The Cardiovascular System at a Glance

Fifth Edition

Philip I. Aaronson
Jeremy P.T. Ward
Michelle J. Connolly

with website

WILEY Blackwell

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Preface

This book is designed to present a concise description of the cardiovascular system which integrates normal structure and function with pathophysiology, pharmacology and therapeutics. We therefore cover in an accessible yet comprehensive manner all of the topics that preclinical medical students and biomedical science students are likely to encounter when they are learning about the cardiovascular system. However, our aims in writing and revising this book have always been more ambitious – we have also sought to provide to our readers a straightforward description of fascinating and important topics that are often neglected or covered only superficially by other textbooks and most university and medical courses. We hope that this book will not only inform you about the cardiovascular system, but enthuse you to look more deeply into at least some of its many remarkable aspects.

In addition to making substantial revisions designed to update the topics, address reviewers' criticisms and simplify some of the diagrams, we have added three chapters to expand our coverage of cardiac arrhythmias and congenital heart disease, myopathies and channelopathies, and have also included a new chapter on stroke.

Philip I. Aaronson
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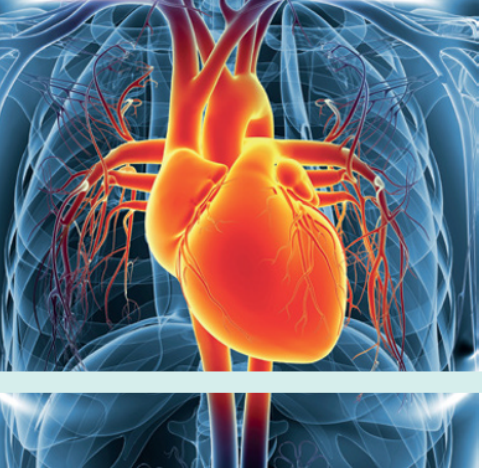

Recommended reading

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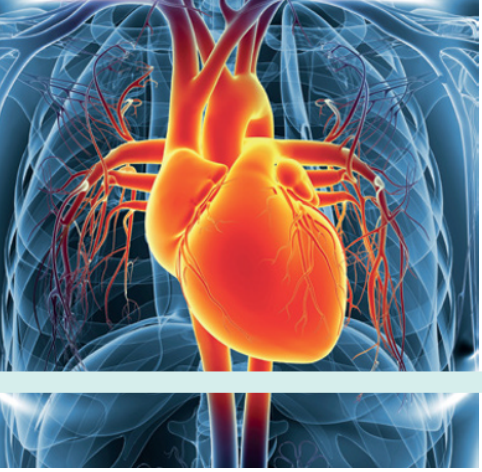

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We would also like to thank our Project Editor Anupama Sreekanth for her assistance in keeping track of our progress and her patience in putting up with our difficulties in meeting our deadlines, and for making sure that this book and its companion website look every bit as good as we were hoping they would. Finally, as always, we thank our readers, particularly our students at King's College London, whose support over the years has encouraged us to keep trying to make this book better.

List of abbreviations

5-HT	5-hydroxytryptamine (serotonin)
AAA	abdominal aortic aneurysm
ABP	arterial blood pressure
AC	adenylate cyclase
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor/s
ACS	acute coronary syndromes
ADH	antidiuretic hormone
ADMA	asymmetrical dimethyl arginine
ADP	adenosine diphosphate
AF	atrial fibrillation
AMP	adenosine monophosphate
ANP	atrial natriuretic peptide
ANS	autonomic nervous system
AP	action potential
APAH	pulmonary hypertension associated with other conditions
APC	active protein C
APD	action potential duration
aPTT	activated partial thromboplastin time
AR	aortic regurgitation
ARB	angiotensin 2 receptor blocker
ARDS	acute respiratory distress syndrome
AS	aortic stenosis
ASD	atrial septal defect
ATP	adenosine triphosphate
AV	atrioventricular
AVA	arteriovenous anastomosis
AVN	atrioventricular node
AVNRT	atrioventricular nodal re-entrant tachycardia
AVRT	atrioventricular re-entrant tachycardia
AVSD	Atrioventricular septal defects
BBB	blood–brain barrier
BP	blood pressure
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CaM	calmodulin
cAMP	cyclic adenosine monophosphate
CCB	calcium-channel blocker
CE	cholesteryl ester
CETP	cholesteryl ester transfer protein
CFU-E	colony-forming unit erythroid cell
cGMP	cyclic guanosine monophosphate
CHB	omplete heart block
CHD	congenital heart disease
CHD	coronary heart disease
CHF	chronic heart failure
CICR	calcium-induced calcium release
CK-MB	creatine kinase MB
CMR	cardiac magnetic resonance imaging
CNS	central nervous system
CO	cardiac output
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
CPVT	catecholaminergic polymorphic ventricular tachycardia
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computed tomography
CTPA	computed tomography pulmonary angiogram
CVD	cardiovascular disease
CVP	central venous pressure
CXR	chest X-ray
DAD	delayed afterdepolarization
DAG	diacylglycerol
DAPT	dual antiplatelet therapy
DBP	diastolic blood pressure
DC	direct current
DCM	dilated cardiomyopathy
DCCV	direct current cardioversion
DHP	dihydropyridine
DIC	disseminated intravascular coagulation
DM2	type 2 diabetes mellitus
DSE	dobutamine stress echocardiography
DVT	deep venous/vein thrombosis
EAD	early afterdepolarization
ECF	extracellular fluid
ECG	electrocardiogram/electrocardiograph (EKG)
ECM	extracellular matrix
EDHF	endothelium-derived hyperpolarizing factor
EDP	end-diastolic pressure
EDRF	endothelium-derived relaxing factor
EDTA	ethylenediaminetetraacetic acid
EDV	end-diastolic volume
EET	epoxyeicosatrienoic acid
EnaC	epithelial sodium channel
eNOS	endothelial NOS
ERP	effective refractory period
ESR	erythrocyte sedimentation rate
FDP	fibrin degradation product
GP	glycoprotein
GPI	glycoprotein inhibitor
GTN	glyceryl trinitrate
Hb	haemoglobin
HCM	hypertrophic cardiomyopathy
HDL	high-density lipoprotein
HEET	hydroxyeicosatetraenoic acid
HMG-CoA	hydroxy-methylglutanyl coenzyme A
hPAH	heritable pulmonary arterial hypertension
HPV	hypoxic pulmonary vasoconstriction

HR	heart rate
IABP	intra-aortic balloon pump
ICD	implantable cardioverter defibrillator
IDL	intermediate-density lipoprotein
Ig	immunoglobulin
IML	intermediolateral
iNOS	inducible NOS
INR	international normalized ratio
IP_3	inisotol 1,4,5-triphosphate
iPAH	idiopathic pulmonary arterial hypertension
ISH	isolated systolic hypertension
IVUS	intravascular ultrasound
JVP	jugular venous pressure
LA	left atrium
LBBB	left bundle branch block
LDL	low-density lipoprotein
LITA	left internal thoracic artery
LMWH	low molecular weight heparin
L-NAME	L-nitro arginine methyl ester
LPL	lipoprotein lipase
LQT	long QT
LV	left ventricle/left ventricular
LVAD	left ventricular assist device
LVH	left ventricular hypertrophy
MABP	mean arterial blood pressure
MCH	mean cell haemoglobin
MCHC	mean cell haemoglobin concentration
MCV	mean cell volume
MI	myocardial infarction
MLCK	myosin light-chain kinase
mPAP	mean pressure in the pulmonary artery
MR	mitral regurgitation
MRI	magnetic resonance imaging
MS	mitral stenosis
MW	molecular weight
NCX	Na^+–Ca^{2+} exchanger
NK	natural killer
NO	nitric oxide
NOS	nitric oxide synthase
nNOS	neuronal nitric oxide synthase
NSAID	non-steroidal anti-inflammatory drug
NSCC	non-selective cation channel
NSTEMI	non-ST segment elevation myocardial infarction
NTS	nucleus tractus solitarius
NYHA	New York Heart Association
OCT	optical coherence tomography
PA	postero-anterior
PA	pulmonary artery
PAH	pulmonary arterial hypertension
PAI-1	plasminogen activator inhibitor-1
PCI	percutaneous coronary intervention
PCV	packed cell volume
PD	potential difference
PDA	patent ductus arteriosus
PDE	phosphodiesterase
PE	pulmonary embolism
PGE_2	prostaglandin E_2
PGI_2	prostacyclin
PH	pulmonary hypertension
PI3K	phosphatidylinositol 3-kinase
PKA	protein kinase A
PKC	protein kinase C
PKG	cyclic GMP-dependent protein kinase
PLD	phospholipid
PMCA	plasma membrane Ca^{2+}-ATPase
PMN	polymorphonuclear leucocyte
PND	paroxysmal nocturnal dyspnoea
PPAR	proliferator-activated receptor
PRU	peripheral resistance unit
PT	prothrombin time
PTCA	percutaneous transcoronary angioplasty
PVC	premature ventricular contraction
PVR	pulmonary vascular resistance
RAA	renin–angiotensin–aldosterone
RBBB	right bundle branch block
RCA	radiofrequency catheter ablation
RCC	red cell count
RGC	receptor-gated channel
RMP	resting membrane potential
RV	right ventricle/right ventricular
RVLM	rostral ventrolateral medulla
RVOT	right ventricular outflow tract tachycardia
RyR	ryanodine receptor
SAN	sinoatrial node
SBP	systolic blood pressure
SERCA	smooth endoplasmic reticulum Ca^{2+}-ATPase
SK	streptokinase
SMTC	S-methyl-L-thiocitrulline
SOC	store-operated Ca^{2+} channel
SPECT	single photon emission computed tomography
SR	sarcoplasmic reticulum
STEMI	ST elevation myocardial infarction
SV	stroke volume
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
TAFI	thrombin activated fibrinolysis inhibitor
TAVI	transcatheter aortic valve implantation
TB	tuberculosis
TEE	transthoracic echocardiogram
TF	tissue factor thromboplastin
TFPI	tissue factor pathway inhibitor
TGF	transforming growth factor
TIA	transient ischaemic attack
TOE	transoesophageal echocardiography/echocardiogram
tPA	tissue plasminogen activator
TPR	total peripheral resistance
TRP	transient receptor potential
TXA_2	thromboxane A_2
UA	unstable angina
uPA	urokinase
VF	ventricular fibrillation
VGC	voltage-gated channel
VLDL	very low density lipoprotein
VSD	ventricular septal defect
VSM	vascular smooth muscle
VT	ventricular tachycardia
VTE	venous thromboembolism
vWF	von Willebrand factor
WBCC	white blood cell count
WPW	Wolff–Parkinson–White

About the companion website

This book is accompanied by a companion website:

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Scan this QR code to visit the companion website:

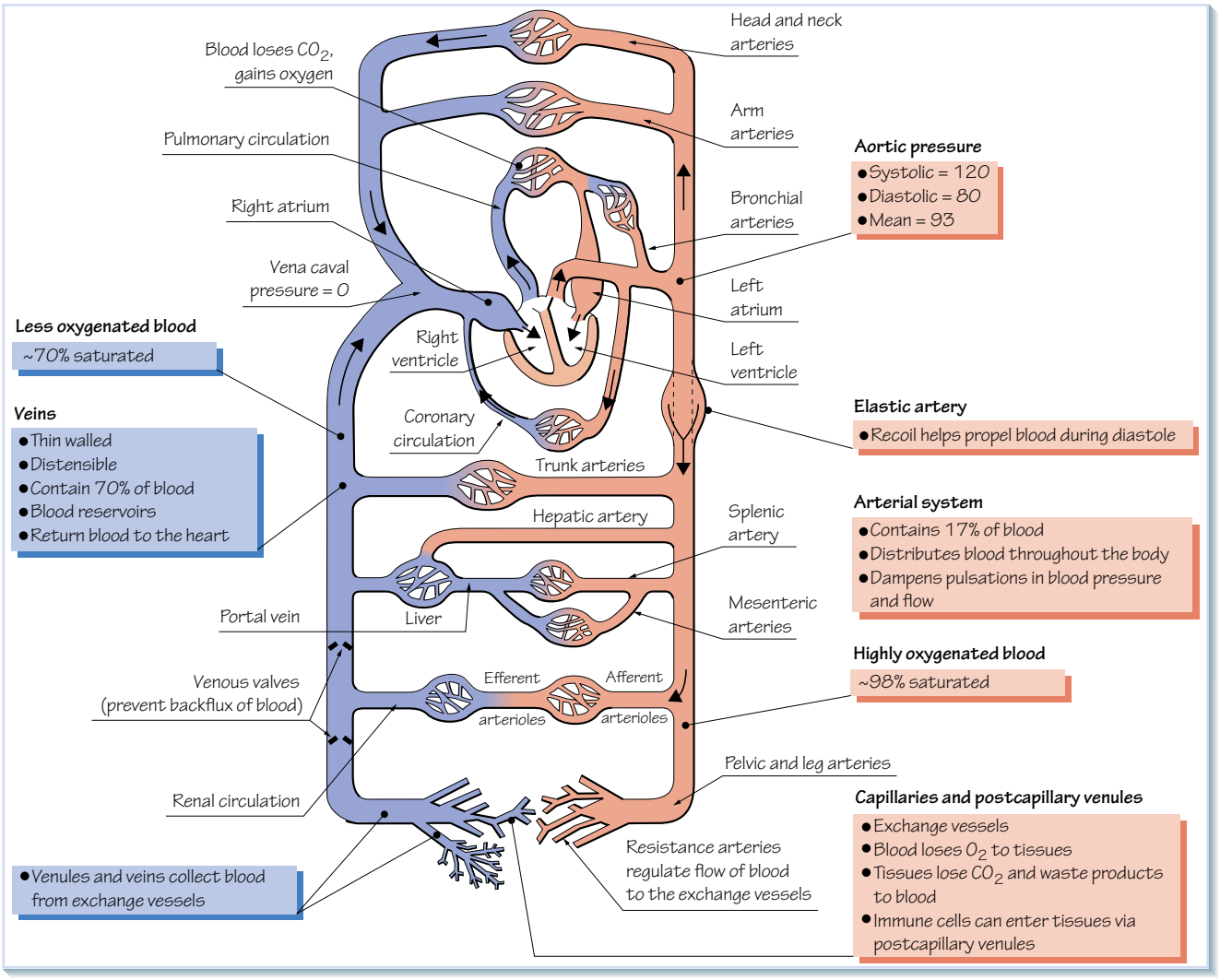
The website includes self-assessment questions and answers

Introduction

Chapter

1 Overview of the cardiovascular system

Figure 1.1 Schematic of the cardiovascular system



The cardiovascular system is composed of the heart, blood vessels and blood. In simple terms, its main functions are:

1. distribution of O_2 and nutrients (e.g. glucose, amino acids) to all body tissues
2. transportation of CO_2 and metabolic waste products (e.g. urea) from the tissues to the lungs and excretory organs
3. distribution of water, electrolytes and hormones throughout the body
4. contributing to the infrastructure of the immune system
5. thermoregulation.

Blood is composed of **plasma**, an aqueous solution containing electrolytes, proteins and other molecules, in which **cells** are suspended. The cells comprise 40–45% of blood volume and are mainly **erythrocytes**, but also **white blood cells** and **platelets**. Blood volume is about 5.5 L in an 'average' 70-kg man.

Figure 1.1 illustrates the 'plumbing' of the cardiovascular system.

Blood is driven through the cardiovascular system by the **heart**, a muscular pump divided into left and right sides. Each side contains two chambers, an **atrium** and a **ventricle**, composed mainly of cardiac muscle cells. The thin-walled atria serve to fill or 'prime' the thick-walled ventricles, which when full constrict forcefully, creating a pressure head that drives the blood out into the body. Blood enters and leaves each chamber of the heart through separate one-way valves, which open and close reciprocally (i.e. one closes before the other opens) to ensure that flow is unidirectional.

Consider the flow of blood, starting with its exit from the left ventricle.

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When the ventricles contract, the left ventricular internal pressure rises from 0 to 120 mmHg (atmospheric pressure = 0). As the pressure rises, the aortic valve opens and blood is expelled into the **aorta**, the first and largest artery of the **systemic circulation**. This period of ventricular contraction is termed **systole**. The maximal pressure during systole is called the **systolic pressure**, and it serves both to drive blood through the aorta and to distend the aorta, which is quite elastic. The aortic valve then closes, and the left ventricle relaxes so that it can be refilled with blood from the left atrium via the mitral valve. The period of relaxation is called **diastole**. During diastole aortic blood flow and pressure diminish but do not fall to zero, because *elastic recoil* of the aorta continues to exert a **diastolic pressure** on the blood, which gradually falls to a minimum level of about 80 mmHg. The difference between systolic and diastolic pressures is termed the **pulse pressure**. **Mean arterial blood pressure** (MABP) is pressure averaged over the entire cardiac cycle. Because the heart spends approximately 60% of the cardiac cycle in diastole, the MABP is approximately equal to the diastolic pressure + one-third of the pulse pressure, rather than to the arithmetic average of the systolic and diastolic pressures.

The blood flows from the aorta into the **major arteries**, each of which supplies blood to an organ or body region. These arteries divide and subdivide into smaller **muscular arteries**, which eventually give rise to the **arterioles** – arteries with diameters of <100 μm. Blood enters the arterioles at a mean pressure of about 60–70 mmHg.

The walls of the arteries and arterioles have circumferentially arranged layers of **smooth muscle cells**. The lumen of the entire vascular system is lined by a monolayer of **endothelial cells**. These cells secrete vasoactive substances and serve as a barrier, restricting and controlling the movement of fluid, molecules and cells into and out of the vasculature.

The arterioles lead to the smallest vessels, the **capillaries**, which form a dense network within all body tissues. The capillary wall is a layer of overlapping endothelial cells, with no smooth muscle cells. The pressure in the capillaries ranges from about 25 mmHg on the arterial side to 15 mmHg at the venous end. The capillaries converge into small **venules**, which also have thin walls of mainly endothelial cells. The venules merge into larger venules, with an increasing content of smooth muscle cells as they widen. These then converge to become **veins**, which progressively join to give rise to the **superior** and **inferior venae cavae**, through which blood returns to the right side of the heart. Veins have a larger diameter than arteries and thus offer relatively little resistance to flow. The small pressure gradient between venules (15 mmHg) and the venae cavae (0 mmHg) is therefore sufficient to drive blood back to the heart.

Blood from the venae cavae enters the **right atrium** and then the **right ventricle** through the **tricuspid valve**. Contraction of the right ventricle, simultaneous with that of the left ventricle, forces blood through the pulmonary valve into the pulmonary artery, which progressively subdivides to form the arteries, arterioles and capillaries of the **pulmonary circulation**. The pulmonary circulation is shorter and has a much lower pressure than the systemic circulation, with systolic and diastolic pressures of about 25 and 10 mmHg, respectively. The pulmonary capillary network within the lungs surrounds the alveoli of the lungs, allowing exchange of CO_2 for O_2. Oxygenated blood enters pulmonary venules and veins and then the **left atrium**, which pumps it into the left ventricle for the next systemic cycle.

The output of the right ventricle is slightly lower than that of the left ventricle. This is because 1–2% of the systemic blood flow never reaches the right atrium but is shunted to the left side of the heart via the bronchial circulation (Figure 1.1), and a small fraction of coronary blood flow drains into the thebesian veins (see Chapter 2).

Blood vessel functions

Each vessel type has important functions in addition to being a conduit for blood.

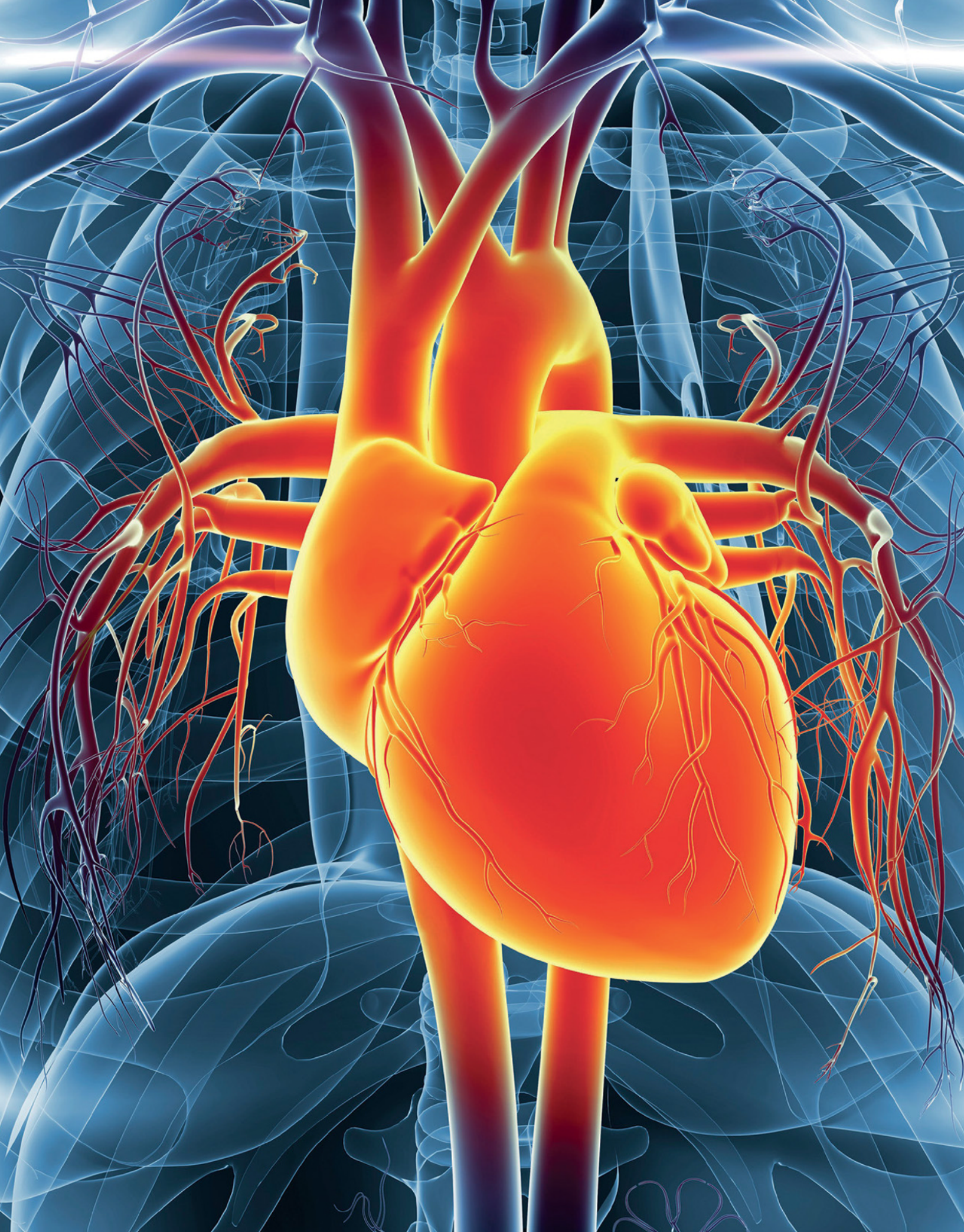
The branching system of elastic and muscular arteries progressively reduces the pulsations in blood pressure and flow imposed by the intermittent ventricular contractions.

The smallest arteries and arterioles have a crucial role in regulating the amount of blood flowing to the tissues by dilating or constricting. This function is regulated by the sympathetic nervous system and factors generated locally in tissues. These vessels are referred to as **resistance arteries**, because their constriction resists the flow of blood.

Capillaries and small venules are the **exchange vessels**. Through their walls, gases, fluids and molecules are transferred between blood and tissues. White blood cells can also pass through the venule walls to fight infection in the tissues.

Venules can constrict to offer resistance to the blood flow, and the ratio of arteriolar and venular resistance exerts an important influence on the movement of fluid between capillaries and tissues, thereby affecting blood volume.

The veins are thin walled and very *distensible*, and therefore contain about 70% of all blood in the cardiovascular system. The arteries contain just 17% of total blood volume. Veins and venules thus serve as volume reservoirs, which can shift blood from the peripheral circulation into the heart and arteries by constricting. In doing so, they can help to increase the **cardiac output** (volume of blood pumped by the heart per unit time), and they are also able to maintain the blood pressure and tissue perfusion in essential organs if **haemorrhage** (blood loss) occurs.

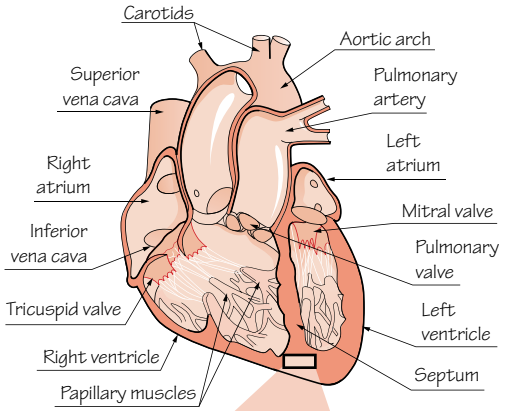


Anatomy and histology

Chapters

2 Gross anatomy and histology of the heart

Figure 2.1 Gross anatomy of the heart



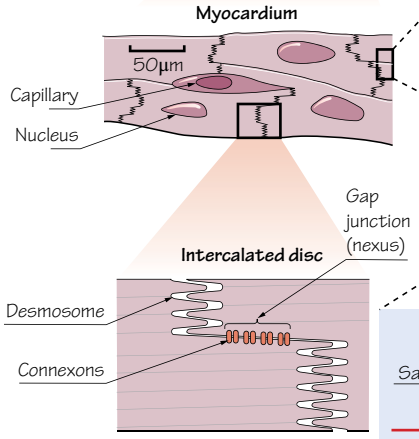
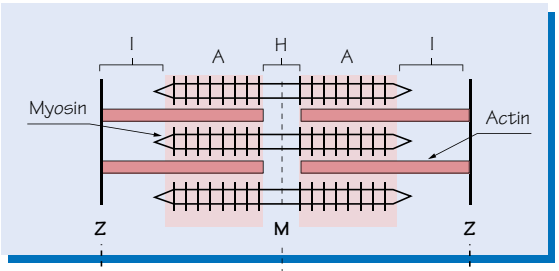


Figure 2.2 Arrangement of intercalated disks

Figure 2.3 Arrangement of sarcomere lines and bands



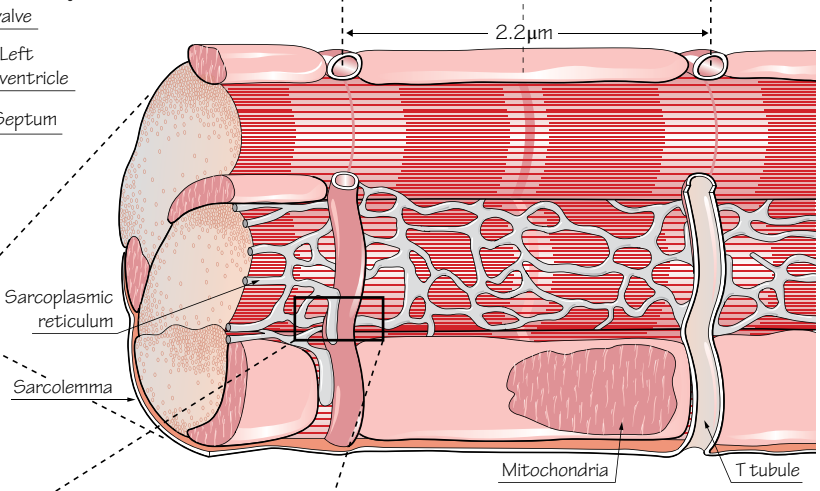


Figure 2.4 Sarcomere structure

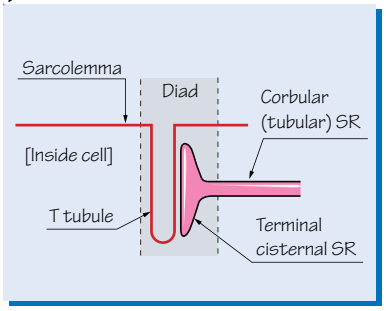


Figure 2.5 Diad structure

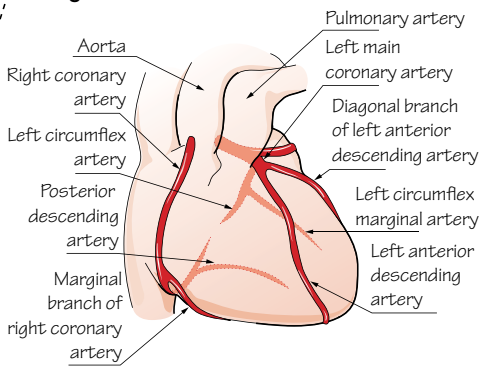


Figure 2.6 Coronary circulation

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Gross anatomy of the heart (Figure 2.1)

The heart consists of four chambers. Blood flows into the right atrium via the superior and inferior venae cavae. The left and right atria connect to the ventricles via the mitral (two cusps) and tricuspid (three cusps) atrioventricular (AV) valves, respectively. The AV valves are passive and closed when the ventricular pressure exceeds that in the atrium. They are prevented from being everted into the atria during systole by fine cords (**chordae tendineae**) attached between the free margins of the cusps and the papillary muscles, which contract during systole. The outflow from the right ventricle passes through the pulmonary semilunar valve to the pulmonary artery, and that from the left ventricle enters the aorta via the aortic semilunar valve. These valves close passively at the end of systole, when ventricular pressure falls below that of the arteries. Both semilunar valves have three cusps.

The cusps or leaflets of the cardiac valves are formed of fibrous connective tissue, covered in a thin layer of cells similar to and contiguous with the **endocardium** (AV valves and ventricular surface of semilunar valves) and **endothelium** (vascular side of semilunar valves). When closed, the cusps form a tight seal (come to apposition) at the **commissures** (line at which the edges of the leaflets meet).

The atria and ventricles are separated by a band of fibrous connective tissue called the **annulus fibrosus**, which provides a skeleton for attachment of the muscle and insertion of the valves. It also prevents electrical conduction between the atria and ventricles except at the **atrioventricular node** (AVN). This is situated near the interatrial septum and the mouth of the coronary sinus and is an important element of the cardiac electrical conduction system (see Chapter 13).

The ventricles fill during diastole; at the initiation of the heartbeat the atria contract and complete ventricular filling. As the ventricles contract the pressure rises sharply, closing the AV valves. When ventricular pressure exceeds the pulmonary artery or aortic pressure, the semilunar valves open and ejection occurs (see Chapter 16). As systole ends and ventricular pressure falls, the semilunar valves are closed by backflow of blood from the arteries.

The force of contraction is generated by the muscle of the heart, the **myocardium**. The atrial walls are thin. The greater pressure generated by the left ventricle compared with the right is reflected by its greater wall thickness. The inside of the heart is covered in a thin layer of cells called the **endocardium**, which is similar to the endothelium of blood vessels. The outer surface of the myocardium is covered by the **epicardium**, a layer of mesothelial cells. The whole heart is enclosed in the **pericardium**, a thin fibrous sheath or sac, which prevents excessive enlargement. The **pericardial space** contains interstitial fluid as a lubricant.

Structure of the myocardium

The myocardium consists of **cardiac myocytes** (*muscle cells*) that show a striated subcellular structure, although they are less organized than skeletal muscle. The cells are relatively small (100 × 20 μm) and branched, with a single nucleus, and are rich in mitochondria. They are connected together as a network by **intercalated discs** (Figure 2.2), where the cell membranes are closely opposed. The intercalated discs provide both a structural attachment by 'glueing' the cells together at **desmosomes**, and an electrical connection through **gap junctions** formed of pores made up of proteins called **connexons**. As a result, the myocardium acts as a **functional syncytium**, in other words as a single functional unit, even though the individual cells are still separate. The gap junctions play a vital part in conduction of the electrical impulse through the myocardium (see Chapter 13).

The myocytes contain **actin** and **myosin** filaments which form the contractile apparatus and exhibit the classic M and Z lines and A, H and I bands (Figure 2.3). The intercalated discs always coincide with a Z line, as it is here that the actin filaments are anchored to the cytoskeleton. At the Z lines the **sarcolemma** (cell membrane) forms tubular invaginations into the cells known as the **transverse** (T) **tubular system**. The **sarcoplasmic reticulum** (SR) is less extensive than in skeletal muscle and runs generally in parallel with the length of the cell (Figure 2.4). Close to the T tubules the SR forms **terminal cisternae** that with the T tubule make up **diads** (Figure 2.5), an important component of excitation–contraction coupling (see Chapter 12). The typical *triad* seen in skeletal muscle is less often present. The T tubules and SR never physically join, but are separated by a narrow gap. The myocardium has an extensive system of capillaries.

Coronary circulation (Figure 2.6)

The heart has a rich blood supply, derived from the **left and right coronary arteries**. These arise separately from the aortic sinus at the base of the aorta, behind the cusps of the aortic valve. They are not blocked by the cusps during systole because of eddy currents, and remain patent throughout the cardiac cycle. The **right coronary artery** runs forward between the pulmonary trunk and right atrium, to the AV sulcus. As it descends to the lower margin of the heart, it divides to **posterior descending** and **right marginal** branches. The **left coronary artery** runs behind the pulmonary trunk and forward between it and the left atrium. It divides into the **circumflex**, **left marginal** and **anterior descending** branches. There are anastomoses between the left and right marginal branches and the anterior and posterior descending arteries, although these are not sufficient to maintain perfusion if one side of the coronary circulation is occluded.

Most of the blood returns to the right atrium via the **coronary sinus**, and **anterior cardiac veins**. The **large** and **small** coronary veins run parallel to the left and right coronary arteries, respectively, and empty into the sinus. Numerous other small vessels empty into the cardiac chambers directly, including **thebesian veins** and **arteriosinusoidal vessels**.

The coronary circulation is capable of developing a good collateral system in ischaemic heart disease, when a branch or branches are occluded by, for example, atheromatous plaques. Most of the left ventricle is supplied by the left coronary artery, and occlusion can therefore be very dangerous. The AVN and **sinus node** are supplied by the right coronary artery in the majority of people; disease in this artery can cause a slow heart rate and AV block (see Chapters 13 and 14).

3 Vascular anatomy

Figure 3.1 Typical dimensions for different types of blood vessels

	Ascending aorta	Muscular artery	Arteriole	Capillary	Venule	Vein	Vena cava
Lumen diameter	25mm	4mm	20µm	5µm	20µm	5mm	30mm
Wall thickness	2mm	1mm	15µm	1µm	2µm	0.5mm	1.5mm

Figure 3.2 Arrangement of the major arteries

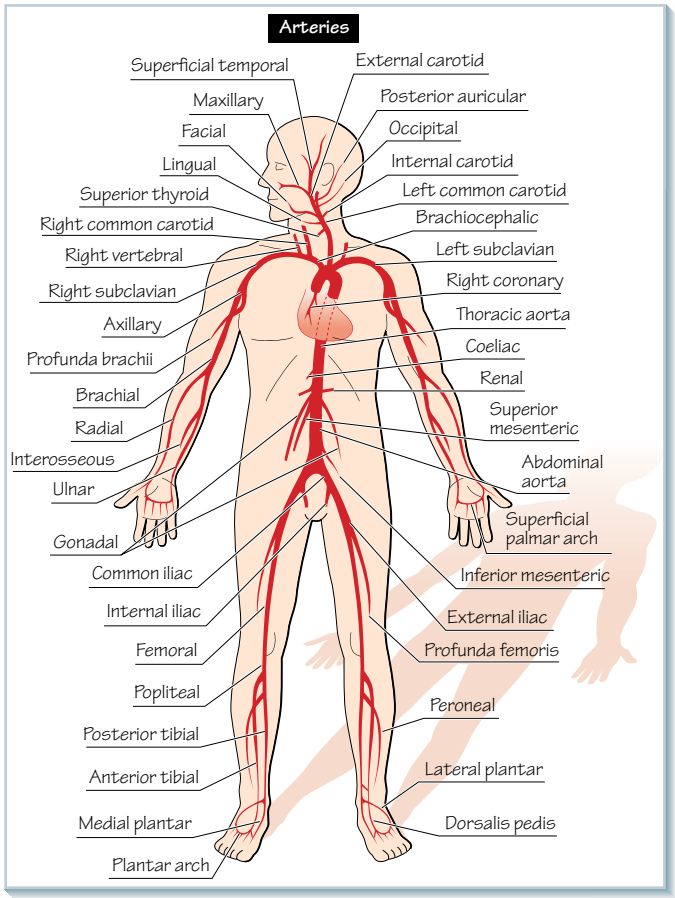
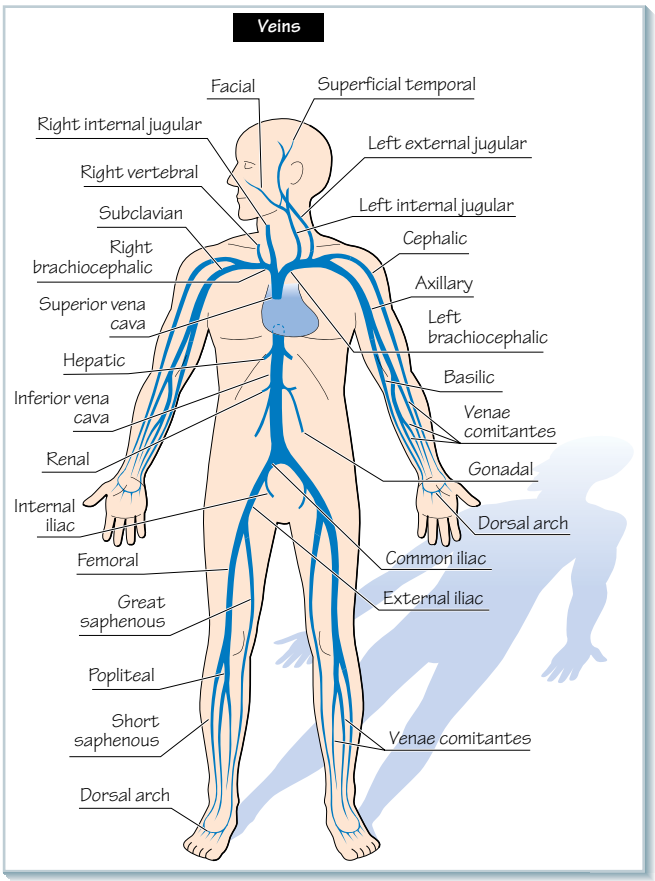


Figure 3.3 Arrangement of the major veins



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The blood vessels of the cardiovascular system are for convenience of description classified into **arteries** (elastic and muscular), **resistance vessels** (small arteries and arterioles), **capillaries**, **venules** and **veins**. Typical dimensions for the different types of vessel are illustrated (Figure 3.1).

The systemic circulation

Arteries (Figure 3.2)

The **systemic (or greater) circulation** begins with the pumping of blood by the left ventricle into the largest artery, the **aorta**. This ascends from the top of the heart, bends downward at the **aortic arch** and descends just anterior to the spinal column. The aorta bifurcates into the left and right **iliac arteries**, which supply the pelvis and legs. The major arteries supplying the head, the arms and the heart arise from the aortic arch, and the main arteries supplying the visceral organs branch from the descending aorta. All of the major organs except the liver (see below) are therefore supplied with blood by arteries that arise from the aorta. The fundamentally *parallel* organization of the systemic vasculature has a number of advantages over the alternative *series* arrangement, in which blood would flow sequentially through one organ after another. The parallel arrangement of the vascular system ensures that the supply of blood to each organ is relatively independent, is driven by a large pressure head, and also that each organ receives highly oxygenated blood.

The aorta and its major branches (**brachiocephalic**, **common carotid**, **subclavian** and **common iliac** arteries) are termed **elastic arteries**. In addition to conducting blood away from the heart, these arteries distend during systole and recoil during diastole, damping the pulse wave and evening out the discontinuous flow of blood created by the heart's intermittent pumping action.

Elastic arteries branch to give rise to **muscular arteries** with relatively thicker walls; this prevents their collapse when joints bend. The muscular arteries give rise to **resistance vessels**, so named because they present the greatest part of the resistance of the vasculature to the flow of blood. These are sometimes subclassified into small arteries, which have multiple layers of smooth muscle cells in their walls, and **arterioles**, which have one or two layers of smooth muscle cells. Resistance vessels have the highest wall to lumen ratio in the vasculature. The degree of constriction or tone of these vessels regulates the amount of blood flowing to each small area of tissue. All but the smallest resistance vessels tend to be heavily innervated (especially in the *splanchnic*, *renal* and *cutaneous* vasculatures) by the **sympathetic nervous system**, the activity of which usually causes them to constrict (see Chapter 28).

Arterial anastomoses

In addition to branching to give rise to smaller vessels, arteries and arterioles may also merge to form **anastomoses**. These are found in many circulations (e.g. the brain, mesentery, uterus, around joints) and provide an alternative supply of blood if one artery is blocked. If this occurs, the anastamosing artery gradually enlarges, providing a **collateral circulation**.

The smallest arterioles, capillaries and postcapillary venules comprise the **microcirculation**, the structure and function of which are described in Chapters 20 and 21.

Veins (Figure 3.3)

The venous system can be divided into the **venules**, which contain one or two layers of smooth muscle cells, and the **veins**. The veins of the limbs, particularly the legs, contain paired **semilunar valves** which ensure that the blood cannot move backwards. These are orientated so that they are pressed against the venous wall when the blood is flowing forward but are forced out to occlude the lumen when the blood flow reverses.

The veins from the head, neck and arms come together to form the **superior vena cava**, and those from the lower part of the body merge into the **inferior vena cava**. These deliver blood to the right atrium, which pumps it into the right ventricle.

The one or two veins draining a body region typically run next to the artery supplying that region. This promotes heat conservation, because at low temperatures the warmer arterial blood gives up its heat to the cooler venous blood, rather than to the external environment. The pulsations of the artery caused by the heartbeat also aid the venous flow of blood.

The pulmonary circulation

The **pulmonary (or lesser) circulation** begins when blood is pumped by the right ventricle into the **main pulmonary artery**, which immediately bifurcates into the **right** and **left pulmonary arteries** supplying each lung. This 'venous' blood is oxygenated during its passage through the pulmonary capillaries. It then returns to the heart via the **pulmonary veins** to the left atrium, which pumps it into the left ventricle. The metabolic demands of the lungs are not met by the pulmonary circulation, but by the **bronchial circulation**. This arises from the **intercostal arteries**, which branch from the aorta. Most of the veins of the bronchial circulation terminate in the right atrium, but some drain into the pulmonary veins.

The splanchnic circulation

The arrangement of the **splanchnic circulation** (liver and digestive organs) is a partial exception to the parallel organization of the systemic vasculature (see Figure 3.1). Although a fraction of the blood supply to the liver is provided by the hepatic artery, the liver receives most (approximately 70%) of its blood via the **portal vein**. This vessel carries venous blood that has passed through the capillary beds of the stomach, spleen, pancreas and intestine. Most of the liver's circulation is therefore *in series* with that of the digestive organs. This arrangement facilitates hepatic uptake of nutrients and detoxification of foreign substances that have been absorbed during digestion. This type of sequential perfusion of two capillary beds is referred to as a **portal circulation**. A somewhat different type of portal circulation is also found within the kidney.

The lymphatic system

The body contains a parallel circulatory system of **lymphatic vessels** and **nodes** (see Chapter 20). The lymphatic system functions to return to the cardiovascular system the approximately 8 L/day of interstitial fluid that leaves the exchange vessels to enter body tissues. The larger lymphatic vessels pass through nodes containing lymphocytes, which act to mount an immune response to microbes, bacterial toxins and other foreign material carried into the lymphatic system with the interstitial fluid.

4 Vascular histology and smooth muscle cell ultrastructure

Figure 4.1 Structure of a typical small muscular artery

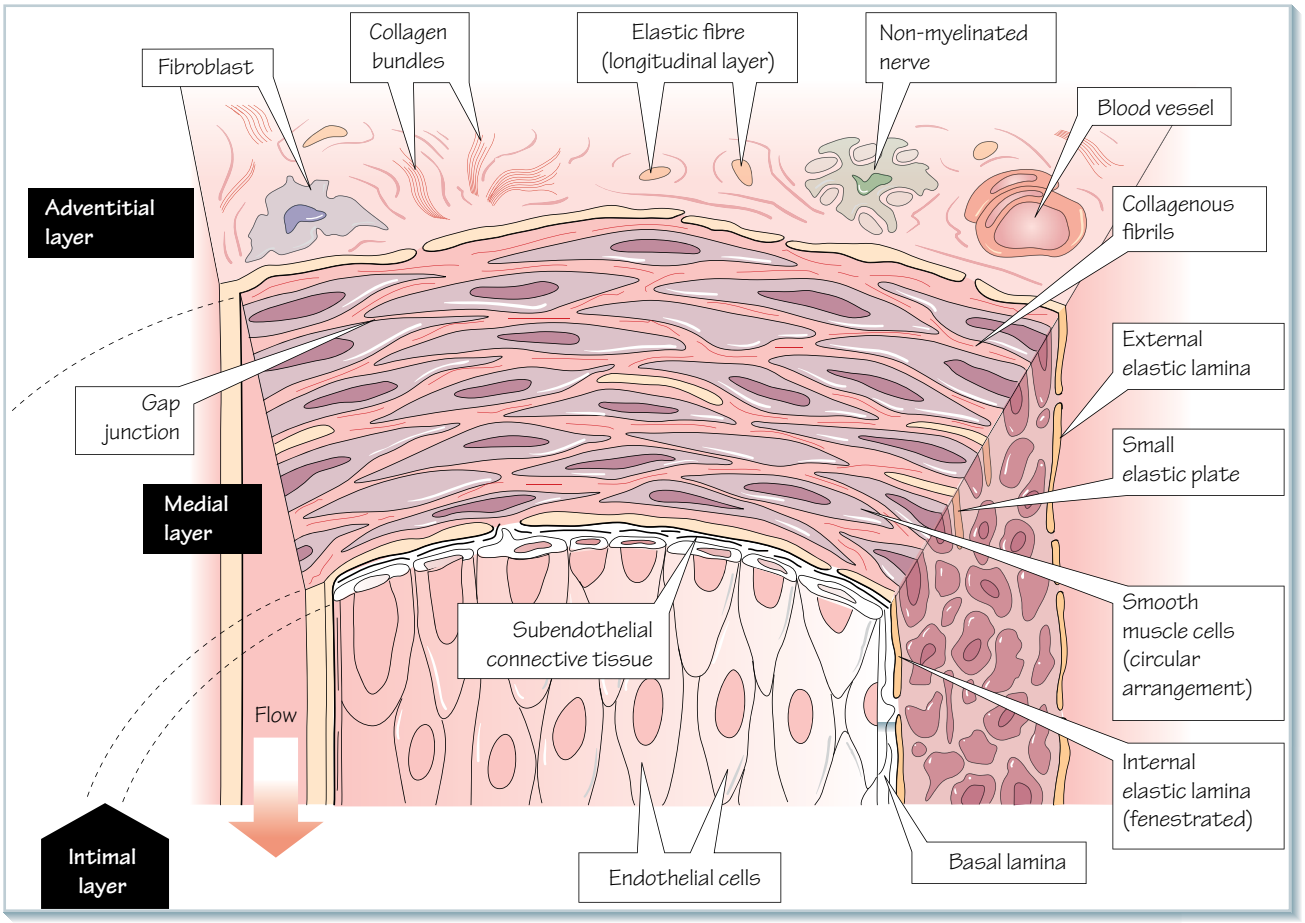
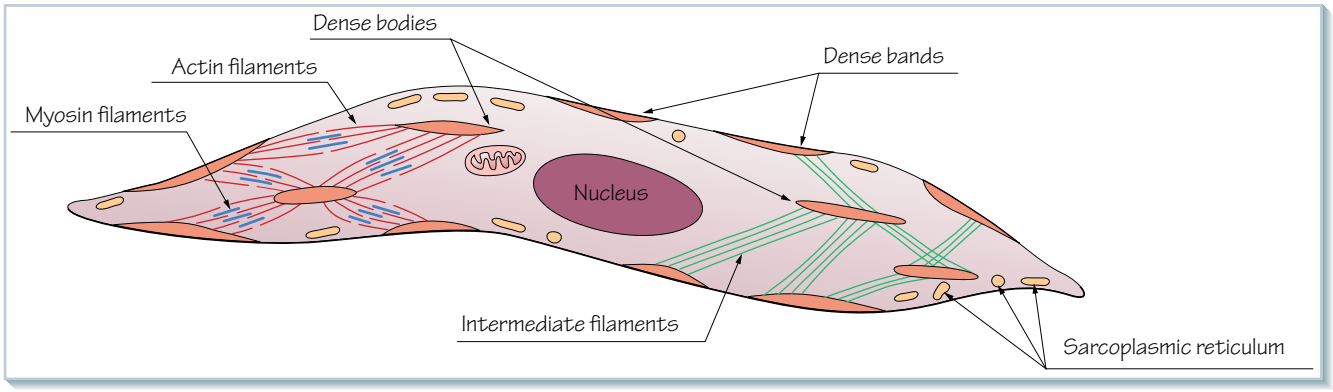


Figure 4.2 Smooth muscle cell ultrastructure



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Larger blood vessels share a common three-layered structure. Figure 4.1 illustrates the arrangement of these layers, or *tunics*, in a muscular artery.

A thin inner layer, the **tunica intima**, comprises an endothelial cell monolayer (**endothelium**) supported by connective tissue. The endothelial cells lining the vascular lumen are sealed to each other by tight **junctions**, which restrict the diffusion of large molecules across the endothelium. The endothelial cells have a crucial role in controlling vascular permeability, vasoconstriction, angiogenesis (growth of new blood vessels) and regulation of haemostasis. The intima is relatively thicker in larger arteries and contains some smooth muscle cells in large and medium-sized arteries and veins.

The thick middle layer, the **tunica media**, is separated from the intima by a fenestrated (perforated) sheath, the **internal elastic lamina**, mostly composed of elastin. The media contains **smooth muscle cells** embedded in an **extracellular matrix** (ECM) composed mainly of collagen, elastin and proteoglycans. The cells are shaped like elongated and irregular spindles or cylinders with tapering ends and are 15–100 μm long. In the arterial system, they are orientated circularly or in a low-pitch spiral, so that the vascular lumen narrows when they contract. Individual cells are long enough to wrap around small arterioles several times.

Adjacent smooth muscle cells form **gap junctions**. These are areas of close cellular contact in which arrays of large channels called **connexons** span both cell membranes, allowing ions to flow from one cell to another. The smooth muscle cells therefore form a **syncytium**, in which depolarization spreads from each cell to its neighbours.

An **external elastic lamina** separates the tunica media from the outer layer, the **tunica adventitia**. This contains collagenous tissue supporting fibroblasts and nerves. In large arteries and veins, the adventitia contains **vasa vasorum**, small blood vessels that also penetrate into the outer portion of the media and supply the vascular wall with oxygen and nutrients.

These three layers are also present in the venous system but are less distinct. Compared with arteries, veins have a thinner tunica media containing a smaller amount of smooth muscle cells, which also tend to have a more random orientation.

The protein **elastin** is found mainly in the arteries. Molecules of elastin are arranged into a network of randomly coiled fibres. These molecular 'springs' allow arteries to expand during systole and then rebound during diastole to keep the blood flowing forward. This is particularly important in the aorta and other large elastic arteries, in which the media contains fenestrated sheets of elastin separating the smooth muscle cells into multiple concentric layers (lamellae).

The fibrous protein **collagen** is present in all three layers of the vascular wall and functions as a framework that anchors the smooth muscle cells in place. At high internal pressures, the collagen network becomes very rigid, limiting vascular distensibility. This is particularly important in veins, which have a higher collagen content than arteries.

Exchange vessel structure

Capillaries and postcapillary venules are tubes formed of a single layer of overlapping endothelial cells. This is supported and surrounded on the external side by the **basal lamina**, a 50–100 nm layer of fibrous proteins including collagen, and glycoproteins. **Pericytes**, isolated cells that can give rise to smooth muscle cells during angiogenesis, adhere to the outside of the basal lamina, especially in postcapillary venules. The luminal side of the endothelium is coated by **glycocalyx**, a dense glycoprotein network attached to the cell membrane.

There are three types of capillaries, and these differ in their locations and permeabilities. Their structures are illustrated in Chapter 20.

Continuous capillaries occur in skin, muscles, lungs and the central nervous system. They have a low permeability to molecules that cannot pass readily through cell membranes, owing to the presence of tight junctions which bring the overlapping membranes of adjacent endothelial cells into close contact. The tight junctions run around the perimeter of each cell, forming a seal restricting the paracellular flow of molecules of molecular weight (MW) >10 000. These junctions are especially tight in most capillaries of the central nervous system and form an integral part of the **blood–brain barrier** (see Chapter 20).

Fenestrated capillaries are much more permeable than continuous capillaries. These are found in endocrine glands, renal glomeruli, intestinal villi and other tissues in which large amounts of fluid or metabolites enter or leave capillaries. In addition to having leakier intercellular junctions, the endothelial cells of these capillaries contain **fenestrae**, circular pores of diameter 50–100 nm spanning areas of the cells where the cytoplasm is thinned. Except in the renal glomeruli, fenestrae are usually covered by a thin perforated diaphragm.

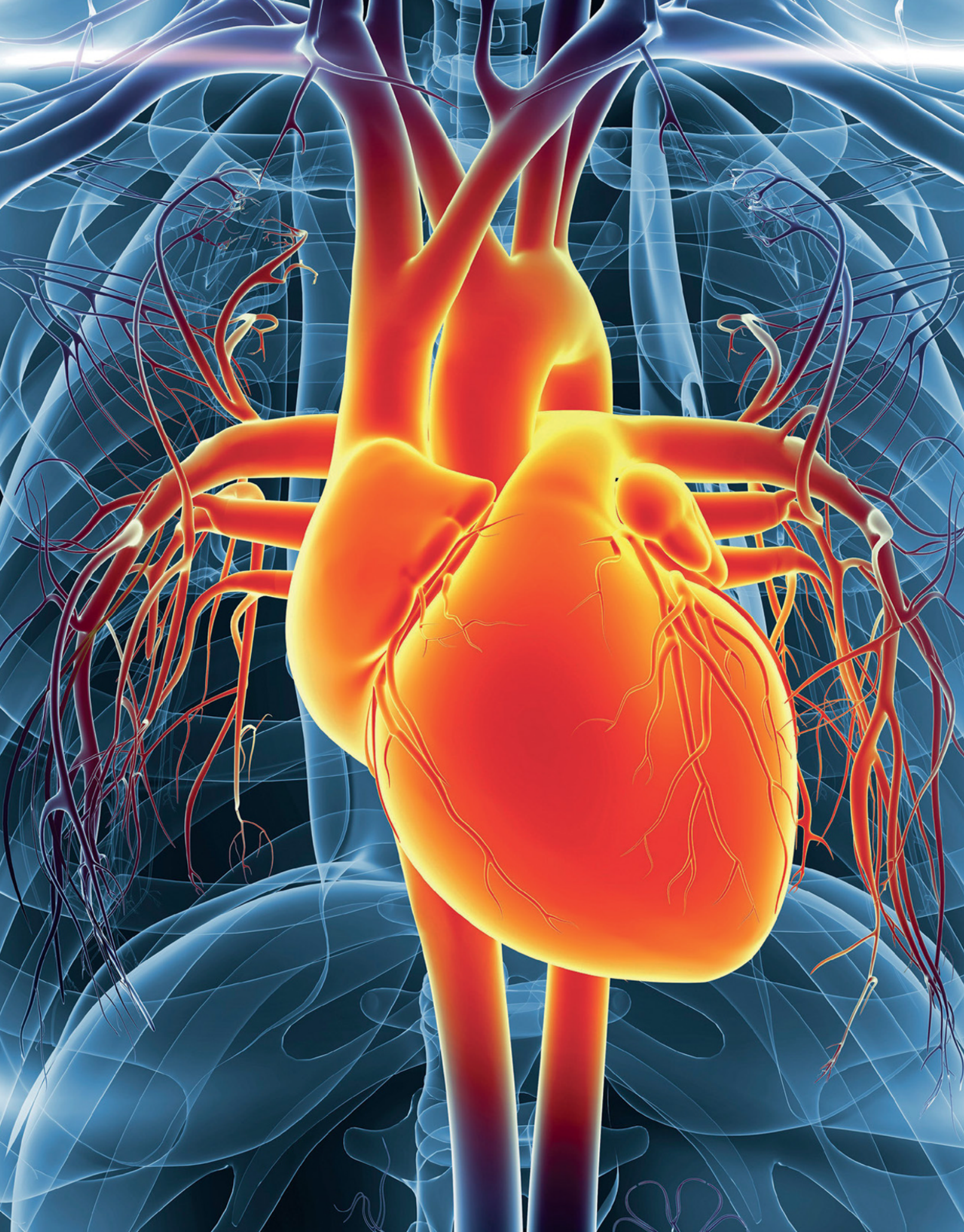
Discontinuous capillaries or **sinusoids** are found in liver, spleen and bone marrow. These are large, irregularly shaped capillaries with gaps between the endothelial cells wide enough to allow large proteins and even erythrocytes to cross the capillary wall.

Smooth muscle cell ultrastructure

The cytoplasm of vascular smooth muscle cells contains thin **actin** and thick **myosin** filaments (Figure 4.2). Instead of being aligned into sarcomeres as in cardiac myocytes, groups of actin filaments running roughly parallel to the long axis of the cell are anchored at one end into elongated **dense bodies** in the cytoplasm and **dense bands** along the inner face of the cell membrane. Dense bodies and bands are linked by bundles of **intermediate filaments** composed mainly of the proteins **desmin** and **vimentin** to form the **cytoskeleton**, an internal scaffold giving the cell its shape. The free ends of the actin filaments interdigitate with myosin filaments. The myosin crossbridges are structured so that the actin filaments on either side of a myosin filament are pulled in opposite directions during crossbridge cycling. This draws the dense bodies towards each other, causing the cytoskeleton, and therefore the cell, to shorten. The dense bands are attached to the ECM by membrane-spanning proteins called **integrins**, allowing force development to be distributed throughout the vascular wall. The interaction between the ECM and integrins is a dynamic process which is affected by forces exerted on the matrix by the pressure inside the vessel. This allows the integrins, which are signalling molecules capable of influencing both cytoskeletal structure and signal transduction, to orchestrate cellular responses to changes in pressure.

The **sarcoplasmic reticulum** (SR, also termed smooth endoplasmic reticulum) occupies 2–6% of cell volume. This network of tubes and flattened sacs permeates the cell and contains a high concentration (~0.5 mmol/L) of free Ca^{2+}. Elements of the SR closely approach the cell membrane. Several types of Ca^{2+}-regulated ion channels and transporters are concentrated in these areas of the plasmalemma, which may have an important role in cellular excitation.

The nucleus is located in the central part of the cell. Organelles including rough endoplasmic reticulum, Golgi complex and mitochondria are mainly found in the perinuclear region.



Blood and body fluids

Chapters

5 Constituents of blood

Figure 5.1 Blood cell centrifugation and PCV

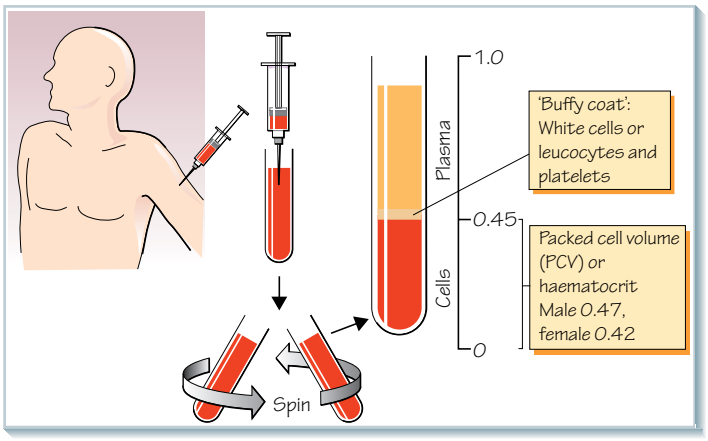
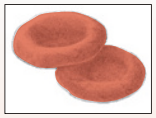


Figure 5.2 Composition of plasma

		Normal range	Units
Osmolality		280–295	mosm/kg H_2O
Electrolytes			
Na^+		135–145	mmol/L
K^+		3.5–5.0	mmol/L
Ca^{2+}	Total	2.2–2.6	mmol/L
	~50% Free	1.0–1.3	mmol/L
Mg^{2+}	Total	0.7–1.1	
	~50% Free	0.3–0.6	mmol/L
Cl^-		98–108	mmol/L
HCO_3^-		22–30	mmol/L
Inorganic phosphate		0.8–1.4	mmol/L
	~85–90% Free		
Proteins (–ve charge)		~14	mmol/L
Cells			
Erythrocytes	male	4.7–6.1	x 10^{-12}/L
	female	4.2–5.4	
Packed cell volume (PCV) (Haematocrit)	male	0.41–0.52	(no unit)
	female	0.36–0.48	
Haemoglobin (Hb)	male	130–180	g/L
	female	120–160	
Leucocytes (total) (White blood cell count, WBCC)		4–11	x 10^9/L
Platelets		150–400	x 10^9/L

Figure 5.4 Erythrocytes (red cells)



Approximate cell diameter = 6.5–8.8μm

Mean cell volume (**MCV**) = $\frac{PCV}{RCC}$ = ~85fL (85 x 10^{-15}L)

Mean cell haemoglobin (**MCH**) = $\frac{Hb}{RCC}$ = ~30pg (30 x 10^{-12}g)

Mean cell haemoglobin concentration (**MCHC**) = $\frac{MCH}{MCV}$ or $\frac{Hb}{PCV}$ = ~350g/L

Figure 5.5 Relative proportion of leucocytes (total count ~ 4-11 x 10^9 per litre)

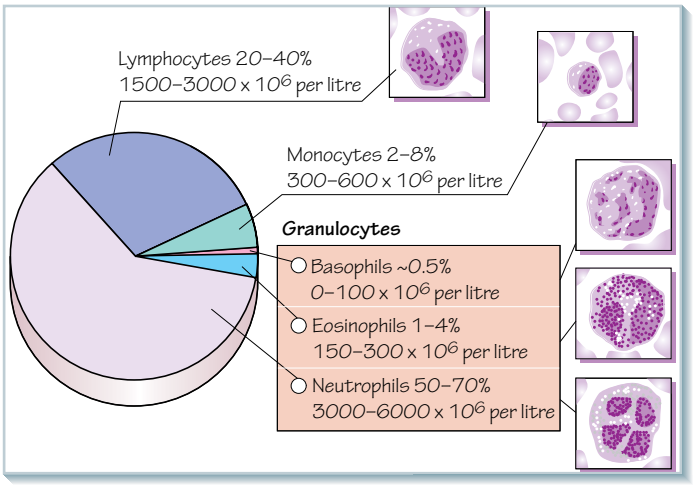


Figure 5.3 Protein composition of plasma

	Average plasma concentration (g/L)	Molecular weight (x 1000)	Functions include
Albumin	48.0	69	Colloidal osmotic pressure; binds hormones, drugs, etc.
α-globulins	5.5	16–90	Copper transport, binds haemoglobin, antiprotease
β-globulins			
Transferrin	3.0	90	Iron transport
Prothrombin	1.0	68	Haemostasis
Plasminogen	0.7	140	Haemostasis
Components of complement	1.6	~200	Immune system
Fibrinogen	3.0	350	Haemostasis
γ-globulins	13.0	150–200 (IgM, 1000)	Immunoglobulins (mostly IgG)

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The primary function of blood is to deliver O_2 and energy sources to the tissues and to remove CO_2 and waste products. It contains elements of the defence and immune systems, is important for regulation of temperature, and transports hormones and other signalling molecules between tissues. In a 70-kg man blood volume is ~5500 mL, or 8% of body weight. Blood consists of **plasma** and **blood cells**. If blood is centrifuged, the cells sediment as the **packed cell volume** (PCV, haematocrit), normally ~45% of total volume (i.e. PCV = 0.45) in men, less in women (Figure 5.1).

Plasma

The plasma volume is ~5% of body weight. It consists of ions in solution and a variety of plasma proteins. Normal ranges for key constituents are shown in Figure 5.2. After clotting, a straw-coloured fluid called **serum** remains, from which fibrinogen and other clotting factors have been removed. The relative osmotic pressures of plasma, interstitial and intracellular fluid are critical for maintenance of tissue cell volume and are related to the amount of osmotically active particles (molecules) per litre, or **osmolarity** (mosmol/L); as plasma is not an ideal fluid (it contains slow diffusing proteins), the term **osmolality** (mosmol/kg H_2O) is often used instead. Plasma **osmolality** is ~290 mosmol/kg H_2O, mostly due to dissolved ions and small diffusible molecules (e.g. glucose and urea). These diffuse easily across capillaries, and the **crystalloid osmotic pressure** they exert is therefore the same either side of the capillary wall. Proteins do not easily pass through capillary walls and are responsible for the **oncotic** (or colloidal osmotic) pressure of the plasma. This is much smaller than crystalloid osmotic pressure but is critical for fluid transfer across capillary walls because it differs between plasma and interstitial fluid (see Chapter 21). Oncotic pressure is expressed in terms of pressure and in plasma is normally ~25 mmHg. Maintenance of plasma osmolality is vital for regulation of blood volume (see Chapter 29).

Ionic composition

Na^+ is the most prevalent ion in plasma and the main determinant of plasma osmolality. Figure 5.2 shows concentrations of the major ions; others are present in smaller amounts. Changes in ionic concentration can have major consequences for excitable tissues (e.g. K^+, Ca^{2+}). Whereas Na^+, K^+ and Cl^- completely dissociate in plasma, Ca^{2+} and Mg^{2+} are partly bound to plasma proteins, so that free concentration is ~50% of the total.

Proteins

Normal total plasma protein concentration is 65–83 g/L. Most plasma proteins other than γ-globulins (see below) are synthesized in the liver. Proteins can ionize as either acids or bases because they have both NH_2 and COOH groups. At pH 7.4 they are mostly in the anionic (acidic) form. Their ability to accept or donate H^+ means they can act as buffers and account for ~15% of the buffering capacity of blood. Plasma proteins have important transport functions. They bind with many hormones (e.g. cortisol, thyroxine), metals (e.g. iron) and drugs and therefore modulate their free concentration and thus biological activity. Plasma proteins encompass **albumin**, **fibrinogen** and **globulins** (Figure 5.3). Globulins are further classified as α-, β- and γ-globulins. β-globulins include transferrin (iron transport), components of complement (immune system), and prothrombin and plasminogen, which with fibrinogen are involved in blood clotting (Chapter 7). The most important γ-globulins are the immunoglobulins (e.g. IgG, IgE, IgM).

Blood cells

In the adult, all blood cells are produced in the **red bone marrow**, although in the fetus, and following bone marrow damage in the adult, they are also produced in the liver and spleen. The marrow contains a small number of **uncommitted stem cells**, which differentiate into specific **committed stem cells** for each blood cell type. **Platelets** are not true cells, but small (~3 μm) vesicle-like structures formed from **megakaryocytes** in the bone marrow, containing clearly visible **dense granules**. Platelets play a key role in haemostasis (Chapter 7) and have a lifespan of ~4 days.

Erythrocytes

Erythrocytes (red cells) are by far the most numerous cells in the blood (Figure 5.4), with ~5.5×10^{12}/L in males (red cell count, RCC). Erythrocytes are biconcave discs with no nucleus, and a mean cell volume (**MCV**) of ~85 fL. Each contains ~30 pg haemoglobin (mean cell haemoglobin, **MCH**), which is responsible for carriage of O_2 and plays an important part in acid–base buffering. Blood contains ~160 g/L (male) and ~140 g/L (female) haemoglobin. The shape and flexibility of erythrocytes allows them to deform easily and pass through the capillaries. When blood is allowed to stand in the presence of anticoagulant, the cells slowly sediment (erythrocyte sedimentation rate, **ESR**). The ESR is increased when cells stack together (form *rouleaux*), and in pregnancy and inflammatory disease, and decreased by low plasma fibrinogen. Erythrocytes have an average lifespan of 120 days. Their formation (erythropoiesis) and related diseases are discussed in Chapter 6.

Leucocytes (white cells) and platelets

Leucocytes defend the body against infection by foreign material. The normal white blood cell count (WBCC, see Figure 5.5) increases greatly in disease (**leucocytosis**). In the newborn infant the WBCC is ~20×10^9/L. Three main types are present in blood: **granulocytes** (polymorphonuclear leucocytes, PMN), **lymphocytes** and **monocytes**. Granulocytes are further classified as **neutrophils** (containing neutral-staining granules), **eosinophils** (acid-staining granules) and **basophils** (basic-staining granules). All contribute to inflammation by releasing mediators (cytokines) when activated.

Neutrophils have a key role in the innate immune system and migrate to areas of infection (**chemotaxis**) within minutes, where they destroy bacteria by **phagocytosis**. They are a major constituent of pus. They have a half-life of ~6 h in blood, days in tissue. *Eosinophils* are less motile and longer lived and phagocytose larger parasites. They increase in allergic reactions and contribute to allergic disease (e.g. asthma) by release of pro-inflammatory cytokines. *Basophils* release histamine and heparin as part of the inflammatory response and are similar to tissue **mast** cells. *Lymphocytes* originate in the marrow but mature in the lymph nodes, thymus and spleen before returning to the circulation. Most remain in the lymphatic system. Lymphocytes are critical components of the **immune** system and are of three main forms: B cells which produce immunoglobulins (antibodies), T cells which coordinate the immune response, and natural killer (NK) cells which kill infected or cancerous cells.

Monocytes are phagocytes with a clear cytoplasm and are larger and longer lived than granulocytes. After formation in the marrow they circulate in the blood for ~72 h before entering the tissues to become **macrophages**, which unlike granulocytes can also dispose of dead cell debris. Macrophages form the **reticuloendothelial system** in liver, spleen and lymph nodes.

6 Erythropoiesis, haemoglobin and anaemia

Figure 6.1 Erythropoiesis and the life cycle of the erythrocyte

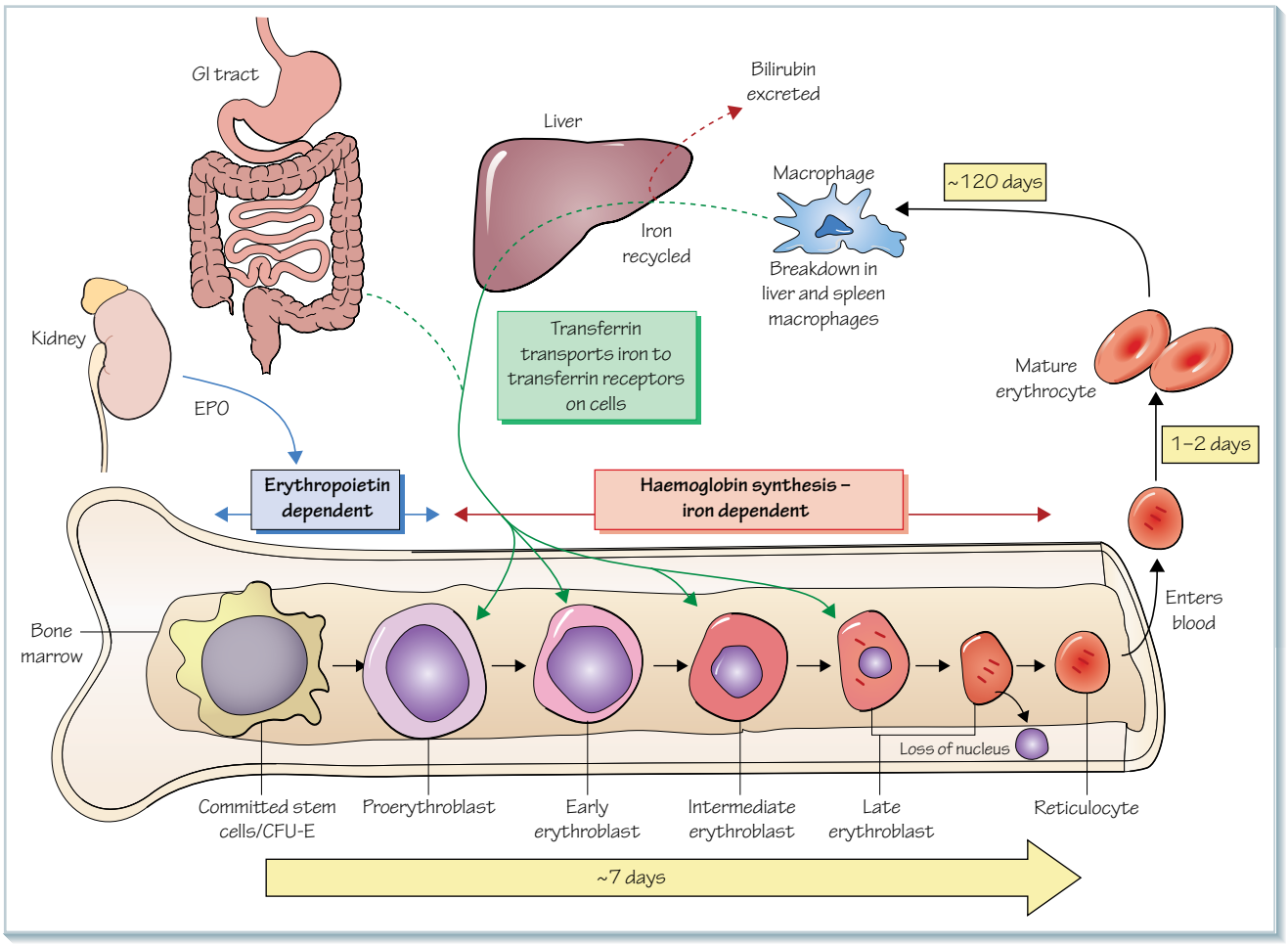

Figure 6.2 Characteristics of types of anaemia

Red cells	Microcytic Low MCV (<80fL)		Macrocytic High MCV (>95fL)		Normal cells	Deformed
Marrow	Ragged erythroblasts Iron content ↓	Hyperplastic Normal iron	Megaloblastic	Normal	Normal	
Example	Iron deficiency (commonest cause)	Thalassaemia Defect of haem synthesis (rare)	B_{12}, folate deficiency	Liver disease Alcohol abuse (Aplastic anaemia)	Acute blood loss Chronic disease	Spherocytosis Sickle cells Schistocytes
Type	Microcytic hypochromic		Macrocytic		Normocytic normochromic	Haemolytic

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Erythropoiesis

Erythropoiesis, the formation of red cells (erythrocytes), occurs in the red bone marrow of adults and the liver and spleen of the fetus. It can also occur in the liver and spleen of adults following bone marrow damage. Erythropoiesis is primarily controlled by **erythropoietin**, a glycoprotein hormone secreted primarily by the kidneys in response to hypoxia; about 10–15% is produced by the liver, the major source for the fetus. Other factors such as corticosteroids and growth hormones can also stimulate erythropoiesis.

Erythropoiesis begins when uncommitted stem cells commit to the erythrocyte lineage and under the influence of erythropoietin transform into rapidly growing precursor cells (colony forming unit erythroid cells, CFU-E) and then **proerythroblasts** (Figure 6.1). These large cells are packed with ribosomes, and it is here that haemoglobin synthesis begins. Development and maturation proceed through early (basophilic), intermediate (polychromatic), and finally late (orthochromatic) **erythroblasts** (or normoblasts) of decreasing size. As cell division ceases, ribosomal content decreases and haemoglobin increases. The late erythroblast finally loses its nucleus to become a **reticulocyte**, a young erythrocyte still retaining the vestiges of a ribosomal reticulum. Reticulocytes enter the blood and, as they age, the reticulum disappears and the characteristic biconcave shape develops. About 2×10^{11} erythrocytes are produced from the marrow each day, and normally 1–2% of circulating red cells are reticulocytes. This increases when erythropoiesis is enhanced, for example after haemorrhage (Chapter 31) or during hypoxia associated with respiratory disease or altitude. This can greatly increase erythrocyte numbers (**polycythaemia**) and haematocrit. Conversely, erythropoietin levels may fall in kidney disease, chronic inflammation and liver cirrhosis, resulting in anaemia.

Erythrocytes are destroyed by **macrophages** in the liver and spleen after ~120 days. The spleen also sequesters and eradicates defective erythrocytes. The haem group is split from haemoglobin and converted to **biliverdin** and then **bilirubin**. The iron is conserved and recycled via **transferrin**, an iron transport protein, or stored in **ferritin**. Bilirubin is a brown–yellow compound that is excreted in the bile. An increased rate of haemoglobin breakdown results in excess bilirubin, which stains the tissues (**jaundice**).

Haemoglobin

Haemoglobin has four subunits, each containing a polypeptide **globin** chain and an iron-containing porphyrin, **haem**, which are synthesized separately. Haem is synthesized from succinic acid and glycine in the mitochondria and contains one atom of iron in the **ferrous** state (Fe^{2+}). One molecule of haemoglobin has therefore four atoms of iron and binds four molecules of O_2. There are several types of haemoglobin, relating to the globin chains; the haem moiety is unchanged. Adult haemoglobin (Hb A) has two α and two β chains. Fetal haemoglobin (Hb F) has two γ chains in place of the β chains, and a high affinity for O_2. **Haemoglobinopathies** are due to abnormal haemoglobins.

Sickle cell anaemia occurs in 10% of the Black population and is caused by substitution of a glutamic acid by valine in the β chain; this haemoglobin is called Hb S. At a low Po_2 Hb S gels, causing deformation (*sickling*) of the erythrocyte. The cell is less flexible and prone to fragmentation, and there is an increased rate of breakdown by macrophages. Heterozygous patients with less than 40% Hb S normally have no symptoms (**sickle cell trait**). Homozygous patients with more than 70% Hb S develop full **sickle cell anaemia**, with acute episodes of pain resulting from blockage of blood vessels, congestion of liver and spleen with red cells, and leg ulcers.

Thalassaemia involves defective synthesis of α- or β-globin chains. Several genes are involved. In β thalassaemia there are fewer or no β chains available, so α chains bind to γ (Hb F) or δ chains (Hb A_2). Thalassaemia major (severe β thalassaemia) causes severe anaemia, and regular transfusions are required, leading to iron overload (haemochromatosis). In heterozygous β thalassaemia minor there are no symptoms, although erythrocytes are **microcytic** and **hypochromic**, that is, **mean cell volume** (MCV), **mean cell haemoglobin content** (MCH) and **mean cell haemoglobin concentration** (MCHC) are reduced. In **α thalassaemia** there are fewer or no α chains. In the latter case haemoglobin does not bind O_2, and infants do not survive (**hydrops fetalis**). When some α chains are present, patients surviving as adults may produce some Hb H (four β chains); this precipitates in the red cells which are then destroyed in the spleen.

Anaemia

Blood loss (e.g. haemorrhage, heavy menstruation) or chronic disease (e.g. infection, tumours, renal failure) may simply reduce the number of erythrocytes. When these have a normal MCV and MCH (Chapter 5), this is termed **normocytic normochromic** anaemia.

Iron deficiency is the most common cause of anemia. The dietary requirement for iron is small, as the body has an efficient recycling system, but is increased with significant blood loss. Women have a higher requirement for dietary iron than men because of menstruation and also during pregnancy. Iron deficiency causes defective haemoglobin formation and a **microcytic hypochromic** anaemia (reduced MCV and MCH).

Vitamin B_{12} (cobalamin) and folate are required for maturation of erythroblasts, and deficiencies of either cause **megaloblastic anaemia**. The erythroblasts are unusually large (megaloblasts), and they mature as erythrocytes with a high MCV and MCH, although MCHC is normal. Erythrocyte numbers are greatly reduced, and rate of destruction increased. Folate deficiency is mostly related to poor diet, particularly in the elderly or poor; folate is commonly given with iron during pregnancy. Alcoholism and some anticonvulsant drugs (e.g. phenytoin) impair folate utilization. **Pernicious anaemia** is caused by defective absorption of vitamin B_{12} from the gut, where it is transported as a complex with intrinsic factor produced by the gastric mucosa. Damage to the latter results in pernicious anaemia. B_{12} deficiency can also occur in strict vegans.

Aplastic anaemia results from aplastic (non-functional) bone marrow and causes **pancytopenia** (reduced red, white and platelet cell count). It is dangerous but uncommon. It can be caused by drugs (particularly anticancer), radiation, infections (e.g. viral hepatitis, TB) and pregnancy, where it has a 90% mortality. A rare inherited condition, **Fanconi's anaemia**, involves defective stem cell production and differentiation.

Haemolytic anaemia involves an excessive rate of erythrocyte destruction and causes jaundice. Causes include blood transfusion mismatch, **haemolytic anaemia of the newborn** (see Chapter 9), abnormal erythrocyte fragility and haemoglobins, and autoimmune, liver and hereditary diseases. In **hereditary haemolytic anaemia** (familial spherocytosis) erythrocytes are more spheroid and fragile and are rapidly destroyed in the spleen. It is relatively common, affecting 1 in 5000 Caucasians. Jaundice is common at birth but may appear after several years. Aplastic anaemia may occur after infections, and megaloblastic anaemia from folate deficiency as a result of high bone marrow activity. Figure 6.2 shows characteristics of types of anaemia.

7 Haemostasis

Figure 7.1 Primary haemostasis, activation of platelets and formation of platelet plug

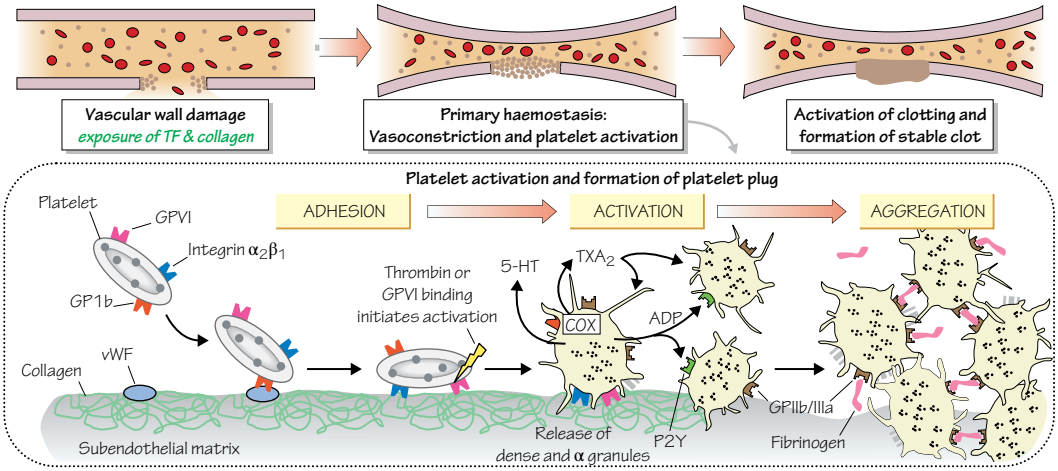


Figure 7.2 Cell-based model of clotting

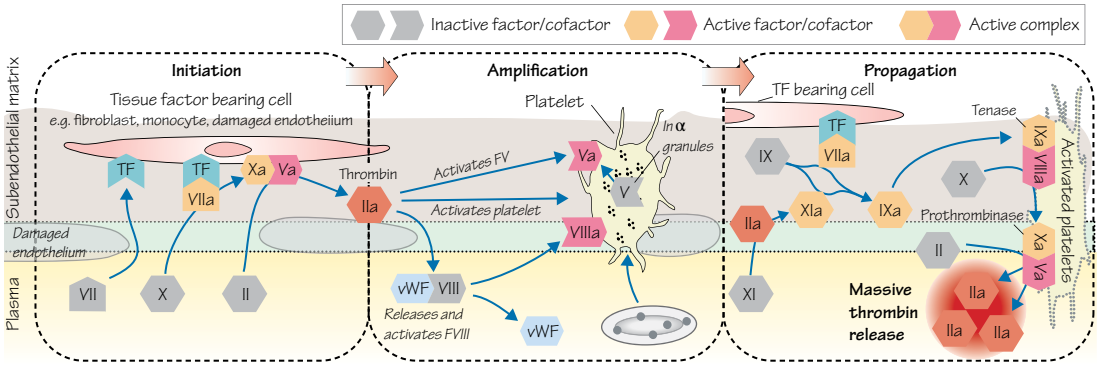


Figure 7.3 Fibrin disposition

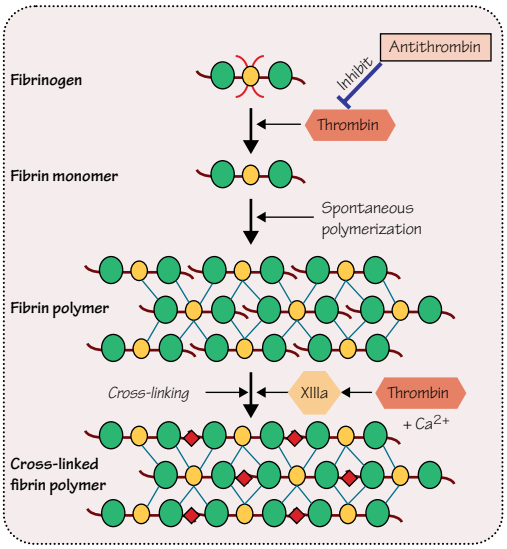
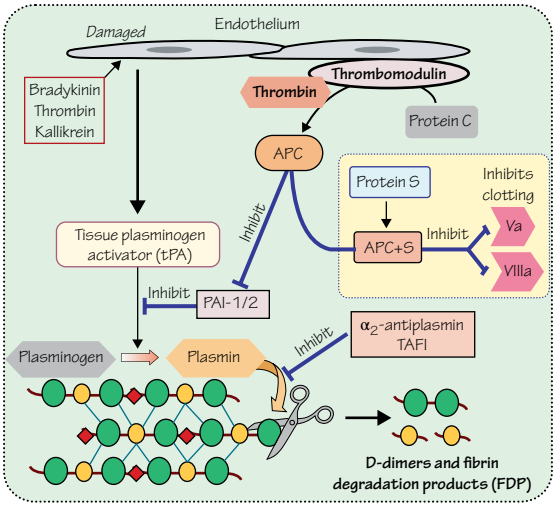


Figure 7.4 Fibrinolysis and active protein C (APC)



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Primary haemostasis (Figure 7.1)

The immediate response to damage of the blood vessel wall is vasoconstriction, which reduces blood flow. This is followed by a sequence of events leading to sealing of the wound by a clot. Collagen in the exposed subendothelial matrix binds **von Willebrand factor** (vWF), which in turn binds to glycoprotein Ib (**GPIb**) receptors on platelets, the first stage of **platelet adhesion**. This initial tethering promotes binding of platelet **integrin $\alpha_2\beta_1$** and **GPVI** receptors directly to collagen. Binding of receptors initiates **activation**, partly by increasing intracellular Ca^{2+}. Platelets change shape, put out pseudopodia and make thromboxane A_2 (**TXA_2**) via cyclooxygenase (**COX**). TXA_2 releases mediators from platelet **dense granules**, including **serotonin** (5-HT) and adenosine diphosphate (**ADP**), and from **α granules** vWF, factor V (see below) and agents that promote vascular repair. TXA_2 and 5-HT also promote vasoconstriction. ADP activates more platelets via **$P2Y_{12}$** purinergic receptors, causing activation of **fibrinogen** (GPIIb/IIIa) receptors and exposure of **phospholipid** (PLD) on the platelet surface. Plasma fibrinogen binds to GPIIb/IIIa receptors causing the platelets to **aggregate** (stick together) forming a soft **platelet plug** (Figure 7.1). This is stabilized with **fibrin** during clotting. Note that **thrombin** (see below) is also a potent platelet activator.

Formation of the blood clot (Figures 7.2, 7.3)

The final stage of blood clotting (coagulation) is formation of the clot – a tight mesh of **fibrin** entrapping platelets and blood cells. The process is complex, involving sequential conversion of proenzymes to active enzymes (**factors**; e.g. factor X → Xa). The ultimate purpose is to produce a massive burst of **thrombin** (factor IIa), a protease that cleaves fibrinogen to fibrin. The **cell-based model** of clotting (Figure 7.2) has replaced the older extrinsic and intrinsic pathways. Most of the action in this model occurs on the cell surface (hence its name).

The **initial phase** of clotting is initiated when cells in the subendothelial matrix that bear **tissue factor** (**TF**; thromboplastin) are exposed to factor VIIa from plasma. Such cells include fibroblasts and monocytes, but damaged endothelium and circulating cell fragments containing TF (microparticles) can also initiate clotting. TF forms a complex with factor VIIa (**TF:VIIa**) which activates **factor X** (and IX, see below). **Factor Xa** with its cofactor Va then converts **prothrombin** (factor II) to thrombin; activation of both factor X and prothrombin require Ca^{2+}. Comparatively little thrombin is produced at this time, but sufficient to initiate the **amplification phase**. Activity of these processes is normally suppressed by tissue factor pathway inhibitor (**TFPI**), which inhibits and forms a complex with factor Xa, which then inhibits TF:VIIa; however, the influx of plasma factors after damage overwhelms this suppression.

The **amplification phase** takes place on platelets (Figure 7.2). Thrombin produced in the initial phase activates further platelets and membrane-bound factor V which is released from platelet α granules. Factor VIII is normally bound to circulating vWF, which protects it from degradation. Thrombin cleaves factor VIII from vWF and activates it, when it binds to the platelet membrane.

The scene is now set for the **propagation phase**. Either factor XIa (itself activated by thrombin) or TF:VIIa can activate factor IX, which binds and forms a complex with factor VIIIa on the platelet membrane called **tenase**; this is a much more powerful activator of factor X than TF:VIIa. Factors Xa and Va then bind to form **prothrombinase** on the platelet membrane. This process leads to a massive burst of thrombin production, 1000-fold greater than in the initial phase and localized to activated platelets.

Factor XII (Hageman factor, not shown) is probably of limited significance, as deficiency does not lead to bleeding. It is activated by negative charge on glass and collagen and can activate factor XI. It may be involved in pathological clotting in the brain.

Thrombin cleaves small fibrinopeptides from fibrinogen to form fibrin monomers (Figure 7.3), which spontaneously **polymerize**. This polymer is **cross-linked** by **factor XIIIa** (activated by thrombin in the presence of Ca^{2+}) to create a tough network of fibrin fibres and a **stable clot**. Retraction of entrapped platelets contracts the clot by ~60%, making it tougher and assisting repair by drawing the edges of the wound together.

Inhibitors of haemostasis and fibrinolysis

Inhibitory mechanisms are vital to prevent inappropriate clotting (**thrombosis**). **Prostacyclin** (PGI_2) and nitric oxide from undamaged endothelium impede platelet adhesion and activation. **Antithrombin** inhibits thrombin, factor Xa and IXa/tenase; its activity is strongly potentiated by **heparin**, a polysaccharide. *Heparan* on endothelial cells is similar. **TFPI** has already been mentioned. **Thrombomodulin** on endothelial cells binds thrombin and prevents it cleaving fibrinogen; instead, it activates **protein C** (**APC**) which with its cofactor **protein S** inactivates cofactors Va and VIIIa, and hence tenase and prothrombinase (Figure 7.4).

Fibrinolysis is the process by which a clot is broken down by **plasmin**, a protease (Figure 7.4). This creates soluble fibrin degradation products (**FDPs**) including small **D-dimers**. **Plasmin** is formed from fibrin-bound **plasminogen** by tissue plasminogen activator (**tPA**), released from damaged endothelial cells in response to bradykinin, thrombin and kallikrein. **Urokinase** (uPA) is similar. **APC** inactivates an inhibitor of plasminogen activator inhibitor (tPA; **PAI-1** and 2), and so promotes fibrinolysis (Figure 7.4). Plasmin is itself inactivated by **α_2-antiplasmin** and inhibited by thrombin activated fibrinolysis inhibitor (**TAFI**).

Defects in haemostasis

The most common hereditary disorder is **haemophilia A**, a deficiency of factor VIII sex linked to males. **Christmas disease** is a deficiency of factor IX, and **von Willebrand disease** a deficiency of vWF. The latter leads to defective platelet adhesion and reduced availability of factor VIII, which is stabilized by vWF. The liver requires **vitamin K** for correct synthesis of prothrombin and factors VII, IX and X. As vitamin K is obtained from intestinal bacteria and food, disorders of fat absorption or liver disease can result in deficiency and defective clotting. **Factor V Leiden** is brought about by a mutant factor V that cannot be inactivated by APC. Five per cent carry the gene, which causes a fivefold increase in the risk of thrombosis. **Antiphospholipid syndrome** is caused by phospholipid-binding antibodies (e.g. cardiolipin, lupus anticoagulant) which may inhibit APC and protein S or facilitate cleavage of prothrombin. It is associated with recurrent thrombosis and linked to 20% of strokes in people under 50 years, more common in females.

8 Thrombosis and anticoagulants

Figure 8.1 Risk factors for thrombosis and embolism

Arterial thrombosis	DVT, VTE and pulmonary embolism	
Endothelial/endocardial damage: Atherosclerotic plaque rupture Myocardial infarct Valve disease Atherosclerosis Haemodynamic stress/Hypertension Catheters	**Low flow states (stasis):** Cardiac failure, immobility, surgery, ***High risk***: Orthopaedic (hip, knee), gynaecological **Vascular injury:** Artherosclerosis, catheters Spinal trauma	**Hypercoagulability:** Thrombocytosis Deficiencies in antithrombin, protein C, protein S Antiphospholipid syndrome Factor V Leiden *-prevents inactivation by protein C*
	General factors: age, obesity, smoking, oral contraceptive pill (link with *Factor V Leiden*)	

Figure 8.2 Antiplatelet drugs: action on platelet activation and aggregation

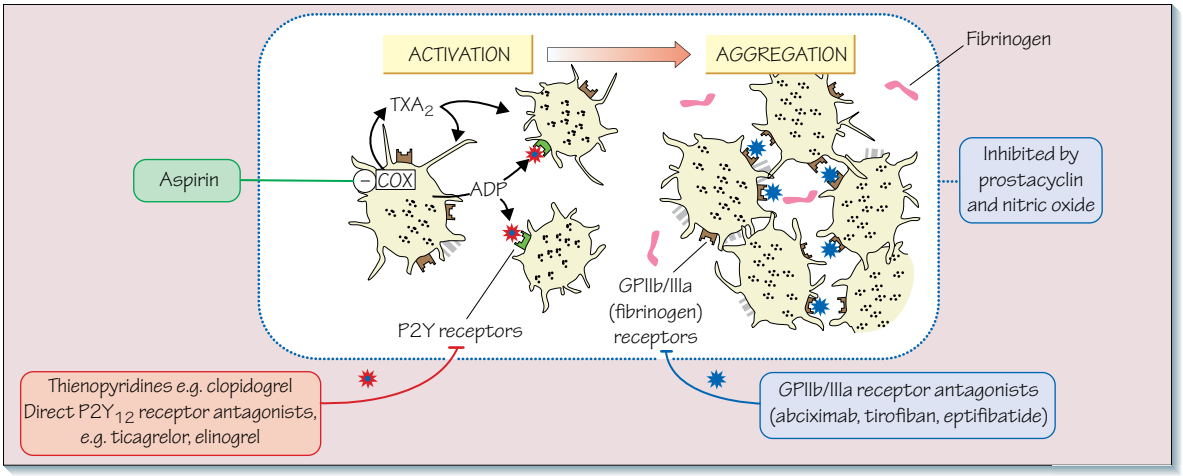
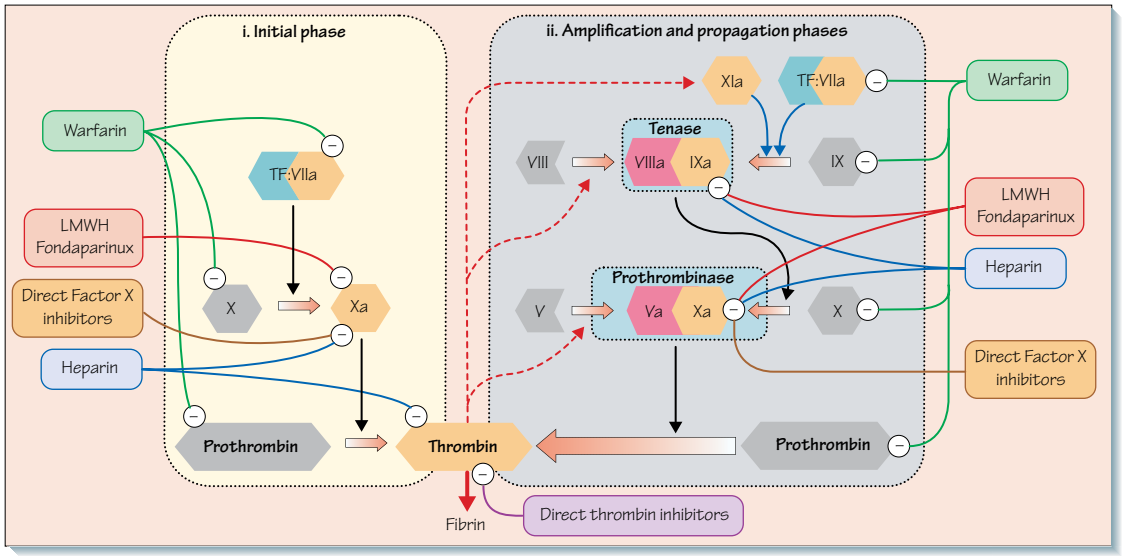


Figure 8.3 Anticoagulant drugs: action on clotting cascade



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Thrombosis

Thrombosis and embolism are ultimately the main cause of death in the industrialized world. Thrombosis is inappropriate activation of haemostasis, with clots (**thrombi**) forming inside blood vessels. If thrombi fragment they can be carried in the blood as **emboli** and block downstream blood vessels causing infarction. Most commonly, fatalities are due to thrombosis as a result of **atherosclerotic plaque rupture** in acute coronary syndromes (see Chapter 42), or venous thromboembolism (**VTE**), particularly **pulmonary embolism**, following **deep vein thrombosis** (**DVT**). **Virchow's triad** of ***endothelial damage, blood stasis*** and ***hypercoagulability*** predisposes to thrombosis. Endothelial (or endocardial) damage is the most common cause of arterial thrombosis. Stasis (poor flow), which allows clotting factors to accumulate and unimpeded formation of thrombi, is the most common cause of DVT and VTE. **Risk factors** are shown in Figure 8.1. Once formed, thrombi can undergo **dissolution** by fibrinolysis, **propagation** by accumulation of more fibrin and platelets, or **organization** with invasion of endothelial or smooth muscle cells and fibrosis. In **recanalization** channels form allowing blood to reflow. If not destroyed, thrombi may be incorporated into the vessel wall.

Arterial (white, platelet-rich) thrombi are primarily treated with antiplatelet drugs, whereas venous (red) thrombi are primarily treated with anticoagulants. All such therapies increase risk of bleeding and may be contraindicated in patients with prior stroke, active ulcers, pregnancy or recent surgery.

Antiplatelet drugs (Figure 8.2)

Aspirin (*acetylsalicylic acid*) is the most important antiplatelet drug. It irreversibly inhibits **cyclooxygenase** (COX), the first enzyme in the sequence leading to formation of **thromboxane A_2** (TXA_2) and **prostacyclin** (PGI_2). TXA_2 is produced by platelets and is a key platelet activator (Chapter 7), whereas endothelium-derived PGI_2 inhibits platelet activation and aggregation. Because aspirin inhibits COX *irreversibly*, production of PGI_2 and TXA_2 recovers only when new COX is produced via gene transcription. This cannot occur in platelets, which lack nuclei (Chapter 5), whereas endothelial cells make new COX within hours. Aspirin therapy therefore produces a sustained increase in the PGI_2: TXA_2 ratio, suppressing platelet activation and aggregation. Aspirin can cause gastrointestinal bleeding.

Thienopyridine derivatives such as **clopidogrel** indirectly and irreversibly block purinergic **P2Y receptors**, and thus ADP-induced platelet activation (Chapter 7); however, they are prodrugs that require metabolism in the liver and so take >24 h for maximal effect. They are useful for aspirin-intolerant patients and preventing thrombi on coronary artery stents (Chapter 42), and long-term treatment with clopidogrel plus aspirin is beneficial in acute coronary syndromes. Direct **$P2Y_{12}$ receptor antagonists** such as ticagrelor and elinogrel have advantages, including reversibility and rapidity of action, and are effective for acute coronary syndrome.

Small peptide glycoprotein receptor inhibitors (**GPI**) such as tirofiban and eptifibatide and the monoclonal antibody abciximab prevent fibrinogen binding to **GPIIb/IIIa receptors** on activated platelets, thus inhibiting aggregation (Chapter 7). In patients with unstable angina or undergoing high-risk angioplasty, a GPI combined with aspirin and heparin reduces short-term mortality and the need for urgent revascularization.

Anticoagulant drugs (Figure 8.3)

Heparin, a mixture of mucopolysaccharides derived from mast cells, activates **antithrombin**, which inhibits thrombin and factors X, IX and XI (Chapter 7). Heparin must bind to both thrombin and antithrombin for inhibition of thrombin, but only antithrombin for inhibition of factor X. *Unfractionated* heparin has a large variability of action and causes thrombocytopenia in some patients. **Low molecular weight heparins** (LMWHs) have largely replaced unfractionated heparin in clinical use, as they have a longer half-life and predictable dose responses; thrombocytopenia is rare. LMWHs bind only to antithrombin and are therefore more effective at inhibiting factor X. They are given subcutaneously and are first-line drugs for routine thromboprophylaxis. **Fondaparinux** is a synthetic pentasaccharide that acts in a similar fashion to LMWH. **Bivalirudin** is a direct thrombin inhibitor delivered intravenously, with benefits of rapidity of action and reversal.

Warfarin (coumarin) is still the most important oral anticoagulant. It inhibits vitamin K reductase and thus γ-carboxylation of prothrombin and factors VII, IX and X in the liver; this prevents tethering to cells and hence activity (Chapter 7). Although slow in onset (~1–2 days), it provides effective support for ~5 days. Numerous factors including disease and drugs affect the sensitivity to warfarin, so blood tests must be used routinely to monitor dosage, which is adjusted to give a **prothrombin time** international normalized ratio (**INR**) of ~3 (see below). Use of warfarin may decline following the advent of direct oral anticoagulants (DOACs), for example **dabigatran** (thrombin antagonist) and **rivaroxaban** (factor Xa antagonist). These have benefits of increased rapidity of action and reduced sensitivity to other drugs and disease and a greatly reduced need for routine blood tests. Both are approved for prevention of VTE following hip and knee replacement surgery and have been shown to be as effective as warfarin for prevention of atrial fibrillation-associated stroke.

Thrombolytic agents induce fibrinolysis by activating plasmin; tissue plasminogen activator (**tPA**) is the most important endogenous agent (Chapter 7), and recombinant tPA the most commonly used clinically. Until relatively recently, thrombolysis was the recognized treatment for dissolution of life-threatening blood clots in coronary artery disease and acute MI, although with a severe risk of gut and intracerebral haemorrhage (stroke). It has now been largely replaced by emergency angioplasty – percutaneous coronary intervention (PCI) (Chapter 43).

Some laboratory investigations

***Prothrombin time (PT)*:** time to clot formation following addition of thromboplastin (TF) (fibrinogen and Ca^{2+} in excess); normally ~14 s. A measure of activity of vitamin K-dependent clotting factors and thus important for titrating dose of **warfarin** (see above). It is expressed as **INR**, the ratio of the patient's PT to that of a standardized reference sample. INR is normally 1.

***Activated partial thromboplastin time (aPTT)*:** time to clot formation following addition of a surface activator (kaolin; activates factor XII), phospholipid and Ca^{2+} to plasma. Measures activity of factors in the amplification phase (i.e. not factor VIIa) (see Figure 7.2). Normally 35–45 s. Prolonged by relevant deficiencies.

***D-dimers and fibrin degradation products (FDPs)*:** indicative of fibrinolysis; raised in disseminated intravascular coagulation (**DIC**) and other thrombotic conditions. False positives common.

9 Blood groups and transfusions

Figure 9.1 Red cell agglutination in incompatible plasma

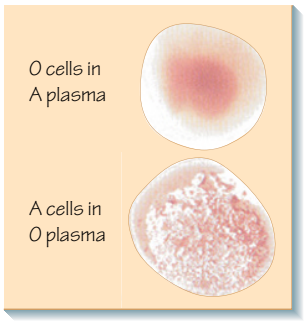

Figure 9.2 ABO phenotypes

Group	Agglutinogens	Agglutinins
AB	A and B	None
A	A	Anti-B
B	B	Anti-A
O	None	Anti-A and Anti-B

Figure 9.4 Relative distribution of ABO blood types by race

Group	Caucasian	Far Eastern	Afro-Caribbean	Native American
A	41%	28%	28%	3%
B	10%	23%	20%	—
AB	4%	13%	5%	—
O	45%	36%	47%	97%

Figure 9.3 Safe transfusion?

Recipient	Donor A	B	AB	O (universal donor)
A	Yes	No	No	Yes
B	No	Yes	No	Yes
AB (universal recipient)	Yes	Yes	Yes	Yes
O	No	No	No	Yes

Figure 9.5 Distribution of Rhesus groups (Caucasians)

Group	Proportion of population	Breakdown of genotypes
RH +	85%	35% DD 48% Dd 2% other + D
RH –	15%	

Blood groups

If samples of blood from different individuals are mixed together, some combinations result in red cells sticking together as clumps (Figure 9.1). This is called **agglutination**, and it occurs when the **blood groups** are incompatible. It is caused when antigens (or **agglutinogens**) on the red cell membrane react with specific antibodies (or **agglutinins**) in the plasma. If the quantity (or **titre**) of antibodies is sufficiently high, they bind to their antigens on several red cells and glue the cells together, which then rupture (**haemolyse**). If this occurs following a blood transfusion it can lead to anaemia and other serious complications. The most important blood groups are the **ABO system** and **Rh** (**Rhesus**) groups.

The ABO system

The **ABO system** consists of four blood groups: A, B, AB and O. The precise group depends on the presence or absence of two antigens, A and B, on the red cells, and their respective antibodies, α and β, in the plasma (Figure 9.2). The A and B antigens on red cells are mostly glycolipids that differ in respect of their terminal sugar. The antigens are also found as glycoproteins in other tissues, including salivary glands, pancreas, lungs and testes, and in saliva and semen.

Group A blood contains the A antigen and β antibody, and group B the B antigen and α antibody. Group AB has both A and B antigens, but neither antibody. Group O blood contains neither antigen, but both α and β antibodies. Group A blood cannot therefore be transfused into people of group B, or vice versa, because antibodies in the recipient react with their respective antigens on the donor red cells and cause agglutination (Figure 9.3). As people of group AB have neither α nor β antibodies in the plasma, they can be transfused with blood from any group, and are called **universal recipients**. Group O red cells have neither antigen and can therefore be transfused into any patient. People of group O are therefore called **universal donors**. Although group O blood contains both antibodies, this can normally be disregarded as they are diluted during transfusion and are bound and neutralized by free A or B antigens in the recipient's plasma. If large or repeated transfusions are required, blood of the same group is used.

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Inheritance of ABO blood groups

The expression of A and B antigens is determined genetically. A and B allelomorphs (alternative gene types) are dominant and O recessive. Therefore AO (**heterozygous**) and AA (**homozygous**) genotypes both have group A phenotypes. An AB genotype produces both antigens and is thus group AB. The proportion of each blood group varies according to race (Figure 9.4), although group O is most common (35–50%). Native Americans are almost exclusively group O.

Rh groups

In ~85% of the population the red cells have a D antigen on the membrane (Figure 9.5). Such people are called Rh+ (Rhesus positive), while those who lack the antigen are Rh– (Rhesus negative). Unlike ABO antigens, the D antigen is not found in other tissues. The antibody to D antigen (**anti-D agglutinin**) is not normally found in the plasma of Rh– individuals, but sensitization and subsequent antibody production occur if a relatively small amount of Rh+ blood is introduced. This can result from transfusion, or when an Rh– mother has an Rh+ child, and fetal red blood cells enter the maternal circulation during birth. Occasionally, fetal cells may cross the placenta earlier in the pregnancy.

Inheritance of Rh groups

The gene corresponding to the D antigen is also called D and is dominant. When D is absent from the chromosome, its place is taken by the allelomorph of D called d, which is recessive. Individuals who are homozygous and heterozygous for D will be Rh+. About 50% of the population are heterozygous for D, and ~35% homozygous. Blood typing for Rh groups is routinely performed for prospective parents to determine the likelihood of **haemolytic disease** in the offspring.

Haemolytic disease of the newborn

Most pregnancies with Rh– mothers and Rh+ fetuses are normal, but in some cases a severe reaction occurs. Anti-D antibody in the mother's blood can cross the placenta and agglutinate fetal red cells expressing D antigen. The titre of antibody is generally too low to be of consequence during a first pregnancy with a Rh+ fetus, but it can be dangerously increased during subsequent pregnancies, or if the mother was previously sensitized with Rh+ blood. Agglutination of the fetal red cells and consequent haemolysis can result in anaemia and other complications. This is known as **haemolytic disease of the newborn** or **erythroblastosis fetalis**. The haemoglobin released is broken down to bilirubin, which in excess results in **jaundice** (yellow staining of the tissues). If the degree of agglutination and anaemia is severe, the fetus develops severe jaundice and is grossly oedematous (**hydrops fetalis**), and often dies in utero or shortly after birth.

Prevention and treatment In previously unsensitized mothers, sensitization can be prevented by treatment with anti-D immunoglobulin after birth. This destroys any fetal Rh+ red cells in the maternal circulation before sensitization of the mother can occur. If haemolytic disease is evident in the fetus or newborn, the Rh+ blood can be replaced by Rh– blood immediately after birth. By the time the newborn infant has regenerated its own Rh+ red cells, the anti-D antibody from the mother will have been reduced to safe levels. Phototherapy is commonly used for jaundice, as light converts bilirubin to a more rapidly eliminated compound.

Other blood groups

Although there are other blood groups, these are of little clinical importance, as humans rarely develop antibodies to the respective antigens. However, they may be of importance in medicolegal situations, such as determination of paternity. An example is the MN group, which is a product of two genes (M and N). A person can therefore be MM, MN or NN, each genome coming from one parent. As with the other groups, analysis of the respective parties' genomes can only determine that the man is *not* the father. This method has been largely superseded by DNA profiling.

Complications of blood transfusions

Blood type incompatibility When the recipient of a blood transfusion has a significant plasma titre of α, β or anti-D antibodies, donor red cells expressing the respective antigen will rapidly agglutinate and haemolyse (**haemolytic transfusion reaction**). If the subsequent accumulation of bilirubin is sufficiently large, **haemolytic jaundice** develops. In severe cases renal failure may develop. Antibodies in the donor blood are rarely problematical, as they are diluted and removed in the recipient.

Transmission of infection as a result of bacteria, viruses and parasites. Most important are hepatitis, HIV, prions and in endemic areas parasites such as malaria.

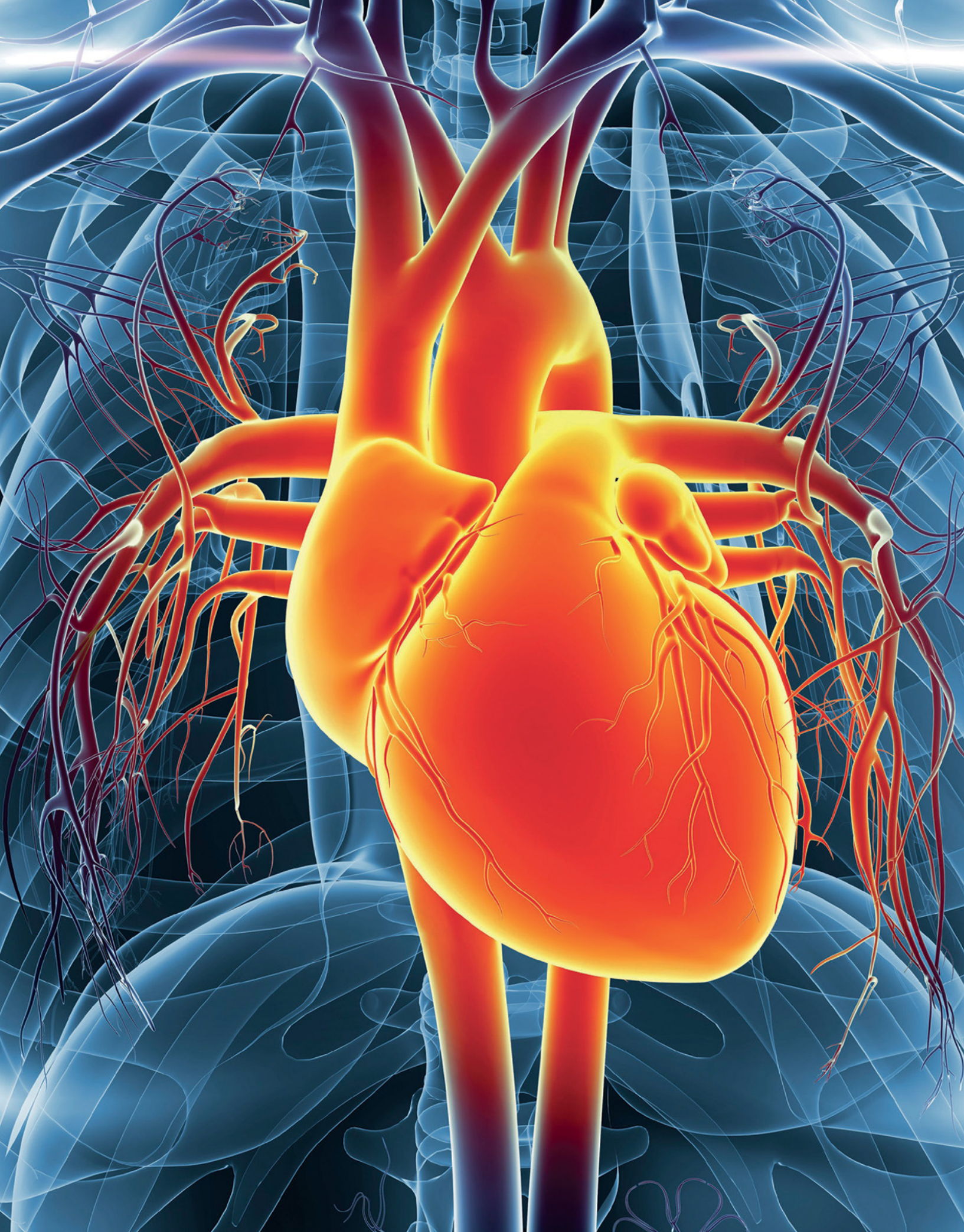
Iron overload resulting from frequent transfusions and breakdown of red cells (*transfusion haemosiderosis*), for example in **thalassaemia** (Chapter 6). Can cause damage to heart, liver, pancreas and glands. Treatment: iron chelators and vitamin C.

Fever resulting from an immune response to transfused leucocytes which release pyrogens. Relatively common but mild in patients who have previously been transfused and in pregnancy.

Electrolyte changes and **suppression of haemostasis** following massive transfusions (e.g. major surgery) with stored blood (see below).

Blood storage

Blood is stored for transfusions at 4°C in the presence of an agent that chelates free Ca^{2+} to prevent clotting; for example, citrate, oxalate and ethylenediaminetetraacetic acid (EDTA; Chapter 7). Even under these conditions the red cells deteriorate, although they last much longer in the presence of glucose, which provides a metabolic substrate. The cell membrane Na^+ pump works more slowly in the cold, with the result that Na^+ enters the cell, and K^+ leaves. This causes water to move into the cell so that it swells and becomes more spherocytic. On prolonged storage the cells become fragile, and **haemolyse** (fragment) easily. Neither leucocytes nor platelets survive storage well and disappear within a day of transfusion. Blood banks normally remove all the donor agglutinins (antibodies), although for small transfusions these would be sufficiently diluted to be of no threat. Great care is taken to screen potential donors for blood-borne diseases (e.g. hepatitis, HIV).



Cellular physiology

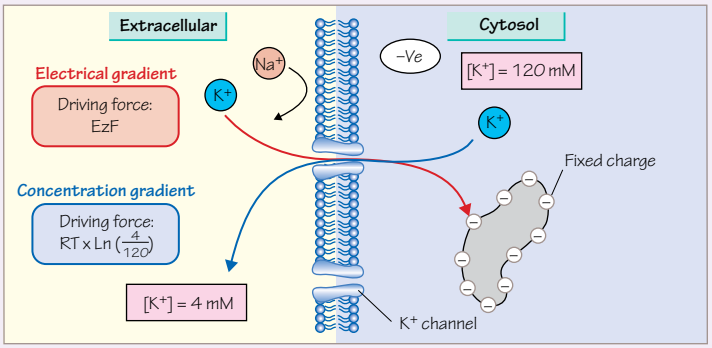
Chapters

10 Membrane potential, ion channels and pumps

Figure 10.1 Nernst equation and K^+ equilibrium potential

E = potential
z = valency (1 for K^+)
F = Faraday (charge per mole) (96 485 coulombs)

R = gas constant (8.314 Joules/mole/degree K)
T = absolute temperature



At equilibrium:

Electrical gradient: Driving force: EzF = Concentration gradient: Driving force: $RT \times Ln(\frac{4}{120})$

Rearrange:

$$E = \frac{RT}{zF} \times Ln(\frac{4}{120})$$

The Nernst equation

Solving for R, z and F, 37°C, and log base 10:

$$E_k = 61 \times Log(\frac{4}{120}) = -90\ mV$$

E_k, the **K^+ equilibrium potential**, is the potential at which equilibrium would be obtained for these intracellular and extracellular [K^+], assuming the membrane is only permeable to K^+

Figure 10.2 Ion channels and gating

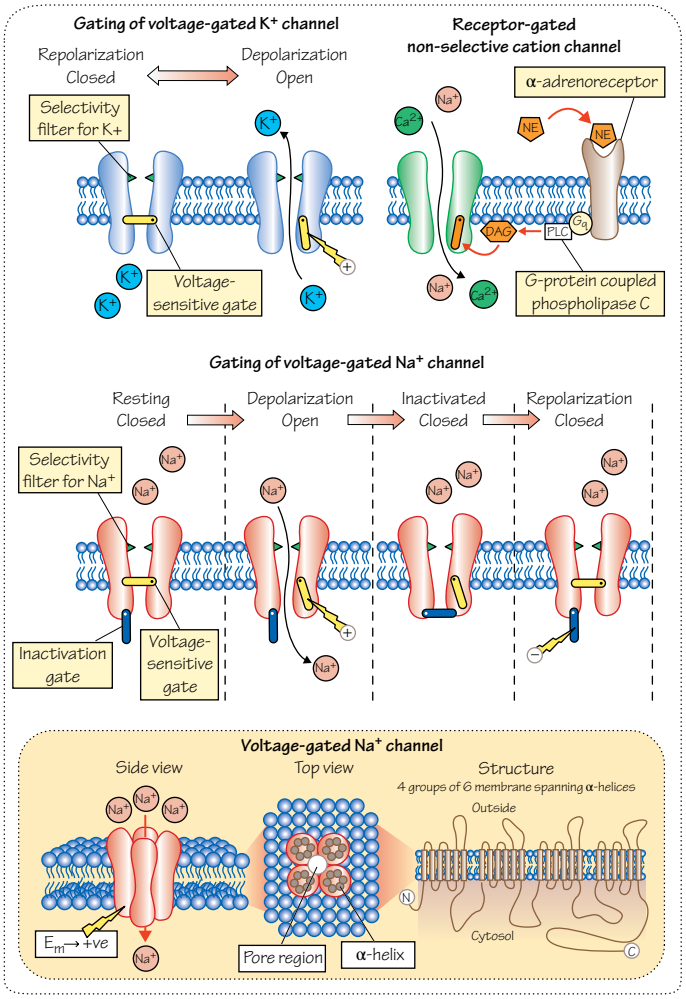
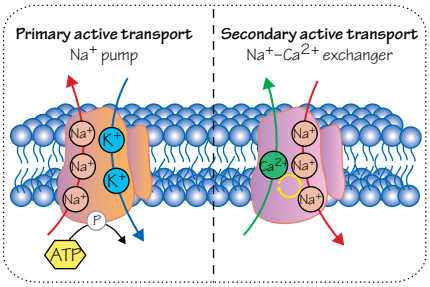


Figure 10.3 Ion pumps and exchangers



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The cell membrane is a lipid bilayer with an intrinsically low permeability to charged ions. However, a variety of structures span the membrane through which ions can enter or leave the cell. These include **ion channels** through which ions passively diffuse and **ion pumps** which actively transport ions across the membrane. Pumps regulate ionic gradients, and channels determine membrane potential and underlie action potentials.

Resting membrane potential (Figure 10.1)

The resting membrane is more permeable to K^+ and Cl^- than other ions and is therefore **semipermeable**. The cell contains negatively charged molecules (e.g. proteins) which cannot cross the membrane. This fixed negative charge attracts K^+ but repels Cl^-, leading to accumulation of K^+ within the cell and loss of Cl^-. However, the consequent increase in K^+ concentration gradient drives K^+ back out of the cell. An equilibrium is reached when the *electrical* forces exactly balance those due to *concentration* differences (**Gibbs–Donnan equilibrium**); the net force or **electrochemical gradient** for K^+ is then zero. The opposing effect of the concentration gradient means fewer K^+ ions move into the cell than are required by the fixed negative charges. The inside of the cell is therefore negatively charged compared to the outside (*charge separation*), and a potential develops across the membrane. Only a small charge separation (e.g. 1 in ~100,000 K^+ ions) is required to cause a potential of ~−100 mV. If the membrane was only permeable to K^+ and no other cations, the potential at equilibrium (**K^+ equilibrium potential**, E_K) would be defined by the K^+ concentration gradient and calculated from the **Nernst equation**. As cardiac muscle intracellular [K^+] is ~120 mmol/L and extracellular [K^+] ~4 mmol/L E_K = ~−90 mV (Figure 10.1).

In real membranes K^+ permeability (P_K) at rest is indeed greater than for other ions, so the **resting membrane potential** (RMP) is close to E_K (~−85 mV). RMP does not equal E_K because there is some permeability to other ions; most notably Na^+ permeability (P_{Na}) is ~1% of P_K. The Na^+ concentration gradient is also opposite to that for K^+ (intracellular [Na^+] ~10 mmol/L, extracellular ~140 mmol/L), because the **Na^+ pump** (see below) actively removes Na^+ from the cell. As a result, the theoretical equilibrium potential for Na^+ (E_{Na}) is ~+65 mV, far from the actual RMP. Both concentration and electrical gradients are therefore in the same direction, and this inward **electrochemical gradient** drives Na^+ into the cell. As P_{Na} at rest is relatively low, the amount of Na^+ leaking into the cell is small but is still sufficient to cause an inward current that slightly depolarizes the membrane. RMP is thus less negative than E_K. RMP can be calculated using the **Goldman equation**, a derivation of the Nernst equation taking into account other ions and their permeabilities.

A consequence of the above is that if P_{Na} was increased to more than P_K, then the membrane potential would shift towards E_{Na}. This is exactly what happens during an action potential, when Na^+ channels open so that P_{Na} becomes 10-fold greater than P_K, and the membrane depolarizes (see Chapter 11). An equivalent situation arises for Ca^{2+}, as intracellular [Ca^{2+}] is ~100 nmol/L at rest, much smaller than the extracellular [Ca^{2+}] of ~1 mmol/L.

Ion channels and gating (Figure 10.2)

Channels differ in ion selectivity and activation mechanisms. They are either **open** or **closed**; transition between these states is called **gating**. When channels open ions move passively down their electrochemical gradient. As ions are charged, this causes an electrical current (***ionic current***); positive ions entering the cell cause **inward currents** and depolarization. Phosphorylation of channel proteins – by protein kinase A/cAMP for example – can modify function, for example Ca^{2+} channels (Chapter 11). There are several types of gating; two are described.

Voltage-gated channels (VGCs) are regulated by membrane potential. Some (e.g. certain K^+ channels) simply switch between **open** and **shut** states according to the potential across them (Figure 10.2). Others, such as the **fast inward Na^+ channel** responsible for the upstroke of the action potential in nerves, skeletal and cardiac muscle (Figure 10b; Chapter 11), have three states: open, shut and **inactive**. When a cell depolarizes sufficiently to activate these Na^+ channels (i.e. reaches their **threshold** potential), they open and the cell depolarizes towards E_{Na}. After a short period (<ms) the channels spontaneously **inactivate**, as though another gate had closed. Inactivated channels can only be reactivated once the membrane potential becomes negative again. This is essential for generation of action potentials (Chapter 11).

Receptor-gated channels (RGCs; important in smooth muscle, Chapter 15) are commonly **non-selective cation channels** (NSCCs; permeable to Na^+ and Ca^{2+}). They open when a hormone or neurotransmitter (e.g. noradrenaline) binds to a receptor and initiates production of a second messenger, such as **diacylglycerol** (DAG, Figure 10.2).

Ion pumps and exchangers (Figure 10.3)

Ion pumps use energy to transfer ions against their electrochemical gradient. **Primary active transport** consumes ATP for energy, the prime example being the **Na^+ pump** (Na^+–K^+-ATPase), which pumps three Na^+ out of the cell in exchange for two K^+. Another is the Ca^{2+}-ATPase that pumps Ca^{2+} into intracellular stores (SERCA; Chapters 12 and 15). **Secondary active transport** uses the Na^+ electrochemical gradient generated by the Na^+ pump to drive the transfer of other ions or molecules across the membrane. An example is the **Na^+–Ca^{2+} exchanger**, which exchanges three Na^+ ions for a Ca^{2+} ion (Chapters 11 and 12). Na^+ pump inhibitors (e.g. **digoxin**) reduce the Na^+ gradient and thus indirectly inhibit secondary transport. Pumps are regulated by ion concentrations and modulated by second messengers.

Ion pumps and membrane potential

The Na^+ pump and Na^+–Ca^{2+} exchanger are **electrogenic** as unequal amounts of charge are transported, and thus a small ionic current is generated. They can therefore both affect, and be affected by, membrane potential. An example is Na^+–Ca^{2+} exchange during the cardiac muscle action potential (Chapters 11 and 12).

11 Electrophysiology of cardiac muscle and origin of the heartbeat

Figure 11.1 Cardiac ventricular muscle AP

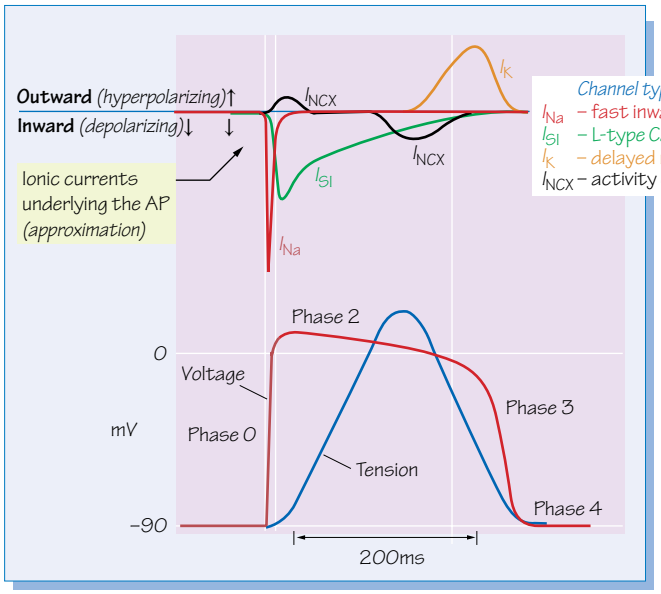


Figure 11.4 Control of heart rate: chronotropic agents

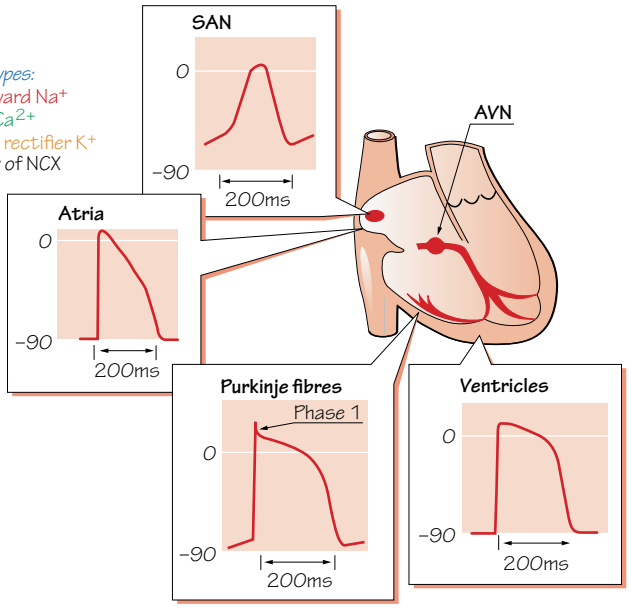


Figure 11.2 AP in different regions

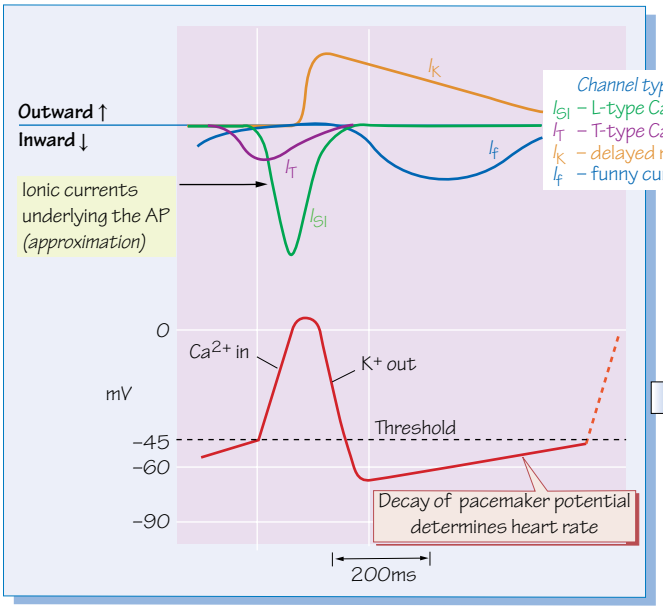
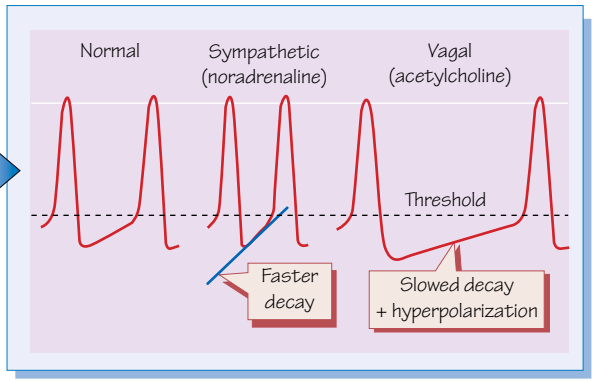


Figure 11.3 Sinoatrial node AP



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An action potential (AP) is the transient depolarization of a cell as a result of activity of ion channels. The cardiac AP is considerably longer than those of nerve or skeletal muscle (~300 vs ~2 ms). This is due to a **plateau phase** in cardiac muscle, lasting for 200–300 ms.

Ventricular muscle action potential

(Figure 11.1)

Initiation of the action potential

At rest, the ventricular cell membrane is most permeable to K^+ and the **resting membrane potential** (RMP) is therefore close to the K^+ equilibrium potential (E_K), ~−90 mV (Chapter 10). An AP is initiated when the membrane is depolarized to the **threshold potential** (~−65 mV). This occurs due to transmission of a depolarizing current from an adjacent activated cell through **gap junctions** (Chapter 2). At threshold, sufficient **voltage-gated Na^+ channels** are activated to initiate a self-regenerating process – the inward current caused by entry of Na^+ (I_{Na}) through these channels causes further depolarization, which activates more Na^+ channels, and so on. The outcome is a very large and fast I_{Na}, and therefore a very rapid AP upstroke (phase 0; ~500 V/s).

Activation of Na^+ channels during phase 0 means that the Na^+ permeability is now much greater than that for K^+, and so the membrane potential moves towards the Na^+ equilibrium potential (E_{Na}, ~+65 mV) (Chapter 10). It does not reach E_{Na} because the Na^+ channels rapidly **inactivate** as the potential nears +40 mV (Chapter 10); this, and activation of a transient outward K^+ current, can lead to a rapid decline in potential, leaving a spike (**phase 1**), best seen in Purkinje fibres (Figure 11.2). The inactivated Na^+ channels cannot be **reactivated** until the potential returns to less than −60 mV, so another AP cannot be initiated until the cell repolarizes (**refractory period**). The refractory period therefore lasts as long as the plateau and contraction (Figure 11.1), so unlike skeletal muscle, cardiac muscle cannot be tetanized.

The plateau (phase 2)

By the end of the upstroke all Na^+ channels are inactivated, and in skeletal muscle the cell would now repolarize. In cardiac muscle, however, the potential remains close to 0 mV for ~250 ms. This **plateau phase** is due to opening of **voltage-gated (L-type) Ca^{2+} channels**, which activate relatively slowly when the membrane potential becomes more positive than ~−35 mV. The resultant Ca^{2+} current (slow inward or $\boldsymbol{I}_{SI}$) is sufficient to slow repolarization until the potential falls to ~−20 mV. The length of the plateau is related to slow **inactivation** of Ca^{2+} channels and the additional Na^+ inward current provided by the Na^+–Ca^{2+} exchanger (see below). Ca^{2+} entry during the plateau is vital for cardiac muscle contraction (Chapter 12).

Repolarization (phase 3)

By the end of the plateau the membrane potential is sufficiently negative to activate *delayed rectifier* K^+ channels, and the associated outward K^+ current (I_K) therefore promotes rapid repolarization. As the membrane potential returns to resting levels (**phase 4**), I_K slowly inactivates again. Factors that influence I_K will affect the rate of repolarization, and hence the AP length (Chapter 52), and mutations in the underlying channels cause long QT syndrome (Chapter 57).

Role of Na^+–Ca^{2+} exchange

The Na^+–Ca^{2+} exchanger (NCX) exchanges three Na^+ for one Ca^{2+} and is thus electrogenic (Chapter 10). In the early plateau, when membrane potential is most positive, the NCX may reverse and contribute to inward current and movement of Ca^{2+}. As the plateau decays and becomes more negative NCX returns to its usual function of expelling Ca^{2+} from the cell in exchange for Na^+, which is potentiated by the high cytosolic [Ca^{2+}]. This influx of Na^+ ions causes an inward current (I_{NCX}) that slows repolarization and lengthens the plateau.

Sinoatrial node

The **sinoatrial node** (SAN) is the origin of the heartbeat, and its AP differs from that of the ventricle (Figure 11.3). The resting potential (phase 4) exhibits a slow depolarization, and the upstroke (phase 0) is much slower. The latter is because there are no functional Na^+ channels, and the upstroke is due instead to activation of slow L-type Ca^{2+} channels. The slow upstroke leads to slower conduction between cells (Chapter 13). This is of particular importance in the **atrioventricular node** (AVN), which has a similar AP to the SAN.

The SAN resting potential slowly depolarizes from ~−60 mV to a threshold of ~−40 mV, at which point L-type channels activate and an AP is initiated; the threshold is more positive because of substitution of L-type for Na^+ channels. The rate of decay determines how long it takes for threshold to be reached and therefore the heart rate. The resting potential is therefore commonly called the **pacemaker potential**. As for ventricular cells, repolarization of the AP in SAN involves activation of I_K, which then slowly inactivates. In addition, there are two inward currents, $\boldsymbol{I}_b$ and $\boldsymbol{I}_f$ ('*funny*'), mostly due to inward movement of Na^+. $\boldsymbol{I}_b$ is stable, and present in other cardiac cells, but $\boldsymbol{I}_f$ is specific to nodal cells and activated at the end of repolarization by negative potentials (Figure 11.2). The combination of inward current from $\boldsymbol{I}_f$ plus $\boldsymbol{I}_b$ and decay in I_K causes the slow depolarization of the pacemaker potential. As this approaches threshold, another type of voltage gated Ca^{2+} channel (transient, T-type) is activated, which contributes to the depolarization and the early part of the upstroke.

Factors influencing $\boldsymbol{I}_K$, $\boldsymbol{I}_b$, or $\boldsymbol{I}_f$ thus alter the slope of the pacemaker and so heart rate and are called **chronotropic agents**. The sympathetic neurotransmitter noradrenaline increases heart rate by increasing the size of I_f. It also reduces AP length by increasing the rate of Ca^{2+} entry and hence the slope of the upstroke. The parasympathetic transmitter acetylcholine reduces the slope of the pacemaker potential and causes a small hyperpolarization, both of which increase the time required to reach threshold and reduce heart rate (Figure 11.4).

Other regions of the heart (Figure 11.2)

Atrial muscle has a similar AP to ventricular muscle, although the shape is more triangular. **Purkinje fibres** in the conduction system have a prominent phase 1, reflecting a greater $\boldsymbol{I}_{Na}$ (due to their large size); the latter causes a more rapid upstroke and faster conduction. APs in the AVN are similar to those of the SAN, although the rate of decay of the resting potential is slower. The resting potential of the bundle of His and Purkinje system may also exhibit an even slower rate of decay (due to decay of $\boldsymbol{I}_K$). All of these could therefore act as pacemakers, but the SAN is normally faster and predominates. This is called **dominance** or **overdrive suppression**.

12 Cardiac muscle excitation–contraction coupling

Figure 12.1 Activation

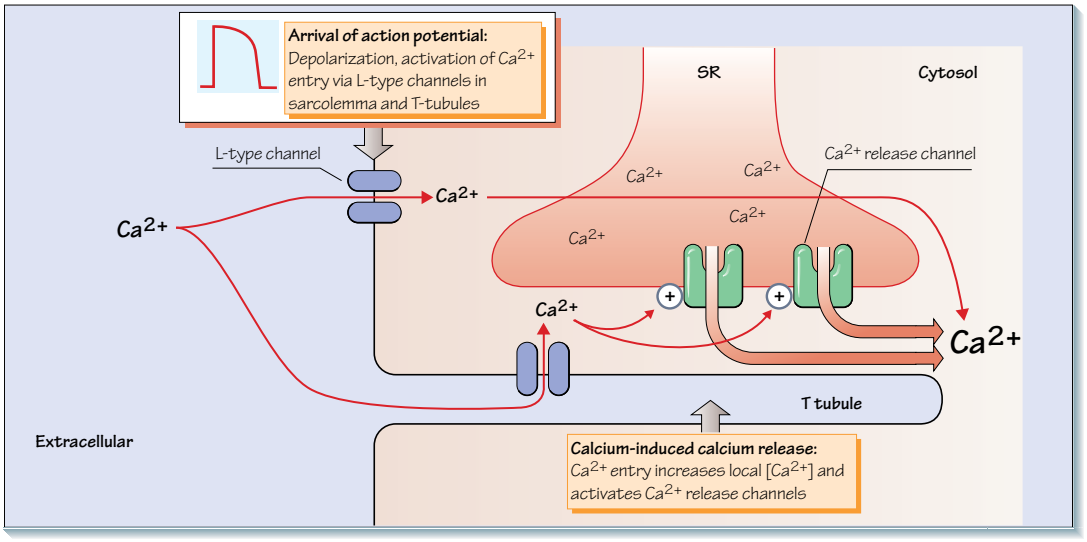


Figure 12.2 Relaxation

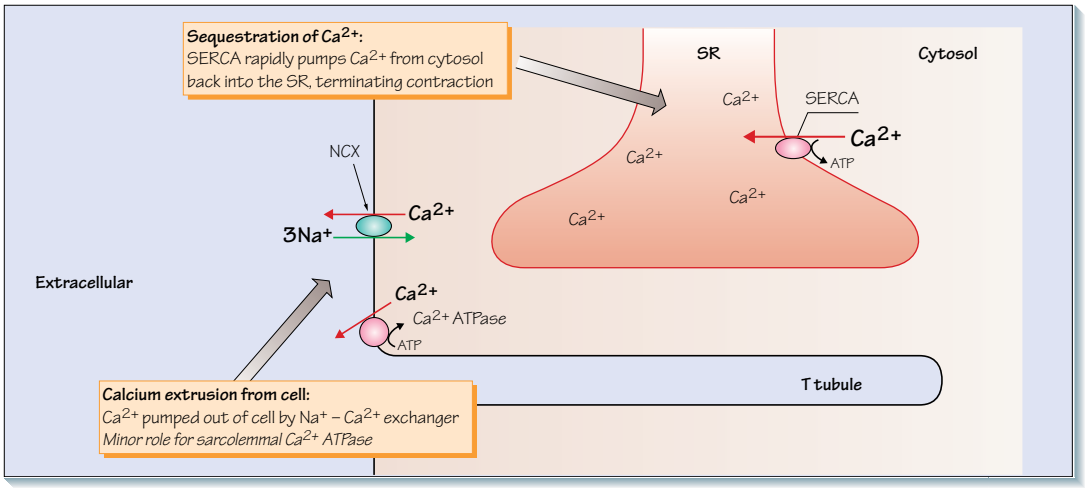
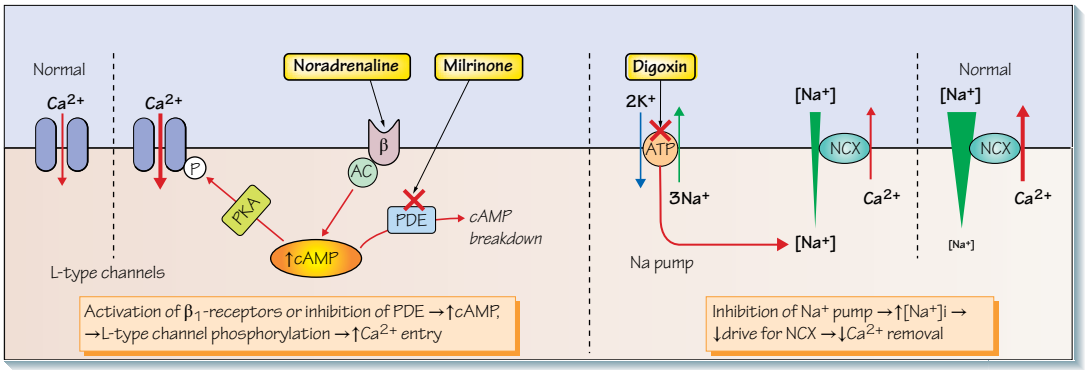


Figure 12.3 Inotropes



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Cardiac muscle contracts when cytosolic [Ca^{2+}] rises above about 100 nmol/L. This rise in [Ca^{2+}] couples the action potential (AP) to contraction, and the mechanisms involved are referred to as **excitation–contraction coupling**. The relationship between cardiac muscle force and stretch is discussed in Chapter 17. The ability of cardiac muscle to generate force *for any given fibre length* is described as its **contractility**. This depends on cytosolic [Ca^{2+}], and to a lesser extent on factors that affect Ca^{2+} sensitivity of the contractile apparatus. The contractility of cardiac muscle is primarily dependent on the way that the cell handles Ca^{2+}.

Initiation of contraction

During the **plateau phase** of the AP, Ca^{2+} enters the cell through **L-type voltage-gated Ca^{2+} channels** (Figure 12.1). L-type channels are specifically blocked by **dihydropyridines** (e.g. *nifedipine*) and *verapamil*. However, the amount of Ca^{2+} that enters the cell is less than 20% of that required for the observed rise in cytosolic [Ca^{2+}] ($[Ca^{2+}]_i$). The rest is released from the **sarcoplasmic reticulum** (SR), where Ca^{2+} is stored in high concentrations by the Ca^{2+} binding protein **calsequestrin**. AP travels down the **T tubules** which are close to, but do not touch, the **terminal cisternae** of the SR (Figure 12.1). During the first 1–2 ms of the plateau Ca^{2+} enters and causes a rise in [Ca^{2+}] in the gap between the T tubule sarcolemma and SR. This rise in [Ca^{2+}] activates Ca^{2+}-sensitive **Ca^{2+} release channels** in the SR, through which stored Ca^{2+} floods into the cytoplasm. This is called **calcium-induced calcium release (CICR)** (Figure 12.1). The amount of Ca^{2+} released depends both on the content of the SR and size of the activating Ca^{2+} entry, and modulation of the latter is the major way by which cardiac function is regulated (see Regulation of contractility below). Ca^{2+} release and entry combine to cause a rapid increase in $[Ca^{2+}]_i$, which initiates contraction. Peak $[Ca^{2+}]_i$ normally rises to ~2 μmol/L, although maximum contraction occurs when $[Ca^{2+}]_i$ rises above 10 μmol/L.

Generation of tension

The arrangement of **actin** and **myosin** filaments is discussed in Chapter 2. Force is generated when myosin heads protruding from thick filaments bind to actin thin filaments to form **crossbridges** and drag the actin past in a ratchet fashion using ATP bound to myosin as an energy source. This is the **sliding filament** or **crossbridge mechanism** of muscle contraction. In cardiac muscle $[Ca^{2+}]_i$ controls crossbridge formation via the regulatory proteins **tropomyosin** and **troponin**. Tropomyosin is a coiled strand which, at rest, lies in the cleft between the two actin chains that form the thin filament helix and covers the myosin binding sites. Myosin therefore cannot bind, and there is no tension. Troponin is a complex of three globular proteins (**troponin C, I and T**), bound to tropomyosin by **troponin T** at intervals of 40 nm. When $[Ca^{2+}]_i$ rises above 100 nmol/L, Ca^{2+} binds to **troponin C** causing a conformational change which allows tropomyosin to shift out of the actin cleft. Myosin binding sites are uncovered, crossbridges form and tension develops. Tension is related to the number of active crossbridges and will increase until all troponin C is bound to Ca^{2+} ($[Ca^{2+}]_i$ >10 μmol/L).

Relaxation mechanisms

When $[Ca^{2+}]_i$ rises above resting levels (~100 nmol/L), ATP-dependent Ca^{2+} pumps in the SR (sarcoendoplasmic reticulum Ca^{2+}-ATPase; **SERCA**) are activated, and start to pump (**sequester**) Ca^{2+} from the cytosol back into the SR (Figure 12.2). As the AP repolarizes and L-type Ca^{2+} channels inactivate, this mechanism reduces $[Ca^{2+}]_i$ towards resting levels, so Ca^{2+} dissociates from troponin C and the muscle relaxes. However, the Ca^{2+} originally entering the cell must now be expelled. Ca^{2+} is transported out of the cell by the membrane **Na^+–Ca^{2+} exchanger (NCX)** (Chapters 10, 11). This uses the inward Na^+ electrochemical gradient as an energy source to pump Ca^{2+} out, and three Na^+ enter the cell for each Ca^{2+} removed (Figure 12.2). Sarcolemmal Ca^{2+}-ATPase pumps are present but less important. At the end of the AP about 80% of the Ca^{2+} will have been resequestered into the SR, and most of the rest ejected from the cell. The remainder is slowly pumped out between beats.

Regulation of contractility

Inotropic agents alter the contractility of cardiac muscle; a positive inotrope increases contractility, while a negative decreases it. Most inotropes act by modulating cell Ca^{2+} handling, although some may alter Ca^{2+} binding to troponin C. A high plasma [Ca^{2+}] increases contractility by increasing Ca^{2+} entry during the AP.

Noradrenaline (norepinephrine) from sympathetic nerve endings, and to a lesser extent circulating **adrenaline (epinephrine)**, are the most important physiological inotropic agents. They also increase heart rate (positive **chronotropes**; Chapter 11). Noradrenaline binds to β_1-adrenoceptors on the sarcolemma and activates adenylate cyclase (AC), causing production of the second messenger cAMP. This activates protein kinase A (PKA), which phosphorylates L-type Ca^{2+} channels so that they allow more Ca^{2+} to enter during the AP (Figure 12.3; Chapter 11). The elevation of $[Ca^{2+}]_i$ is thus potentiated and more force develops. Any agent that increases cAMP will act as a positive inotrope, for example milrinone, an inhibitor of the phosphodiesterase that breaks down cAMP. Noradrenaline (and cAMP) also increase the rate of Ca^{2+} reuptake into the SR, mediated by PKA and phosphorylation of **phospholamban**, a SERCA regulatory protein. While not affecting contractility, this assists removal of the additional Ca^{2+} and shortens contraction, which is useful for high heart rates.

The classic positive inotropic drug is **digoxin**, a **cardiac glycoside.** Digoxin inhibits the **Na^+ pump** (Na^+-K^+ ATPase) which removes [Na^+] from cells. Intracellular [Na^+] therefore increases, so reducing the Na^+ gradient that drives NCX (Chapter 11). Consequently, less Ca^{2+} is removed from the cell by the NCX (Figure 12.3) and peak $[Ca^{2+}]_i$ and force increase.

Overstimulation by positive inotropes can lead to **Ca^{2+} overload**, and damage due to excessive uptake of Ca^{2+} by the SR and mitochondria. This can contribute to the progressive decline in myocardial function in **chronic heart failure** (Chapter 46), when sympathetic stimulation is high.

Acidosis is *negatively* inotropic, largely by interfering with the actions of Ca^{2+}. This is important in **myocardial ischaemia** and **heart failure**, where poor perfusion can lead to **lactic acidosis** and so depress cardiac function.

Influence of heart rate

When heart rate increases there is a proportional rise in cardiac muscle force. This phenomenon is known as the **staircase**, **Treppe** or **Bowditch** effect. It can be attributed both to an increase in cytosolic [Na^+] due to the greater frequency of APs, with a consequent inhibition of NCX (see above), and to a decreased diastolic interval, which limits the time between beats for Ca^{2+} to be extruded from the cell.

13 Electrical conduction system in the heart

Figure 13.1 Conduction mechanism

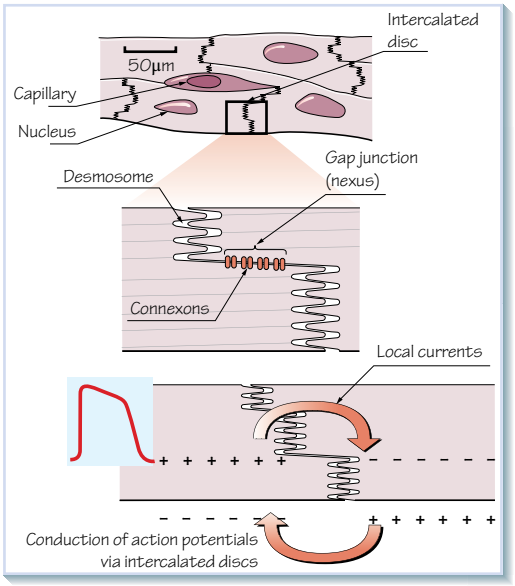


Figure 13.2 Conduction pathways

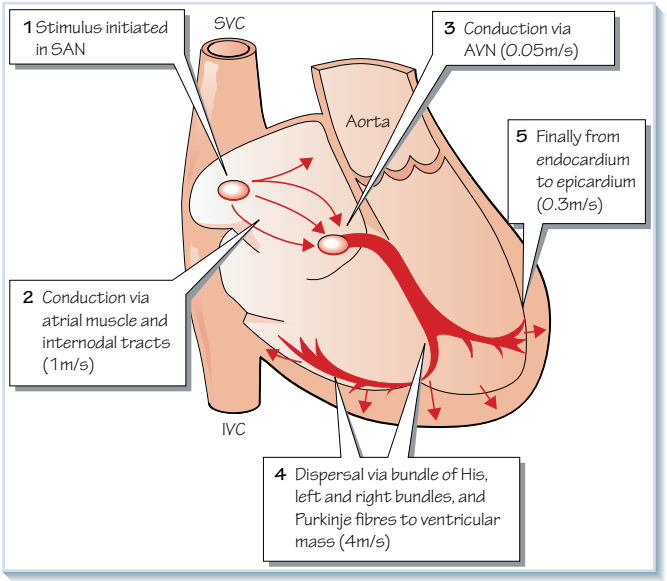


Figure 13.3 Example ECGs for SA node conductions defects

Figure 13.3.1 Sinus rhythm

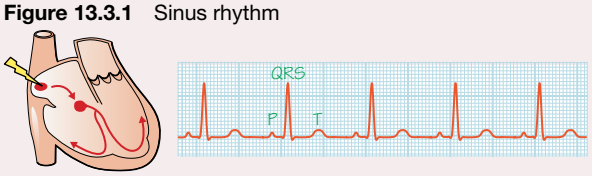


Figure 13.3.2 Sick sinus syndrome (AVN escape)

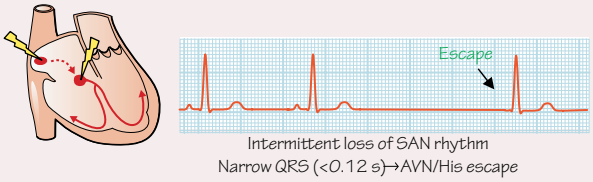


Figure 13.3.3 1st-degree heart block

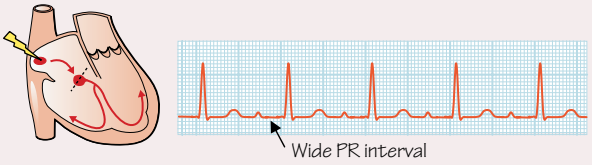


Figure 13.3.4 2nd-degree heart block (2:1; Mobitz II)

Figure 13.3.5 2nd-degree heart block (Mobitz I)

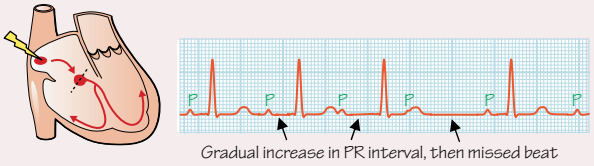


Figure 13.3.6 3rd-degree heart block (AVN escape)

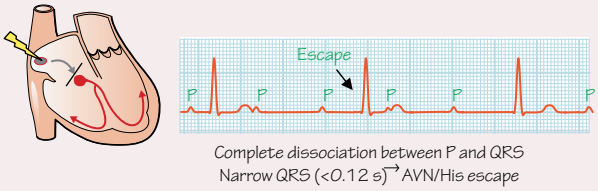
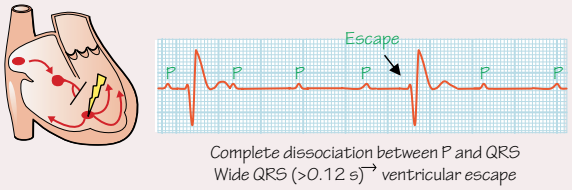


Figure 13.3.7 3rd-degree heart block (ventricular escape)



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Electrical conduction in cardiac muscle

(Figure 13.1)

Cardiac muscle cells are connected via **intercalated discs** (Chapter 2). These incorporate regions where the membranes of adjacent cells are very close, called **gap junctions.** Gap junctions consist of proteins known as **connexons**, which form low-resistance junctions between cells. They allow the transfer of small ions and thus electrical current. As all cells are therefore electrically connected, cardiac muscle is said to be a **functional** (or electrical) **syncytium**. If an action potential (AP) is initiated in one cell, local currents via gap junctions will cause adjacent cells to depolarize, initiating their own AP. A wave of depolarization will therefore be conducted from cell to cell throughout the myocardium. The rate of conduction is partly dependent on gap junction resistance and the *size of the depolarizing current*. This is related to the **upstroke velocity of the AP** (phase 0). Drugs that slow phase 0 therefore slow conduction (e.g. lidocaine, class I antiarrhythmics). Pathological conditions such as ischaemia may increase gap junction resistance and slow or abolish conduction. Retrograde conduction does not normally occur because the original cell is refractory (Chapter 11). Transfer of the pacemaker signal from the sinoatrial node (SAN) and synchronous contraction of the ventricles is facilitated by **conduction pathways** formed from specialized muscle cells.

Conduction pathways in the heart (Figure 13.2)

Sinoatrial node

The heartbeat is normally initiated in the **SAN**, located at the junction of the superior vena cava and right atrium. The SAN is a ~2-mm-wide group of small elongated muscle cells that extends for ~2 cm down the sulcus terminalis. It has a rich capillary supply and sympathetic and parasympathetic (right vagal) nerve endings. The SAN generates an AP about once a second (sinus rhythm, Figure 13.3.1; Chapter 11).

Atrial conduction

The impulse spreads from the SAN across the atria at ~1 m/s. Conduction to the **atrioventricular node** (AVN) is facilitated by larger cells in the three **internodal tracts** of Bachmann (anterior), Wenckebach (middle) and Thorel (posterior).

The atrioventricular node

The atria and ventricles are separated by the non-conducting **annulus fibrosus**. The AVN marks the upper region of the only conducting route through this band. It is similar in structure to the SAN, situated near the interatrial septum and mouth of the coronary sinus, and innervated by sympathetic and left vagal nerves. The complex arrangement of small cells and slow AP upstroke (Chapter 11) result in a very slow conduction velocity (~0.05 m/s). This provides a functionally significant delay of ~0.1 s between contraction of the atria and ventricles, reflected by the **PR interval** of the electrocardiogram (**ECG;** Chapter 14). Sympathetic stimulation increases conduction velocity and reduces the delay, whereas vagal stimulation slows conduction and increases the delay.

Bundle of His and Purkinje system

The **bundle of His** transfers the impulse from the AVN to the top of the interventricular septum. Close to the attachment of the tricuspid septal cusp it branches to form the **left** and **right bundle branches**. The left bundle divides into the posterior and anterior fascicles. The bundles travel under the endocardium down the walls of the septum and at the base divide into the multiple fibres of the **Purkinje system**. This distributes the impulse over the inner walls of the ventricles. Cells in the bundle of His and Purkinje system have large diameters (~40 μm) and rapid AP upstroke and consequently fast conduction (~4 m/s). The impulse spreads from the Purkinje cells through the endocardium towards the epicardium at 0.3–1 m/s, thereby initiating contraction.

Abnormalities of impulse generation or conduction (see also Chapters 48–53)

Sinus tachycardia (100–200 beats/min) is normal in exercise or excitement, but also occurs when pathological stimuli (e.g. phaeochromocytoma, heart failure, thyrotoxicosis) elevate sympathetic tone and accelerate SAN firing. Sinus tachycardia generally starts and stops gradually. Treatment, if required, involves removing the underlying cause. The ECG is otherwise normal. Conversely, **sick sinus syndrome**, generally caused by SAN fibrosis, causes slowed impulse generation and **bradycardia** (slow heart rate), or a sustained or intermittent failure of the impulse to reach the AVN, termed **sinoatrial block** (Figure 13.3.2). Because other parts of the conduction system also exhibit pacemaking activity (Chapter 11), sick sinus syndrome can result in the emergence of **escape** beats or rhythms in which impulses arising elsewhere (usually the AVN) can activate ventricular depolarization. Sick sinus syndrome can be treated by implantation of a pacemaker.

Heart block Abnormally slow conduction in the AVN can result in incomplete (**first-degree**) heart block (*AV block*; Figure 13.3.3), where the delay is greater than normal, resulting in an extended PR interval. **Second-degree** heart block occurs when only a fraction of impulses from the atria are conducted; for example, ventricular contraction is only initiated every second or third atrial contraction (**2:1 or 3:1** block; **Mobitz II**; Figure 13.3.4). **Mobitz I block** (Wenckebach) is another type of second-degree block, in which the PR interval progressively lengthens until there is no transmission from atria to ventricles and a QRS complex is missed; the cycle then begins again (Figure 13.3.5). Patients with first- or second-degree block are often asymptomatic. Complete (**third-degree**) heart block occurs when conduction between atria and ventricles is abolished (Figure 13.3.6, 13.3.7). This can result from ischaemic damage to nodal tissue or the bundle of His. In the absence of a signal from the SAN, the AVN and bundle of His can generate a heart rate of ~40 beats/min (Chapter 11). Some ventricular cells spontaneously generate APs, but at a rate less than 20/min.

Bundle branch block When one branch of the bundle of His does not conduct (*left or right bundle branch block*), the part of the ventricle that it serves is stimulated by conduction through the myocardium from unaffected areas. As this form of conduction is slower, activation is delayed (see Chapter 53).

14 The electrocardiogram

Figure 14.1 Bipolar limb leads

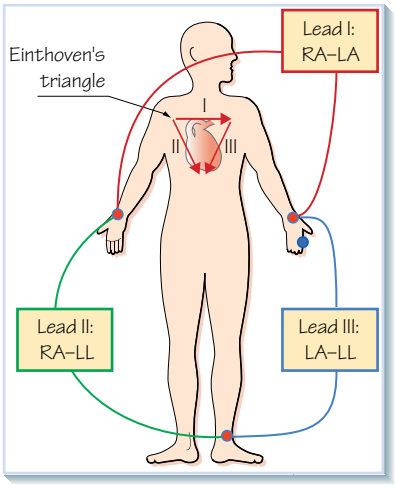


Figure 14.2 Depolarization and the ECG complex

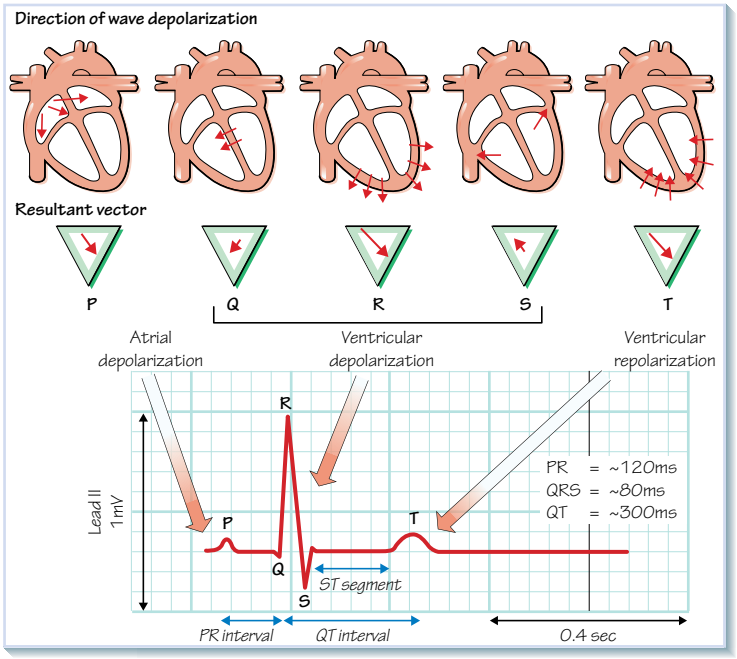


Figure 14.3 Precordial (chest) leads

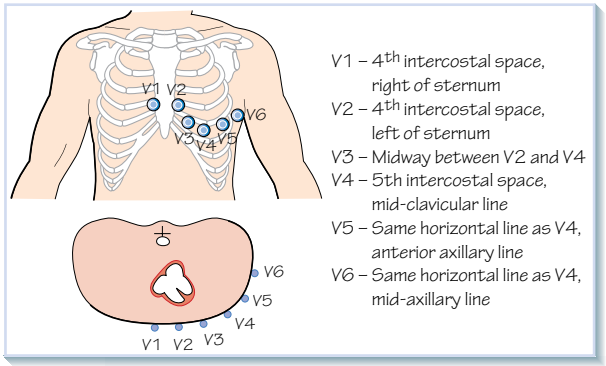


Figure 14.4 Hexaxial reference and cardiac axis

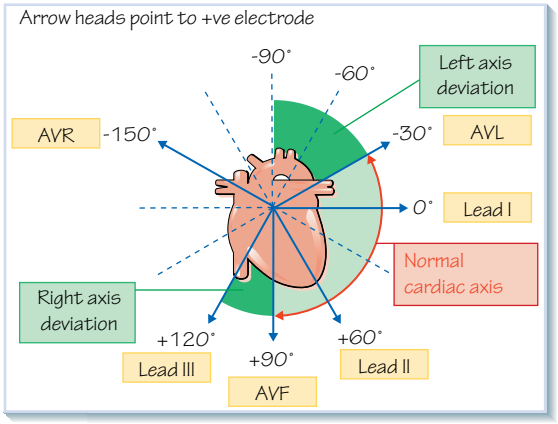


Figure 14.5 12 lead ECG

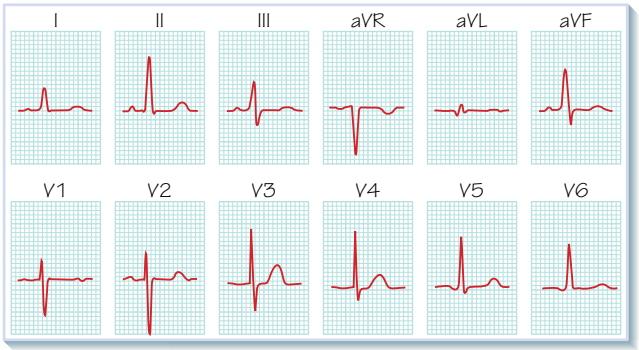
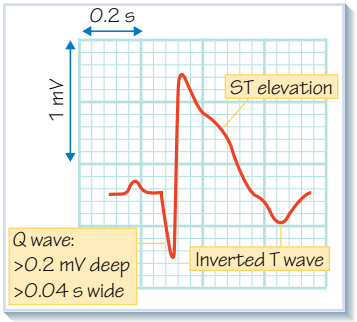


Figure 14.6 Typical changes associated with MI



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The **electrocardiogram** (ECG) is the surface recording of electrical activity of the heart as the cardiac muscle depolarizes and repolarizes (see Chapters 11 and 13). The recorded voltage (1–2 mV) is much smaller than that of the action potential and reflects the *vector sum* of currents between depolarized and resting cells, thus providing both **amplitude** and **directional** information. Identification of intermittent events such as paroxysmal arrhythmias may require ambulatory ECG recording over 24 hours (**Holter** test), or an **exercise tolerance test** where workload is progressively increased to elicit events related to coronary artery disease for example.

Recording the ECG

The ECG is based around the concept of an equilateral triangle (**Einthoven's triangle**; Figure 14.1). The points of the triangle are approximated by placing electrodes on the right arm (RA), left arm (LA) and left leg (LL). The right leg is commonly used as an earth to minimize interference. The voltage between any two electrodes will depend on the amplitude of the current, which is related to muscle mass, and the mean direction of current; it is thus a **vector quantity** (Figure 14.2). The greatest voltage and thus deflection are therefore seen when the wave of depolarization is directly towards or away from the respective electrodes. By convention, the ECG is connected such that a wave of depolarization towards the positive electrode causes an upward deflection, and the paper speed of the recorder is normally 25 or 50 mm/s.

The various combinations of electrodes are called **leads** (not to be confused with the cables connecting the electrodes). The three **bipolar limb leads** each approximate the potential difference (PD) between two corners of Einthoven's triangle and are essentially looking at electrical activity in the heart from three different directions, separated by 60°. **Lead I** measures the PD between RA (positive electrode) and LA (negative electrode); **lead II**, RA (negative) and LL (positive); and **lead III**, LA (negative) and LL (positive).

The **unipolar leads** use a single sensing electrode and measure the PD between this and an **indifferent electrode** representing the average potential of the whole body (i.e. zero). Practically, this is obtained by connecting RA, LA and LL together, which approximates the centre of Einthoven's triangle (i.e. the heart). The six **precordial** (chest) leads use a separate *sensing* (positive) electrode placed on the chest so as to accentuate activity in particular regions of the heart (Figure 14.3): V1 and V2, right ventricle; V3 and V4, interventricular septum; V5 and V6, left ventricle. However, the **augmented** limb leads use one limb connection as the sensing electrode (aVR, RA; aVL, LA; aVF, LL), with the remaining two connected together as the indifferent electrode. As they therefore measure from each corner of Einthoven's triangle towards the centre, they 'see' the heart at angles rotated by 30° compared with the bipolar leads. The six limb leads therefore give a view of the electrical activity of the heart every 30° (**hexaxial reference system**; Figure 14.4). Lead II and AVR normally shows the tallest QRS, as they lie closest to the mean direction of ventricular depolarization; as the ventricles have the greatest muscle mass, they generate the largest current. Together, the limb and precordial leads provide the standard **12 lead ECG** (Figure 14.5).

General features of the ECG (Figure 14.2)

The **P wave** (≤0.12 s duration) is a small deflection due to depolarization of the atria (atrial systole). The **QRS complex** is normally <0.08 s in duration and reflects ventricular depolarization; it is largest because of the large ventricular mass. The relative size of the individual components varies between leads. In lead II the **Q wave** is a small downward deflection, reflecting left to right depolarization of the interventricular septum. The **R wave** is a strong upwards deflection, reflecting depolarization of the main ventricular mass. The **S wave** is a small downward deflection in lead II and reflects depolarization of the last part of the ventricle close to the base of the heart. The **T wave** reflects ventricular repolarization and is normally in the same direction as the R wave (e.g. upwards deflection in lead II). This is because although it is opposite in polarity, its *direction* is the opposite of that for depolarization (Figure 14.2), as the length of action potential in the epicardium is shorter than that in the endocardium, so although the epicardium depolarizes last it repolarizes first. The reversal in direction therefore cancels out the reversal in polarity. Note that atrial repolarization is too small and diffuse to be seen, and the conducting system (see Chapter 13) has too small a mass to generate any significant voltage.

The **PR interval** represents the delay between atrial and ventricular depolarization, mostly in the atrioventricular node (AVN), and is measured from the start of P to the start of QRS. Normal duration is 0.12–0.20 s. The **ST segment** (~0.25 s) is normally **isoelectric** (i.e. at zero potential), because all ventricular muscle is depolarized and so there can be no current flow between cells. The **QT interval**, from the start of QRS to the end of T, represents the duration of ventricular activation. It is strongly dependent on heart rate and is generally corrected by the **Bazett formula** (QT_C = QT/square root of R–R interval). QT_C is normally <0.44 s, slightly longer in females.

Basic interpretation of the ECG (Figure 14.5)

Rate and rhythm Heart rate in beats/min is 1/RR interval × 60. At a paper speed of 25 mm/s one large square = 0.2 s, one small square = 0.04 s. A heart rate above 100 beats/min is **tachycardia**, and below 60 beats/min **bradycardia**. A regular rhythm with a constant normal PR interval is **sinus rhythm**. A prolonged PR interval or disassociation of P and QRS waves suggests impaired conduction in the AVN or bundle of His (see Chapter 13).

QRS A broad and negative **Q wave** (sometimes normal in AVR and V1) or broad and misshapen QRS can be caused by a number of defects, including bundle branch block (see Chapter 13) or a ventricular origin of the heartbeat (e.g. ectopic beats). A slowly developing Q wave may indicate a full wall-thickness **myocardial infarction** (MI; Figure 14.6; see Chapter 45).

Cardiac axis The direction of maximum ECG amplitude (mean vector) and thus of the sum of currents generated by the ventricles. It is calculated from the relative size of the QRS for each limb lead, and ranges from +90° to −30° (Figure 14.4). It depends on the orientation of the heart and so varies during breathing. **Left axis deviation** (−30° to −90°) may reflect left ventricular hypertrophy, and **right axis deviation** (+90° to +120°) right ventricular hypertrophy.

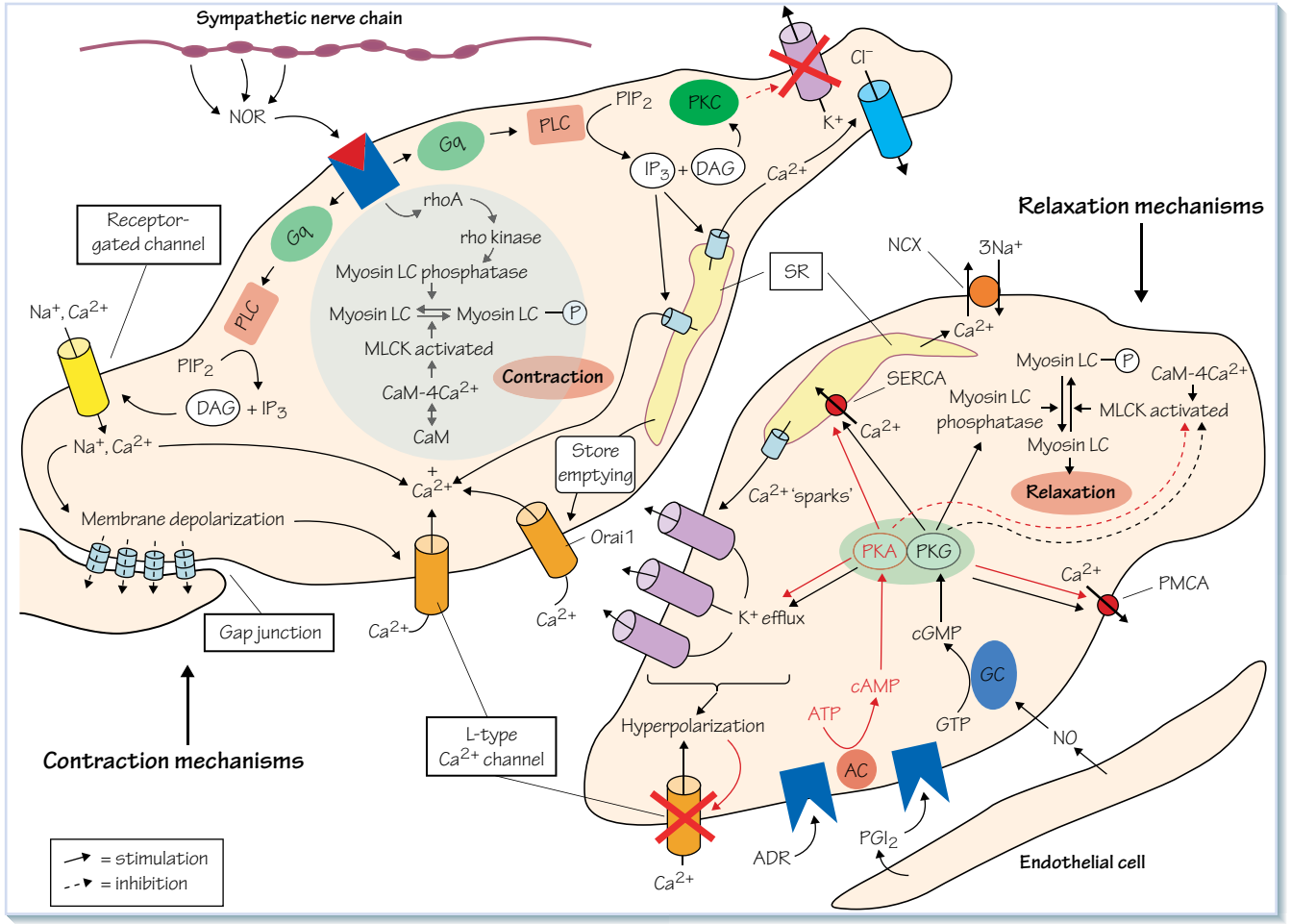
ST segment elevation Due to **injury currents** between damaged and undamaged cells, normally transient and indicative of recent MI (Figure 14.6; see Chapter 45). Subendocardial MI may cause ST segment **depression**.

T wave inversion Often normal in lead III and V1, but in other leads may reflect MI and slowed conduction, such that repolarization of the epicardium occurs before repolarization of the endocardium. A **tall peaked T wave** can be caused by hyperkalaemia.

Prolonged QT_C Reflects delayed repolarisation and can be caused by class IA and III antiarrhythmic drugs, heart failure and inherited long QT syndrome (see Chapters 46, 51 and 54).

15 Vascular smooth muscle excitation–contraction coupling

Figure 15.1 Vasoconstricting and vasodilating mechanisms of vascular smooth muscle cells



Vascular smooth muscle (VSM) contraction is, like that of cardiac muscle, controlled by the *intracellular Ca^{2+} concentration* $[Ca^{2+}]_i$. Unlike cardiac muscle cells, however, VSM cells lack troponin and utilize a *myosin-based system* to regulate contraction.

Regulation of contraction by Ca^{2+} and myosin phosphorylation (see shaded area in left cell of Figure 15.1)

Vasoconstricting stimuli initiate VSM cell contraction by increasing $[Ca^{2+}]_i$ from its basal level of ~100 nmol/L. Force development is proportional to the increase in $[Ca^{2+}]_i$, with maximal contraction occurring at ~1 μmol/L $[Ca^{2+}]_i$. The rise in $[Ca^{2+}]_i$ promotes its binding to the cytoplasmic regulatory protein **calmodulin (CaM)**. Once a calmodulin molecule has bound four Ca^{2+} ions, it can activate the enzyme **myosin light-chain kinase** (MLCK). MLCK in turn phosphorylates two 20-kDa subunits (**'light chains'**) contained within the 'head' of each myosin molecule. Phosphorylated myosin then forms crossbridges with actin, using ATP hydrolysis as an energy source to produce contraction. Actin–myosin interactions during crossbridge cycling are similar to those in cardiac myocytes (Chapter 12).

The degree of myosin light-chain phosphorylation, which determines crossbridge turnover, is a balance between the activity of MLCK and a **myosin light-chain phosphatase** which dephosphorylates the light chains. Once $[Ca^{2+}]_i$ falls, MLCK activity diminishes and relaxation occurs as light-chain phosphorylation is returned to basal levels by the phosphatase.

VSM cells *in vivo* maintain a tonic level of partial contraction that varies with fluctuations in the vasoconstricting and vasodilating influences to which they are exposed. VSM cells

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avoid fatigue during prolonged contractions because their rate of ATP consumption is 300-fold lower than that of skeletal muscle fibres. This is possible because the maximum cross-bridge cycling rate of smooth muscle during shortening is only about one-tenth of that in striated muscles due to differences in the types of myosin present. Once VSM cells have shortened, their ATP expenditure is further reduced because the myosin crossbridges remain attached to actin for a longer time, thus 'locking in' shortening.

Vasoconstricting mechanisms

The binding to receptors of **noradrenaline (norepinephrine)** and other important vasoconstrictors such as **endothelin, thromboxane A_2, angiotensin 2** and **vasopressin** stimulates VSM contraction via common **G-protein-mediated** pathways (see left cell).

Effects of IP_3 and diacylglycerol

Binding of vasoconstrictors to receptors activates the G-protein $G_{q/11}$, which stimulates the enzyme **phospholipase C**. Phospholipase C splits the membrane phospholipid phosphatidylinositol 1,4 bisphosphate (PIP_2), generating the second messengers inositol 1,4,5-triphosphate (**IP_3**) and diacylglycerol (**DAG**). IP_3 binds to and opens Ca^{2+} channels on the membrane of the **sarcoplasmic reticulum** (SR). This allows Ca^{2+}, which is stored in high concentrations within the SR, to flood out into the cytoplasm. DAG activates **protein kinase C** (PKC). This activates the protein **CPI-17**, which phosphorylates and inhibits myosin phosphatase, promoting contraction.

Ca^{2+} influx mechanisms

Vasoconstrictors also cause **membrane depolarization** via several mechanisms. First, the release of SR Ca^{2+} they initiate causes the opening of plasmalemmal **Ca^{2+}-activated chloride channels**, which are thought to be formed of the protein **anoctamin**. Second, vasoconstrictors may act via DAG and PKC to *inhibit* the activity of **K^+ channels**. Third, vasoconstrictors act through DAG to open **receptor-gated cation channels**, which allow the influx of both Na^+ and Ca^{2+} ions. These channels are formed from tetramers of **TRPC** (transient receptor potential canonical) proteins, with TRPC 3, 6 and 7 isoforms thought to be the main isoforms involved.

The membrane depolarization elicited by vasoconstrictors opens **L-type voltage-gated Ca^{2+} channels** (also termed $Ca_v1.2$ channels) similar to those found in cardiac myocytes. With sufficient depolarization, some blood vessels may fire brief Ca^{2+} channel-mediated APs that cause transient contractions. More often, however, vasoconstrictors cause graded depolarizations, during which sufficient Ca^{2+} influx occurs to cause more sustained contractions. Vasoconstrictors further enhance Ca^{2+} influx through L-type channels by evoking channel phosphorylation. Furthermore, depletion of SR Ca^{2+} due to its release causes the activation of STIM1, an SR protein which then binds to and stimulates the opening of plasmalemmal **store-operated Ca^{2+}** (SOC) **channels,** which mediate the influx of both Ca^{2+} and Na^+. The molecular correlate of SOC channels is probably the plasmalemmal protein **Orai1**, although this concept is disputed because Orai1 is Ca^{2+} selective and it may be that non-selective cation channels formed by the protein TRPC1 are also involved.

As well as raising $[Ca^{2+}]_i$, vasoconstrictors also promote contraction by a process termed **Ca^{2+} sensitization**. Ca^{2+} sensitization is caused by the inhibition of myosin phosphatase. This increases myosin light-chain phosphorylation, and therefore force development, even with minimal increases in $[Ca^{2+}]_i$ and MLCK activity. Although PKC has this effect (see above), phosphatase inhibition is primarily caused by **RhoA kinase**, an enzyme stimulated by the *ras* type G-protein **RhoA**, which is activated by vasoconstrictors via $G_{q/11}$.

The relative importance of the excitatory mechanisms listed above varies between different vasoconstrictors and vascular beds. In resistance arteries depolarization and Ca^{2+} influx through voltage-gated channels are probably most important.

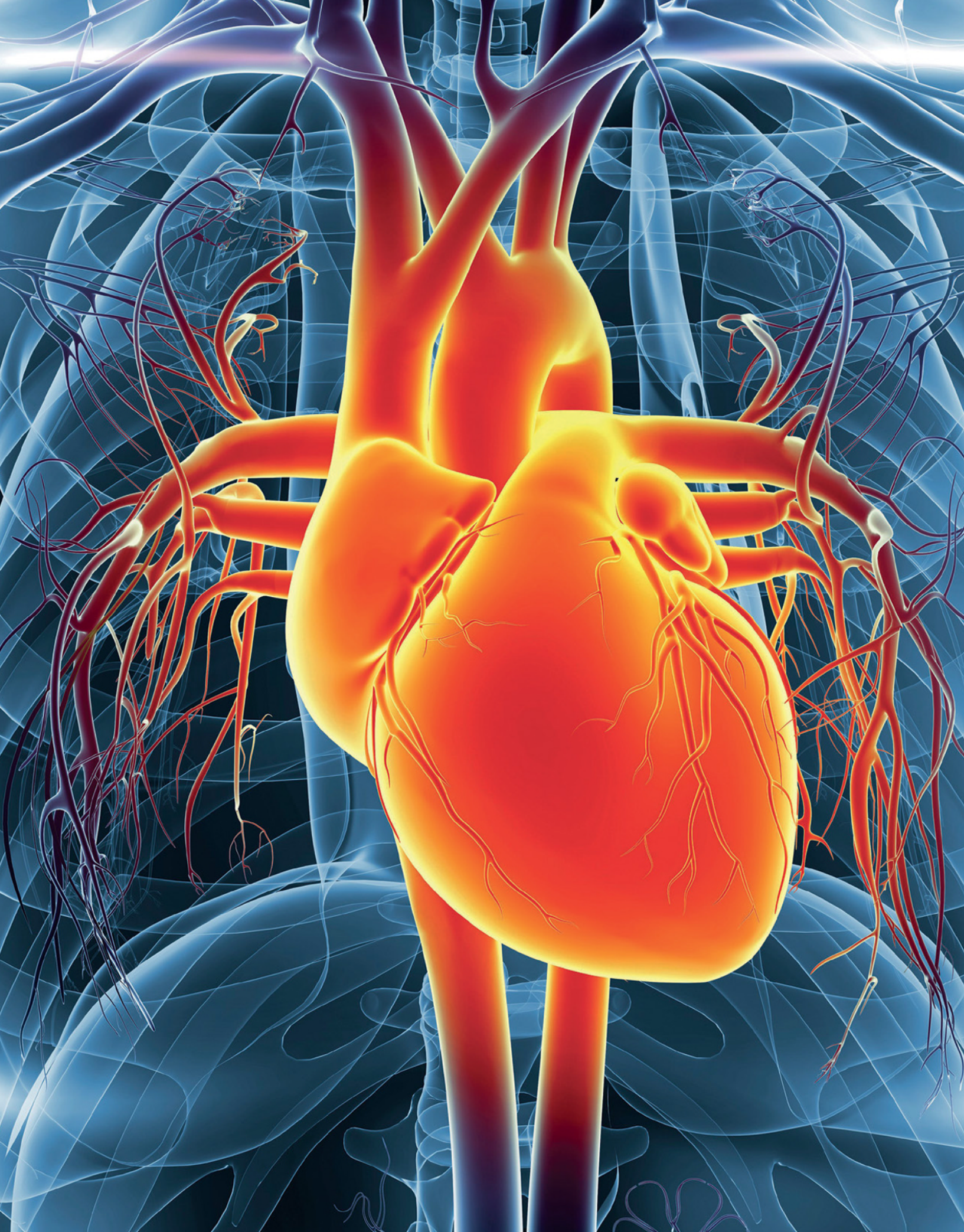
Ca^{2+} removal and vasodilator mechanisms

(see right cell of Figure 15.1)

Several mechanisms serve to remove Ca^{2+} from the cytoplasm. These are continually active, allowing cells both to recover from stimulation and to maintain a low basal $[Ca^{2+}]_i$ despite the enormous electrochemical gradient tending to drive Ca^{2+} into cells. The **smooth endoplasmic reticulum Ca^{2+}-ATPase (SERCA)** pumps Ca^{2+} from the cytoplasm into the SR, a process referred to as **Ca^{2+} sequestration**. An analogous **plasma membrane Ca^{2+}-ATPase (PMCA)** pumps Ca^{2+} from the cytoplasm into the extracellular space **(Ca^{2+} extrusion)**. Cells also extrude Ca^{2+} via a **Na^+-Ca^{2+} exchanger (NCX)** located in the cell membrane, which is similar to that found in cardiac cells (Chapter 12). The NCX may be localized to areas of the plasma membrane that are approached closely by the SR, allowing any Ca^{2+} leaking from the SR to be quickly ejected from the cell without causing tension development. Interestingly, when the intracellular Na^+ concentration near the cell membrane is sufficiently raised due to the opening of receptor-gated or store-operated channels, the NCX may act in *reverse mode,* thereby becoming a pathway for Ca^{2+}influx rather than extrusion.

Most vasodilators cause relaxation by activating either the **cyclic GMP** (e.g. nitric oxide, atrial natriuretic peptide) or **cyclic AMP** (e.g. adenosine, prostacyclin, β-receptor agonists) second messenger systems. Both second messengers activate kinases, which, by phosphorylating overlapping sets of cellular proteins, stimulate numerous vasodilating pathways. cGMP activates **cyclic GMP-dependent protein kinase (protein kinase G, PKG)**. PKG causes vasodilation by phosphorylating and activating **Ca^{2+}-activated K^+ (BK_{Ca}) channels**; this leads to a membrane hyperpolarization which inhibits Ca^{2+} influx by switching off voltage-gated Ca^{2+} channels, some of which are open even at the resting membrane potential. PKG also stimulates Ca^{2+} removal from the cytoplasm by SERCA, PMCA and NCX, and suppresses Ca^{2+} sensitization by inhibiting Rho kinase.

Cyclic AMP exerts its effects via **cyclic AMP-dependent protein kinase** (**protein kinase A**, **PKA**), although high levels of cAMP have also been shown to stimulate PKG. PKA lowers $[Ca^{2+}]_i$ by activating SERCA, and also by opening voltage-gated K^+ channels and BK_{Ca}. Stimulation of SERCA by PKA, which loads the SR with Ca^{2+}, may also indirectly activate BK_{Ca} channels by increasing the frequency of 'Ca^{2+} sparks'. These are transient elevations of $[Ca^{2+}]_i$ near the cell membrane caused by the spontaneous opening of clusters of ryanodine receptors (RyRs) and the consequent release of Ca^{2+} from the SR. PKA can also phosphorylate and inhibit MLCK, although the contribution of this mechanism to relaxation under physiological conditions is controversial. Both PKG and PKA also have been proposed to cause relaxation by phosphorylating **heat shock protein 20**, thereby causing actin depolymerization and/or dissociation from the cytoskeleton.



Form and function

Chapters

16 Cardiac cycle

Figure 16.1 Pressures, volumes and key events during the cardiac cycle

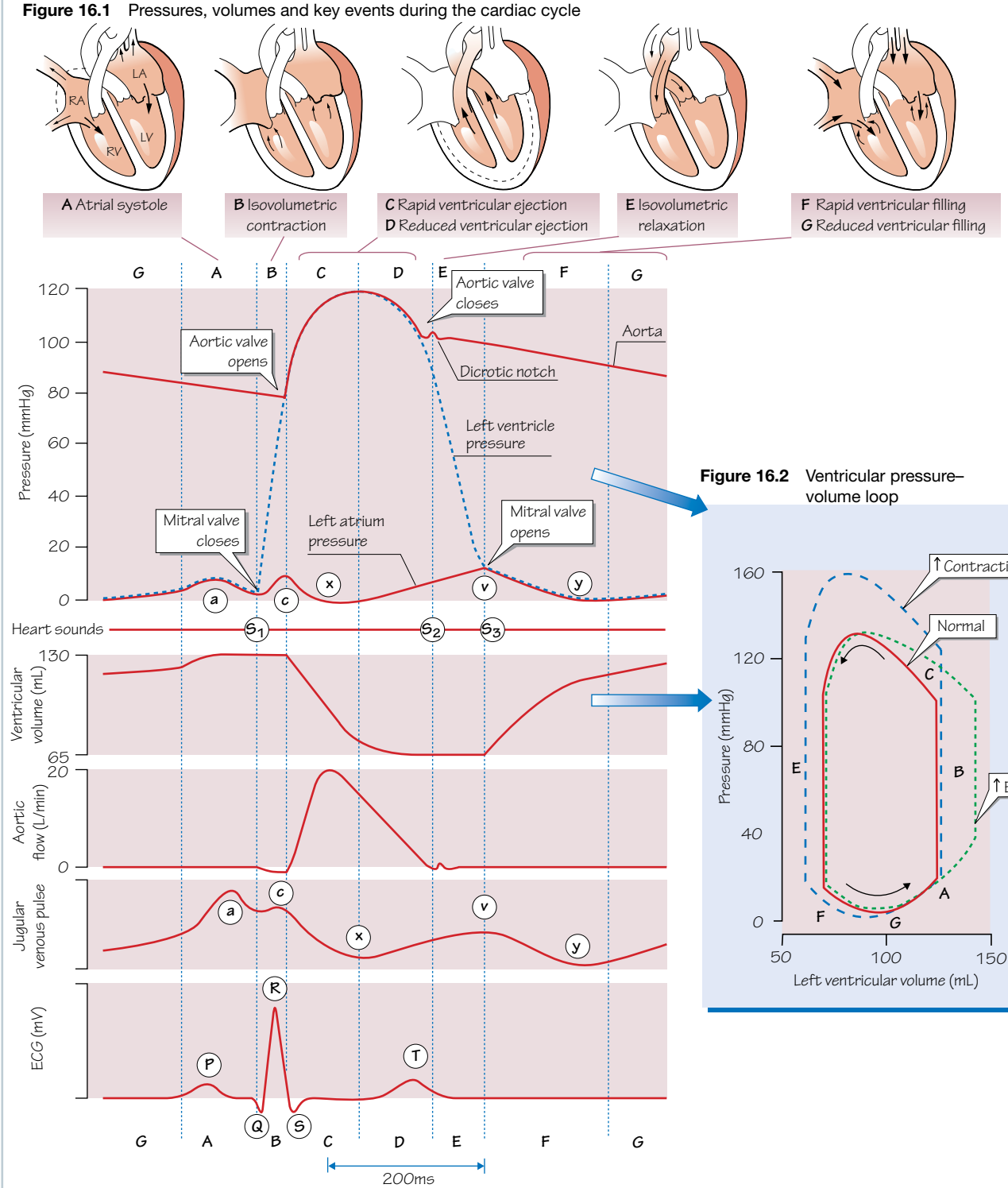


Figure 16.2 Ventricular pressure–volume loop

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The **cardiac cycle** is the sequence of events that occurs during a heartbeat (Figure 16.1). The amount of blood ejected by the ventricle in this process is the **stroke volume** (SV), ~70 mL, and **cardiac output** is the volume ejected per minute (SV × heart rate).

Towards the end of **diastole** (G) all chambers of the heart are relaxed. The valves between the atria and ventricles are open (**AV valves**: right, **tricuspid**; left, **mitral**), because atrial pressure remains slightly greater than ventricular pressure until the ventricles are fully distended. The **pulmonary** and **aortic** (semilunar) **outflow valves** are closed, as pulmonary artery and aortic pressure are greater than the respective ventricular pressures. The cycle begins when the **sinoatrial node** initiates the heartbeat (Chapter 11).

Atrial systole (A)

Contraction of the atria completes ventricular filling. At rest, the atria contribute less than 20% of ventricular volume, but this proportion increases with heart rate, as diastole shortens and there is less time for ventricular filling. There are no valves between the veins and atria, so some blood regurgitates into the veins. The **a wave** of atrial and venous pressure traces reflects atrial systole. Ventricular volume after filling is known as **end-diastolic volume** (EDV) and is ~120–140 mL. The equivalent pressure (**end-diastolic pressure**, EDP) is <10 mmHg and is higher in the left ventricle than in the right due to the more muscular and therefore stiffer left ventricular wall. EDV is an important determinant of the strength of the subsequent contraction (Starling's law; Chapter 17). Atrial depolarization causes the **P wave** of the ECG.

Ventricular systole

Ventricular contraction causes a sharp rise in ventricular pressure, and the atrioventricular (AV) valves close once this exceeds atrial pressure. Closure of the AV valves causes the **first heart sound** ($\mathbf{S_1}$; see below). Ventricular depolarization is associated with the **QRS complex** of the ECG. During the initial phase of ventricular contraction pressure is less than that in the pulmonary artery and aorta, so the outflow valves remain closed. This is **isovolumetric contraction** (B), as ventricular volume does not change. The increasing pressure causes the AV valves to bulge into the atria, resulting in the small atrial pressure wave (**c wave**), followed by a fall (**x descent**). Note the **jugular venous pulse** reflects the right atrial pressure and has corresponding **a, c** and **v waves**, and **x** and **y descents**.

Ejection

The outflow valves open when pressure in the ventricle exceeds that in its respective artery. Note that mean pulmonary artery pressure (~15 mmHg) is considerably less than that in the aorta (~80 mmHg). Flow into the arteries is initially very rapid (**rapid ejection phase**, C), but as contraction wanes ejection is reduced (**reduced ejection phase**, D). Rapid ejection can sometimes be heard as a **murmur**. Active contraction ceases during the second half of ejection, and the muscle repolarizes. This is associated with the **T wave** of the ECG. Ventricular pressure towards the end of the reduced ejection phase is slightly less than that in the artery, but blood continues to flow out of the ventricle because of momentum. Eventually the flow briefly reverses, causing closure of the outflow valve and a small increase in aortic pressure, the **dicrotic notch**. Closure of the semilunar valves is associated with the second heart sound ($\mathbf{S_2}$).

The ventricle ejects ~70 mL of blood (SV), so if EDV is 120 mL, 50 mL is left in the ventricle at the end of systole (**end-systolic volume**). The proportion of EDV that is ejected (stroke volume/EDV) is the **ejection fraction**. During the last two-thirds of systole atrial pressure rises as a result of filling from the veins (**v wave**).

Diastole – relaxation and refilling

Following closure of the outflow valves the ventricles are rapidly relaxing. Ventricular pressure is still greater than atrial pressure, however, and the AV valves remain closed. This is **isovolumetric relaxation** (E). When ventricular pressure falls below atrial pressure, the AV valves open, and atrial pressure falls (**y descent**) as the ventricles refill (**rapid ventricular refilling**, F). This is assisted by elastic recoil of the ventricular walls, essentially sucking in the blood. A **third heart sound** ($\mathbf{S_3}$) may be heard. As the ventricles relax completely refilling slows (**reduced refilling**, G). This continues during the last two-thirds of diastole due to venous flow. At rest, diastole is twice the length of systole, but decreases proportionately during exercise and as heart rate increases.

The pressure–volume loop

Ventricular pressure plotted against volume generates a loop (Figure 16.2). The shape of the loop is affected by **contractility** (Chapters 12, 17) and **compliance** ('*stretchiness*') of the ventricle and factors that alter **refilling** or **ejection** (e.g. central venous pressure, afterload). The bottom dotted line shows the passive elastic properties of the ventricle (compliance). If compliance was decreased as a result of fibrotic damage following an infarct, the curve would be steeper. The area of the loop (Δ pressure × Δ volume) is a measure of work done during a beat and is an indicator of cardiac function. A clinical estimate of **stroke work** is calculated from mean arterial pressure × stroke volume.

Heart sounds and murmurs

Heart sounds are caused by **vibrations in the blood**. S_1 and S_2 are each formed of two components (one for each valve). Normally, these may not be distinguishable, but they can 'split', so two distinct sounds are heard. S_1 is comprised of M_1 and T_1, due to closure of the mitral and tricuspid valves, respectively. Splitting of S_1 is always pathological, and commonly due to conduction defects (Chapter 13). S_2 is comprised of A_2 and P_2, closure of aortic and pulmonary valves. A_2 slightly precedes P_2, and a split is often heard in healthy young people, especially during inspiration and exercise. A large split may relate to conduction defects or high outflow pressures. S_3 is due to rapid ventricular filling and is often heard in young healthy people or when EDP is high (e.g. heart failure). S_4 (not shown) is associated with atrial systole, and rarely heard unless EDP is high.

Murmurs are caused by turbulence. **Valve stenosis** (narrowing; Chapters 54 and 55) increases blood velocity and thus turbulence. Stenosis of the AV valves causes a soft **diastolic murmur** during ventricular filling. Semilunar valve stenosis causes a loud **systolic murmur** during ejection. Valve leakage (**regurgitation**, *incompetence*) also causes murmurs. AV valve regurgitation causes a **pansystolic** murmur (throughout systole) as blood leaks back into the atria, whereas semilunar valve regurgitation causes **early diastolic** murmurs as arterial blood leaks back into the ventricle.

17 Control of cardiac output

Figure 17.1 Factors affecting cardiac output

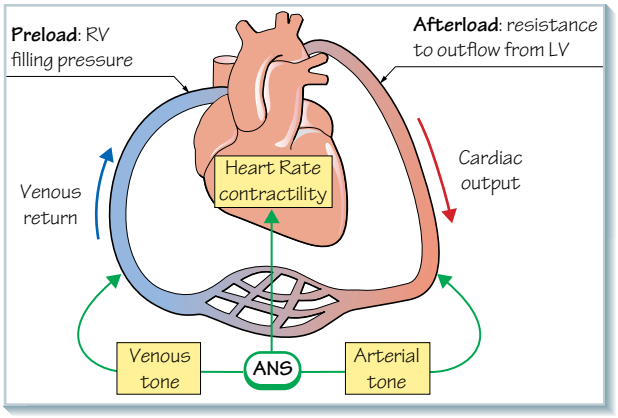


Figure 17.2 Ventricular function curves

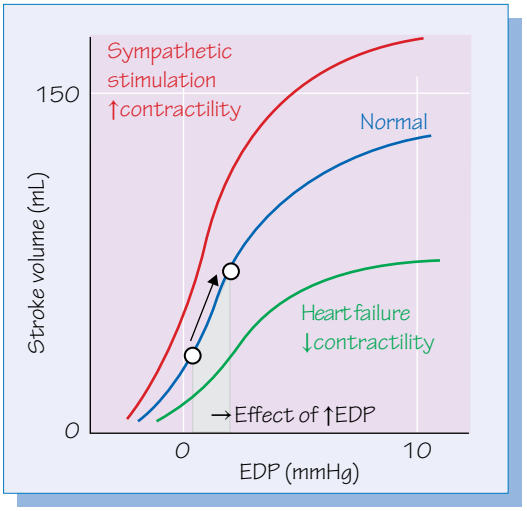


Figure 17.3 Vascular function curves

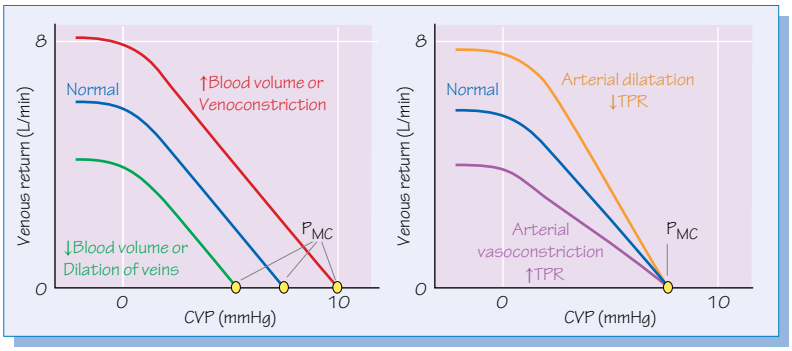
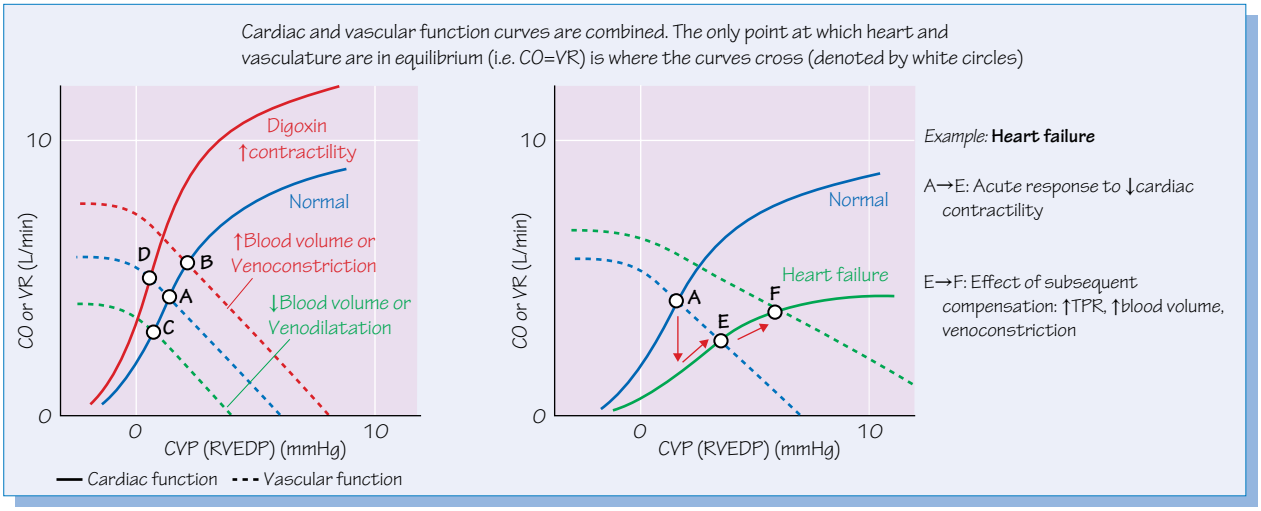


Figure 17.4 Guyton's analysis



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Cardiac output (CO) is stroke volume (SV) × heart rate (HR), and at rest ~5 L/min; during strenuous exercise this can rise to >25 L/min. SV is influenced by the filling pressure (**preload**), cardiac muscle force, and pressure against which the heart has to pump (**afterload**), which are all modulated by the autonomic nervous system (ANS) (Figure 17.1). The heart and vasculature form a closed system, so except for transient perturbations **venous return** *must* equal CO.

Filling pressure and Starling's law of the heart

Right ventricular (RV) **end-diastolic pressure** (**EDP**) is dependent on right atrial and therefore central venous pressure (**CVP**); left ventricular (LV) EDP is dependent on **pulmonary venous pressure**. EDP and the compliance of the ventricle (how easy it is to inflate) determine ventricular **end-diastolic volume** (EDV). As EDP (and so EDV) increases, the force of the following contraction, and thus SV, increases (Figure 17.2). This is known as the **Frank–Starling** relationship, and the graph relating SV to EDP is called a **ventricular function** curve. The force of contraction is dependent on muscle stretch, and **Starling's law of the heart** states '*The energy released during contraction depends on the initial fibre length.*'

As muscle is stretched more myosin crossbridges can form, increasing force. Cardiac muscle has a steeper relationship between stretch and force than skeletal muscle, because in the heart stretch also increases Ca^{2+} sensitivity of troponin C (Chapter 12). The function curve is therefore steep, so small changes in EDP can lead to large increases in SV (Figure 17.2).

Importance of Starling's law

The most important consequence of Starling's law is that **SV is matched between right and left ventricles**. If, for example, RV SV increases, the amount of blood in the lungs and thus pulmonary vascular pressure will also increase. As the latter determines LV EDP, LV SV increases due to Starling's law, until it again matches that of the RV when input to and output from the lungs equalize and the pressure stops rising. This represents a rightward shift along the function curve (Figure 17.2). Starling's law thus explains how CVP, although only perceived by the RV, also influences LV function and CO, and why postural hypotension and haemorrhage reduce CO. It also allows the heart to sustain output against an increased afterload (e.g. hypertension, valve stenosis), as this leads to accumulation of venous blood and a raised EDP/EDV. Ventricular force therefore increases according to Starling's law, until CO is restored at the expense of an increased EDP. The same occurs when *contractility* is reduced, which is why EDP is high in heart failure (Figure 17.2; Chapter 46). As an increase in LV EDP represents an increase in RV afterload, for the same reasons CVP may also rise (Figure 17.3). A consequence of the above is that the **ejection fraction** (SV/EDV) will be reduced; this and an **enlarged heart** (high EDV) are characteristic of systolic heart failure (Chapter 46).

The autonomic nervous system

The ANS strongly influences CO and is central to control of blood pressure (Chapters 27, 28). **Sympathetic** stimulation increases heart rate whereas parasympathetic stimulation decreases it (Chapter 11). Sympathetic stimulation also increases cardiac muscle force (*without any change in EDV*), termed an increase in **contractility** (Chapter 12); the function curve therefore shifts upwards (Figure 17.2). Agents that affect contractility are called **inotropes** (Chapter 12). Parasympathetic stimulation does not affect ventricular contractility.

Sympathetic stimulation also causes arterial and venous vasoconstriction (Chapter 28). An often overlooked point is that these differ in effect. Arterial vasoconstriction increases total peripheral resistance (**TPR**) and thus reduces flow, so downstream pressure and venous return fall. However, unlike arteries veins are highly **compliant** (stretch easily) and contain ~70% of blood volume. Venoconstriction reduces venous compliance and hence **capacity** (amount of blood they contain), and therefore has the same effect as increasing blood volume, that is, **CVP increases**. Venoconstriction does not significantly impede flow because venous resistance is very low compared to TPR. Sympathetic stimulation can thus increase CO by increasing heart rate, contractility and CVP.

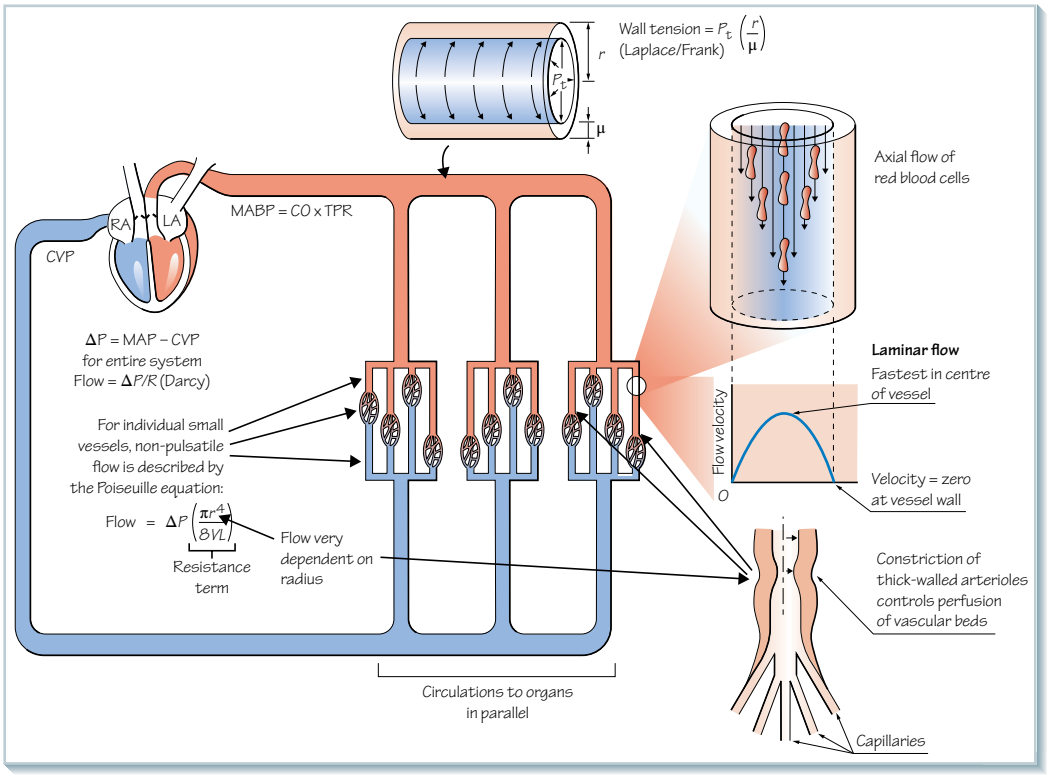
Venous return and vascular function curves

Blood flow is driven by the arterial–venous pressure difference, so venous return will be impeded by a rise in CVP. This is at first glance inconsistent with Starling's law if CO must equal venous return. However, factors that affect CVP (blood volume, venoconstriction) also affect the relationship between CVP and venous return (**vascular function curves**; Figure 17.3). If the heart stops, pressure will equalize between the arterial and venous circulations (**mean circulatory pressure,** P_{MC}), which depends on the volume and compliance of the vasculature, primarily the veins. By definition CVP equals P_{MC} when venous return (i.e. CO) is zero. The curve levels off at negative CVP due to venous collapse. Increasing blood volume or venoconstriction increases P_{MC} and so shifts the curve to the right, whereas blood loss does the reverse. Arterial vasoconstriction and an increase in TPR on the other hand reduces blood flow and venous return (see above), but as resistance arteries contain little of the blood volume, and the decrease in diameter required to increase their resistance is small (Chapter 18), there is an insignificant change in vascular volume or P_{MC}. Thus, the net effect is to reduce the slope of the curve. A reduction in TPR does the opposite.

Guyton's analysis helps us to understand the function of the cardiovascular system by combining vascular and cardiac function curves into one graph (Figure 17.4). The cardiac function curve is now shown as CO plotted against CVP (i.e. RV EDP). The only point at which CO and venous return are equal, and so the only point where the system is in equilibrium, is where the two function curves cross (A), the **equilibrium** (or *operating*) point. Thus, **increasing blood volume** or **venoconstriction** shifts the equilibrium point (B) and CO and CVP are both increased. Blood loss or venous dilatation do the opposite (C), which is why nitrovasodilators, which primarily dilate veins, reduce cardiac work (Chapter 41). **Positive inotropes** (e.g. digoxin) increase cardiac contractility and shift the cardiac function curve upwards. At equilibrium (D) CO is thus increased but CVP *reduced*, explaining why digoxin reduces symptoms in heart failure (Chapter 46). Analysis of **heart failure** is illuminating. The initial fall in CO is limited by an elevated CVP (Figure 17.4, E; see Starling's law above). Central mechanisms mediated via the ANS then provide further compensation to maintain blood pressure, by increasing TPR, venoconstriction and renal retention of salt and water (Chapter 46). Combined, these raise and flatten the vascular function curve (see above), so at equilibrium CO may be largely restored, but at the expense of a greatly increased CVP (F).

18 Haemodynamics

Figure 18.1 Pressure, resistance and flow in the vascular system.



Relationships between pressure, resistance and flow

Haemodynamics is the study of the relationships between **pressure**, **resistance** and the **flow of blood** in the cardiovascular system. Although the properties of this flow are enormously complex, they can largely be derived from simpler physical laws governing the flow of liquids through single tubes (Figure 18.1).

When a fluid is pumped through a closed system, its flow (Q) is determined by the pressure head developed by the pump (P_1–P_2 or ΔP), and by the resistance (R) to that flow, according to **Darcy's law** (analogous to Ohm's law):

$$Q = \Delta P/R$$

or for the systemic circulation as a whole:

$$CO = \left(MABP - CVP\right)/TPR,$$

where CO is cardiac output, $MABP$ is mean arterial blood pressure, TPR is total peripheral resistance (also referred to as the systemic vascular resistance, SVR) and CVP is central venous pressure. Because CVP is ordinarily close to zero, this equation is typically simplified to $MABP \approx CO \times TPR$.

MABP is the arterial blood pressure averaged over the cardiac cycle, and since diastole lasts roughly twice as long as systole, it can be approximated as $MABP \approx (DBP + (SBP - DBP)/3)$ where SBP and DBP refer to the systolic and diastolic arterial blood pressures, respectively.

TPR cannot be measured and is calculated as:

$$\text{TPR} = \left(\text{MABP} - \text{CVP}\right)/\text{CO or TPR} \approx \text{MABP/CO}$$

TPR can be expressed in peripheral resistance units (PRU, also termed Wood units) as pressure in mmHg divided by cardiac output in mL/min (i.e. mmHg × min × L^{-1}). However, pressure and flow can also be expressed as dynes/cm^2 and cm^3/sec, respectively, such that resistance in cgs units is dynes × sec × cm^{-5}. Taking into account that 1 mmHg = 1330 dynes/cm^2, the value of TPR in cgs units can be calculated from that in PRU by multiplying by 80. Thus, for example, if $MABP$ is 95 mm/Hg and CO is 5200 mL/min, the TPR in PRU is ~18 and in cgp units is ~1460.

Resistance to flow is caused by frictional forces within a fluid and depends on the viscosity of the fluid and the dimensions of the tube, as described by **Poiseuille's law**:

$$\text{resistance} = 8VL/\pi r^4$$

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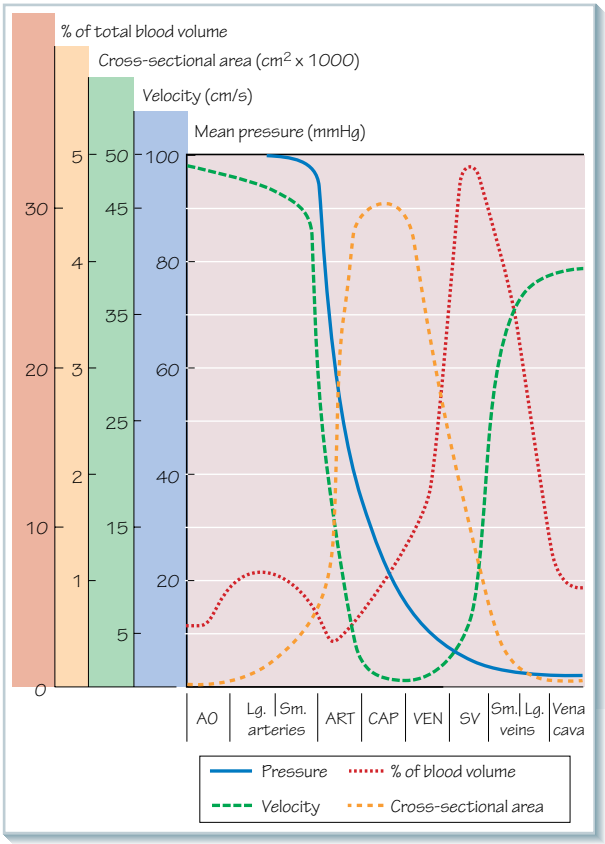
Figure 18.2 Blood pressure and velocity along the vascular system



so that:

$$\text{flow} = \Delta P\left(\pi r^4 / 8VL\right).$$

Here, V is the viscosity of the fluid, L is the tube length and r is the inner radius (= ½ the diameter) of the tube. Because flow depends on the fourth power of the tube radius in this equation, *small changes in radius have a powerful effect on flow*. For example, a 20% decrease in radius reduces flow by about 60%.

Considering the cardiovascular system as a whole, the different types or sizes of blood vessels (e.g. arteries, arterioles, capillaries) are arranged sequentially, or in ***series***. In this case, the resistance of the entire system is equal to the *sum of all the resistances* offered by each type of vessel:

$$R_{\text{total}} = R_{\text{arteries}} + R_{\text{arterioles}} + R_{\text{capillaries}} + R_{\text{venules}} + R_{\text{veins}}.$$

Calculations taking into account the estimated lengths, radii and numbers of the various sizes of blood vessels show that the arterioles, and to a lesser extent the capillaries and venules, are primarily responsible for the resistance of the cardiovascular system to the flow of blood. In other words, $R_{\text{arteriole}}$ makes the largest contribution to R_{total}. Because according to Darcy's law the pressure drop in any section of the system is proportional to the resistance of that section, the steepest fall in pressure is in the arterioles (Figure 18.2).

Although the various sizes of blood vessel are arranged in series, each organ or region of the body is supplied by its own major arteries which emerge from the aorta. The vascular beds for the various organs are therefore arranged in *parallel* with each other. Similarly, the vascular beds within each organ are mainly arranged into parallel subdivisions (e.g. the arteriolar resistances $R_{\text{arteriole}}$ are in parallel with each other). For 'n' vascular beds arranged in parallel:

$$1/R_{\text{total}} = 1/R_1 + 1/R_2 + 1/R_3 + 1/R_4 \ldots 1/R_n.$$

An important consequence of this relationship is that the blood flow to a particular organ can be altered (by adjustments of the resistances of the arterioles in that organ) without greatly affecting pressures and flows in the rest of the system. This can be accomplished, as a consequence of Poiseuille's law, by relatively small dilatations or constrictions of the arterioles within an organ or vascular bed.

Because there are so many small blood vessels (e.g. millions of arterioles, billions of venules, trillions of capillaries), the overall cross-sectional area of the vasculature reaches its peak in the microcirculation. As the velocity of the blood at any level in the system is equal to the total flow (the cardiac output) divided by the cross-sectional area at that level, the blood flow is slowest in the capillaries (Figure 18.2), favouring O_2–CO_2 exchange and tissue absorption of nutrients. The capillary transit time at rest is 0.5–2 s.

Blood viscosity

Very viscous fluids like motor oil flow more slowly than less viscous fluids like water. **Viscosity** is caused by frictional forces within a fluid that resist flow. Although the viscosity of plasma is similar to that of water, the viscosity of blood is normally three to four times that of water, because of the presence of blood cells, mainly erythrocytes. In **anaemia**, where the cell concentration (haematocrit) is low, viscosity and therefore vascular resistance decrease and CO rises. Conversely, in the high-haematocrit condition **polycythaemia**, vascular resistance and blood pressure are increased.

Laminar flow

As liquid flows steadily through a long tube, frictional forces are exerted by the tube wall. These, in addition to viscous forces within the liquid, set up a velocity gradient across the tube (Figure 18.1) in which the fluid adjacent to the wall is motionless, and the flow velocity is greatest at the centre of the tube. This is termed **laminar flow** and occurs in the microcirculation, except in the smallest capillaries. One consequence of laminar flow is that erythrocytes tend to move away from the vessel wall and align themselves edgewise in the flow stream. This reduces the effective viscosity of the blood in the microcirculation (the **Fåhraeus–Lindqvist effect**), helping to minimize resistance.

Wall tension

In addition to the pressure gradient along the length of blood vessels, there exists a pressure difference across the wall of a blood vessel. This transmural pressure is equal to the pressure inside the vessel minus the interstitial pressure. The transmural pressure exerts a circumferential tension on the wall of the blood vessel that tends to distend it, much as high pressure within a balloon stretches it. According to the **Laplace/Frank law**:

$$\text{wall tension} = P_t\left(r/\mu\right),$$

where P_t is the transmural pressure, r is the vessel radius and μ is the wall thickness. In the aorta, where P_t and r are high, atherosclerosis may cause thinning of the arterial wall and the development of a bulge or **aneurysm** (see Chapter 37). This increases r and decreases μ, setting up a vicious cycle of increasing wall tension which, if not treated, may result in vessel rupture.

19 Blood pressure and flow in the arteries and arterioles

Figure 19.1 Pressure (above) and velocity (below) in the aorta and arterial branches in the dog, showing amplification of the pressure pulses by reflected waves

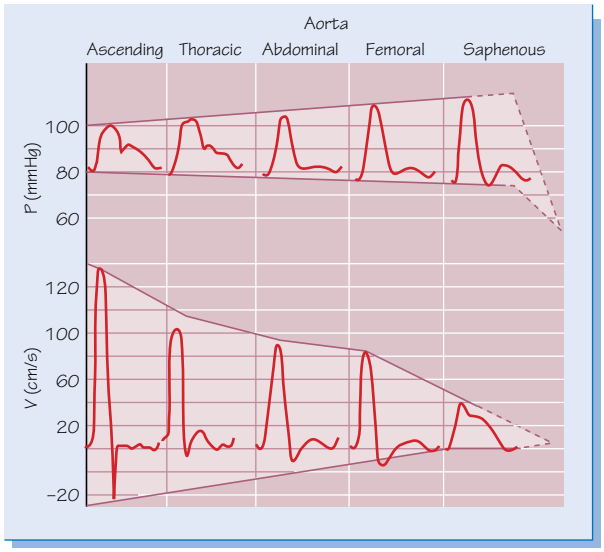


Figure 19.2 Arterial elasticity and resistance regulate dynamic changes in blood pressure and flow during the cardiac cycle

Factors controlling arterial blood pressure

The mean arterial blood pressure is equal to the product of the cardiac output (about 5 L/min at rest) and the total peripheral resistance (TPR). Because the total drop of mean pressure across the systemic circulation is about 100 mmHg, TPR is calculated to be 100 mmHg/5000 mL/min, or 0.02 mmHg/mL/min. The unit mmHg/mL/min is referred to as a **peripheral resistance unit** (PRU), so that TPR is normally about 0.02 PRU.

Systolic pressure is mainly influenced by the *stroke volume*, the *left ventricular ejection velocity* and *aortic/arterial stiffness* and rises when any of these increase. Conversely, diastolic pressure rises with an *increase in TPR*. Arterial pressure falls progressively during diastole (see Figure 16.1), so that a shortening of the diastolic interval associated with a rise in the heart rate also increases diastolic pressure.

Blood pressure and flow in the arteries

The blood flow in the aorta and the larger arteries is pulsatile, as a result of the rhythmic emptying of the left ventricle.

As blood is ejected from the left ventricle during systole, it hits the column of blood already present in the ascending aorta, creating

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Table 19.1 Endogenous substances and other factors affecting arteriolar tone

	Vasoconstrictors	Vasodilators
Neurotransmitters	Sympathetic Noradrenaline ATP Neuropeptide Y	Parasympathetic and sensory (limited distribution) Acetylcholine (acts via NO) Substance P Calcitonin gene-related peptide Vasoactive intestinal peptide
Hormones	Adrenaline (most blood vessels) Angiotensin 2 Vasopressin (antidiuretic hormone)	Adrenaline (in skeletal muscle, coronary, hepatic arteries) Atrial natriuretic peptide
Endothelium-derived substances	Endothelin Endothelium-derived constricting factor (chemical identity unknown)	Endothelium-derived relaxing factor (NO) Prostaglandin I_2 (prostacyclin)
Metabolites and related factors	Hypoxia (pulmonary arteries only)	Endothelium-derived hyperpolarizing factor (chemical identity unknown) Hypoxia (other vessels) Adenosine, hyperosmolarity, H^+ ions, lactic acid, K^+ ions, CO_2
Other locally produced factors	Histamine (veins, pulmonary arteries) Prostaglandin $F_{2\alpha}$, thromboxane A_2 5-Hydroxytryptamine Growth factors (e.g. PDGF)	Histamine (arterioles) Prostaglandin E_2 Bradykinin Adipocyte derived relaxing factors (ADRFs)
Other factors	Pressure (myogenic response) Moderate cold (skin)	Increased flow Heat (skin)

NO, nitric oxide; PDGF, platelet-derived growth factor.

a pressure wave in the aortic blood which is rapidly (at between 4 and 10 m/s) conducted towards the arterioles. As this pulse pressure wave passes each point along the aorta and the major arteries, it sets up a transient pressure gradient that briefly propels the blood at that point forward, causing a pulsatile flow wave. The blood in the arteries therefore moves forward in short bursts, separated by longer periods of stasis, so that its average velocity in the aorta is about 0.2 m/s (Figure 19.1).

The pressure wave also causes the elastic arterial wall to bulge out, thereby storing some of the energy of the wave. The arterial wall then rebounds, releasing part of this energy to drive the blood forward during diastole (**diastolic run-off**). This pumping mechanism of the elastic arteries is termed the **Windkessel** function (Figure 19.2).

The large arteries also absorb and dissipate some of the energy of the pressure wave. This progressively damps the oscillations in flow, as shown by the lower traces in the inset to Figure 19.2. However, as the upper traces illustrate, the pulse pressure wave becomes somewhat *larger* as it moves down the aorta and major arteries (e.g. the saphenous artery), before it then progressively dies out along the smaller arteries. This occurs in part because a fraction of the pressure wave is *reflected* back towards the heart at arterial branch points. In the aorta and large arteries, the reflected wave *summates* with the forward-moving pulse pressure wave, increasing its amplitude. Once the blood has entered the smaller arteries, however, the damping properties of the arterial wall predominate and progressively depress the oscillations in flow and pressure, so that in most organs these die out completely by the time the blood reaches the microcirculation.

In contrast, the brain and the kidneys receive a very high blood flow and correspondingly have a relatively low vascular resistance. There is thus less pulse wave reflection and damping in these organs, so that pressure and flow pulsations penetrate into their capillaries and veins. This renders the delicate microcirculation in these organs liable to damage in **isolated systolic hypertension** (ISH), a condition in which the systolic BP is increased with no change or a fall in the diastolic BP pulsatility, such that pulsatility is enhanced. ISH, which becomes increasingly common after middle age (Chapter 39), occurs for two reasons. Firstly, large arteries lose their elasticity and are therefore less able to dissipate the pressure wave and to maintain their Windkessel function. Secondly, **the resistance vessels** (the small arteries and arterioles) become narrowed. This causes the pressure wave to be reflected back more quickly and to a greater extent, such that its summation with the forward-going wave increases the systolic blood pressure.

Arterioles and vascular resistance

The mean blood pressure falls progressively along the arterial system. The decline is particularly steep in the smallest arteries and the arterioles (diameter <100 μm) because these vessels present the greatest resistance to flow (Figure 18.2); they are therefore often termed the **resistance vessels**. The walls of the arterioles are very thick in relation to the diameter of the lumen, and these vessels can therefore constrict powerfully, dramatically increasing this resistance. Because the arterioles are normally partially constricted, their resistance can also be decreased by vasodilating stimuli.

The role of the arterioles in setting the vascular resistance has several important implications.

1. Constriction or dilatation of a large proportion of the arterioles in the body will affect the TPR and the blood pressure.
2. Constriction of the arterioles in one organ or region will selectively direct the flow of blood away from that region, while dilatation will have the opposite effect.
3. Changes in arteriolar resistance in a region affect the 'downstream' hydrostatic pressure within the capillary beds and veins in that region. Changes in the pressure within the capillaries affect the movement of fluid from the blood to the tissues (see Chapter 21). Because the veins are very compliant, their volume is very sensitive to alterations in pressure (see Chapter 22). Thus, arteriolar constriction in a region of the body will both promote the movement of fluid from its tissue spaces into its exchange vessels and also decrease its venous volume. Both effects work to increase the blood supply to other parts of the body.

Table 19.1 lists important endogenous substances and factors that affect arteriolar tone.

20 The microcirculation and lymphatic system and diapedesis

Figure 20.1 Structure of the microcirculation

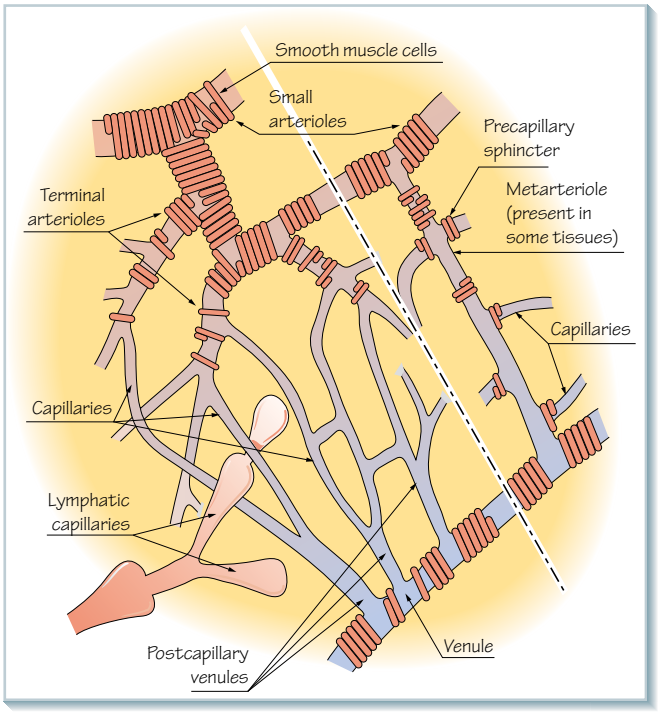


Figure 20.2 Capillary structure

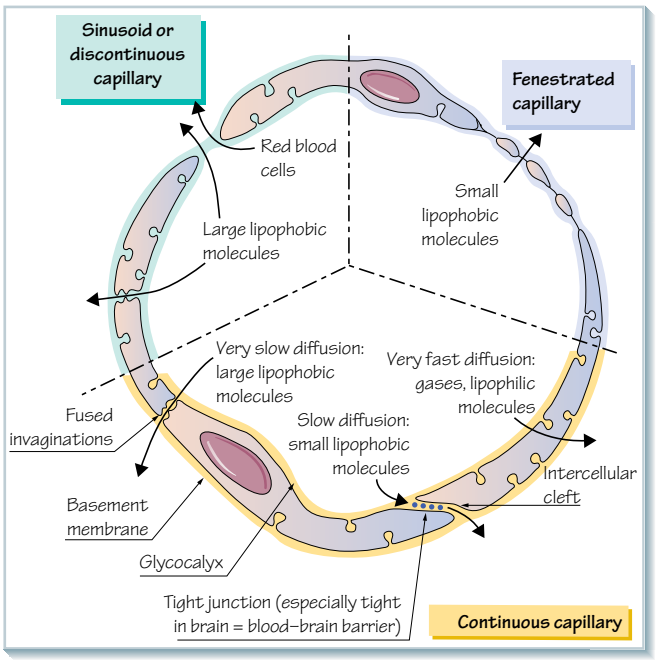
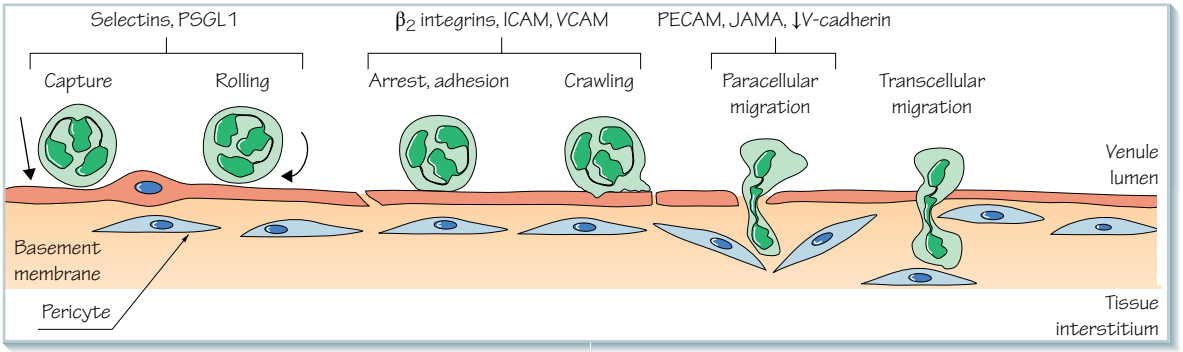


Figure 20.3 Diapedesis



The **microcirculation** comprises the **smallest arterioles** and the **exchange vessels**, including the **capillaries** and the **postcapillary venules**. The transfer of gases, water, nutrients, waste materials and other substances between the blood and body tissues carried out by the exchange vessels is the ultimate function of the cardiovascular system.

Organization of the microcirculation

Blood enters the microcirculation via small arterioles, the walls of which contain smooth muscle cells. These vessels are densely innervated by the sympathetic system, particularly in the splanchnic and cutaneous vascular beds. Sympathetically mediated constriction of each small arteriole reduces the blood flow to many capillaries.

In the vast majority of tissues, the smallest or **terminal** arterioles divide to give rise to sets of capillaries (Figure 20.1, left). The terminal arteriole itself acts as a functional precapillary sphincter for its entire cluster of capillaries. Terminal arterioles are not innervated, and their tone is controlled by local metabolic factors (see Chapter 23). Under basal conditions, terminal arterioles constrict and relax periodically. This **vasomotion** causes the flow of blood through the cluster of capillaries to fluctuate.

In a few tissues, however (e.g. mesentery), capillaries branch from thoroughfare vessels which run from small arterioles to

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venules (Figure 20.1, right). The proximal (arteriolar) end of such a vessel is termed a **metarteriole**, and it is wrapped intermittently in smooth muscle cells. The capillaries have a ring of smooth muscle called a **precapillary sphincter** at their origin, but thereafter lack smooth muscle cells. Constriction of the precapillary sphincter controls the flow of blood through that capillary.

The capillaries join to form postcapillary venules, which also lack smooth muscle cells. These merge to form venules, which contain smooth muscle cells and are sympathetically innervated.

Movement of solutes across the capillary wall

Water, gases and solutes (e.g. electrolytes, glucose, proteins) cross the walls of exchange vessels mainly by **diffusion**, a passive process by which substances move down their concentration gradients. O_2 and CO_2 can diffuse through the lipid bilayers of the endothelial cells. These and other **lipophilic** substances (e.g. general anaesthetics) therefore cross the capillary wall very rapidly. However, the lipid bilayer is impermeable to electrolytes and small **hydrophilic** (lipid-insoluble) molecules such as glucose, which therefore cross the walls of **continuous** capillaries (Figure 20.2, bottom) 1000–10 000 times more slowly than does O_2. Hydrophilic molecules cross the capillary wall mainly by diffusing between the endothelial cells. This process is slowed by tight junctions between the endothelial cells which impede diffusion through the intercellular clefts. Diffusion is also retarded by the **glycocalyx**, a dense network of fibrous macromolecules coating the luminal side of the endothelium. This tortuous diffusion pathway (the **small pore** system) acts as a sieve which admits molecules of molecular weight (MW) less than 10 000.

Even large proteins (e.g. albumin, MW 69 000) can cross the capillary wall, albeit very slowly. This suggests that the capillary wall also contains a small number of **large pores**, although these have never been directly visualized. It has been proposed that large pores exist transiently when membrane invaginations on either side of the endothelial cell fuse, temporarily creating a channel through which large molecules diffuse.

The endothelial cells of **fenestrated** capillaries (found in kidneys, intestines and joints) contain pores called **fenestrae** (Figure 20.2, upper right) which render them ~10 times more permeable than continuous capillaries to small hydrophilic molecules, which can move through the fenestrae. **Sinusoidal** or **discontinuous** capillaries (liver, bone marrow, spleen) are very highly permeable, because they have wide spaces between adjacent endothelial cells through which proteins and even erythrocytes can pass (Figure 20.2, upper left).

The blood–brain barrier

The composition of the extracellular fluid in the brain must be kept extremely constant in order to allow stable neuronal function. This is made possible by the existence of the **blood–brain barrier** (BBB), which tightly controls the movement of ions and solutes across the walls of the continuous capillaries within the brain and the choroid plexus. The BBB has two important features. First, the junctions between the endothelial cells of cerebral capillaries are extremely tight (resembling the zonae occludens of epithelia), preventing any significant movement of hydrophilic solutes. Second, specialized membrane transporters exist in cerebral endothelial cells which allow the controlled movement of inorganic ions, glucose, amino acids and other substances across the capillary wall. Thus, the relatively uncontrolled diffusion of solutes present in other vascular beds is replaced in the brain by a number of specific transport processes. This can present a therapeutic problem, as most drugs are excluded from the brain (e.g. many antibiotics).

The BBB is interrupted in the **circumventricular organs**, areas of the brain that need to be influenced by blood-borne factors or to release substances into the blood. These include the **pituitary** and **pineal** glands, the **median eminence**, the **area postrema** and the **choroid plexus**. The BBB can break down with large elevations of blood pressure, osmolarity or PCO_2, and in infected areas of the brain.

Diapedesis

In order to cause local inflammation in infected or damaged tissue, leucocytes must leave the blood by migrating across the endothelium of nearby venules, a process termed **diapedesis** (Figure 20.3). Inflammatory mediators released at the site of infection induce venular endothelial cells to express E- and P-selectins and other adhesion molecules on their luminal surfaces. Leucocytes express complementary surface adhesion molecules such as VLA_4 and P-selectin glycoprotein ligand 1, and many leucocytes are therefore captured as they flow by, at first rolling along the endothelial surface and then stopping as their interaction with the endothelium and exposure to locally released cytokines causes the expression and activation of additional adhesion molecules on both types of cells (e.g. VCAM1 on endothelial cells; β_2 integrins on leucocytes). The leucocytes flatten and send out protrusions allowing them to creep over the endothelium, seeking 'permissive' sites at which they can enter the tissue by squeezing themselves through the junctions *between* adjacent endothelial cells (**paracellular transendothelial migration**). Endothelial cells aid this process by down-regulating the function of the junctional plasmalemmal protein VE-cadherin which normally acts to hold the adjacent cells close together at the junctions, and by transiently increasing the expression of junctional adhesion molecules such as PECAM and JAM-A, which the leucocytes use to pull themselves through. Alternatively, leucocytes are able to undergo **transcellular transendothelial migration**, a process by which they tunnel directly *through* rather than between endothelial cells to reach the interstitium. Following endothelial transmigration, leucocytes are able to propel themselves through weak spots in the layer of basement membrane and pericytes, gaining access to the tissue.

The lymphatic system

Approximately 8 L of fluid containing solutes and plasma proteins is filtered from the microcirculation into the tissue spaces each day. This returns to the blood via the **lymphatic system**. Most body tissues contain lymphatic capillaries (Figure 20.1). These are blind-ended bulbous tubes 15–75 μm in diameter, with walls formed of a monolayer of endothelial cells. Interstitial fluid, plasma proteins and bacteria can easily enter the lymphatic capillaries via the gaps between these cells, the arrangement of which then prevents these substances from escaping. These vessels merge to form **collecting lymphatics**, the walls of which contain smooth muscle cells and one-way valves (as do the larger lymphatic vessels). The sections between these valves, termed lymphangions, constrict strongly, forcing the lymph towards the blood. Lymph is also propelled by compression of the vessels by muscular contraction, body movement and tissue compression. Lymph then enters the larger **afferent lymphatics**, which flow into the **lymph nodes**. Here, foreign particles and bacteria are scavenged by phagocytes and can initiate the production of activated lymphocytes. These enter the lymph for transport into the circulation, where they mount an immune response. Much of the lymph returns to the blood via capillary absorption in the lymph nodes. The rest enters **efferent lymphatics**, most of which eventually merge into the **thoracic duct**. This duct empties into the left subclavian vein in the neck. Lymphatics from parts of the thorax, the right arm and the right sides of the head and neck merge forming the **right lymph duct**, which enters the right subclavian vein. The lymphatic system is also important in the absorption of lipids from the intestines. The **lacteal** lymphatics are responsible for transporting about 60% of digested fat into the venous blood.

21 Fluid filtration in the microcirculation

Figure 21.1 Movement of water across the capillary wall is determined by the balance between hydrostatic and osmotic pressure gradients

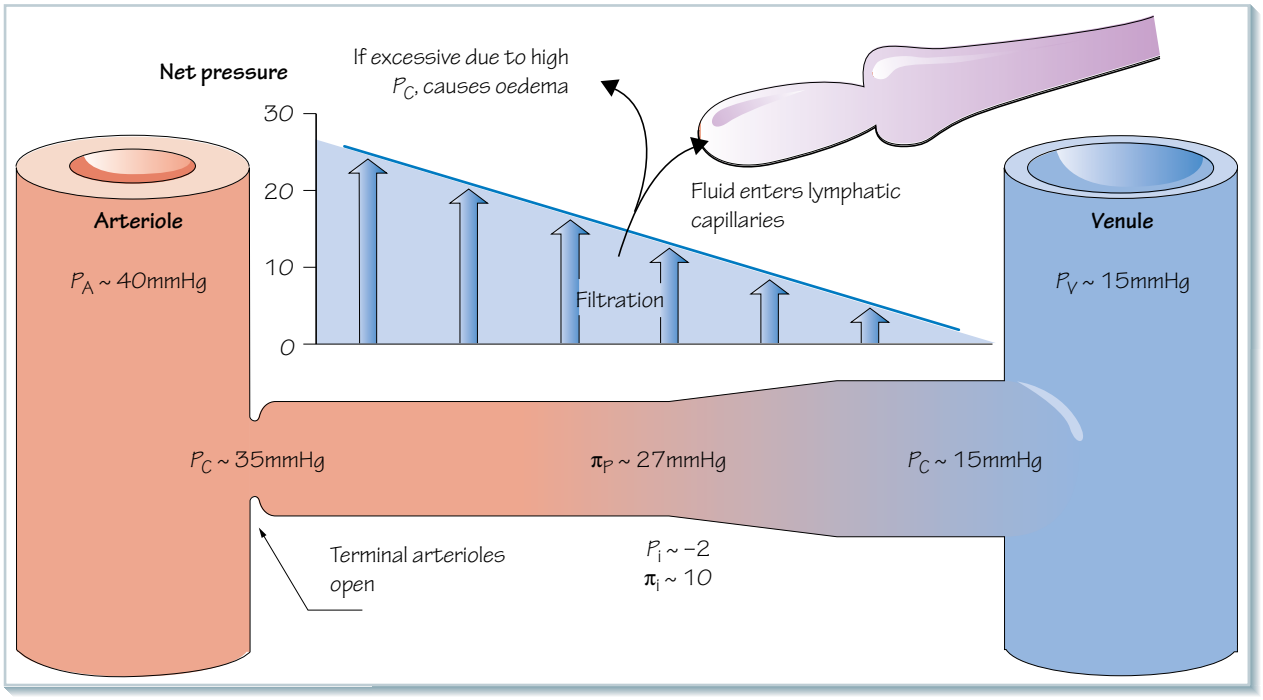
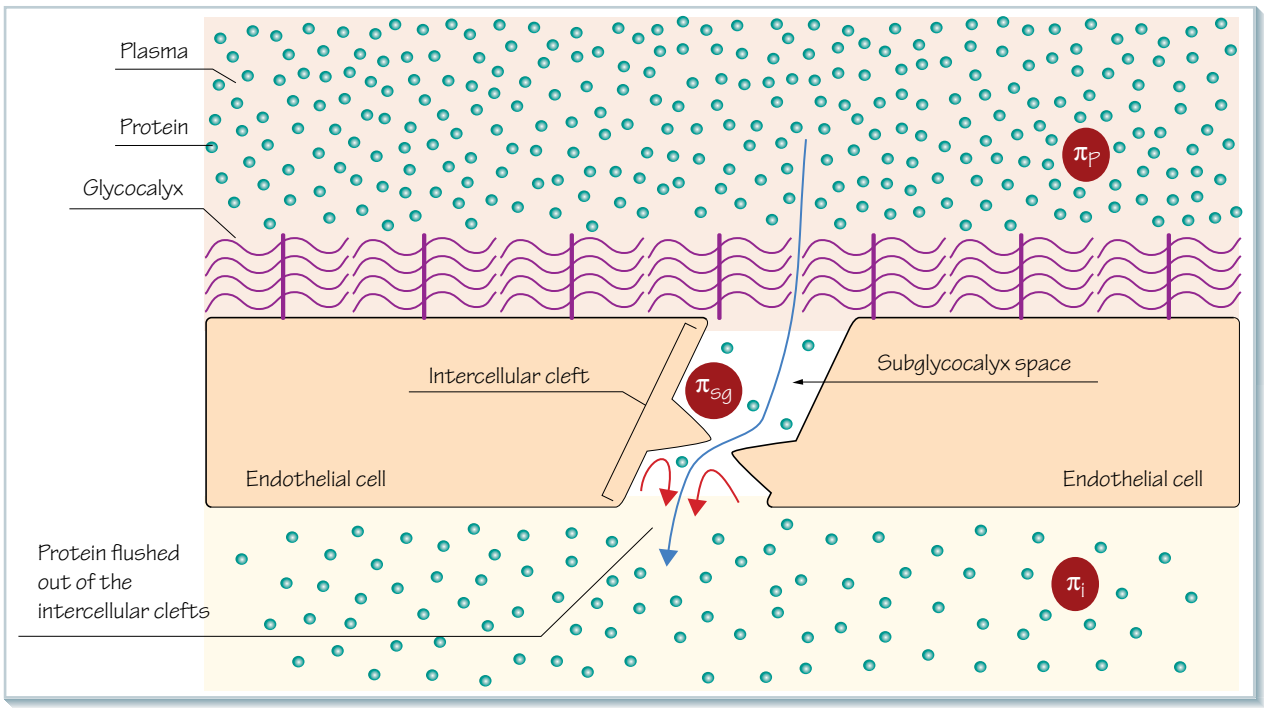


Figure 21.2 Flushing of protein from intracellular clefts may influence fluid filtration



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Movement of water across the capillary wall

The capillary wall (here taken to include the wall of postcapillary venules) is very permeable to water. However, although individual water molecules can move freely between the plasma and the tissue spaces, the *net* flow of water across the capillary wall is very small. This flow is determined by a balance between two forces or pressures that are exerted across the wall of the capillaries. These are **hydrostatic pressure**, which tends to drive water out of the capillary, and **colloid osmotic pressure**, which tends to draw water into capillaries from the surrounding tissue spaces. The sum of these two pressures at each point along the capillary is equal to a **net pressure** that will be directed either out of or into the capillary, and the net flow of water is proportional to this net pressure. The classic **Starling equation** describes the relationship between net flow (J_v) and the hydrostatic and osmotic pressures:

$$J_v \propto \left[\left(P_c - P_i\right) - \sigma\left(\pi_p - \pi_i\right)\right]$$

The **hydrostatic force** ($P_c - P_i$) is equal to the difference between the blood pressure inside the capillary (P_c) and the pressure in the interstitium around the capillary (P_i). P_c in blood-perfused capillaries ranges from about 35 mmHg at the arteriolar end of the capillaries to about 15 mmHg in the venules. P_i is slightly subatmospheric in many tissues (−5 to 0 mmHg), due to a suction of fluid from the interstitium by the lymphatic capillaries. The greater pressure inside the capillary tends to drive **filtration**, the movement of water out into the tissues.

As described in Chapter 20, the capillary wall acts as a *semipermeable membrane* or barrier to free diffusion, across which electrolytes and small molecules pass with much greater ease than plasma proteins. A substance dissolved on one side of a semipermeable membrane exerts an osmotic pressure that draws water across the membrane from the other side. This osmotic pressure is proportional to the concentration of the substance in solution and is also a function of its permeability. Substances that can easily permeate a barrier (in this case the capillary wall) exert little osmotic pressure across it, whereas those that permeate less readily exert a larger osmotic pressure. For this reason, the osmotic force across the capillary wall is largely a result of the relatively impermeant plasma proteins, in particular albumin. The osmotic pressure exerted by plasma proteins is referred to as the **colloid osmotic** or **oncotic** pressure.

The osmotic force across the capillary wall tends to cause **absorption**, the movement of water into capillaries. This force has classically been equated with the difference between the colloid osmotic pressure of the plasma (π_p) and that of the interstitium (π_i), multiplied by the **reflection coefficient** (σ), a factor that is a measure of how difficult it is for the proteins to cross the capillary wall. Substances that cannot cross the membrane at all have a reflection coefficient of 1, whereas those that pass freely have a reflection coefficient of zero. σ ranges from 0.8 to 0.95 for most plasma proteins, whereas ($\pi_p - \pi_i$) is typically about 13 mmHg.

Water filtration and absorption

Given the balance of hydrostatic and osmotic pressures acting on fluid in the microcirculation, capillaries and venules that are perfused with blood will be mainly filtering plasma (Figure 21.1), so that normally there is a slight predominance of filtration over absorption in the body as a whole. Therefore, of about 4000 L plasma entering the capillaries daily as the blood recirculates, a *net* filtration of 8 L occurs. This fluid is returned from the interstitium to the vascular compartment through the lymphatic system.

On the other hand, certain sites such as the kidneys or the intestinal mucosa are specialized for water reabsorption. Here the osmotic pressure term is large, because plasma proteins are continually being washed out of the interstitium, so that net reabsorption occurs.

It is also the case that the balance between filtration and reabsorption is a dynamic one, mainly because the hydrostatic pressure within the capillaries is variable. Arteriolar vasodilatation, which increases intracapillary hydrostatic pressure, increases filtration, whereas arteriolar vasoconstriction favours absorption. For example, arterioles generally demonstrate **vasomotion** (spontaneous rhythmic oscillations in diameter which occur 1 – 20 times a minute). During periods of arteriolar constriction, capillary pressure falls, favouring the absorption of interstitial fluid. This absorption tends to be transient, however, because as fluid is absorbed into the capillaries, local P_i falls and π_i increases. These effects progressively diminish absorption.

Assumption of the upright posture increases the transcapillary hydrostatic pressure gradient in the lower extremities, thereby immediately increasing filtration in these regions. However, this effect is partially compensated for by a rapid constriction of the arterioles of the leg, which is mediated by a local sympathetic axon reflex. This reduces blood flow and attenuates the rise in capillary hydrostatic pressure in these areas.

By the same token, fluid tends to accumulate in the tissue spaces of the upper body and face during the night, because assumption of the supine position increases capillary hydrostatic pressures above the heart. This causes morning 'puffiness'.

Although the principle on which the Starling equation is based is universally accepted, studies in many types of tissue have shown that net filtration is less than would be predicted from measurements of π_i. This discrepancy is explained by the Michel–Weinbaum hypothesis (Figure 21.2). According to this proposal, the glycocalyx coating the luminal endothelial wall constitutes the semipermeable diffusion barrier described above. Because water crosses the endothelium mainly through the glycocalyx and intercellular clefts, it is not the osmotic pressure exerted by the [protein] in the tissue interstitium (π_i), but rather the osmotic pressure exerted by the [protein] *within the intracellular clefts just beneath the glycocalyx*, which should be used to calculate the osmotic force term in the Starling equation. Importantly, this 'subglycocalyx' protein concentration (π_{sg}) is lower than that in the bulk interstitium because as water streams out through the clefts, it is funnelled through narrow gaps in the junctional strands that hold the walls of the clefts together, creating a current that opposes the diffusion of interstitial protein into the cleft which also occurs through these gaps. Modifying the Starling equation by replacing π_i with π_{sg} increases the size of the osmotic term in the equation (i.e. $\sigma(\pi_p - \pi_{sg})$ is larger than $\sigma(\pi_p - \pi_i)$ because $\pi_{sg} < \pi_i$) meaning that net filtration will be smaller than is predicted by the classic Starling equation.

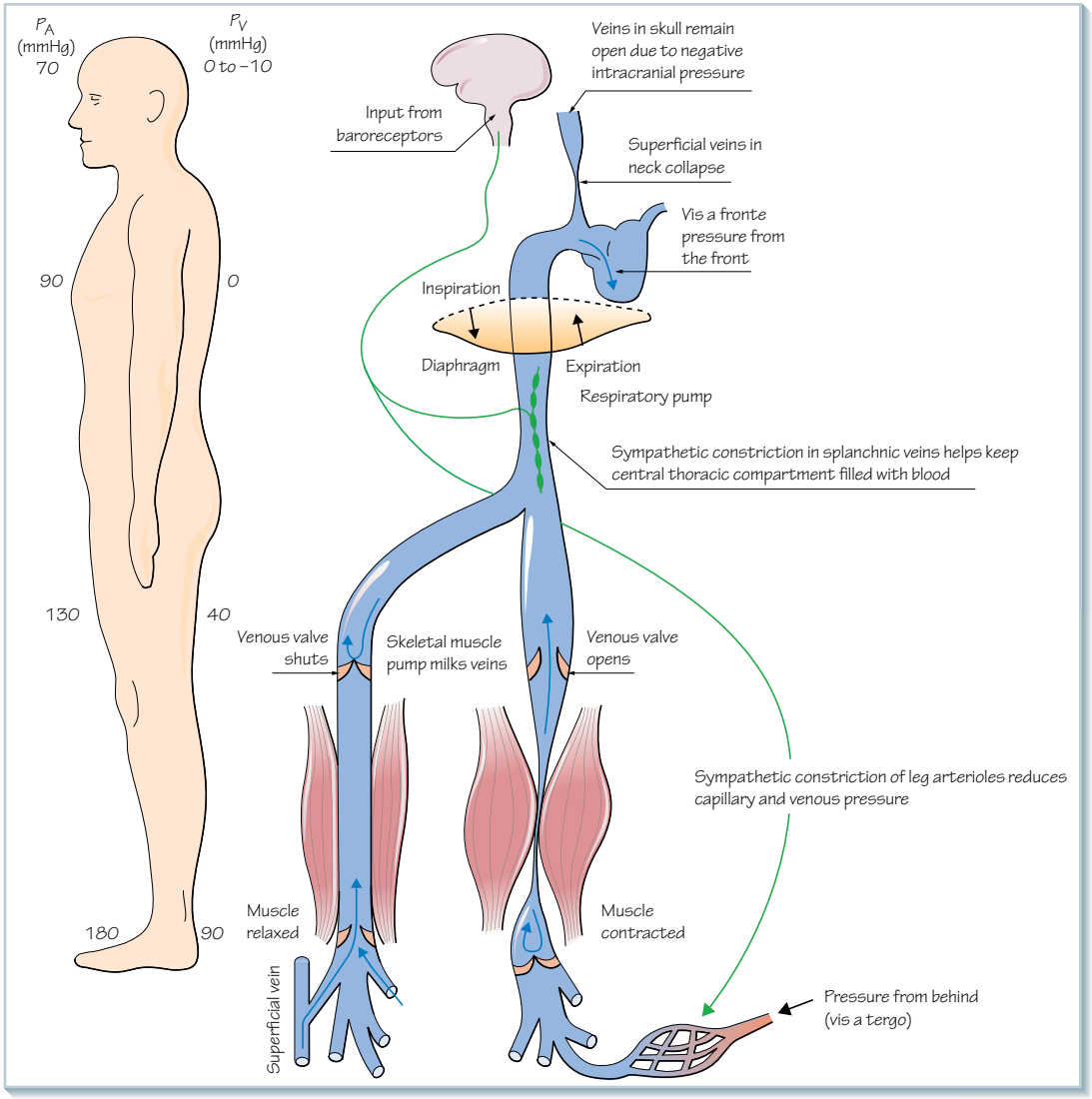
Pulmonary and systemic oedema

The hydrostatic and osmotic pressures in the capillaries of the pulmonary circulation are atypical. Both P_c (~7 mmHg) and P_i (~8 mmHg) are low, whereas π_i is high (~18 mmHg), because these vessels are highly permeable to plasma proteins. The balance of forces slightly favours filtration. In **congestive heart failure**, the output of both the left and right ventricles is markedly reduced (see Chapter 46). Failure of the left ventricle results in an increase in left ventricular end-diastolic pressure. This pressure backs up into the lungs, causing increased pulmonary venular and capillary pressures. This promotes filtration in these vessels, causing an accumulation of fluid in the lungs (**pulmonary oedema**), which dramatically worsens the dyspnoea (breathlessness) and inadequate tissue oxygenation characteristic of congestive heart failure. Similarly, failure of the right ventricle increases systemic venous and therefore capillary pressure, leading to systemic oedema, particularly of the lower extremities.

Oedema of the legs is also caused by **varicose veins**, a condition in which the venous valves are unable to operate properly because the veins become swollen and overstretched. By interfering with the effectiveness of the skeletal muscle pump, the incompetence of the valves leads to increases in venous and capillary hydrostatic pressure, resulting in the rapid development of oedema during standing.

22 The venous system

Figure 22.1 Determinants of venous pressure and flow



The venules and veins convey the blood from the microcirculation to the right atrium. In doing so, they are subject to regulation by several mechanisms (Figure 22.1) that allow them to influence the right atrial pressure and therefore the cardiac output (see Chapter 17).

The venous system differs from the arterial system in two important respects. First, the total volume (and cross-sectional area) of the venous system is much greater than that of the arterial system. This is because there are many more venules than arterioles; venules also tend to have larger internal diameters than arterioles. Second, the veins are quite thin walled and can therefore expand greatly to hold more blood if their internal pressure rises.

As a result of its large cross-sectional area, the venous system offers much less resistance to flow than the arterial system. The pressure gradient required to drive the blood through the venous system (15 mmHg) is therefore much smaller than the pressure needed in the arterial system (80 mmHg). The average pressure in the venae cavae at the level of the heart (the **central venous pressure**) is usually close to 0 mmHg (i.e. atmospheric pressure). The flow of blood back to the heart is aided by the presence of one-way **venous valves** in the arms and especially the legs, which prevent backflow.

Venous and arterial compliance

Figure 22.2 illustrates the relationship between pressure and volume in a typical vein and artery. The slope of the volume–pressure curve is referred to as the **compliance**. Compliance is a measure of **expandability**. Veins are much more compliant than arteries at low pressures (0–10 mmHg). Small increases in venous pressure in this range therefore cause large increases in venous blood volume.

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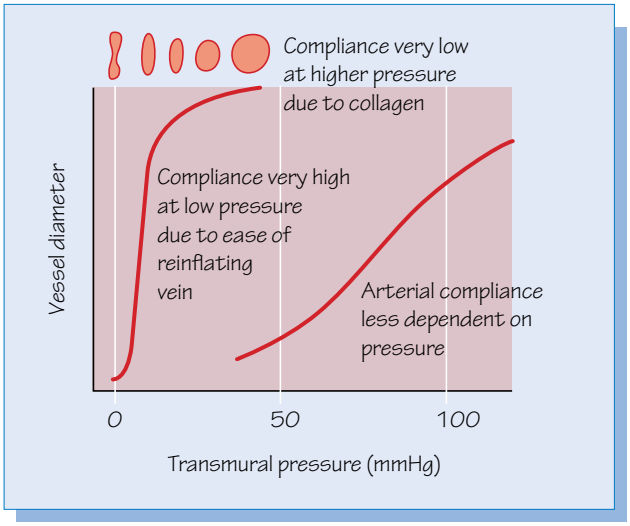
Figure 22.2 Venous and arterial compliance



One result of high venous compliance is that their thin walls allow veins to collapse at low internal pressures. Only small increases in pressure are needed to 'reinflate' a collapsed vein with blood until it has nearly rounded up. At higher pressures, however, venous compliance decreases dramatically (see Figure 22.2) because the slack in rigid collagen fibres in the venous wall is rapidly taken up. This limit on the expandability of the veins is important in limiting the pooling of blood in the veins of the legs that occurs during standing.

The veins as capacitance vessels

Because of their large volumes and high compliance, the veins/venules accommodate a much larger volume of the blood (60–70% of the total) than do the arteries/arterioles (~12%). They are therefore termed **capacitance vessels** and are able to serve as blood volume reservoirs. During exercise, and in hypotensive states (e.g. during haemorrhage), sympathetically mediated constriction of the veins/venules, notably in the splanchnic (including the gastrointestinal tract and liver) and cutaneous circulations, displaces blood into the rest of the cardiovascular system. In particular, the resulting reduction of the venous volume increases the volume of blood in the central thoracic compartment (i.e. the heart and pulmonary circulation), thereby boosting cardiac output, assisting perfusion of other essential vascular beds and helping to maintain the blood pressure.

Effects of posture

When the upright position is assumed (orthostasis), the pull of gravity increases the absolute pressures within *both* the arteries and veins of the lower extremities. The average arterial and venous blood pressures in a normal adult standing quietly are about 100 and 2 mmHg, respectively, at the level of the heart, while in the feet the pressures are about 190 and 90 mmHg, respectively. However, gravity does not affect the *pressure gradient* driving the blood circulation, because the *difference* between the arterial and venous pressures is similar (100 mmHg) at both levels. Therefore standing does not stop blood from flowing back to the heart (Figure 22.1, left).

However, orthostasis does cause important haemodynamic effects. The increased pressure within the veins of the lower extremities causes them to distend, so that about 500 mL blood is shifted into this part of the circulation. The rise in hydrostatic pressure within the capillaries of the lower extremities increases fluid filtration, causing a progressive loss of plasma volume into the tissues of the legs and feet. The resulting loss of fluid from the central thoracic compartment lowers central venous pressure and therefore CO (see Chapter 17).

The fall in CO causes an immediate decrease in the pulse pressure and the mean arterial blood pressure (MABP). However, this is rapidly compensated for by activation of the baroreceptor and cardiopulmonary reflexes (see Chapter 27), which respond to the fall in both parameters by causing an *increased heart rate* and widespread constriction of the veins limits the loss of blood from the central thoracic compartment, and of the arteries/arterioles, causes a 30–40% increase in total peripheral resistance. Since the CO remains depressed by ~20%, the MABP (which is equal CO x TPR) is restored to a level slightly higher than it was before standing up. A local *sympathetic axon reflex* which is triggered by the increase in venous pressure also reduces blood flow and pressure in the lower extremities, limiting fluid filtration.

In the upright position, the reduction of intravascular pressures above the heart causes the partial collapse of superficial veins. This prevents their internal pressure from falling below zero, while allowing blood flow to continue. Deeper veins remain partly open because their walls are anchored to surrounding tissues. Standing also causes a downward displacement into the spinal canal of the cerebrospinal fluid bathing the central nervous system (CNS). This creates a negative pressure inside the rigid cranium that prevents cerebral veins from collapsing, such that their internal pressure falls below zero. However, because cerebral venous pressure is not able to fall as much as arterial pressure (see Figure 22.1), the pressure gradient driving blood flow above the heart decreases and cerebral blood flow falls by 10–20%.

The skeletal muscle pump

Even during quiet standing, the leg muscles are stimulated by reflexes to contract and relax rhythmically, causing swaying. During contraction, veins within the muscles are squeezed, forcing blood towards the heart, as the venous valves prevent retrograde flow. Upon relaxation, these veins expand, drawing in blood from venules and from superficial veins that communicate with the muscle veins via collaterals (Figure 22.1). This *skeletal muscle pump* thus 'milks' the veins, driving blood towards the heart to assist venous return. The skeletal muscle pump is greatly potentiated during walking and running, dramatically lowering the venous pressure in the foot to levels as low as 30 mmHg. Functional incompetence of the valves in superficial tributary veins of the legs, which becomes more common with ageing, renders the skeletal muscle pump less effective. This exposes these vessels to higher internal pressures during orthostasis, causing them to become chronically dilated (**varicose veins**).

The respiratory pump

During inspiration, downward displacement of the diaphragm causes the intrathoracic pressure to fall and the intra-abdominal pressure to rise. This increases the pressure gradient favouring venous return, and vena caval flow rises. An opposite effect occurs during expiration. During straining movements in which there is forced expiration against a closed glottis (e.g. the Valsalva manoeuvre), the rise in intrathoracic pressure severely reduces venous return.

Effect of cardiac contraction

Downward displacement of the ventricles during systole pulls on the atria, expanding them and drawing in blood from the venae cavae and pulmonary veins. When the valves between the atria and ventricles then open during diastole, the blood is drawn in from these veins by the expansion of the ventricles, further aiding venous return. Venous return is therefore driven not only by the upstream pressure but also (to a smaller extent) by downstream suction.

23 Local control of blood flow

Figure 23.1 Autoregulation

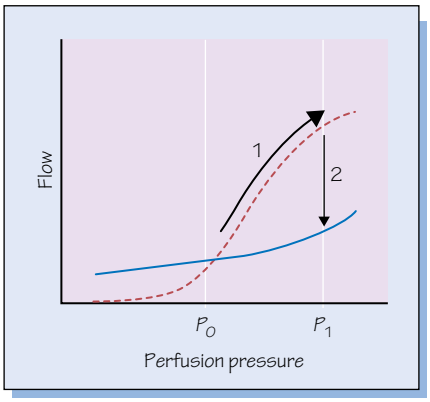


Figure 23.2 Mechanisms of autoregulation

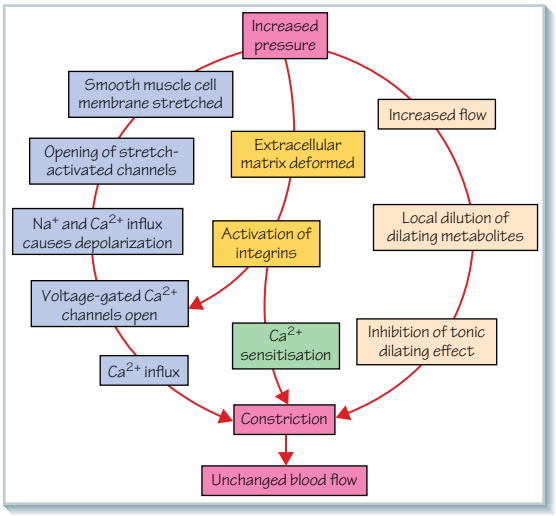
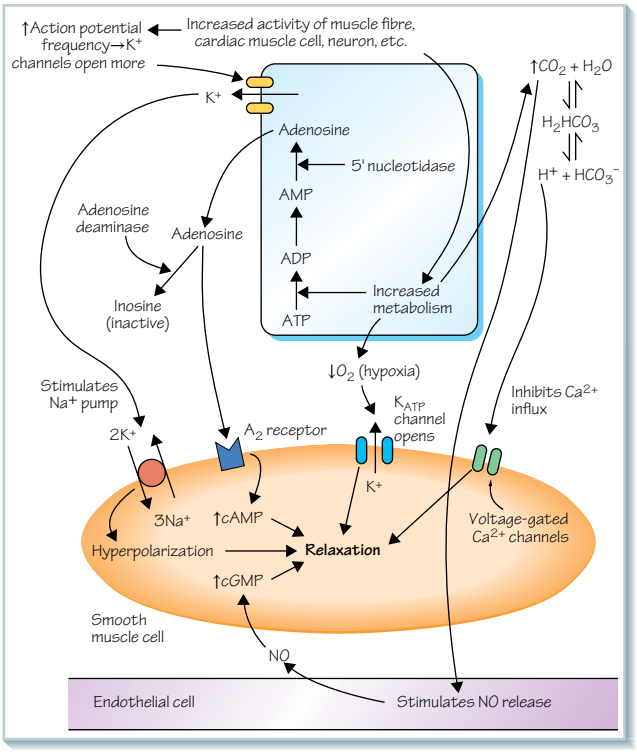


Figure 23.3 Effects of vasodilating metabolites



The activity of the sympathetic nervous system provides for centrally coordinated control of vascular tone (see Chapters 27 and 28) and serves to maintain constant arterial blood pressure. However, there are additional mechanisms that regulate vascular tone. Local mechanisms arise either from within the blood vessel itself or from the surrounding tissue. These local mechanisms function primarily to regulate flow. Regulation tends to be most important in organs that require a constant blood supply or in which metabolic needs can increase markedly (brain, kidneys, heart, skeletal muscles).

Local mechanisms have two main functions. First, under basal conditions they regulate local vascular resistance to maintain the blood flow in many types of vascular beds at a nearly constant level over a large range of arterial pressures (50–170 mmHg). This tendency to minimise changes in flow during variations in pressure is termed **autoregulation**. Autoregulation prevents major fluctuations in capillary pressure which would lead to uncontrolled movement of fluid into the tissues.

Second, when a tissue requires more blood to meet its metabolic needs, local mechanisms cause dilatation of resistance vessels and upregulate blood flow. This response is referred to as **metabolic vasodilatation**. Autoregulation may persist under these conditions but is adjusted to maintain flow around the new set point.

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Autoregulation

Figure 23.1 illustrates the phenomenon of autoregulation. When the upstream pressure driving blood through a resistance artery is suddenly increased to P_1 from its starting level P_0, the artery dilates passively and blood flow immediately rises as predicted by Poiseuille's law (arrow 1). However, within a minute the resistance artery responds to the increased pressure by *actively constricting* (arrow 2), thereby bringing blood flow back down towards its initial level (solid line). Similarly, decreases in upstream pressure cause rapid compensatory dilatations to maintain flow. Autoregulation ensures that under basal conditions blood flow remains nearly constant over a wide range of pressures and is particularly important in the heart, the brain and the kidneys. Two homeostatic negative feedback mechanisms are involved: the **myogenic response** (Figure 23.2) and the effect of **vasodilating metabolites** (Figure 23.3).

The myogenic response is thought to be controlled by sensors in the plasma membrane of vascular smooth muscle cells which react to changes in pressure and/or stretch. **Integrins**, membrane-spanning proteins that act as adhesion molecules linking the extracellular matrix with the cytoskeleton (see Chapter 4), constitute one class of such sensors. Integrins have two subunits (i.e. they are *dimers*), designated α and β, and there are multiple isoforms of each subunit. Studies indicate that integrins consisting of $\alpha_5\beta_1$ and $\alpha_v\beta_3$ dimers are necessary for the myogenic response. Increases in pressure cause changes in the conformation of extracellular matrix proteins which activate these integrins. This in turn induces the opening of L-type voltage-gated Ca^{2+} channels, causing Ca^{2+} influx and vasoconstriction. Increased pressure also stimulates **stretch-activated channels**, leading to Na^+ and Ca^{2+} influx and cell depolarization which is an additional stimulus for opening L-type Ca^{2+} channels. The identities of the stretch-activated channels involved are uncertain, but there is evidence supporting the involvement of two types of **transient receptor potential** (TRP) channels: TRPC6 and TRPM4. In addition to activation of these Ca^{2+}-dependent pathways, the myogenic response to increased pressure also involves **Ca^{2+} sensitization** (see Chapter 15) which is initiated when the monomeric G protein RhoA is stimulated. This can be caused both by the $\alpha_5\beta_1$ integrin dimer and also by the angiotensin 2 AT_1 receptor, which can be shifted into an active conformation by membrane stretch even in the absence of its ligand.

The opposite processes occur when pressure falls, causing vasodilatation.

Cellular metabolism results in the production of **vasodilating metabolites** or **factors** (Figure 23.3) that diffuse into the tissue spaces and affect neighbouring arterioles. If blood flow increases, these substances tend to be washed out of the tissue, leading to an inhibition of vasodilatation that counteracts the rise in blood flow. Conversely, decreased blood flow causes a local accumulation of metabolites, leading to a homeostatic vasodilatation.

Metabolic and reactive hyperaemia

When metabolism in cardiac and skeletal muscle increases during exercise, tissue concentrations of vasodilating metabolites rise markedly. Similarly, focal changes in brain metabolism accompany diverse types of mental activity, causing enhanced local production of metabolites. The increased presence of such factors in the interstitium causes a powerful vasodilatation, termed **metabolic** or **functional hyperaemia**, allowing the rises in blood flow necessary to supply the increased metabolic demand.

An accumulation of vasodilating metabolites also occurs during flow occlusion (e.g. caused by thrombosis). Release of occlusion then results in **reactive hyperaemia**; this is a large increase in blood flow that hastens the re-establishment of cellular energy stores. This response is transient, persisting until levels of these metabolites fall back to normal.

Metabolic factors

Many factors contribute to metabolic vasodilatation. The most important factors are thought to be **adenosine**, **K^+ ions** and **hypercapnia** (increased PCO_2). Local **hypoxia** (reduced PO_2) can also relax vascular smooth muscle cells, partly by opening adenosine triphosphate (ATP) sensitive K^+ channels. **Inorganic phosphate**, **hyperosmolarity** and **lactic acid** may also act as metabolic vasodilators (not shown), although this is less well established.

Adenosine is a potent vasodilator that is released from the heart, skeletal muscles and brain during increased metabolism and hypoxia. It is thought to contribute to metabolic control of blood flow in these organs. Adenosine is produced when adenosine monophosphate (AMP), which accumulates as a result of increased ATP breakdown, is dephosphorylated by the cell membrane enzyme **5′-nucleotidase**. It passes into the extracellular space, dilating neighbouring arterioles before being broken down to inosine by **adenosine deaminase**. It causes vasodilatation by acting on **A_2 receptors** to increase cyclic AMP (cAMP) levels in vascular myocytes. Adenosine also has other actions in the body (e.g. inhibiting conduction in the atrioventricular node), some of which are mediated by **A_1 receptors** (which lower cAMP).

Ischaemia or increased activation of muscles and nerves causes K^+ ions to move out of cells. Resulting increases in the extracellular K^+ concentration (up to 10–15 mmol/L) dilate arterioles, partly by stimulating the Na^+–K^+-ATPase, during functional hyperaemia in skeletal muscle and brain tissue. **Hypercapnia** associated with **acidosis** occurs in brain tissue during stimulation of local metabolism and also during **cerebral ischaemia** (stroke). These are thought to provide a powerful vasodilating stimulus, both by releasing **nitric oxide** from endothelial cells, and by directly inhibiting Ca^{2+} influx into arteriolar cells.

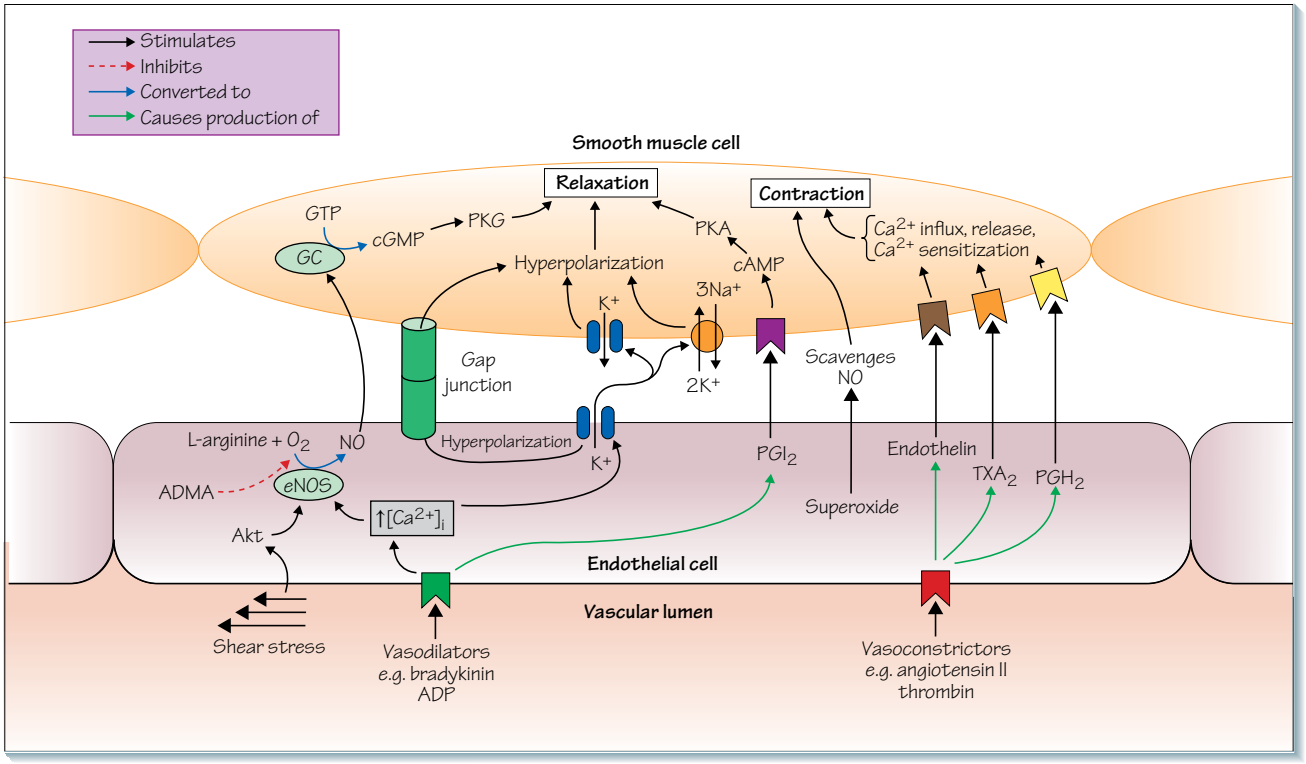
Other local mechanisms

There are also a number of mechanisms acting locally in selected vascular beds under specific circumstances. For example, during the inflammatory reaction, local infection or trauma causes the release of various **autacoids** (local hormones), including the arteriolar dilators **histamine**, **prostaglandin E_2**, **bradykinin** and **platelet activating factor**. These increase local blood flow and increase postcapillary venular permeability, thereby facilitating the access of leucocytes and antibodies to damaged and infected tissues. The generation of **bradykinin** by sweat glands during sweating promotes cutaneous vasodilatation. **Prostaglandin I_2** (PGI_2, prostacyclin) is synthesized and released in the renal cortex under conditions where renal blood flow is reduced by vasoconstrictors. Prostacyclin has a vasodilating action that helps to maintain renal blood flow. Conversely, the release of **serotonin** (5-hydroxytryptamine) and **thromboxane A_2** (TXA_2) from platelets during haemostasis causes vasospasm, which helps to reduce bleeding (see Chapter 7).

There is increasing interest in the regulation of vascular tone by **perivascular adipose tissue** (PVAT; the fat cells surrounding many blood vessels). PVAT can release diverse substances as that may directly affect vascular tone, or modulate the effects of other vasoactive agents. Factors released by PVAT which cause or promote constriction include **chemerin**, **TNF-α**, and **leptin**, whereas **adipocyte-derived relaxing factors** include **adiponectin**, **angiotensin 1-7** and **hydrogen sulfide**. It has been proposed that the net effect of the various factors released by PVAT normally favours vasorelaxation, but that in conditions such as diabetes and hypertension the overall balance shifts to promote constriction.

24 Regulation of the vasculature by the endothelium

Figure 24.1 Regulation of vascular tone by the endothelium



The entire vascular lumen is lined by a monolayer of endothelial cells which are crucial in regulating vascular tone. Endothelial cells can release both constricting and dilating substances when stimulated by blood-borne substances or by shear stress associated with the flow of blood (Figure 24.1). Important endothelial vasodilators include **nitric oxide** (termed **endothelium-derived relaxing factor** prior to its identification in 1987), **prostacyclin** (PGI_2), and **endothelium-derived hyperpolarizing factors** (EDHFs). The major endothelial vasoconstrictors are **endothelin-1, thromboxane A_2** (TXA_2) and **prostaglandin H_2**.

Endothelial cells also have a crucial role in suppressing platelet aggregation and thereby regulating haemostasis (see Chapter 7) and, as the major constituents of the capillary wall, control vascular permeability to many substances (see Chapter 21).

Nitric oxide

Nitric oxide (chemical formula NO) is the major vasodilator released by endothelial cells. NO is synthesized from the amino acid L-arginine and O_2 by nitric oxide synthase (NOS). The most important form of NOS in the cardiovascular system is **endothelial NOS** (eNOS, also NOS-3), which is thought to be responsible for a continual basal production and release of NO by endothelial cells (also by platelets and the heart). eNOS is further activated by a variety of substances that act on their receptors to increase the endothelial cell intracellular $Ca^{2+}[Ca^{2+}]_i$, leading to raised levels of the Ca^{2+} – calmodulin complex which stimulates the enzyme. The rise in $[Ca^{2+}]_i$ is initiated by Ca^{2+} release from the endoplasmic reticulum, and is subsequently sustained at a lower but still elevated level by Ca^{2+} influx via store-operated Ca^{2+} channels (see Chapter 15). Substances that cause vasodilatation in this way include locally released factors such as bradykinin, adenine, adenosine nucleotides, histamine, serotonin and the neurotransmitter substance P. Acetylcholine has a similar effect, although this probably has little physiological importance in humans.

Shear forces exerted on the endothelium by the flow of blood also activate eNOS, and this contributes to both basal NO release and local regulation of blood flow. This effect is not caused by a rise in $[Ca^{2+}]_i$, but by cellular pathways activated by shear force-induced deformation of the endothelial cell cytoskeleton. One such pathway involves the sequential activation of the enzymes **phosphatidylinositol 3-kinase** (**PI3K**) and **Akt**, the latter of which stimulates eNOS via phosphorylation.

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Once released from the endothelium, NO diffuses through the vascular wall and into the smooth muscle cells, where it activates the cytosolic enzyme **guanylyl cyclase**. This increases levels of cellular cyclic GMP, which causes relaxation as described in Chapter 15.

NO is a free radical (i.e. it contains an unpaired electron) and is therefore very reactive. In particular, upon its release NO reacts very rapidly with **superoxide**, another free radical which is continually being produced by a variety of enzymes (e.g. NADPH oxidase) to form **peroxynitrite**, a substance that does not cause vasodilatation, and which in excess may damage cells. Because any given molecule of NO therefore survives for only a few seconds, the effects of NO are exerted locally and require its continued production.

Neuronal NOS (nNOS, also NOS-1) is expressed by multiple types of cells, including autonomic and sensory nerves, vascular smooth muscle and skeletal muscle fibres. Local release of NO by nNOS in the macula densa is important in regulating renal blood flow, and recent findings indicate that continual NO production by nNOS in arteries and/or skeletal muscle probably acts as a tonic vasodilating influence on arteries and arterioles throughout the body.

Inducible NOS (iNOS, also NOS-2) is expressed in macrophages, lymphocytes, vascular smooth muscle and other types of cells during inflammation. iNOS is capable of producing much greater amounts of NO and probably aids destruction of foreign organisms by the immune system. An overproduction of NO by iNOS in septic shock is thought to contribute to the severe hypotension characterizing this condition.

The formation of NO is competitively antagonized by drugs such as the non-selective NOS inhibitor L-nitro arginine methyl ester (L-NAME) and the selective nNOS blocker S-methyl-L-thiocitrulline (SMTC). These are useful experimental tools for evaluating the roles of NO *in vitro* and *in vivo*. Remarkably, an *endogenous* competitive inhibitor of eNOS called **ADMA** (asymmetric dimethyl arginine) is normally present in the plasma at a concentration of ~1 μmol/L and is formed by **protein arginine methyltransferases**, enzymes in the nucleus that attach methyl groups to arginine residues in proteins. Subsequent protein hydrolysis then releases ADMA. ADMA is metabolized by the ubiquitous enzyme **dimethylarginine dimethylaminohydrolase** and is also excreted by the kidneys. Elevated plasma levels of ADMA are a cardiovascular risk factor and occur in diabetes mellitus, hyperhomocysteinaemia and preeclampsia.

Other endothelium-derived relaxing mechanisms

Many of the factors that evoke endothelial NO production also stimulate the endothelial release of prostacyclin and EDHF. Prostacyclin promotes vasodilatation by increasing smooth muscle cell cyclic AMP levels, but its most important role is in limiting platelet attachment and aggregation.

EDHF was originally defined as a substance or substances released from the endothelium that cause(s) smooth muscle hyperpolarization (and therefore relaxation, see Chapter 15) by opening K^+ channels and/or stimulating the activity of the Na^+ pump, and is particularly important in causing dilatation of arterioles, where its influence may exceed that of NO. The EDHF response is now thought to occur because the rises in endothelial cell $[Ca^{2+}]$ that trigger NO and PGI_2 synthesis also open Ca^{2+} activated K^+ channels in these cells. This causes a hyperpolarization of the endothelial cells which is transmitted directly to the surrounding smooth muscle cells through **myoendothelial gap junctions** which connect these two types of cells and allow current to flow between them. The opening of endothelial cell K^+ channels also raises the extracellular $[K^+]$ around the smooth muscle cells that are adjacent to the endothelium, and this further promotes smooth muscle cell hyperpolarization by activating both the Na^+ pump and the **inward rectifier** (K_{IR}), a type of K^+ channel that has the unusual property of allowing a greater efflux of K^+ when the extracellular $[K^+]$ increases. **Hydrogen peroxide** and **epoxyeicosatrienoic acids**, which are produced from arachidonic acid by the enzyme cytochrome P450, have also been proposed as EDHFs. However, recent work indicates that they both act in an autocrine manner on endothelial cells to promote rises in $[Ca^{2+}]_i$ and therefore K^+ efflux, thereby enhancing rather than causing the EDHF response.

Endothelium-derived constricting factors

Endothelin-1 is a 21 amino acid peptide that is released from the endothelium by many vasoconstrictors, including angiotensin, vasopressin, thrombin and adrenaline. Endothelin is a potent vasoconstricting agent, particularly in veins and arterioles, and stimulates two subtypes of receptor on vascular smooth muscle cells, designated ET_A and ET_B Endothelin causes vasoconstriction via G-protein-linked mechanisms similar to those activated by noradrenaline. The infusion of endothelin receptor antagonists into humans causes a sustained fall in total peripheral resistance, implying that ongoing endothelin release contributes to maintaining the blood pressure.

Endothelial cells can also release other vasoconstricting substances, including **prostanoids** (thromboxane A_2 and prostaglandin H_2), and superoxide anions which may enhance constriction by breaking down NO. In addition, **angiotensin-converting enzyme** (ACE) present on the surface of endothelial cells is responsible for both the production of the vasoconstrictor angiotensin 2 (see Chapters 29 and 35) and the breakdown of the potent vasodilator bradykinin.

Endothelium in cardiovascular disease

Many diseases that disturb vascular function are associated with abnormalities of the endothelium. Dysfunction of the endothelium is thought to contribute to the early stages of **atherosclerosis**, whereas damage to the endothelium is a crucial factor leading to thrombus formation in the advanced atherosclerotic lesion (see Chapter 37). Plasma from patients with **diabetes mellitus** contains abnormally high levels of biochemical markers indicative of endothelial damage, and there is evidence, both in animal models of insulin-dependent diabetes and in patients with this disorder, for blunted endothelium-dependent relaxation. This deficit in endothelial function is thought to contribute to the increased risks of atherosclerosis, neuropathy and hypertension that are associated with diabetes. The mechanisms leading to diabetes-associated endothelial dysfunction remain incompletely defined, but may include damage by raised levels of glucose and/or oxidized low-density lipoproteins.

Endothelial dysfunction may also be important in causing **preeclampsia**, a disorder of pregnancy characterized by hypertension and increased blood clotting, which is the leading cause of maternal mortality. The endothelium is thought to have an important role in causing the fall in maternal blood pressure that normally occurs during pregnancy. However, this protective function may be disrupted in patients with preeclampsia, possibly because of the release of substances from the placenta that damage the endothelial cells.

25 The pulmonary, skeletal muscle and fetal circulations

Figure 25.1 Effects of the upright position on pulmonary pressures and blood flow

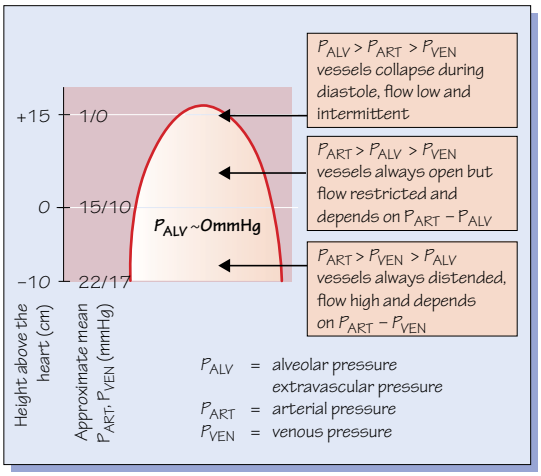
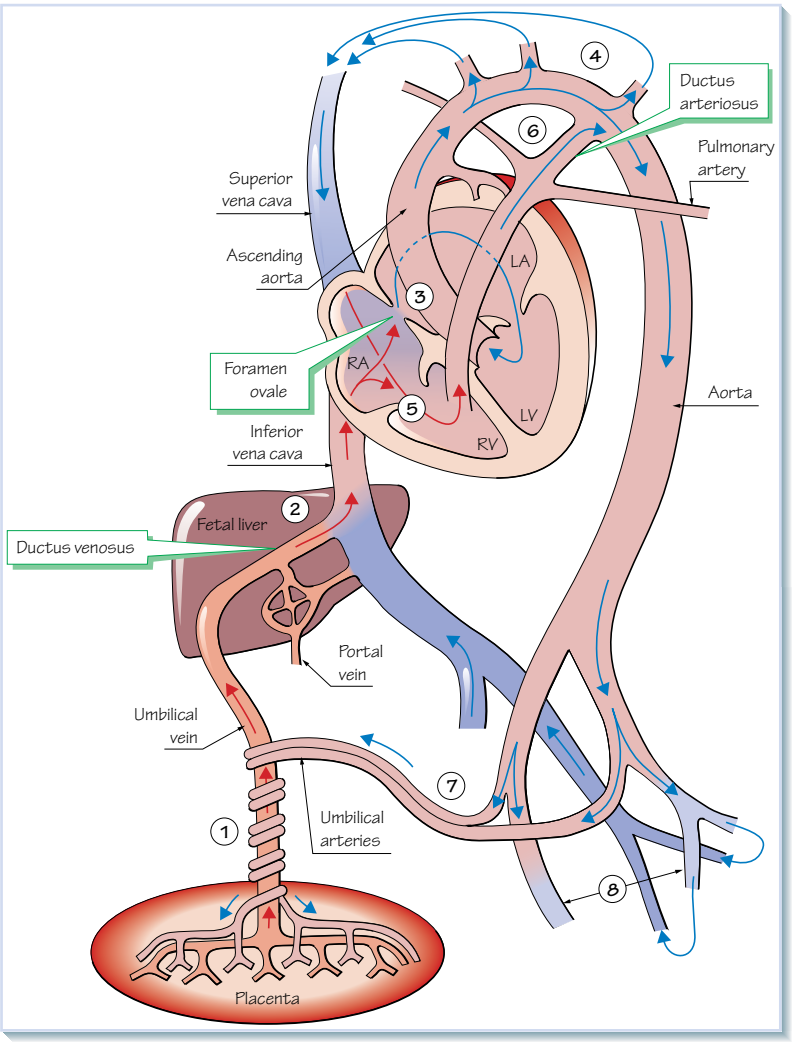


Figure 25.2 The fetal circulation



The vascular beds supplying the different organs of the body are structurally and functionally specialized, allowing an optimal matching of blood flow with their individual requirements.

The pulmonary circulation

As described in Chapter 1, the **pulmonary circulation** receives the entire output of the right ventricle. Its high-density capillary network surrounds the lung alveoli, allowing the O_2-poor blood from the pulmonary arteries to exchange CO_2 for O_2. The pulmonary veins return highly oxygenated blood to the left atrium. The pulmonary circulation contains about 800 mL of blood in recumbent subjects, falling to about 450 mL during quiet standing.

Mean pulmonary arterial pressure is ~15 mmHg, and left atrial pressure is ~5 mmHg. The right ventricle is able to drive its entire output through the pulmonary circulation utilizing a pressure head of only 10 mmHg because the resistance of the pulmonary circulation is only 10–15% that of the systemic circulation. This arises because the vessels of the pulmonary microcirculation are short and of relatively wide bore, with little resting tone. They are also very numerous, so that their total cross-section is similar to that of the systemic circulation. The walls of both arteries and veins are thin and distensible and contain comparatively little smooth muscle.

The low pressure within the pulmonary circulation means that regional perfusion of the lungs in the upright position is greatly affected by gravity (Figure 25.1). The extravascular pressure throughout the lungs is similar to the alveolar pressure (~0 mmHg). However, the intravascular pressure is low in the lung apices, which are above the heart, and high in the lung bases, which are below the heart. Pulmonary

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vessels in the lung apices therefore collapse during diastole, causing intermittent flow. Conversely, vessels in the bases of the lungs are perfused throughout the cardiac cycle and are distended. A small increase in pulmonary arterial pressure during exercise is sufficient to open up apical capillaries, allowing more O_2 uptake by the blood.

The low hydrostatic pressure in pulmonary capillaries (mean of 7–10 mmHg) does not lead to net fluid resorption, because it is balanced by a low extravascular hydrostatic pressure and an unusually high interstitial plasma protein oncotic pressure (~18 mmHg). The lung capillaries therefore produce a small net flow of lymph, which is drained by an extensive pulmonary lymphatic network. During left ventricular failure or mitral stenosis, however, the increased left atrial pressure backs up into the pulmonary circulation, increasing fluid filtration and leading to **pulmonary oedema**.

Neither the sympathetic nervous system nor myogenic/metabolic autoregulation have much of a role in regulating pulmonary vascular resistance or flow. However, the pulmonary vasculature is well supplied with sympathetic nerves. When stimulated, these decrease the compliance of the vessels, limiting the pulmonary blood volume so that more blood is available to the systemic circulation.

The most important mechanism regulating pulmonary vascular tone is **hypoxic pulmonary vasoconstriction** (HPV), a process by which pulmonary vessels *constrict* in response to alveolar **hypoxia**. This unique mechanism (systemic vessels typically *dilate* to hypoxia) diverts blood away from poorly ventilated regions of the lungs, thereby maximizing the **ventilation–perfusion ratio**. HPV is probably caused mainly by hypoxia-induced release of Ca^{2+} from the sarcoplasmic reticulum within the smooth muscle cells of the pulmonary vasculature.

The skeletal muscle circulation

The skeletal muscles comprise about 50% of body weight and at rest receive 15–20% of cardiac output. At rest, skeletal muscle arterioles have a high basal tone as a result of tonic sympathetic vasoconstriction. At any one time, most muscle capillaries are not perfused, due to intermittent constriction of precapillary sphincters (vasomotion).

Because the muscles form such a large tissue mass, their arterioles make a major contribution to total peripheral resistance (TPR). Sympathetically mediated alterations in their arteriolar tone therefore have a crucial role in regulating TPR and blood pressure during operation of the baroreceptor reflex. The muscles thus serve as a '*pressure valve*' that can be closed to increase blood pressure and opened to lower it.

With *rhythmic* exercise, compression of blood vessels during the contraction phase causes the blood flow to become intermittent. However, increased muscle metabolism causes the generation of *vasodilating factors*; these factors cause an enormous increase in blood flow during the relaxation phase, especially to the white or phasic fibres involved in movement. With maximal exercise, the skeletal muscles receive 80–90% of cardiac output. Vasodilating factors include **K^+ ions**, **CO_2** and **hyperosmolarity**. In working muscle their effects completely *override* sympathetic vasoconstriction, while arterioles in non-working muscle remain sympathetically constricted so that their blood flow does not increase.

Sustained compression of blood vessels during *static* (isometric) muscle contractions causes an occlusion of flow that rapidly results in muscle fatigue.

The fetal circulation

A diagram of the fetal circulation is shown in Figure 25.2. The fetus receives O_2 and nutrients from, and discharges CO_2 and metabolic waste products into, the maternal circulation. This exchange occurs in the **placenta**, a thick spongy pancake-shaped structure lying between the fetus and the uterine wall. The placenta is composed of a space containing maternal blood, which is packed with **fetal villi**, branching treelike structures containing fetal arteries, capillaries and veins. They receive the fetal blood from branches of the two **umbilical arteries** and drain back into the fetus via the **umbilical vein**. Gas and nutrient exchange occurs between the fetal capillaries in the villi and the maternal blood surrounding and bathing the villi.

The fetal circulation differs from that of adults in that *the right and left ventricles pump the blood in parallel rather than in series*. This arrangement allows the heart and head to receive more highly oxygenated blood and is made possible by three structural *shunts* unique to the fetus: the **ductus venosus**, the **foramen ovale** and the **ductus arteriosus** (highlighted in Figure 25.2).

Blood leaving the placenta (**1**) via the umbilical vein is 80% saturated with O_2. About half of this flows into the fetal liver. The rest is diverted into the inferior vena cava via the **ductus venosus** (**2**), mixing with poorly oxygenated venous blood returning from the fetus' lower body. When the resulting relatively oxygen-rich mixture (about 67% saturated) enters the right atrium, most of it does not pass into the right ventricle as it would in the adult, but is directed into the left atrium via the **foramen ovale**, an opening between the fetal atria (**3**). Blood then flows into the left ventricle, and is pumped into the ascending aorta, from which it perfuses the head, the coronary circulation and the arms (**4**). Venous blood from these areas re-enters the heart via the superior vena cava. This blood, now about 35% saturated with O_2, mixes with the fraction of blood from the inferior vena cava not entering the foramen ovale (**5**), and flows into the right ventricle, which pumps it into the pulmonary artery. Instead of then entering the lungs, as it would in the adult, about 90% of the blood leaving the right ventricle is diverted into the descending aorta through the **ductus arteriosus** (**6**). This occurs because pressure in the pulmonary circulation is higher than that in the systemic circulation, as a result of pulmonary vasoconstriction and the collapsed state of the lungs. About 60% of blood entering the descending aorta then flows back to the placenta for oxygenation (**7**). The rest, now 58% saturated with O_2, supplies the fetus' trunk and legs (**8**).

Circulatory changes at birth

Two events at birth quickly cause the fetal circulation to assume a quasi-adult pattern. First, the pulmonary vascular pressure falls well below the systemic pressure because of the initiation of breathing and the resulting pulmonary vasodilatation. Together with constriction of the ductus arteriosus caused by increased blood O_2 levels, this reversal of the pulmonary–systemic pressure gradient, which is aided by the loss of the low-resistance placental circulation, abolishes the blood flow from the pulmonary artery into the aorta within 30 min after delivery.

Second, tying off the umbilical cord stops venous return from the placenta, abruptly lowering inferior vena caval pressure. Together with the fall in pulmonary resistance, this lowers right atrial pressure, causing within hours functional closure of the foramen ovale. The ductus venosus also closes with the abolition of venous return from the placenta.

Although these fetal circulatory shunts are *functionally* closed soon after birth, complete *structural* closure occurs only after several months. In 20% of adults, the structural closure of the foramen ovale remains incomplete, although this is of no haemodynamic consequence.

26 The coronary, cutaneous and cerebral circulations

Figure 26.1 Coronary circulation

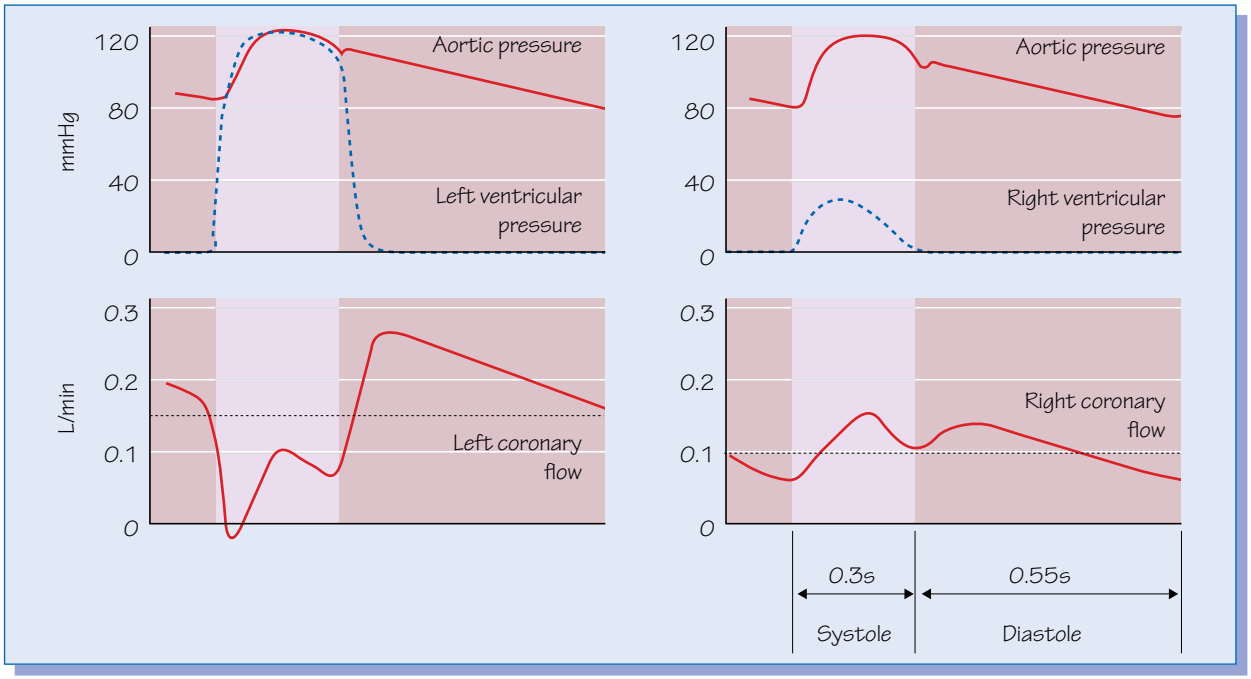


Figure 26.2 Cutaneous circulation

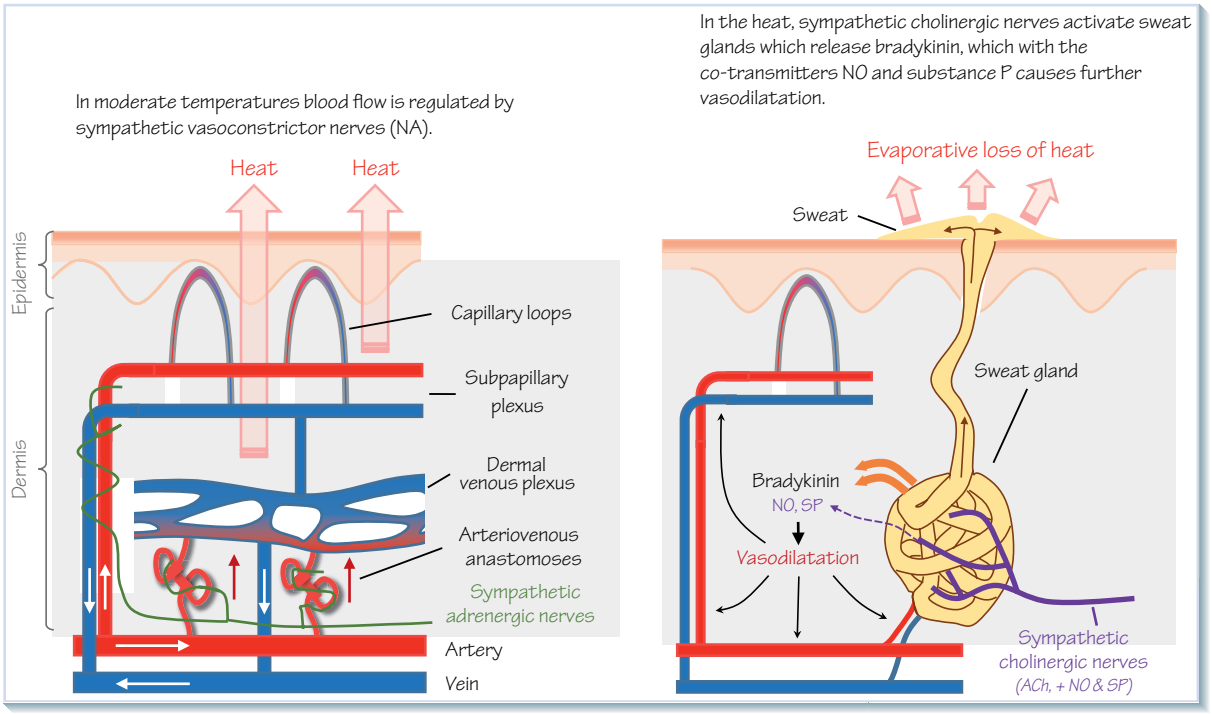
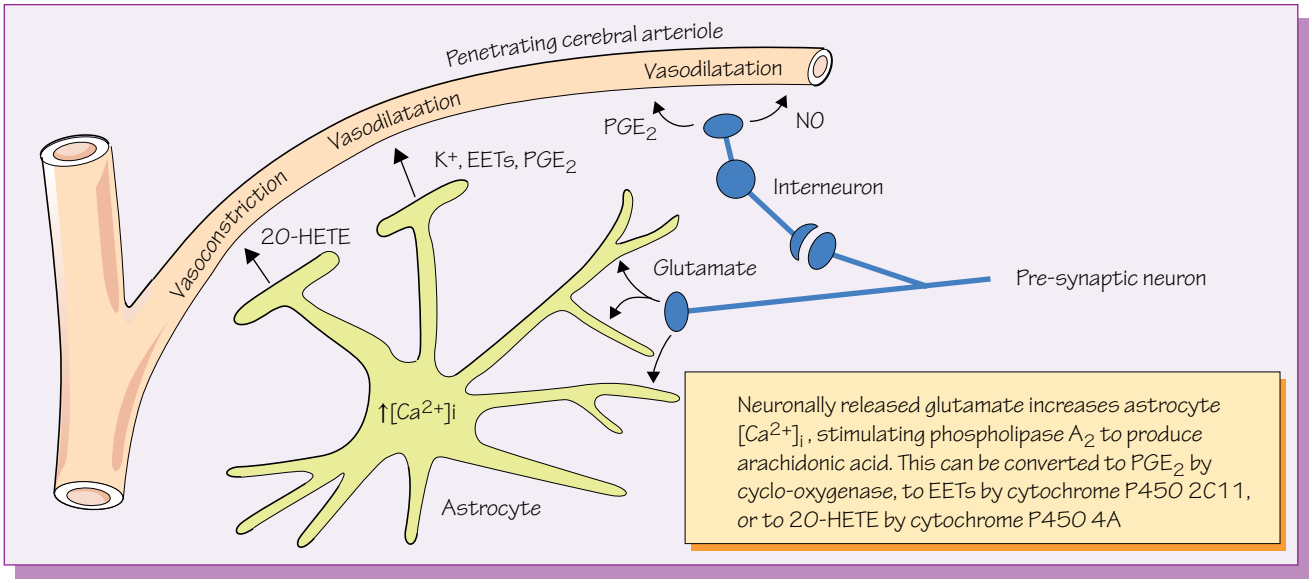


Figure 26.3 Cerebral circulation



Coronary circulation

The anatomy of the coronary circulation is described in Chapter 2. The *high capillary density* of the myocardium (~1 capillary per muscle cell) allows it to extract an unusually large fraction (about 75%) of the oxygen from its blood supply. The resting blood flow to the heart is relatively high and moreover increases approximately five-fold during strenuous exercise.

Figure 26.1 shows left and right coronary blood flow during the cardiac cycle at a resting heart rate (HR) of 70 beats/min. During systole, the branches of the left coronary artery that penetrate the myocardial wall to supply the subendocardium of the left ventricle are strongly compressed by the high pressure within the ventricle and its wall. Left coronary blood flow is therefore almost abolished during systole, so that 85% of flow occurs during diastole. Conversely, right coronary arterial flow rate is highest during systole, because the aortic pressure driving flow increases more during systole (from 80 to 120 mmHg) than the right ventricular pressure which opposes flow (from 0 to 25 mmHg).

With a HR of 70 beats/min, systole and diastole last 0.3 and 0.55 s, respectively. As the HR increases during exercise or excitement, however, the duration of diastole shortens more than that of systole. At 200 beats/min, for example, systole and diastole both last for 0.15 s. In order to cope with the greatly increased oxygen demand of the heart, which occurs simultaneously with a marked reduction in the time available for left coronary perfusion, the coronary arteries/arterioles dilate dramatically to allow for a pronounced rise in blood flow. The mechanism of this **exercise hyperaemia** in humans is unknown. However, in the porcine coronary circulation, which seems to be regulated in a manner similar to that of humans, coronary exercise hyperaemia is probably caused by reduction of endothelin release from the coronary endothelium, plus a sympathetically mediated β-receptor activation of coronary artery smooth muscle which results in a rise in cellular cyclic AMP (cAMP) and the opening of BK_{Ca} channels.

Cutaneous circulation

Apart from supplying the modest metabolic requirements of the skin, the main function of the cutaneous vasculature is **thermoregulation**. **Venous plexuses** (networks) facilitate heat transfer from blood to the surface, and in **glabrous** (hairless) skin of hands, feet and areas of the face, coiled, thick-walled **arteriovenous anastomoses** (AVAs) directly link arterial and venous vessels and enable high blood flows through the venous plexus and increased radiation of heat (Figure 26.2).

Cutaneous blood flow is primarily controlled by the central thermoregulator in the **hypothalamus**. In moderate conditions (**thermoneutral zone**) core temperature is maintained solely by adjusting cutaneous blood flow. Tonic activity of sympathetic adrenergic nerves releases noradrenaline which activates α_1 and α_2 adrenoceptors to induce graded vasoconstriction and thus heat loss. A fall in body temperature increases neural activity and vasoconstriction, so blood flow and heat loss decrease. An increase in temperature does the opposite, and specifically involves opening of AVAs, which are particularly sensitive to sympathetic stimulation and normally strongly vasoconstricted. At higher temperatures **sympathetic cholinergic nerves** release **acetylcholine** to activate **sweat glands** and sweating; co-transmitters (NO, substance P) cause local vasodilatation. Sweat glands themselves release the powerful vasodilator **bradykinin** (Figure 26.3). These mechanisms increase blood flow to support production of sweat and contribute to radiative heat loss. Skin blood flow can increase 30-fold in very hot conditions.

Local skin temperature also directly affects blood flow. Local heating causes vasodilatation, probably due to NO and a local sensory nerve reflex. Local cooling enhances vasoconstriction by causing translocation of intracellular α_{2C} adrenoceptors into the vascular smooth muscle cell membrane, effectively increasing sensitivity to noradrenaline. In cold conditions cutaneous blood flow can fall by 90%, though prolonged cold causes transient paradoxical vasodilation, particularly in the hands. **Raynaud's phenomenon** is an exaggerated vasoconstrictor response to cold in the skin of extremities, especially fingers, causing pain and occasionally ulceration. Prevalence is ~5-10%, and is more common in premenopausal women than men. Most cases are idiopathic (Primary Raynaud's phenomenon), but ~15% are secondary to other conditions (e.g. connective tissue diseases), drug treatment (e.g. chemotherapy, β-blockers) or toxins (e.g. smoking, PVC).

The baroreceptor reflex also constricts cutaneous vessels, helping to increase total peripheral resistance (TPR) and shift blood to vital organs during haemorrhage or shock. This is particularly important at elevated body temperatures, when >50% of the cardiac output may be directed to the skin.

Cerebral circulation

The brain receives about 15% of cardiac output. The **basilar** and **internal carotid arteries** entering the cranium join to form an arterial ring, the **circle of Willis**, from which arise the **anterior**, **middle** and **posterior cerebral arteries** which supply the cranium. This arrangement helps to defend the cerebral blood supply, which if occluded causes immediate unconsciousness and irreversible tissue damage within minutes.

The brain, especially the neuronal grey matter, has a very high capillary density (~3000–4000 capillaries/mm^3) and blood flow. Coupled with a large (~35%) fractional O_2 extraction, this allows it to sustain the high rate of oxidative metabolism it requires to function. The arteriolar myogenic response is well developed, allowing cerebral blood flow to be maintained constant at arterial pressures between about 50 and 170 mmHg. **CO_2** concentrations in the surrounding brain are particularly important in causing vasodilatation (see Chapter 23). The effect of CO_2 is in part caused by NO release from endothelial cells. Hyperventilation, which reduces arterial CO_2, can cause a marked cerebral vasoconstriction and temporary unconsciousness. Sympathetic regulation of cerebral blood flow is probably of minor importance.

Increased neuronal activity dilates local arterioles within seconds through several mechanisms (Figure 26.3). Some neurones release transmitters such as NO, vasoactive intestinal peptide or prostaglandin E_2 (PGE_2), which are vasodilators. Neuronal activity also regulates intracerebral arterioles indirectly via effects on **astrocytes**. These are glial cells that have 'endfeet' that are in close contact with adjacent arterioles (in fact arterioles within the brain are almost completely encased in astrocytic endfeet). Astocytes also have multitudinous projections that surround and monitor the activity of >100 000 neuronal synapses and respond to increased activity in their synaptic 'domain' by raising their intracellular Ca^{2+} concentration. This is thought to induce them to release substances such as K^+, PGE_2 and epoxyeicosatrienoic acids (EETs) from their endfeet onto the arterioles, causing them to dilate. They may also be able to elicit vasoconstriction by releasing 20-hydroxyeicosatetraenoic acid (20-HETE). Astrocytes are coupled to each other electrically by gap junctions, forming a network that may act to spread the vasodilating 'message' upstream so that the larger arteries feeding regions of increased neuronal activity also dilate.

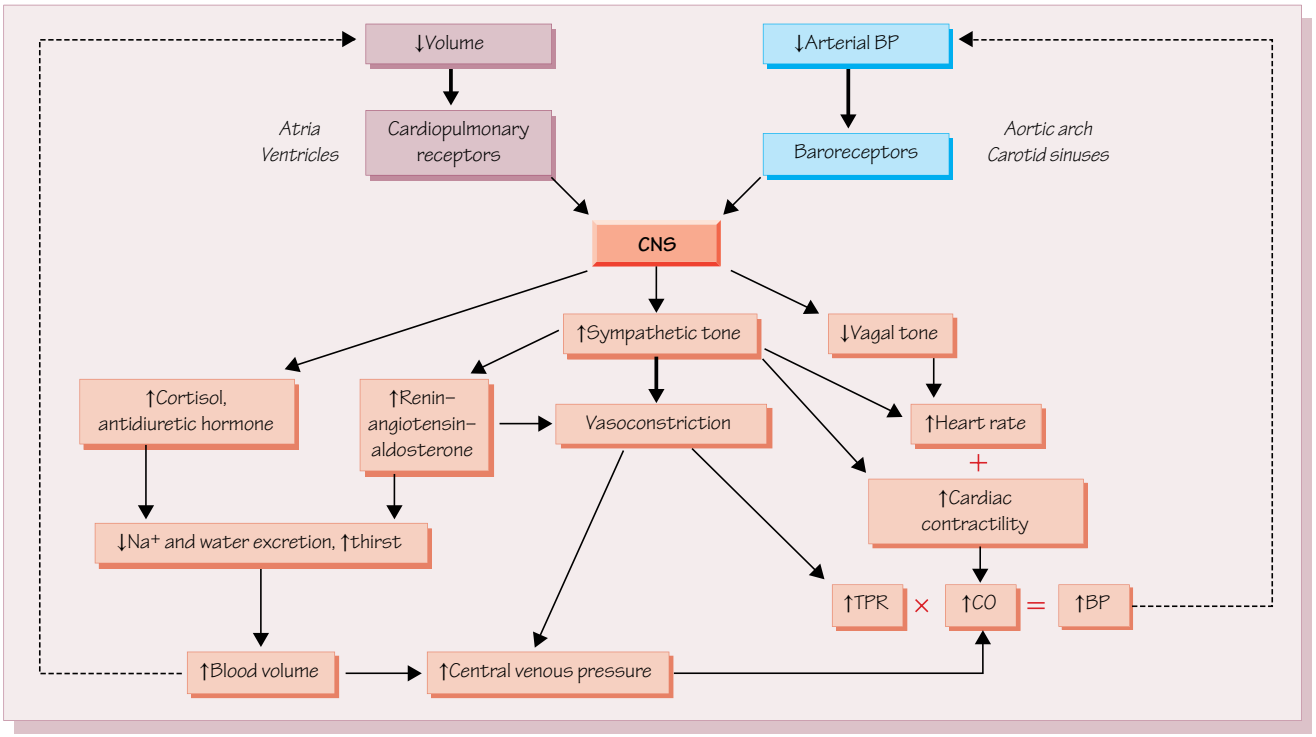
The brain and spinal cord float in the **cerebrospinal fluid** (CSF), which is contained within the rigid cranium and the spinal canal. Because the cranium is rigid and its contents are incompressible, the volume of blood within the brain remains roughly constant, and increases in arterial inflow are compensated for by decreases in venous volume. By increasing the tissue mass, brain tumours increase the intracerebral pressure and reduce cerebral blood flow. Increased intracerebral pressure is partially compensated for by the **Cushing reflex**, a characteristic rise in arterial pressure associated with a reflex bradycardia.

Integration and regulation

Chapters

27 Cardiovascular reflexes

Figure 27.1 Cardiovascular reflexes regulating blood pressure and volume



The cardiovascular system is centrally regulated by **autonomic reflexes**. These work with local mechanisms (see Chapter 23) and the **renin–angiotensin–aldosterone** and **antidiuretic hormone** systems (see Chapter 29) to minimize fluctuations in the mean arterial blood pressure (MABP) and volume and to maintain adequate cerebral and coronary perfusion. **Intrinsic** reflexes, including the **baroreceptor**, **cardiopulmonary** and **chemoreceptor** reflexes, respond to stimuli originating within the cardiovascular system. Less important **extrinsic** reflexes mediate the cardiovascular response to stimuli originating elsewhere (e.g. pain, temperature changes). Figure 27.1 illustrates the responses of the baroreceptor and cardiopulmonary reflexes to reduced blood pressure and volume, as would occur, for example, during haemorrhage.

Cardiovascular reflexes involve three components:

1. Afferent nerves ('receptors') sense a change in the state of the system and communicate this to the brain, which
2. Processes this information and implements an appropriate response, by
3. Altering the activity of efferent nerves controlling cardiac, vascular and renal function, thereby causing homeostatic responses that reverse the change in state.

Intrinsic cardiovascular reflexes

The baroreceptor reflex

This reflex acts rapidly to minimize moment-to-moment fluctuations in the MABP. **Baroreceptors** are afferent (sensory) nerve endings in the walls of the **carotid sinuses** (thin-walled dilatations at the origins of the internal carotid arteries) and the **aortic arch**. These **mechanoreceptors** sense alterations in wall stretch caused by pressure changes, and respond by modifying the frequency at which they fire action potentials. Pressure elevations increase impulse frequency; pressure decreases have the opposite effect.

When MABP decreases, the fall in baroreceptor impulse frequency causes the brain to *reduce* the firing of vagal efferents supplying the sinoatrial node, thus causing tachycardia. Simultaneously, the activity of sympathetic nerves innervating the heart and most blood vessels is *increased*, causing increased cardiac contractility and constriction of arteries and veins. Stimulation of renal sympathetic nerves increases renin release, and consequently angiotensin 2 production and aldosterone secretion (see Chapter 29). The resulting tachycardia, vasoconstriction and fluid retention act together to raise MABP. Opposite effects occur when arterial blood pressure rises.

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There are two types of baroreceptors. **A fibres** have large, myelinated axons and are activated over lower levels of pressure. **C fibres** have small, unmyelinated axons and respond over higher levels of pressure. Together, these provide an input to the brain which is most sensitive to pressure changes between 80 and 150 mmHg. The brain is able to reset the baroreflex to allow increases in MABP to occur (e.g. during exercise and the defence reaction). Ageing, hypertension and atherosclerosis decrease arterial wall compliance, reducing baroreceptor reflex sensitivity.

The baroreceptors quickly show partial *adaptation* to new pressure levels. Therefore alterations in baroreceptor firing frequency are greatest while pressure is changing and tend to moderate when a new steady-state pressure level is established. If unable to prevent a change in MABP, the reflex will within several hours tend to *reset* to maintain pressure around the new level. This finding, together with studies by Cowley and coworkers in the 1970s showing that destroying baroreceptor function increased the variability of MABP but had little effect on its average value measured over a long time, led to general acceptance of the idea that baroreceptors have no role in long-term regulation of MABP. However, it has more recently been shown that electrical stimulation of baroreceptors using implanted electrodes (**barostimulation**) results in a reduction in MABP which is indefinitely sustained. It is therefore now clear that the baroreceptor reflex does contribute to the long-term regulation of MABP, although the extent to which it normally does so remains to be clarified.

Cardiopulmonary reflexes

Diverse intrinsic cardiovascular reflexes originate in the heart and lungs. Cutting the vagal afferent fibres mediating these **cardiopulmonary reflexes** causes an increased heart rate and vasoconstriction, especially in muscle, renal and mesenteric vascular beds. Cardiopulmonary reflexes are therefore thought to exert a *net tonic depression of the heart rate and vascular tone*. Receptors for these reflexes are located mainly in *low-pressure regions* of the cardiovascular system and are well placed to sense the *blood volume* in the central thoracic compartment. These reflexes are thought to be particularly important in controlling blood volume, as well as vascular tone, and act together with the baroreceptors to stabilize the MABP. However, these reflexes have been studied mainly in animals, and their specific individual roles in humans are incompletely understood.

Specific components of the cardiopulmonary reflexes include the following.

1. Atrial mechanoreceptors with non-myelinated vagal afferents which respond to increased atrial volume/pressure by causing bradycardia and vasodilatation.
2. Mechanoreceptors in the left ventricle and coronary arteries with mainly non-myelinated vagal afferents which respond to increased ventricular diastolic pressure and afterload by causing a vasodilatation.
3. Ventricular chemoreceptors which are stimulated by substances such as bradykinin and prostaglandins released during cardiac ischaemia. These receptors activate the **coronary chemoreflex**. This response, also termed the **Bezold–Jarisch effect**, occurs after the intravenous injection of many drugs and involves marked bradycardia and widespread vasodilatation.
4. Pulmonary mechanoreceptors, which when activated by marked lung inflation, especially if oedema is present, cause tachycardia and vasodilatation.
5. Mechanoreceptors with myelinated vagal afferents, located mainly at the juncture of the atria and great veins, which respond to increased atrial volume and pressure by causing a sympathetically mediated tachycardia (**Bainbridge reflex**). This reflex also helps to control blood volume; its activation decreases the secretion of **antidiuretic hormone** (vasopressin), **cortisol** and **renin**, causing a diuresis. Although powerful in dogs, this reflex has been difficult to demonstrate in humans.

Chemoreceptor reflexes

Chemoreceptors activated by **hypoxia**, **hypocapnia** and **acidosis** are located in the aortic and carotid bodies. These are stimulated during asphyxia, hypoxia and severe hypotension. The resulting **chemoreceptor reflex** is mainly involved in stimulating breathing, but also has cardiovascular effects. These include sympathetic constriction of (mainly skeletal muscle) arterioles, splanchnic venoconstriction and a tachycardia resulting indirectly from the increased lung inflation. This reflex is important in maintaining blood flow to the brain at arterial pressures too low to affect baroreceptor activity.

The CNS ischaemic response

Brainstem hypoxia stimulates a powerful generalized peripheral vasoconstriction. This response develops during severe hypotension, helping to maintain the flow of blood to the brain during shock. It also causes the **Cushing reflex**, in which vasoconstriction and hypertension develop when increased cerebrospinal fluid pressure (e.g. due to a brain tumour) produces brainstem hypoxia.

Extrinsic reflexes

Stimuli that are external to the cardiovascular system also exert effects on the heart and vasculature via extrinsic reflexes. Moderate pain causes tachycardia and increases MABP; however, severe pain has the opposite effects. Cold causes cutaneous and coronary vasoconstriction, possibly precipitating angina in susceptible individuals.

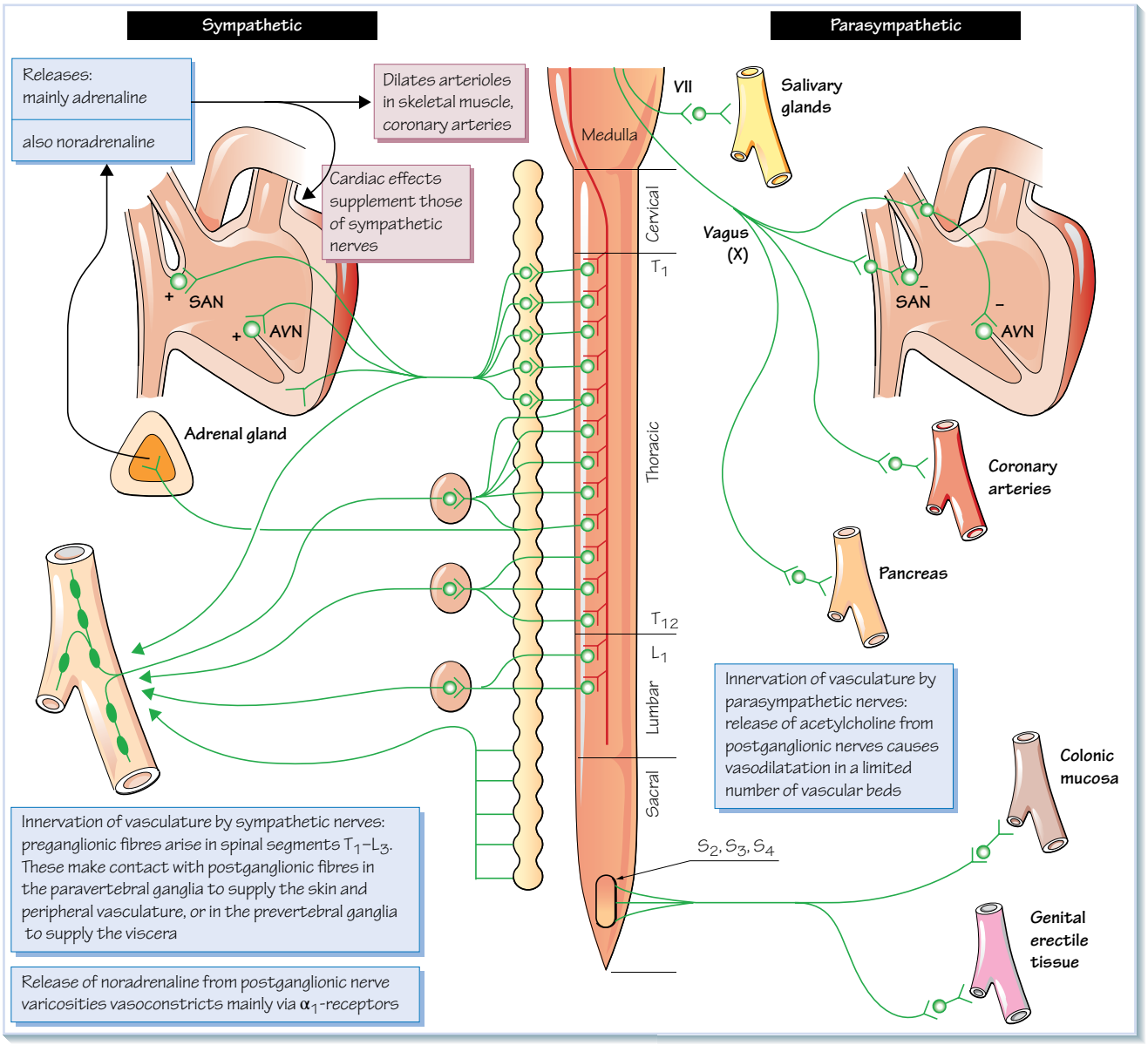
Central regulation of cardiovascular reflexes

The afferent nerves carrying impulses from cardiovascular receptors terminate in the **nucleus tractus solitarius** (NTS) of the medulla. Neurones from the NTS project to areas of the brainstem that control both parasympathetic and sympathetic outflow, influencing their level of activation. The **nucleus ambiguus** and **dorsal motor nucleus** contain the cell bodies of the preganglionic vagal parasympathetic neurones, which slow the heart when the cardiovascular receptors report an increased blood pressure to the NTS. Neurones from the NTS also project to areas of **ventrolateral medulla**; from these descend bulbospinal fibres which influence the firing of the sympathetic preganglionic neurons in the intermediolateral (IML) columns of the spinal cord.

These neural circuits are capable of mediating the basic cardiovascular reflexes. However, the NTS, the other brainstem centres and the IML neurones receive descending inputs from the hypothalamus, which in turn is influenced by impulses from the limbic system of the cerebral cortex. Input from these higher centres modifies the activity of the brainstem centres, allowing the generation of integrated responses in which the functions of the cardiovascular system and other organs are coordinated in such a way that the appropriate responses to changing conditions can be orchestrated. The hypothalamus also receives input from the **subfornical organ**, one of the *circumventricular organs* lacking a blood–brain barrier (see Chapter 20). Circulating factors such as angiotensin 2 and leptin are able to act via the subfornical organ to influence hypothalamic activity, thereby modulating sympathetic outflow and MABP.

28 Autonomic control of the cardiovascular system

Figure 28.1 Autonomic regulation of the cardiovascular system



The **autonomic nervous system** (ANS) comprises a *system of efferent nerves* that regulate the involuntary functioning of most organs, including the heart and vasculature. The cardiovascular effects of the ANS are deployed for two purposes.

First, the ANS provides the effector arm of the cardiovascular *reflexes*, which respond mainly to activation of receptors in the cardiovascular system (see Chapter 27). They are designed to maintain an *appropriate blood pressure* and have a crucial role in homeostatic adjustments to *postural changes* (see Chapter 22), *haemorrhage* (see Chapter 31) and *changes in blood gases*. The autonomic circulation is able to override local vascular control mechanisms in order to serve the needs of the body as a whole.

Second, ANS function is also regulated by signals initiated within the brain as it reacts to *environmental stimuli* or *emotional stress*. The brain can selectively modify or override the cardiovascular reflexes, producing specific patterns of cardiovascular

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adjustments, which are sometimes coupled with behavioural responses. Complex responses of this type are involved in *exercise* (see Chapter 30), *thermoregulation* (see Chapter 26), the '*fight or flight' (defence) response* and '*playing dead*'.

The ANS is divided into **sympathetic** and **parasympathetic** branches. The nervous pathways of both branches of the ANS consist of two sets of neurons arranged in series. **Preganglionic neurons** originate in the central nervous system and terminate in peripheral **ganglia**, where they synapse with **postganglionic neurons** innervating the target organs.

The sympathetic system

Sympathetic preganglionic neurons originate in the **intermediolateral** (IML) columns of the spinal cord. These neurons exit the spinal cord through ventral roots of segments T_1–L_2 and synapse with the postganglionic fibres in either **paravertebral** or **prevertebral** ganglia. The paravertebral ganglia are arranged in two sympathetic chains, one of which is shown in Figure 28.1. These are located on either side of the spinal cord and usually contain 22 or 23 ganglia. The prevertebral ganglia, shown to the left of the sympathetic chain, are diffuse structures that form part of the visceral autonomic plexuses of the abdomen and pelvis. The ganglionic neurotransmitter is **acetylcholine**, and it activates postganglionic **nicotinic cholinergic** receptors.

The postganglionic fibres terminate in the effector organs, where they release **noradrenaline (norepinephrine)**. Preganglionic sympathetic fibres also control the **adrenal medulla**, which releases **adrenaline (epinephrine)** and noradrenaline into the blood. Under physiological conditions, the effect of neuronal noradrenaline release is more important than that of adrenaline and noradrenaline released by the adrenal medulla.

Adrenaline and noradrenaline are **catecholamines** and activate **adrenergic** receptors in the effector organs. These receptors are *g-protein-linked* and exist as three types.

1. **α_1-receptors** are linked to G_q and have subtypes α_{1A}, α_{1B} and α_{1D}. Adrenaline and noradrenaline activate α_1-receptors with similar potencies.
2. **α_2-receptors** are linked to $G_{i/o}$ and have subtypes α_{2A}, α_{2B} and α_{2C}. Adrenaline activates α_2-receptors more potently than does noradrenaline.
3. **β-receptors** are linked to G_s and have subtypes β_1, β_2 and β_3. Noradrenaline is more potent than adrenaline at β_1- and β_3-receptors, whereas adrenaline is more potent at β_2-receptors.

Effects on the heart

Catecholamines acting via cardiac **β_1-receptors** have positive inotropic and chronotropic effects via mechanisms described in Chapters 12 and 13. At rest, cardiac sympathetic nerves exert a tonic accelerating influence on the sinoatrial node, which is, however, overshadowed in younger people by the opposite and dominant effect of parasympathetic vagal tone. Vagal tone decreases progressively with age, as does sympathetic control of the heart: thus the cardiac response to exercise is reduced.

Effects on the vasculature

At rest, vascular sympathetic nerves fire impulses at a rate of 1–2 impulses/s, thereby tonically vasoconstricting the arteries, arterioles and veins. Increasing activation of the sympathetic system causes further vasoconstriction. Vasoconstriction is mediated mainly by **α_1-receptors** on the vascular smooth muscle cells. The arterial system, particularly the arterioles, is more densely innervated by the sympathetic system than is the venous system. Sympathetic vasoconstriction is particularly marked in the splanchnic, renal, cutaneous and skeletal muscle vascular beds.

The vasculature also contains both β_1- and β_2-receptors, which when stimulated exert a *vasodilating* influence, especially in the *skeletal* and *coronary* circulations. These may have a limited role in dilating these vascular beds in response to adrenaline release, for example during mental stress. In some species, sympathetic *cholinergic* fibres innervate skeletal muscle blood vessels and cause vasodilatation during the defence reaction. A similar but minor role for such nerves in humans has been proposed, but is unproven.

It is a common fallacy that the sympathetic nerves are always activated *en masse*. In reality, changes in sympathetic vasoconstrictor activity can be limited to certain regions (e.g. to the skin during thermoregulation). Similarly, a sympathetically mediated tachycardia occurs with no change in inotropy or vascular resistance during the Bainbridge reflex (see Chapter 27).

The parasympathetic system

The parasympathetic preganglionic neurones involved in regulating the heart have their cell bodies in the **nucleus ambiguus** and the **dorsal motor nucleus** of the medulla. Their axons run in the **vagus** nerve (cranial nerve X) and release acetylcholine onto nicotinic receptors on short postganglionic neurones originating in the cardiac plexus. These innervate the *sinoatrial node (SAN)*, the *atrioventricular node (AVN)* and the *atria*.

Effects on the heart

Basal acetylcholine release by vagal nerve terminals acts on muscarinic receptors to slow the discharge of the SAN. Increased vagal tone further decreases the heart rate and the speed of impulse conduction through the AVN and also decreases the force of atrial contraction when activated.

Effects on the vasculature

Although vagal slowing of the heart can decrease the blood pressure by lowering cardiac output, the parasympathetic system has no effect on total peripheral resistance, because it innervates only a limited number of vascular beds. In particular, activation of parasympathetic fibres in the pelvic nerve causes **erection** by vasodilating arterioles in the erectile tissue of the genitalia. Parasympathetic nerves also cause vasodilatation in the pancreas and salivary glands.

29 The control of blood volume

Figure 29.1 Control of osmolality

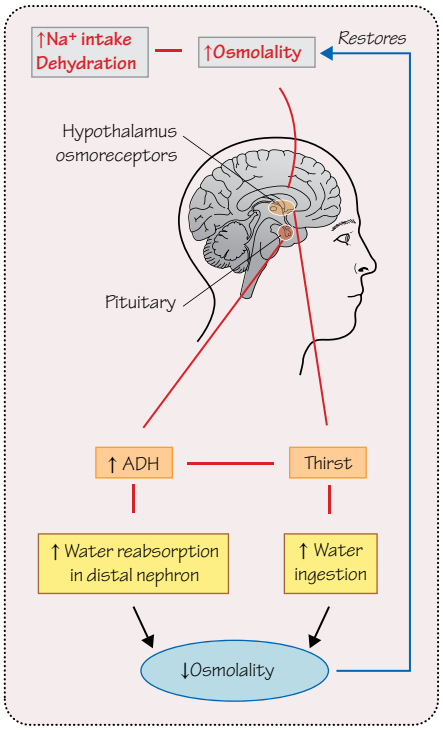


Figure 29.2 Effect of osmolality, pressure and volume on ADH secretion

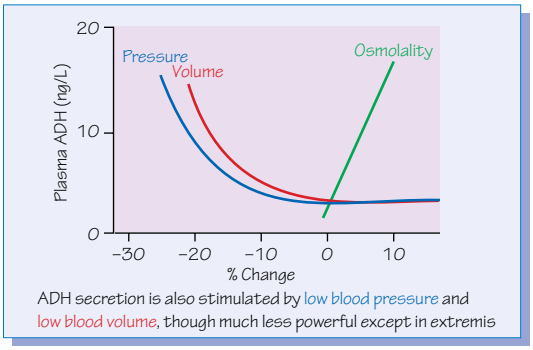


Figure 29.4 Pressure natriuresis

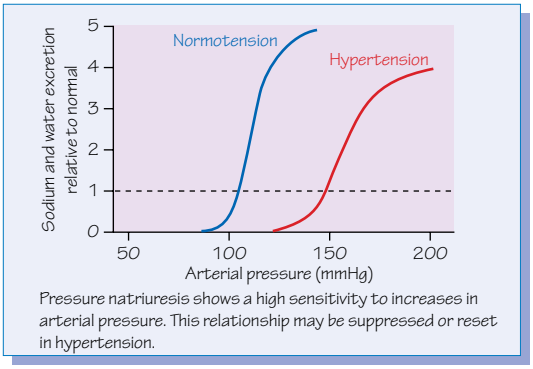
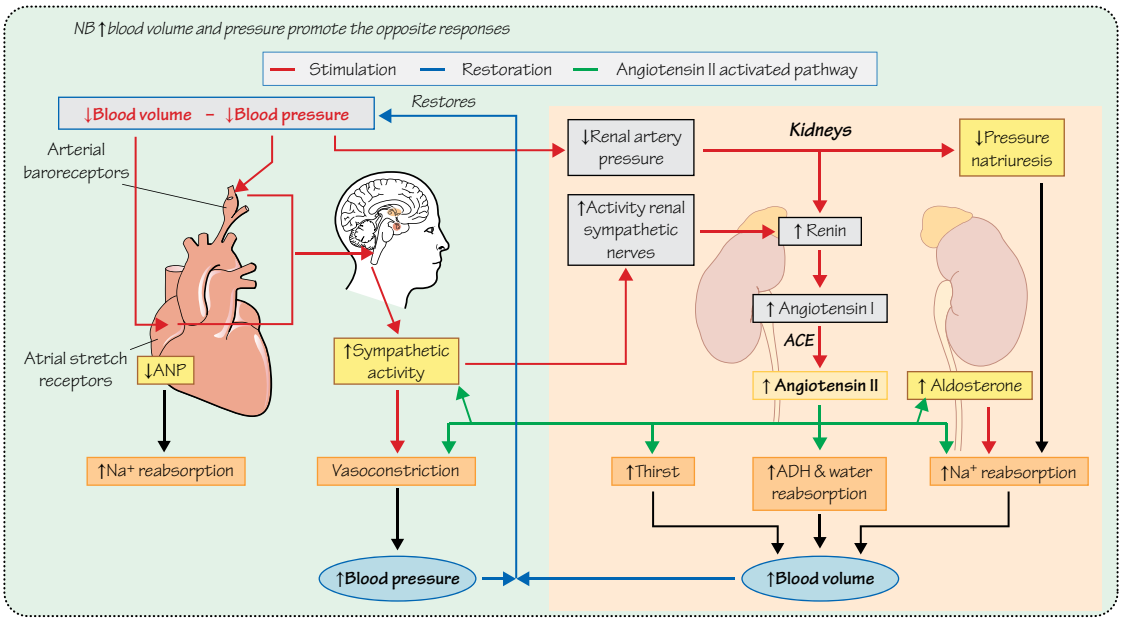


Figure 29.3 Control of blood volume and pressure



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The baroreceptor system effectively minimizes short-term fluctuations in the arterial blood pressure. Over the longer term, however, the ability to sustain a constant blood pressure depends on maintenance of a *constant blood volume*. This dependency arises because alterations in blood volume affect central venous pressure (CVP) and therefore cardiac output (CO) (see Chapter 17). Changes in CO also ultimately lead to adaptive effects on the vasculature which increase peripheral resistance and therefore blood pressure (see Chapter 38).

Blood volume is affected by changes in total body Na^+ and water, which are mainly controlled by the kidneys. Maintenance of blood pressure therefore involves mechanisms that adjust renal excretion of Na^+ and water.

Role of sodium and osmoregulation

Alterations in body salt and water content, caused for example by variations in salt or fluid intake or perspiration, result in changes in plasma **osmolality** (see Chapter 5). Any deviation of plasma osmolality from its normal value of *~290 mosmol/kg* is sensed by *hypothalamic osmoreceptors*, which regulate thirst and release of the peptide **antidiuretic hormone** (**ADH**, or *vasopressin*) from the posterior pituitary. ADH enhances reabsorption of water by activating V2 receptors in *principal cells* of the renal collecting duct. This causes **aquaporins** (water channels) to be inserted into their apical membranes, so increasing their permeability to water. Urine is therefore concentrated and water excretion reduced. ADH also affects thirst. Thus, an increase in plasma osmolality due to dehydration causes increased thirst and enhanced release of ADH. Both act to bring plasma osmolality back to normal by restoring body water content (Figure 29.1). Opposite effects are stimulated by a reduction in osmolality. ADH secretion is inhibited by alcohol and emotional stress and strongly stimulated by nausea. Osmoregulation is extremely sensitive to small changes in osmolality (Figure 29.2) and normally takes precedence over the control of blood volume because of the utmost importance of controlling osmolality tightly for cell function (see Chapter 5).

An important consequence of the above is that blood volume is primarily controlled by the Na^+ content of extracellular fluid (ECF), of which plasma is a part. Na^+ and its associated anions Cl^- and HCO_3^- account for about 95% of the osmolality of ECF, thus any change in body Na^+ content (e.g. after eating a salty meal) quickly affects plasma osmolality. The osmoregulatory system responds by readjusting body water content (and therefore plasma volume) in order to restore plasma osmolality. Under normal conditions, therefore, alterations in body Na^+ lead to changes in blood volume. It follows that control of blood volume requires regulation of body (and therefore ECF) Na^+ content, a function carried out by the kidneys.

Control of Na^+ and blood volume by the kidneys

Blood volume directly affects CVP and indirectly affects arterial blood pressure (see Chapter 17). CVP therefore provides a measure of blood volume and is detected by **stretch receptors** primarily in the atria and venoatrial junction. Arterial blood pressure is detected by the **baroreceptors** (see Chapter 27) and also directly affects renal function via **pressure natriuresis**. Integration of several mechanisms leads to regulation of Na^+ and therefore blood volume (Figure 29.3).

Pressure natriuresis is an intrinsic renal process whereby increases in arterial blood pressure strongly promote diuresis and **natriuresis** (Na^+ excretion in the urine). While the precise mechanisms remain unclear, it is believed that vasodilator prostanoids and nitric oxide increase blood flow in the renal medulla, thereby reducing the osmotic gradient that allows concentration of urine. Na^+ and water reabsorption are therefore suppressed, so more is lost in the urine and blood volume and pressure are restored. Opposite effects occur when pressure is decreased. Pressure natriuresis may be impaired in hypertension, such that maintenance of an appropriate level of Na^+ excretion requires a raised blood pressure (Figure 29.4; see Chapter 38).

An increase in blood volume causes stretch of the atria, activating the stretch receptors and also causing release of **atrial natriuretic peptide** (ANP). Increased atrial receptor activity is integrated in the brainstem with baroreceptor activity, and leads to decreased sympathetic outflow to the heart and vasculature and an immediate reduction in arterial blood pressure. Importantly, sympathetic stimulation of the kidney is also reduced, supressing activity of the **renin–angiotensin–aldosterone** (RAA) **system**; increased renal perfusion pressure does the same. **Renin** is a protease stored in *granular cells* within the juxtaglomerular apparatus. It cleaves the plasma α_2-globulin **angiotensinogen** to form **angiotensin 1**, which is subsequently is converted to the octapeptide **angiotensin 2** by **angiotensin-converting enzyme** (ACE) on the surface of endothelial cells, largely in the lungs. ACE also degrades **bradykinin**, which is why ACE inhibitors cause intractable cough in some patients.

Angiotensin 2 has a number of actions that elevate blood pressure and volume. These include increasing Na^+ reabsorption by the proximal tubule, stimulating thirst, stimulating ADH release, increasing activation of the sympathetic nervous system, and causing a direct vasoconstriction. Importantly, it also promotes release of the steroid **aldosterone** from the adrenal cortex zona glomerulosa. Aldosterone increases Na^+ reabsorption by principal cells in the distal nephron by stimulating synthesis of basolateral Na^+ pumps and Na^+ channels (**ENaC**) in the apical membrane. It also conserves body Na^+ by enhancing its reabsorption from several types of glands, including salivary and sweat glands.

ANP is a 28-amino-acid peptide released from atrial myocytes when they are stretched. ANP causes diuresis and natriuresis by inhibiting ENaC, increasing glomerular filtration rate by dilating renal afferent arterioles, and decreasing renin and aldosterone secretion. It also dilates systemic arterioles and increases capillary permeability. On a cellular level, ANP stimulates membrane-associated guanylyl cyclase and increases intracellular cyclic GMP.

Figure 29.3 summarizes the response of the above mechanisms to a fall in blood volume and pressure. An elevation would induce the opposite effects.

Although pressure natriuresis has been promoted as the primary mechanism controlling blood volume and long-term blood pressure, more recent evidence suggests that the RAA system may be of predominant importance. This concept is consistent with the effectiveness of ACE inhibitors in clinical practice (e.g. Chapters 39 and 47). ANP and other mechanisms seem to have a more limited role and may be involved chiefly in the response to volume overload.

Antidiuretic hormone in volume regulation

Under emergency conditions, blood pressure and volume are maintained at the expense of osmoregulation. Thus, a large fall in blood volume or pressure, sensed by the atrial receptors or arterial baroreceptors, causes increased ADH release (Figure 29.2) and renal water retention. The ADH system is also rendered more sensitive, so that ADH release is increased at normal osmolality.

30 Cardiovascular effects of exercise

Figure 30.1 Changes in haemodynamic parameters with increasing levels of dynamic exercise

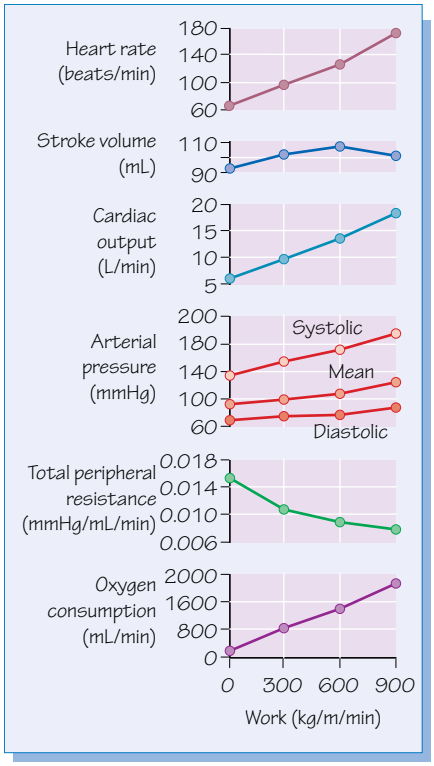

Figure 30.3 Regulation and coordination of the cardiovascular adaptation to exercise

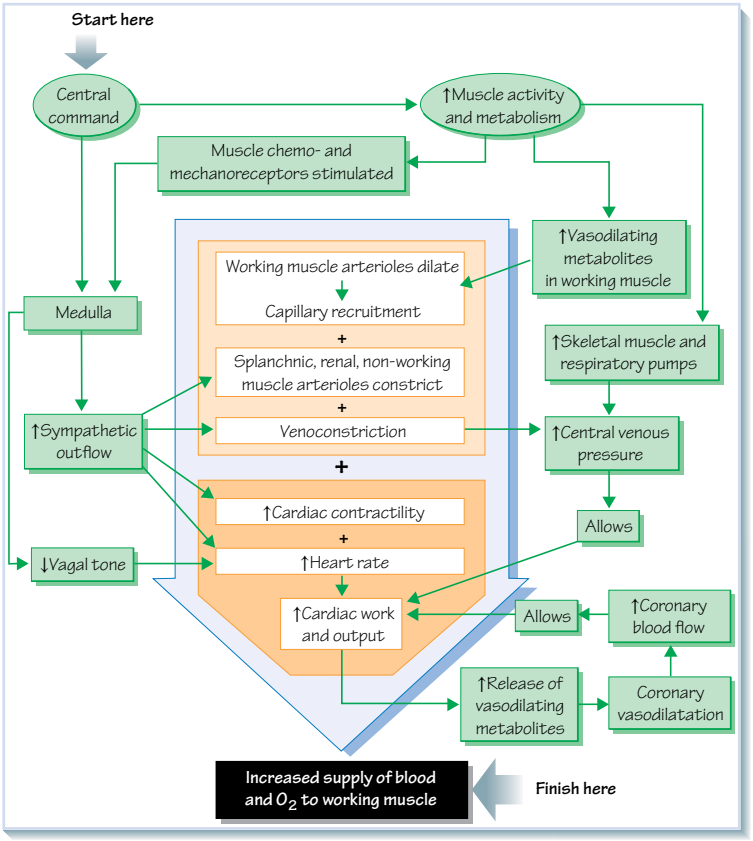

Figure 30.2 Guyton's analysis of exercise

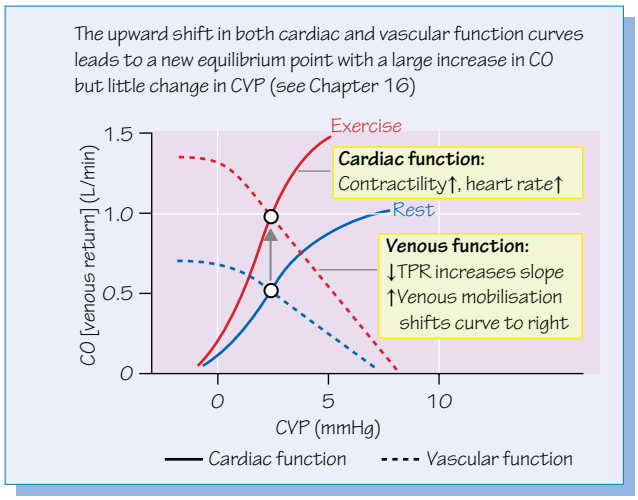

Table 30.1 Approximate values for cardiac output and regional blood flow at rest and during exercise

	Quiet standing	Exercise
Cardiac output	5900	24 000
Blood flow to:		
Heart	250	1000
Brain	750	750
Active skeletal muscle	650	20 850
Inactive skeletal muscle	650	300
Skin	500	500
Kidney, liver, gastrointestinal tract, etc.	3100	600

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Figure 30.1 summarizes important cardiovascular adaptations that occur at increasing levels of dynamic (rhythmic) exercise, thereby allowing working muscles to be supplied with the increased amount of O_2 they require. By far the most important of these adaptations is an increase in cardiac output (CO), which rises almost linearly with the rate of muscle O_2 consumption (level of work) as a result of increases in both *heart rate* and to a lesser extent *stroke volume*. The heart rate is accelerated by a reduction in vagal tone and by increases in sympathetic nerve firing and circulating catecholamines. The resulting stimulation of cardiac β-adrenoceptors increases stroke volume by *increasing myocardial contractility* and enabling more complete systolic emptying of the ventricles. CO is the limiting factor determining the maximum exercise capacity.

Table 30.1 shows that the increased CO is channelled mainly to the active muscles, which may receive 85% of CO against about 15–20% at rest, and to the heart. This is caused by a profound arteriolar vasodilatation in these organs. Dilatation of terminal arterioles causes **capillary recruitment**, a large increase in the number of open capillaries, which shortens the diffusion distance between capillaries and muscle fibres. This, combined with increases in P_{CO_2}, temperature and acidity, promotes the release of O_2 from haemoglobin, allowing skeletal muscle to increase its O_2 extraction from the basal level of 25–30% to about 90% during maximal exercise.

Increased firing of sympathetic nerves and levels of circulating catecholamines constrict arterioles in the *splanchnic* and *renal* vascular beds, and in *non-exercising muscle*, reducing the blood flow to these organs. Cutaneous blood flow is also initially reduced. As core body temperature rises, however, cutaneous blood flow increases as autonomically mediated vasodilatation occurs to promote cooling (see Chapter 26). With very strenuous exercise, cutaneous perfusion again falls as vasoconstriction diverts blood to the muscles. Blood flow to the crucial cerebral vasculature remains constant.

Vasodilatation of the skeletal and cutaneous vascular beds decreases total peripheral resistance (TPR). This is sufficient to balance the effect of the increased CO on diastolic blood pressure, which rises only slightly and may even fall, depending on the balance between skeletal muscle vasodilatation and splanchnic/renal vasoconstriction. However, significant rises in the systolic and pulse pressures are caused by the more rapid and forceful ejection of blood by the left ventricle, leading to some elevation of the mean arterial blood pressure.

Increased sympathetic outflow also causes venoconstriction. This, together with the increased action of skeletal muscle and respiratory pumps and the fall in TPR, maintains the central venous pressure, allowing the large increase in CO to occur (Figure 30.2; see Chapter 17).

Effects of exercise on plasma volume

Arteriolar dilatation in skeletal muscles increases capillary hydrostatic pressure, while capillary recruitment vastly increases the surface area of the microcirculation available to exchange fluid. These effects, coupled with a rise in interstitial osmolarity caused by an increased production of metabolites within the muscle fibres, lead via the Starling mechanism to *extravasation of fluid into muscles* (Chapter 20). Taking into account also fluid losses caused by sweating, plasma volume may decrease by 15% during strenuous exercise. This fluid loss is partially compensated by enhanced fluid reabsorption in the vasoconstricted vascular beds, where capillary pressure decreases.

Regulation and coordination of the cardiovascular adaptation to exercise

In anticipation of exercise, and during its initial stages, a process termed **central command** (Figure 30.3, upper left) initiates the cardiovascular adaptations necessary for increased effort. Impulses from the cerebral cortex act on the medulla to suppress vagal tone, thereby increasing the heart rate and CO. Central command is also thought to raise the set point of the baroreceptor reflex. This allows the blood pressure to be regulated around a higher set point, resulting in an increased sympathetic outflow which contributes to the rise in CO and causes constriction of the splanchnic and renal circulations. An increase in circulating adrenaline also vasodilates skeletal muscle arterioles via β_2-receptors. The magnitude of these anticipatory effects increases in proportion to the degree of perceived effort.

As exercise continues, cardiovascular regulation by central command is supplemented by two further control systems which are activated and become crucial. These involve (i) autonomic reflexes (Figure 30.3, left) and (ii) direct effects of metabolites generated locally in working skeletal and cardiac muscle (right).

Systemic effects mediated by autonomic reflexes

Nervous impulses originating mainly from receptors in working muscle which respond to contraction (mechanoreceptors) and locally generated metabolites and ischaemia (chemoreceptors) are carried to the CNS via afferent nerves. CNS autonomic control centres respond by suppressing vagal tone and causing graded increases in sympathetic outflow which are matched to the ongoing level of exercise. An increased release of adrenaline and noradrenaline from the adrenal glands causes plasma catecholamines to rise by as much as 10- to 20-fold.

Effects of local metabolites on muscle and heart

The autonomic reflexes described above are responsible for most of the cardiac and vasoconstricting adaptations to exercise. However, the marked vasodilatation of coronary and skeletal muscle arterioles is almost entirely caused by *local metabolites* generated in the heart and working skeletal muscle. This **metabolic hyperaemia** (see Chapter 23) causes decreased vascular resistance and increased blood flow. Capillary recruitment (see above) is an important consequence of metabolic hyperaemia.

Static exercises such as lifting and carrying involve maintained muscle contractions with no joint movement. This results in vascular compression and a decreased muscle blood flow, leading to a build-up of muscle metabolites. These activate muscle chemoreceptors, resulting in a *pressor reflex* involving *tachycardia*, and *increases* in *CO* and *TPR*. The resulting rise in blood pressure is much greater than in dynamic exercise causing the same rise in O_2 consumption.

Effects of training

Athletic training has effects on the cardiovascular system that improve delivery of O_2 to muscle cells, allowing them to work harder. The ventricular walls thicken and the cavities become larger, increasing the stroke volume from about 75 to 120 mL. The resting heart rate may fall as low as 45 beats/min, due to an increase in vagal tone, while the maximal rate remains near 180 beats/min. These changes allow CO, the crucial determinant of exercise capacity, to increase more during strenuous exercise, reaching levels of 35 L/min or more. TPR falls, in part due to a decreased sympathetic outflow. The capillary density of skeletal muscle increases, and the muscle fibres contain more mitochondria, promoting oxygen extraction and utilization.

31 Shock and haemorrhage

Figure 31.1 Conditions associated with shock

Hypovolaemic (CVP↓)
- Haemorrhage
- Burns
- Surgery or trauma
- Loss of fluids and electrolytes from gut

Low resistance
- Sepsis
- Anaphylaxis

Cardiogenic (CVP↑)
- Heart failure
- Myocardial infarction

Obstructive (CVP↑)
- Pulmonary embolism
- Pneumothorax
- Cardiac tamponade

Figure 31.2 Treatment of shock (begin within 1 hour)

1. Determine and correct cause (e.g. stop blood loss)
2. Fluid replacement if CVP low (blood, plasma, etc.)
3. Vasoconstrictors/ inotropes if required to support BP and cardiac function
4. Give oxygen ventilation

Figure 31.3 Relationship between degree of blood loss and fall in CO and BP

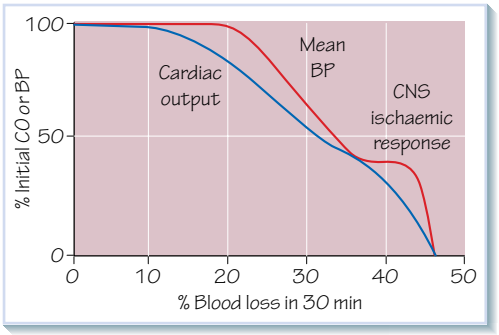

Figure 31.4 Recovery from mild (20%) blood loss

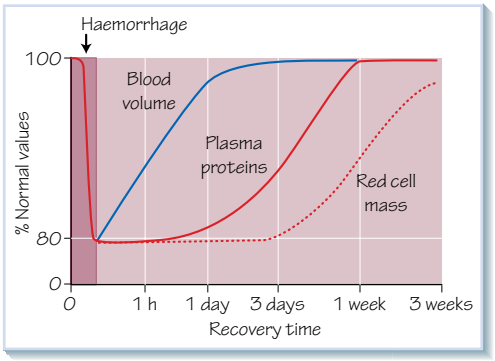

Figure 31.5 Effects of severe (45%) blood loss: progressive, reversible and irreversible shock

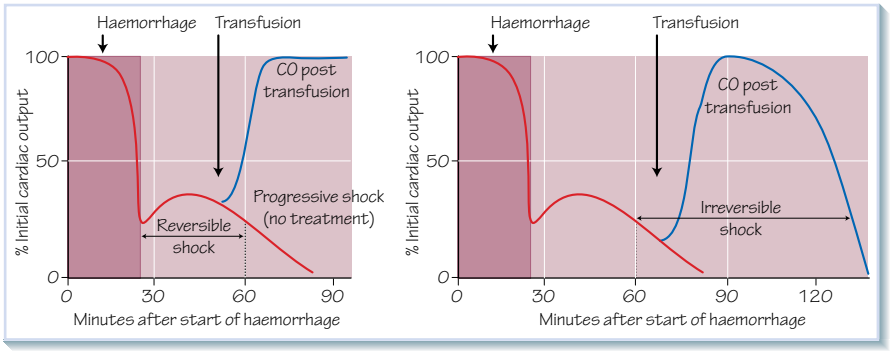

Figure 31.6 Cycle of events leading to progressive and irreversible shock

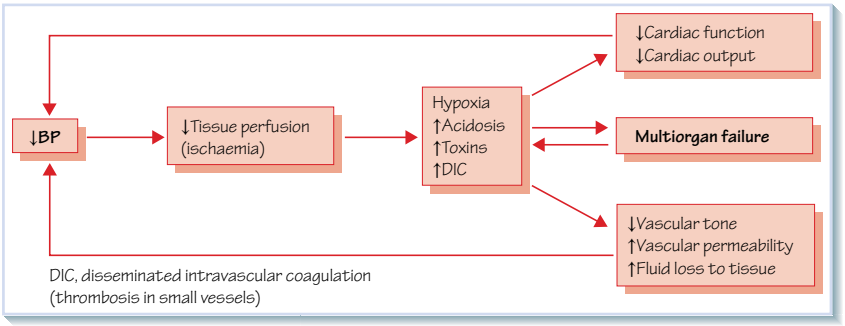

Figure 31.7 A classification of shock

Symptoms may depend on rate as well as volume of blood loss, and general health and fitness. Note that an increased heart rate may be the only overt symptom of quite significant cardiovascular shock

	Class 1	Class 2	Class 3	Class 4
Blood loss (%)	Up to 15%	15-30%	30-40%	>40%
Heart rate	Normal or ↑	↑	↑↑	↑↑↑
Blood pressure	Normal	Normal or ↓	↓	↓↓
Respiratory rate	Normal	↑	↑↑	↑↑
Urine output	Normal	↓	↓↓	Negligible
Mental status	Slightly anxious	Mildly anxious	Anxious/confused	Confused/ lethargic

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Cardiovascular or **circulatory shock** is an acute condition where there is a generalized inadequacy of tissue blood flow. The patient appears pale, grey or cyanotic, with cold clammy skin, a weak rapid pulse and rapid shallow breathing. Urine output is reduced and blood pressure (BP) is generally low. Conscious patients may develop intense thirst. Cardiovascular shock may be caused by a reduced blood volume (**hypovolaemic shock**), profound vasodilatation (**low-resistance shock**), acute failure of the heart to maintain output (**cardiogenic shock**) or blockage of the cardiopulmonary circuit (e.g. pulmonary embolism) (Figures 31.1, 31.2).

Haemorrhagic shock

Blood loss (**haemorrhage**) is the most common cause of **hypovolaemic** shock. Loss of 15% of total blood volume is unlikely to elicit shock in a fit person. Shock is normally induced if 15–30% of blood volume is lost, though blood pressure may be normal. Loss of 30–50% of volume, however, causes a reduction in BP and cardiac output which can be profound (Figure 31.3). Severe shock may become **irreversible** or **refractory** (see below); death is generally inevitable if blood loss is >50%. Figure 31.7 shows a common classification of shock, but severity is also related to rate of blood loss – a very rapid loss of 30% can be fatal, whereas 50% over 24 h may be survived.

Immediate compensation

The initial fall in BP is detected by the **baroreceptors**, and reduced blood flow activates peripheral **chemoreceptors**. These cause a reflex increase in sympathetic and decrease in parasympathetic drive, with a subsequent increase in heart rate, venoconstriction (to restore central venous pressure, CVP), and vasoconstriction of splanchnic, cutaneous, renal and skeletal muscle circulations which helps restore BP. This leads to pallor, reduced urine production and lactic acidosis. Increased sympathetic discharge also causes sweating and characteristic clammy skin. Sympathetic vasoconstriction of renal arteries plus reduced renal artery pressure stimulates the **renin–angiotensin system** (Chapter 29), and production of **angiotensin 2**, a powerful vasoconstrictor. This has an important role in the recovery of BP and stimulates thirst. In more severe blood loss, reduction in atrial stretch receptor output stimulates production of **ADH** (antidiuretic hormone, vasopressin) and adrenal production of **adrenaline (epinephrine)**, both of which contribute to vasoconstriction. These initial mechanisms may prevent any significant fall in BP or cardiac output following moderate blood loss, even though the degree of shock may be serious. If BP falls below 50 mmHg the **CNS ischaemic response** is activated, with powerful sympathetic activation (Figure 31.3).

Medium- and long-term mechanisms

Vasoconstriction and/or fall in BP decreases capillary hydrostatic pressure, resulting in fluid movement from the interstitium back into the vasculature (Chapter 21). This '**internal transfusion**' may increase blood volume by ~0.5 L and takes hours to develop. Increased glucose production by the liver may contribute by raising plasma and interstitial fluid osmolarity, thus drawing water from intracellular compartments. This process results in haemodilution, and patients with severe shock often present with a reduced haematocrit (a warning sign for internal haemorrhage). Fluid volume is restored over a few days by increased fluid intake (thirst), decreased urine production (**oliguria**; due to renal vasoconstriction), increased Na^+ reabsorption due to production of **aldosterone** (stimulated by angiotensin 2) and a fall in atrial natriuretic peptide (**ANP**), and an ADH-mediated increase in water reabsorption (Figure 31.4). The liver replaces plasma proteins within a week, and haematocrit is restored within 6 weeks due to stimulation of **erythropoiesis** (Figure 31.4; Chapter 6).

Other responses to haemorrhage are *increased ventilation* due to reduced flow through **chemoreceptors** (carotid body) and/or acidosis; *decreased blood coagulation time* during a rapid but transient increase in platelets and fibrinogen (Chapter 7); and *increased white cell (neutrophil) count* after 2–5 h.

Complications and irreversible (refractory) shock

When blood loss exceeds 30%, cardiac output may temporarily improve before declining again (**progressive shock**; Figure 31.5). This is due to a vicious circle initiated by circulatory failure and tissue hypoxia/ischaemia, leading to acidosis, toxin release and eventually **multiorgan failure**, including **depression of cardiac muscle function**, acute respiratory distress syndrome (**ARDS**), **renal failure**, disseminated intravascular coagulation (**DIC**), **hepatic failure** and damage to **intestinal mucosa**. Increased vascular permeability further decreases blood volume as fluid is lost to the tissues, and vascular tone is depressed. These complications lead to further tissue damage, impairment of tissue perfusion and gas exchange (Figure 31.6). Rapid treatment (e.g. transfusion) is essential; after 1 h ('*the golden hour*') mortality increases sharply if the patient is still in shock, as transfusion and vasoconstrictor drugs may then cause only a temporary respite before cardiac output falls irrevocably. This is **irreversible** or **refractory** shock (Figure 31.5), primarily related to irretrievable damage to the heart.

Other types of hypovolaemic shock

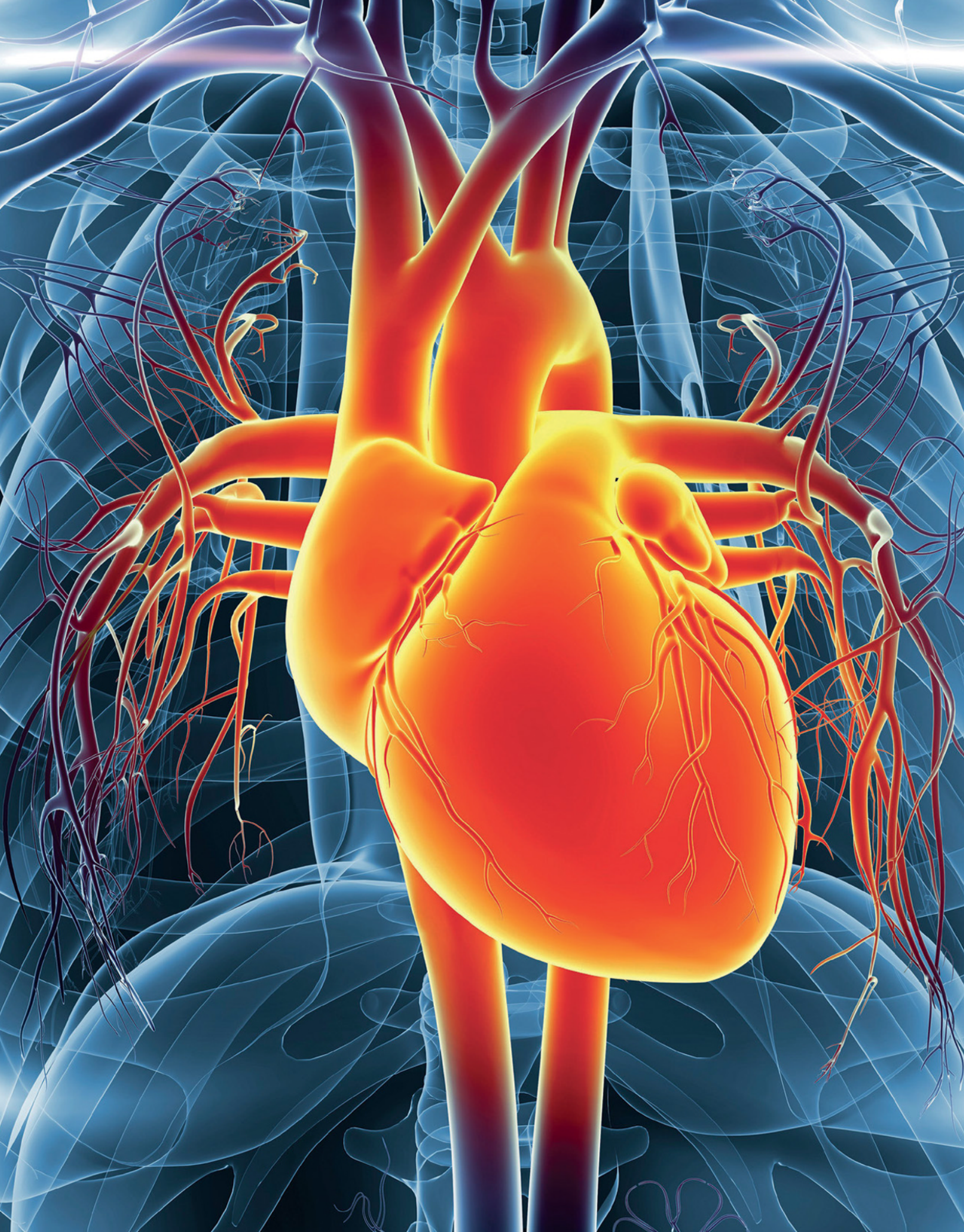
Severe burns cause loss of plasma in exudate from damaged tissue. As red cells are not lost, there is **haemoconcentration**, which increases blood viscosity. Treatment of burns-related shock therefore involves infusion of plasma rather than whole blood. **Traumatic and surgical shock** can occur after major injury or surgery. Although partly due to external blood loss, blood and plasma can also be lost into the tissues, and there may be dehydration. **Other conditions** include severe diarrhoea or vomiting and loss of Na^+ (e.g. **cholera**) with a consequent reduction in blood volume even if water is given, unless electrolytes are replenished.

Low-resistance shock

Unlike hypovolaemic shock, low-resistance shock may present with warm skin due to profound peripheral vasodilatation.

Septic shock is caused by profound vasodilatation due to endotoxins released by infecting bacteria, partly via induction of inducible nitric oxide synthase (Chapter 24). Capillary permeability and cardiac function may be impaired, with consequent loss of fluid to the tissues and depressed cardiac output.

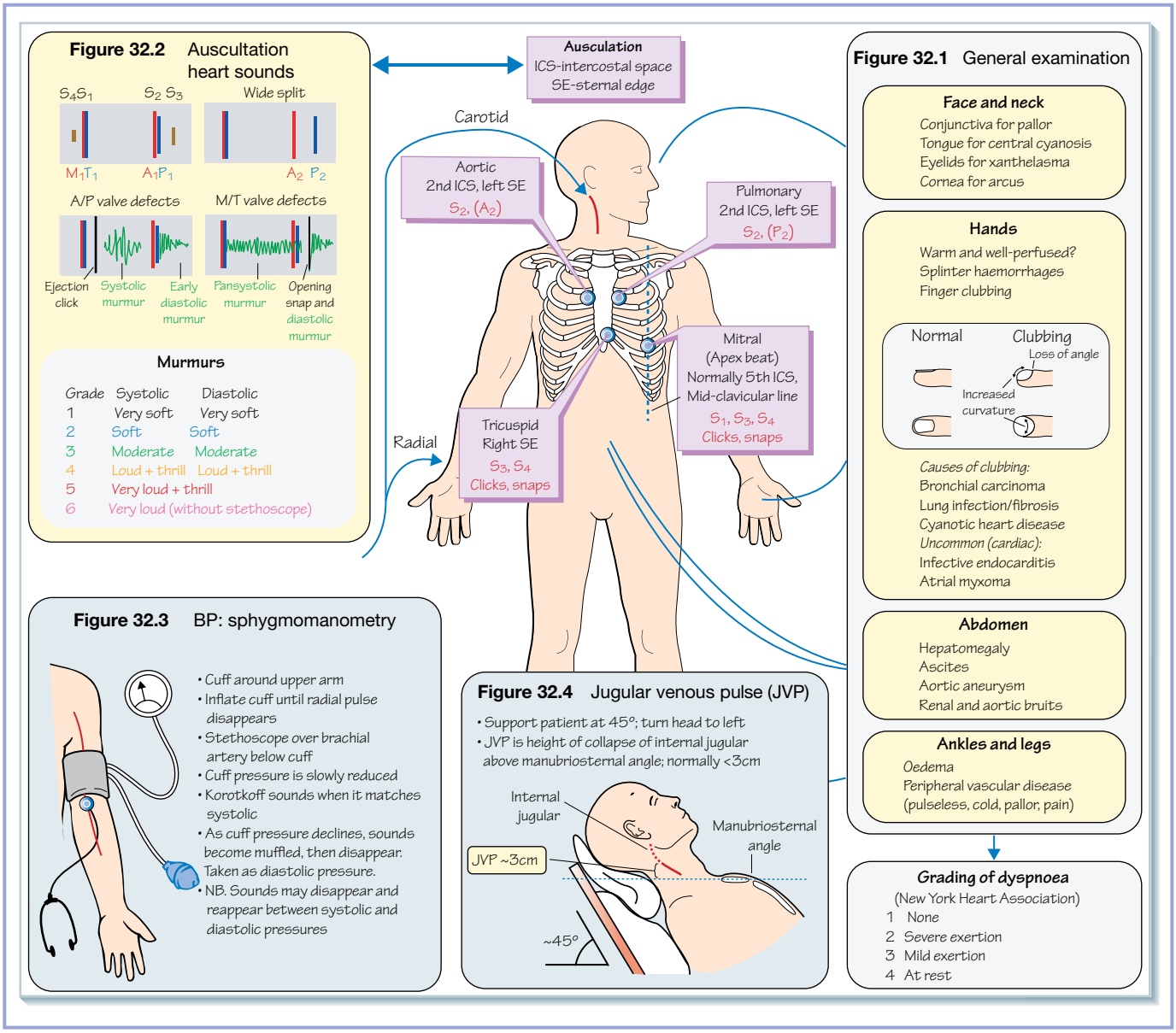
Anaphylactic shock is a rapidly developing and life-threatening condition resulting from presentation of antigen to a sensitized individual (e.g. bee stings or peanut allergy). A severe **allergic reaction** may result, with release of large amounts of histamine. This causes profound vasodilatation and increased microvasculature permeability, leading to protein and fluid loss to tissues (oedema). Rapid treatment with antihistamines and glucocorticoids is necessary, but immediate application of a vasoconstrictor (adrenaline) may be required to save the patient's life.



History, examination and investigations

Chapters

32 History and examination of the cardiovascular system



History

Presenting complaint The reason for seeking medical attention. Examples are chest pain or discomfort, shortness of breath (dyspnoea), palpitations, oedema, and dizziness (presyncope) or collapse/blackouts (syncope).

History of presenting complaint Explore the features of the presenting complaint, such as onset, progression, severity, and aggravating and relieving factors (Figure 32.1).

When eliciting a history from a patient with chest pain, the goal is to ascertain whether the pain is cardiac in origin or not. Pain that is sharp, pleuritic or reproducible on palpation of the chest wall is usually noncardiac, whereas pain that radiates to either arm or shoulders or is exertional is more likely to be cardiac. A notable exception is the sharp pleuritic pain of pericarditis that is classically relieved by leaning forwards as this separates the inflamed pericardial layers.

- **Dyspnoea:** Establish whether it occurs at rest, on exertion, on lying flat (**orthopnoea**) or at night. Ask how far the patient can walk without being breathless. Determine the rate of onset (sudden, gradual). Sudden onset dyspnoea is suggestive of myocardial damage or pulmonary embolism. Gradual onset is suggestive of heart failure or valve disease. Dyspnoea due to pulmonary oedema may cause **paroxysmal nocturnal dyspnoea**, a frightening experience in which the patient wakes at night, gasping for breath.
- **Palpitations:** increased awareness of the heartbeat. Ask the patient to tap out the rhythm – is it regular or irregular, slow or

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fast? Do the palpitations have associated features, that is, chest pain, dyspnoea, presyncope or syncope?

- **Syncope:** transient loss of consciousness caused by global cerebral hypoperfusion. Establish whether the 3 Ps are present – *position* (e.g. syncope brought on by standing for extended periods), *provoking features* (e.g. dehydration), *prodrome* (e.g. dizziness)? If they are then a vasovagal episode (neurocardiogenic syncope) is most likely; if not then the cause may be cardiogenic.
- **Others:** fatigue – heart failure, arrhythmias and drugs (e.g. β-blockers). Oedema and abdominal discomfort – raised central venous pressure (CVP), heart failure. Leg pain on walking that is relieved by rest (**intermittent claudication**) is due to peripheral vascular disease.

Past medical history Ask specifically about myocardial infarction, stroke, hypertension, diabetes, rheumatic fever. Also recent blood pressure measurements and lipid levels, and any cardiac investigations.

Drug history Prescribed and over-the-counter medications. Ascertain compliance. Ask about **drug allergies/sensitivities** and their effect(s).

Family, occupational and social history Family history of premature cardiovascular disease, hypertension, diabetes, stroke or sudden cardiac death? **Smoking:** quantify in pack years; **alcohol** consumption. **Occupation**: sedentary or active.

Examination

General examination (Figure 32.1)

Assess general appearance: obesity, cachexia (wasting). Note any scars; for example, a sternotomy scar (coronary artery bypass graft, CABG; valve surgery). If a sternotomy scar is present, inspect the legs for a saphenous vein graft scar.

- **Hands:** warm and well perfused or cold and shut down? Peripheral cyanosis (dusky blue discolouration, deoxyhaemoglobin >5 g/dL, that is, vasoconstriction, shock, heart failure); assess capillary refill by pressing on the nail bed for 5 s and releasing. Normal is <2 s. Inspect nails for clubbing (Figure 32.1), tar stains, splinter haemorrhages (infective endocarditis). Inspect the palms for Janeway lesions and Osler's nodes (also found in infective endocarditis but these signs are rare).
- **Pulses:** radial pulse; assess rate and character (regular or irregular). Feel for a collapsing pulse (aortic regurgitation). Is there radio-radial delay (coarctation of the aorta)?
- **Blood pressure:** measure the blood pressure over the brachial artery in both arms and take the highest reading.
- **Face and neck:** locate the jugular venous pressure (JVP) wave. It aids in the estimation of volume status. Determine whether or not it is raised. It is raised if the tip of the pulsation in the internal jugular vein is >3 cm above the angle of Louis (where the manubrium meets the sternum). In overweight individuals the JVP may not be visible. Feel the carotid pulse and assess its volume and character. Inspect the conjunctivae for pallor (anaemia); cornea for arcus (hyperlipidaemia, although normal in old age); eyelids for xanthelasma (soft yellow plaques: hyperlipidaemia); tongue for central cyanosis (significant right-to-left shunting); dental hygiene (infective endocarditis); is the palate high arched? (Marfan's); cheeks for malar flush (mitral valve disease); perform fundoscopy looking for hypertensive or diabetic retinopathy.

Examination of the praecordium

- **Palpation: apex beat**, usually at fifth intercostal space, midclavicular line (mitral area). *Non-palpable*: obesity, hyperinflated lungs of chronic obstructive airways disease, pleural effusion. *Displaced*: cardiomegaly, dilated cardiomyopathy, pneumothorax. *Tapping*: mitral stenosis. *Double impulse*: ventricular hypertrophy. *Heaving* (forceful and sustained): pressure overload – hypertension, aortic stenosis. *Parasternal* ***heave***: right ventricular hypertrophy. **Thrills** are palpable (therefore forceful) murmurs (see below). Is there an implanted pacemaker or defibrillator?
- **Auscultation** (Figure 32.2; see Chapters 14, 54–55): correlate with radial or carotid pulse. **First heart sound** (**S1**): closure of mitral and tricuspid valves. *Loud*: atrioventricular valve stenosis, short PR interval; *soft*: mitral regurgitation, long PR interval, heart failure. **Second heart sound** (**S2**): closure of aortic (A2) and pulmonary (P2) valves, A2 louder and preceding P2. *Loud* A2/P2: systemic/pulmonary hypertension. *Splitting*: normal during inspiration or exercise, particularly in the young. *Wide splitting*: delayed activation (e.g. right bundle branch block) or termination (pulmonary hypertension, stenosis) of RV systole. *Reverse splitting*: delayed activation (e.g. left bundle branch block) or termination (hypertension, aortic stenosis) of LV systole. **Others**: **S3** – rapid ventricular filling, common in the young but may reflect heart failure in older patients. **S4** – precedes S1, due to ventricular stiffness and abnormal filling during atrial systole. Presence of S3 and/or S4 gives a **gallop rhythm**. **Ejection click**: after S1, opening of stenotic semilunar valve. **Opening snap**: after S2, opening of stenotic atrioventricular valve.
- **Murmurs** (Figure 32.2): added sounds due to turbulent blood flow. Soft systolic murmurs are common and innocent in the young (~40% children aged 3–8 years) and in exercise; **diastolic murmurs** are pathological. Most nonbenign murmurs are due to **valve defects** (Chapters 54–55) but can be due to a hyperdynamic circulation and atrial or ventricular septal defects.
- **Abdomen:** palpate for liver enlargement (**hepatomegaly**), ascites (raised JVP, heart failure), splenomegaly (infective endocarditis). The **abdominal aorta** is pulsatile in thin individuals but not expansile (indicates **abdominal aortic aneurysm**).
- **Lower limbs:** pitting oedema; arterial and venous ulcers of peripheral vascular disease.

Pulse

Resting rate 60–90 beats/min, slows with age and fitness. Compare radial with apex beat (delay: e.g. atrial fibrillation) and femoral/lower limbs (delay: atherosclerosis, aortic stenosis). Changes in rate with breathing are normal (**sinus arrhythmia**).

- **Irregular beats** *Regularly irregular*: that is, extrasystoles (disappear on exertion), second degree heart block. *Irregularly irregular*: that is, atrial fibrillation (unchanged by exertion).
- **Character** (carotid): *thready or weak*: heart failure, shock, valve disease; *slow rising*: aortic stenosis. *Bounding*: high output; followed by *sharp fall* (***collapsing***): very high output, aortic regurgitation. *Alternating weak–strong* (***pulsus alternans***): left heart failure; distinguish from **pulsus bigeminus**, normal beat followed by weak premature beat. ***Pulsus paradoxus****, accentuated weakening of pulse on inspiration*: cardiac tamponade, severe asthma, restrictive pericarditis.

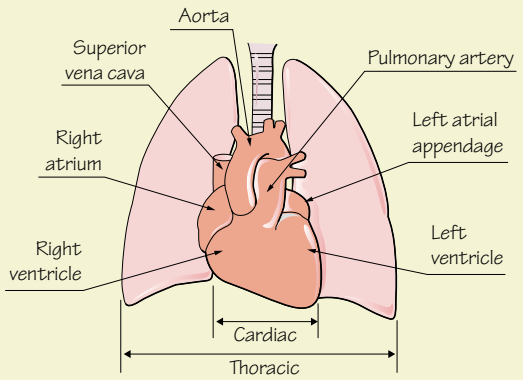
Blood pressure (Figure 32.3)

At rest, adult arterial systolic pressure is normally <140 mmHg and the diastolic pressure is usually <90 mmHg. Systolic pressure rises with age.

- **JVP** (Figure 32.4): Indirect measure of right atrial pressure. Raised in heart failure and volume overload. Large 'a' wave (see Chapter 16): pulmonary hypertension, pulmonary valve stenosis, tricuspid stenosis; large 'v' wave: tricuspid regurgitation. Absent 'a' wave: atrial fibrillation.

33 Cardiac imaging

Figure 33.1 Major structures discernible in a posteroanterior (PA) chest radiograph, measurements for calculation of cardiothoracic ratio (cardiac/thoracic x 100), and normal PA chest radiograph



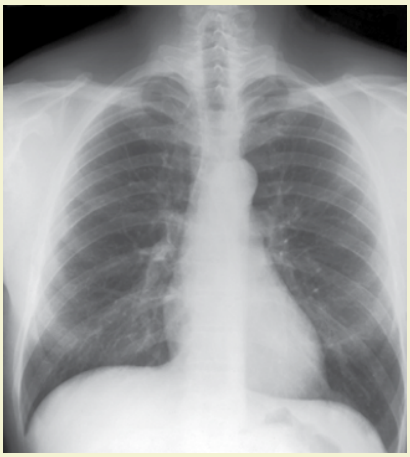


Figure 33.3 Normal transoesophageal echo-cardiogram during diastole

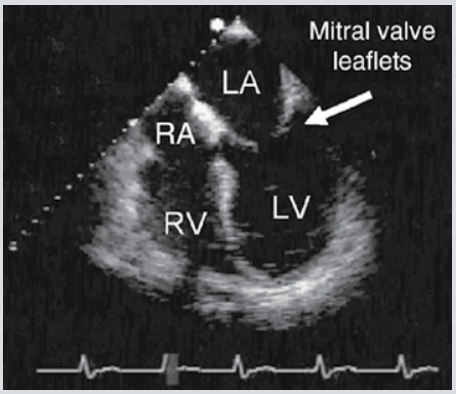
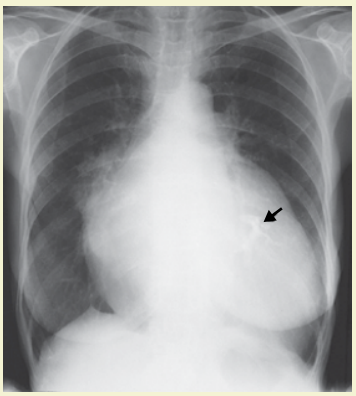


Figure 33.2 Enlarged cardiac silhouette due to mitral valve disease, showing valve calcification (arrow)



There is an array of imaging techniques available to cardiologists.

Chest radiograph (CXR) The CXR is ideally taken in the posteroanterior (PA) direction, with the patient upright and at full inspiration. Figure 33.1 shows the major structures in which abnormalities can be detected, such as enlargement of the heart chambers and major vessels, and a normal PA CXR. Heart size and **cardiothoracic ratio** (size of heart relative to thoracic cavity) can also be estimated. This ratio is normally <50%, except in infants and athletes, for example, due to mitral valve disease, but may be greatly increased in heart failure (Figure 33.2 and Chapters 46 and 55).

Transthoracic echocardiography is the most widely used imaging modality in cardiology as it is noninvasive and can be performed quickly at the bedside. It provides a wealth of structural and functional information, that is, quantification of chamber size, location of areas of reduced contractility, estimation of left ventricular ejection fraction, detection of valvular disease, abnormalities in blood flow such as regurgitation, and detection of pericardial effusion. Echocardiography uses ultrasound to produce images. An ultrasound pulse of 1–10 MHz is emitted from piezoelectric crystals inside a transducer which is moved by the operator on the chest wall. The ultrasound waves are reflected back by internal structures and processed to generate the real time image.

Transoesophageal echocardiography (TOE). A specialised probe with an ultrasound transducer at its tip is passed into the patient's oesophagus. This provides greater resolution (Figure 33.3) and improved access to the pulmonary artery, aorta and atria. The commonest indications for TOE are to confirm the presence of a vegetation or other mass that may have been identified during a transthoracic echocardiogram and to assess valves prior to surgery.

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Figure 33.4 Cardiac magnetic resonance imaging scan with late gadolinium enhancement showing sites of infarction (arrows)

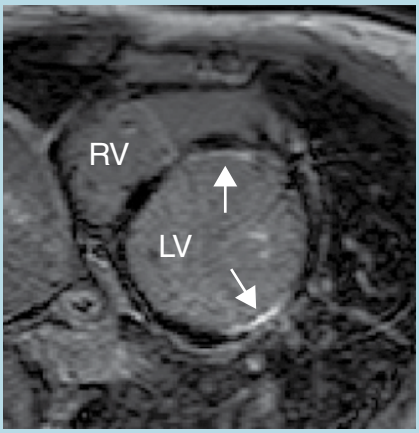
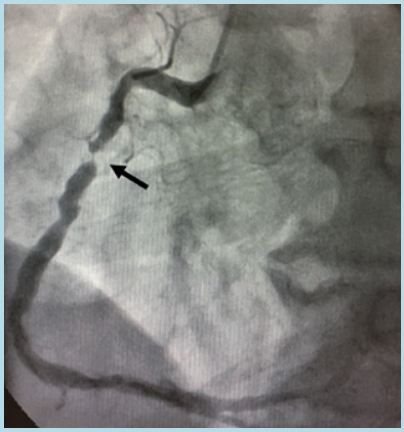


Figure 33.5 Angiogram of the right coronary artery showing a critical lesion (arrow)



Dobutamine stress echocardiography (DSE) is used in patients with angina to see how the heart performs under stress induced by the intravenously administered β1 agonist dobutamine, which increases contractility and cardiac output. DSE is used to diagnose the location and severity of ischaemia. Patients with a moderate to high burden of ischaemia are then offered invasive coronary angiography.

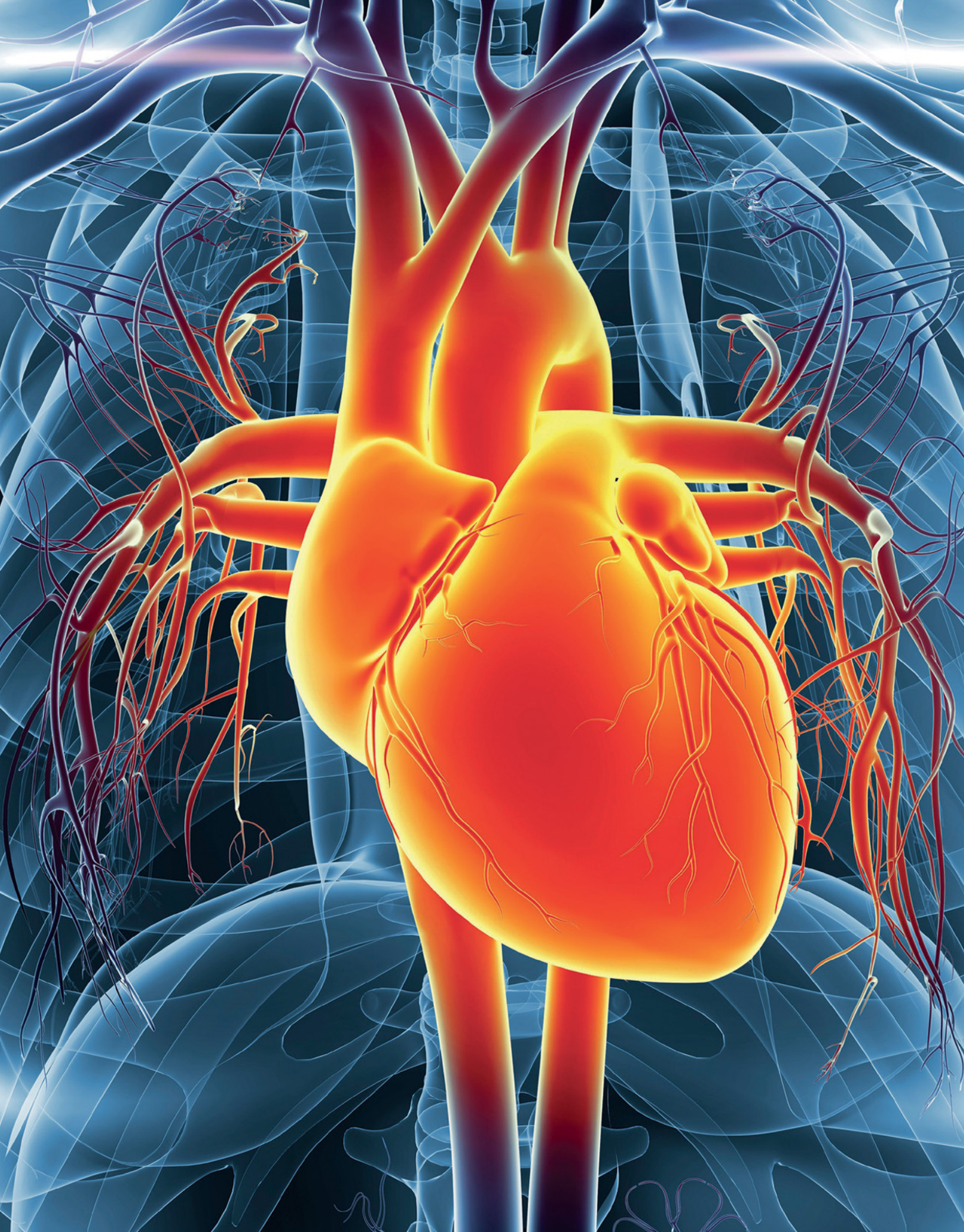
Cardiac CT There are two modalities of cardiac CT: coronary artery calcium score (CAC), which quantifies coronary artery calcification, and CT coronary angiography (CTCA), which provides 3D visualisation of the coronary arteries and any obstructive CAD. A normal CAC is zero, indicating that the patient has no calcified atheroma that can be resolved by the test. Patients with a calcium score of >100 are offered invasive coronary angiography as high CAC scores are an independent predictor of myocardial infarction and death. CTCA is useful in the exclusion of coronary artery disease in low-risk patients.

Cardiac magnetic resonance imaging (CMR) is an advanced imaging modality for the functional and anatomical assessment of many diseases of the cardiovascular system. The commonest indications are the assessment of myocardial ischaemia and viability, heart failure, cardiomyopathies and congenital heart disease. Radiofrequency stimulation of protons held in a strong magnetic field emits energy which can be used to generate a high resolution image that reflects tissue density. Unlike CT and nuclear imaging, CMR uses no ionising radiation. Gadolinium-based contrast agents are administered to detect areas of infarcted and viable myocardium in symptomatic patients and so guide revascularisation. Gadolinium has a rapid washout period in healthy tissue, which appears black on the images obtained. Conversely, infarcted nonviable tissue demonstrates delayed washout and the tissue appears white; this is termed late gadolinium enhancement (Figure 33.4).

Nuclear imaging The main application for nuclear imaging is to detect ischaemia. Radiopharmaceuticals introduced into the circulation are detected by a gamma camera, and their distribution can be used to measure or detect cardiac muscle perfusion, damage and function. 3D information can be obtained in a similar fashion using single photon emission computed tomography (**SPECT**). The nuclear tracers are distributed according to perfusion and taken up by cardiac myocytes. These show up brightly immediately after infusion; ischaemic and infarcted areas remain dark because of poor perfusion.

Coronary angiography is the most sensitive and specific test for the diagnosis of obstructive coronary artery disease. The commonest indication is for diagnosis of coronary artery disease in symptomatic patients. The aortic root gives off two branches which supply the heart. These are the left main stem (also called the left coronary artery) and the right coronary artery. The left main stem bifurcates into the left anterior descending artery (LAD) and the left circumflex artery (LCx), which supply the anterior and posterolateral left ventricle. The right coronary artery (RCA) supplies the right heart and the inferior wall of the left ventricle. A catheter introduced via the radial or femoral artery is guided under fluoroscopy into the aortic root. The operator then manipulates the catheter into the left main stem and a syringe with contrast dye is attached to the end of the catheter. Contrast is then injected directly into the left main stem and its branches. Images are then taken and stored (Figure 33.5). A separate catheter designed to access the RCA is then used to take images of the RCA and its branches.

Intracoronary imaging allows realtime visualisation of plaques inside coronary arteries. There are two techniques: **intravascular ultrasound** (IVUS) and **optical coherence tomography** (OCT). IVUS uses an ultrasound probe mounted on the end of a catheter which is positioned in the coronary artery of interest. It is able to show the lumen, intima, media and adventitia of that artery. This cross-sectional view can assist in choosing the correct sized stent and in confirming that the stent is correctly positioned. OCT uses near infrared light instead of sound waves for image acquisition. Owing to the shorter wavelength of infrared light compared to ultrasound, OCT has a 10-fold higher resolution than IVUS and is therefore able to provide higher quality imaging of the arterial wall.

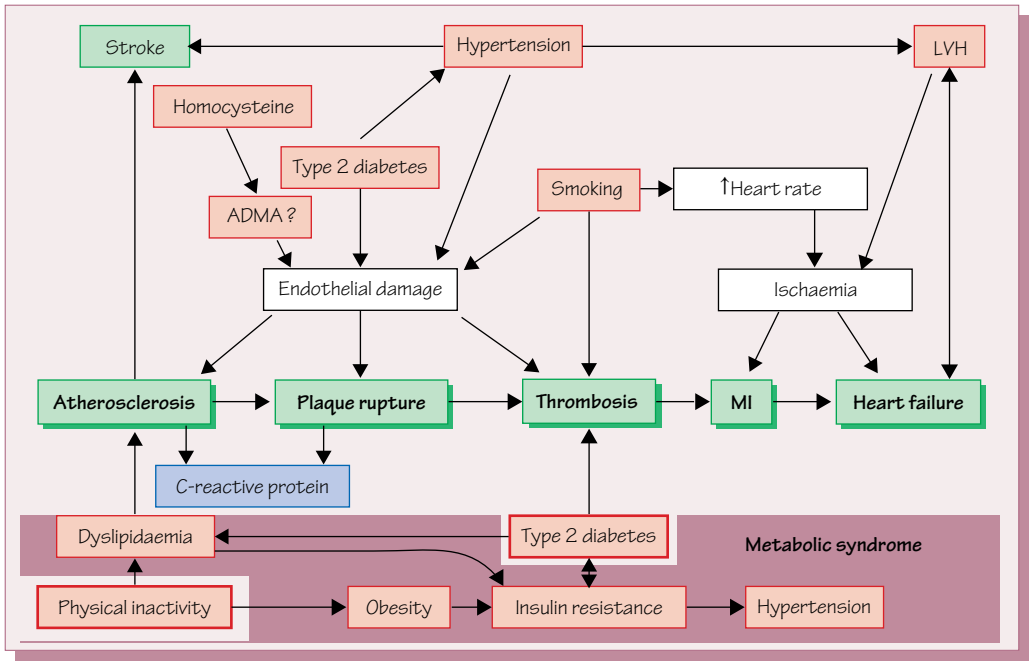


Pathology and therapeutics

Chapters

34 Risk factors for cardiovascular disease

Figure 34.1 Relationships between risk factors and cardiovascular disease



The main manifestations of cardiovascular disease (CVD) are coronary heart disease (CHD), cerebrovascular disease (stroke) and peripheral vascular disease, and the underlying cause of these is most often atherosclerosis (see Chapter 37). Numerous factors or conditions are known to increase (or decrease) the probability that atherosclerosis will develop, and the presence in an individual of these **cardiovascular risk factors** can be used to assess the likelihood that overt cardiovascular morbidity and death will occur in the medium term (Figure 34.1).

Some risk factors such as *age*, *male sex* and *family history of CVD* are **fixed**. However, others, including *dyslipidaemias*, *smoking*, *hypertension*, *diabetes mellitus*, *obesity* and *physical inactivity*, are **modifiable.** These probably account for over 90% of the risk of developing atherosclerotic CVD. The attempt to prevent CVD by targeting modifiable risk factors has become a cornerstone of modern disease management because the occurrence of overt CVD is preceded by the development of subclinical atherosclerosis which takes many years to progress.

Figure 34.1 illustrates the main mechanisms by which major risk factors are thought to promote the development of atherosclerosis and its most important consequence, CHD. Additional aspects of dyslipidaemias and hypertension are described in Chapters 36–39.

Modifiable risk factors

Dyslipidaemias are a heterogeneous group of conditions characterized by abnormal levels of one or more **lipoproteins**. Lipoproteins are blood-borne particles that contain cholesterol and other lipids. They function to transfer lipids between the intestines, liver and other organs (see Chapter 36).

Dyslipidaemias involving excessive plasma concentrations of **low-density lipoprotein (LDL)** are associated with rises in plasma cholesterol levels, because LDL contains 70% of total plasma cholesterol. As the level of plasma cholesterol rises there is a progressive increase in the risk of CVD due to the attendant rise in LDL levels. LDL has a pivotal role in causing atherosclerosis because it can be converted to an oxidized form, which damages the vascular wall (see Chapter 37). Drugs that lower plasma LDL (and therefore oxidized LDL) slow the progression of atherosclerosis and reduce the occurrence of CVD. Elevated levels of **lipoprotein (a)**, a form of LDL containing the unique protein **apo(a)**, have been reported to confer additional cardiovascular risk. Apo(a) contains a structural component closely resembling plasminogen, and it may inhibit fibrinolysis (see Chapters 8 and 45) by competing with plasminogen for endogenous activators. High levels of plasma **triglycerides** may also be correlated with CVD, although this remains controversial.

On the other hand, the risk of CVD is *inversely* related to the plasma concentration of **high-density lipoprotein (HDL)**, possibly because HDL functions to remove cholesterol from body tissues, and may act to inhibit lipoprotein oxidation. The LDL+HDL (total cholesterol): HDL cholesterol ratio is therefore a better predictor of risk than the LDL level. **Hypertension** occurs in almost 30% of the population and in more than half of people who are

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middle aged or older. Hypertension promotes atherogenesis, probably by damaging the endothelium and causing other deleterious effects on the walls of large arteries. Hypertension damages blood vessels of the brain and kidneys, increasing the risk of stroke and renal failure. The higher cardiac workload imposed by the increased arterial pressure also causes a thickening of the left ventricular wall. This process, termed **left ventricular hypertrophy (LVH)**, is both a cause and harbinger of more serious cardiovascular damage. LVH predisposes the myocardium to arrhythmias and ischaemia and is a major contributor to heart failure, myocardial infarction (MI) and sudden death.

Physical inactivity promotes CVD via multiple mechanisms. Low fitness is associated with reduced plasma HDL, higher levels of blood pressure and insulin resistance, and **obesity**, itself a CVD risk factor. Studies show that a moderate to high level of fitness is associated with a halving of CVD mortality.

Diabetes mellitus is a metabolic disease present in approximately 5% of the population. Diabetics either lack the hormone **insulin** entirely or become resistant to its actions. The latter condition, which usually develops in adulthood, is termed type 2 diabetes mellitus (DM2), and accounts for 95% of diabetics. Diabetes causes progressive damage to both the microvasculature and larger arteries over many years. Approximately 75% of diabetics eventually die from CVD.

There is evidence that patients with DM2 have both endothelial damage and increased levels of oxidized LDL. Both effects may be a result of mechanisms associated with the hyperglycaemia characteristic of this condition. Also, blood coagulability is increased in DM2 because of elevated plasminogen activator inhibitor 1 (PAI-1) and increased platelet aggregability.

A set of cardiovascular risk factors including high plasma triglycerides, low plasma HDL, hypertension, hyperglycaemia and obesity (particularly abdominal) are often associated with each other. This combination of risk factors is closely linked to, and could arise as a result of, **insulin resistance**. Individuals with three or more of these risk factors are said to have **metabolic syndrome**.

Atherosclerosis can be viewed as a chronic low-grade inflammation which is localized to certain sites of the vascular wall. This causes the release into the plasma of numerous inflammatory mediators and related substances. Many studies have shown that an elevated serum level of one of these, the acute phase reactant **C-reactive protein (CRP)**, is *predictive* of future CVD, although epidemiological studies, which have taken advantage of the fact that differences in the basal levels of serum CRP occur naturally in the population due to genetic variation, show that CRP does not *cause* CVD. Although proposed to be a potentially valuable risk marker that could be used to predict future CVD (and therefore indicate the need for preventative treatment) even in apparently healthy people with low LDL, many question whether CRP levels are truly independent of other established risk factors.

Tobacco smoking causes CVD by lowering HDL, increasing blood coagulability and damaging the endothelium, thereby promoting atherosclerosis. In addition, nicotine-induced cardiac stimulation and a carbon monoxide-mediated reduction of the oxygen-carrying capacity of the blood also occur. These effects, coupled with an increased occurrence of coronary spasm, set the stage for cardiac ischaemia and MI. Epidemiological evidence suggests that CVD risk is not reduced with low tar cigarettes.

High plasma levels of **homocysteine**, a metabolite of the amino acid methionine, are proposed to be a CVD risk factor, although the evidence for this association is controversial. Hyperhomocysteinaemia may increase cardiovascular risk by causing overproduction of the endogenous endothelial nitric oxide synthase (eNOS) inhibitor asymmetrical dimethyl arginine (**ADMA;** see Chapter 24), because homocysteine can serve as a donor of methyl groups that are enzymatically transferred to arginine to form ADMA.

Epidemiological studies show that **psychosocial stress** (e.g. depression, anxiety, anger) can substantially increase the risk of the development and recurrence of CVD. For example, the INTERHEART study reported in 2004 that people who had had an MI were more than 2.5 times as likely to report pre-existing psychosocial stress than age-matched controls. Although the reasons for this have not been definitively established, it is known that negative emotions can result in activation of the sympathetic nervous system (which can cause various deleterious effects on the cardiovascular system including a raised blood pressure and more frequent cardiac arrhythmias), and also that anxiety and depression engender unhealthy lifestyles. However, the effectiveness of psychological treatments in improving outcomes in those who have already have CVD is uncertain, as a recent Cochrane meta-analysis concluded that whereas psychological interventions reduced MI-related deaths in those who had suffered an MI or undergone revascularization, total mortality was unchanged.

Social deprivation, as assessed in the UK by the **Townsend score**, is also an important cardiovascular risk factor.

Fixed risk factors

Family history of CVD

Numerous epidemiological surveys have shown the existence of a familial predisposition to CVD. This arises in part because many CVD risk factors (e.g. hypertension) have a *multifactorial genetic basis* (are due to multiple abnormal genes interacting with environmental influences). Additional deleterious genetic influences are also probably involved, because the familial predisposition remains if epidemiological data are corrected for known risk factors. For example, the angiotensin-converting enzyme (ACE) gene can exist in two forms, characterized by the insertion or deletion of a 287-base-pair DNA segment within intron 16. Those homozygous for the deletion polymorphism have higher plasma ACE concentrations, which may modestly increase the risk of MI.

Male sex

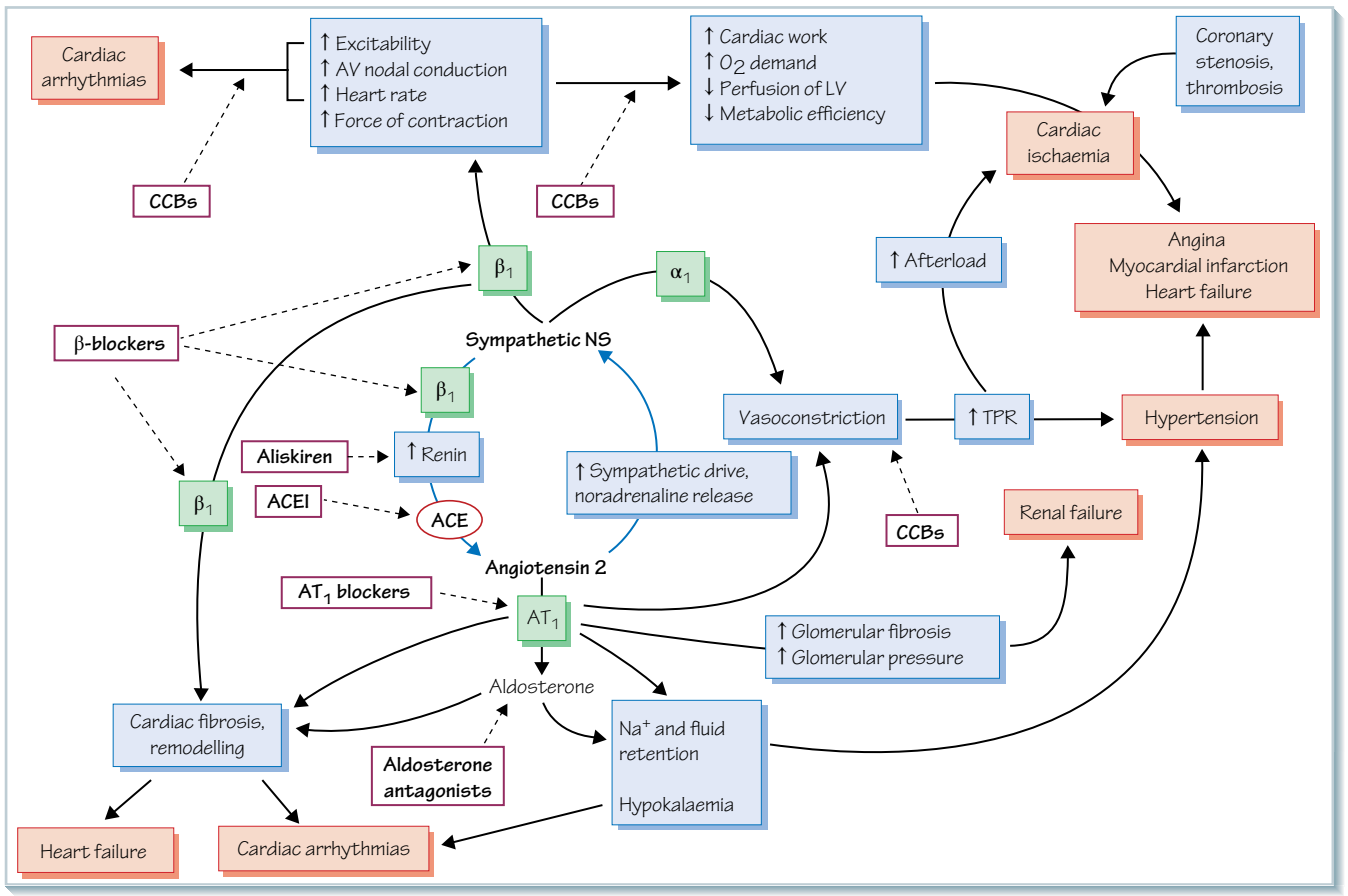
In youth and middle age, CVD is less common in women than in men. This difference progressively narrows after the menopause and is mainly oestrogen mediated. The potentially beneficial actions of oestrogen include acting as an antioxidant, lowering LDL and raising HDL, stimulating the expression and activity of nitric oxide synthase, causing vasodilatation and increasing the production of plasminogen.

Risk scoring in clinical practice

Epidemiological studies of the relationships between particular risk factors and the incidence of CVD have enabled the development of algorithms which can predict the likelihood that an individual will develop a specific cardiovascular disorder, or CVD in general. These scoring systems allow clinicians to determine which patients should be treated prophylactically, to prevent or ameliorate cardiovascular events before they occur. The algorithm QRisk®3 is widely used in UK health practices to predict the likelihood of developing MI or stroke over 10 years based on the presence of risk factors such as age, family history, gender, ethnicity, Townsend score, diabetes, systolic blood pressure, cholesterol/HDL ratio, smoking status, body mass index and the presence of chronic kidney disease and atrial fibrillation.

35 β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and Ca^{2+} channel blockers

Figure 35.1 Mechanisms by which β-blockers, Ca^{2+} channel blockers and drugs antagonising the renin-angiotensin-aldosterone axis ameliorate cardiovascular disease



The four classes of drugs described in this chapter each stand out as being useful in treating multiple disorders of the cardiovascular system. Core aspects of their mechanisms of action and properties are illustrated in Figure 35.1 and described below. Further details on their use are presented in the chapters dealing specifically with their use.

β-adrenoceptor antagonists (β-blockers)

β-blockers are used to treat angina, cardiac arrhythmias, myocardial infarction and chronic heart failure. Once a first-line treatment for hypertension, they are now used only in combination with other antihypertensive drugs if these fail to lower blood pressure sufficiently. Their usefulness derives mainly from their blockade of cardiac *β_1-receptors* (Figure 35.1). When stimulated by noradrenaline released from sympathetic nerves, and by blood-borne adrenaline, these receptors increase the rate and force of carvdiac contraction, thereby increasing the output, work and O_2 requirement of the heart. Although these responses are important for the normal physiological response to stress, they have the undesirable effect of promoting cardiac ischaemia and its downstream effects if coronary blood flow is compromised by atherosclerotic stenosis or thrombosis (see Chapters 40 and 45). Activation of β_1-receptors also increases atrioventricular (AV) nodal conduction and the excitability of the heart, effects that can sometimes cause or promote cardiac arrhythmias (see Chapters 48 and 52). Chronic activation of the sympathetic system, as in congestive heart failure, causes cardiac fibrosis and remodelling, leading to a progressive deterioration of cardiac function and increasing the occurrence of life-threatening arrhythmias (see Chapters 46 and 48).

β-Blockers have additional useful effects. Importantly, renal afferent arterioles contain *renin-producing granular cells* which are stimulated by sympathetic nerves to release renin via their β_1-receptors. Thus, the renin–angiotensin–aldosterone (RAA) axis (see Chapter 29) can be stimulated by the sympathetic system, an effect that β-blockers inhibit. β-Blockers also decrease the release of noradrenaline from sympathetic nerves by inhibiting presynaptic β-receptors on sympathetic varicosities that act to facilitate its release.

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Propranolol, a 'first generation' β-blocker, acts on both β_1 and β_2-receptors, whereas second generation β-blockers (e.g. **atenolol, metoprolol, bisoprolol**) selectively antagonize β_1-receptors. Third generation β-blockers also cause vasodilatation; for example, **carvedilol** does this by blocking α-receptors and by releasing nitric oxide. **Pindolol** belongs to a fourth group of β-blockers with *intrinsic sympathomimetic activity*; it antagonizes β_1-receptors but stimulates β_2-receptors, thereby causing vasodilatation. Although in all cases the main therapeutic effect of these drugs lies in their effect on β_1-receptors, these various properties, as well as differences between β-blockers with respect to their pharmacokinetics and adverse effects (see below) mean that specific β-blockers may be more or less appropriate for individual patients. Adverse effects of β-blockers as a class include exercise intolerance, as well as excessive bradycardia and negative inotropy, all due to their cardiosuppressive effects. Their block of vascular β-receptors, which promote blood flow to skeletal muscle by causing vasodilatation, can also cause fatigue and cold or tingling extremities. β-blockers also can cause bronchospasm and are contraindicated in asthma. These drugs can also have the potentially dangerous effect of masking the perception of hypoglycaemia in diabetics.

Angiotensin-converting enzyme inhibitors and angiotensin 2 receptor blockers

The RAA system, acting through its effectors angiotensin 2 and aldosterone, has a crucial role in conserving body Na^+ and fluid, thereby acting to maintain blood volume and pressure (see Chapter 29). However, even this normal functioning of the RAA system contributes to raised blood pressure in many hypertensives (see Chapter 38), and abnormal activation of this system in those with heart failure (see Chapter 46) leads to additional adverse effects shown in the lower part of Figure 35.1. Angiotensin 2 also enhances sympathetic neurotransmission by promoting noradrenaline release and by stimulating the CNS to increase sympathetic drive, leading to further increases in blood pressure. The activity of angiotensin 2 can be suppressed by angiotensin-converting enzyme inhibitors (ACEI), which block its synthesis by ACE (see Chapter 29), by angiotensin 2 receptor blockers (ARBs) that inhibit its action at AT_1 receptors (which mediate its various deleterious effects), and by direct renin inhibitors.

Because both block RAA system function, ACEI and ARBs suppress the various vasoconstricting effects of angiotensin 2 on the vasculature, thereby reducing total peripheral resistance and blood pressure. Both also cause natriuresis and diuresis which contribute to their blood pressure lowering effects and also help to reverse the pulmonary and systemic oedema and cardiac remodelling which contribute to the symptoms and progression of chronic heart failure. ACEI have the additional effect of preventing the breakdown of the peptide **bradykinin**, which is synthesized in the plasma by ACE and causes vasodilatation by releasing nitric oxide, prostacyclin and endothelium-derived hyperpolarizing factor (EDHF) from the endothelium. Increases in bradykinin may contribute to the ability of ACEI to reduce blood pressure and possibly to prevent cardiac remodelling, but may also cause the chronic cough that ACEI evoke in ~10% of people. ARBs differ from ACEI in that they do not increase bradykinin, and also in that they may cause a greater functional suppression of the RAA system because ACEI do not block *chymase*, another enzyme that synthesizes angiotensin 2. Excepting the fact that ARBs cause less cough than do ACEI, the extent to which these mechanistic differences between the two types of drug are therapeutically relevant remains to be fully elucidated. At present, both ACEI and ARBs are used to treat hypertension, heart failure, myocardial infarction, and to protect against renal complications in diabetes.

The vast majority of ACEI (e.g. **enalapril**, **ramipril**, **trandolapril**; Class II) are taken orally as inactive *prodrugs* which, being lipophilic, are processed in the liver to produce an active metabolite (e.g. enalapril yields *enalaprilat*). **Captopril** (Class 1), the oldest ACEI, is itself active but is also acted on by the liver to give active metabolites. **Lisinopril** (Class III) is active and, being water soluble, is excreted by the kidneys rather than being metabolized in the liver. Examples of ARBs include **losartan** and **candesartan**. Apart from cough, ACEI and ARBs share common contraindications and side effects. They should not be used by pregnant women because they retard fetal growth, or by those with bilateral renal stenosis, because in these individuals decreased renal blood flow typically leads to a powerful activation of the RAA system which is crucial for maintaining glomerular filtration. Because they diminish levels of aldosterone, which promotes renal K^+ excretion, both also can elevate the plasma K^+ concentration (hyperkalaemia).

The therapeutic effects of ACEI and ARB often wane with time, in part because both types of drugs increase renin synthesis and therefore plasma renin activity (PRA), which counters their effects. This occurs because angiotensin 2 exerts a feedback inhibition of renin synthesis *via* an action at AT_1 receptors. The direct renin inhibitor **aliskiren** was developed in an effort to prevent this phenomenon, termed **escape**. Although aliskiren also interrupts this negative pathway on renin synthesis by lowering angiotensin 2 levels, its very high efficacy as a renin antagonist means that PRA and therefore the activity of the RAA system is strongly reduced even though renin levels are increased.

Ca^{2+} channel blockers

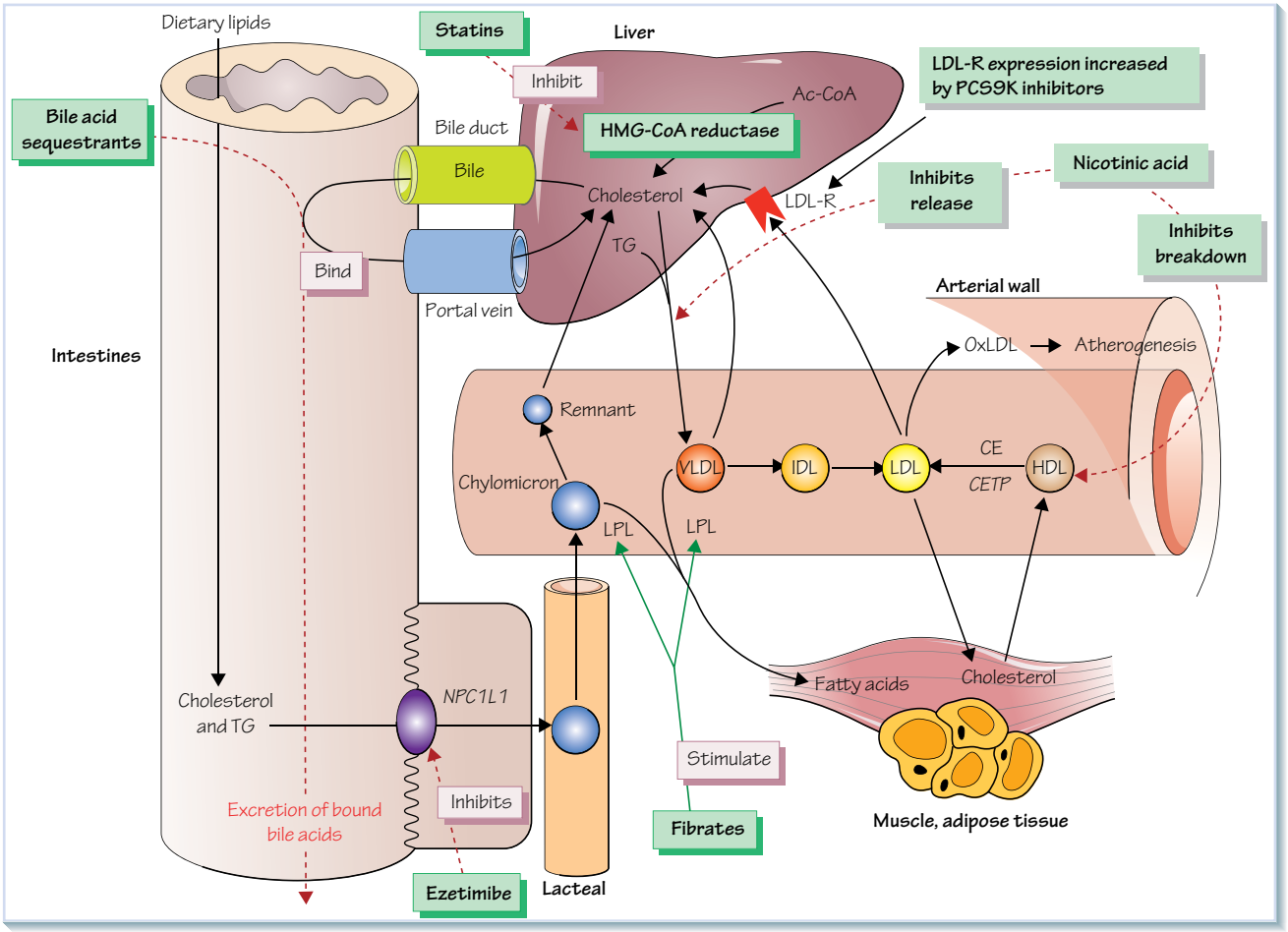
Ca^{2+} channel blockers (CCBs) inhibit the influx of Ca^{2+} into cells through L-type Ca^{2+} channels. The interaction of blocker and Ca^{2+} channel is best understood for the *dihydropyridines* (DHPs), which include **nifedipine**, **amlodipine** and **felodipine**. The affinity of DHPs for the channel increases enormously when the channel is in its *inactivated* state (see Chapter 10). Channel inactivation is favoured by a less negative membrane potential (E_m). DHPs therefore have a relatively selective effect on vascular muscle (E_m ~–50) compared with cardiac muscle (E_m ~–90). This functional selectivity is further enhanced because DHP-mediated vasodilatation stimulates the baroreceptor reflex and increases sympathetic drive, overcoming any direct negative inotropic effects of these drugs. If rapid, such sympathetic activation is thought to lead to cardiac ischaemia and unstable angina, and therefore the DHPs in current use have a slow onset and prolonged effect.

The phenylalkylamine **verapamil** interacts preferentially with the channel in its *open* state. Verapamil binding is therefore less dependent on E_m; thus both cardiac and vascular Ca^{2+} channels are blocked. In addition to its vasodilating properties, verapamil therefore has negative inotropic effects and severely depresses AV nodal conduction. The benzothiazepine **diltiazem** has similar properties; at therapeutic doses it vasodilates but also depresses AV conduction and has negative inotropic/chronotropic effects.

The DHPs are currently first line agents for treating hypertension (see Chapter 39) and angina pectoris (see Chapters 40 and 41). The non-DHPs (verapamil and diltiazem) are also used for these conditions, and for *supraventricular cardiac arrhythmias*, based on their ability to suppress AV nodal conduction (see Chapters 49, 50 and 52). Adverse effects of the DHPs are due to their profound vasodilating properties and include headache, flushing and oedema. The non-DHPs can cause powerful negative inotropic and chronotropic effects, and verapamil can cause constipation.

36 Hyperlipidaemias

Figure 36.1 Mechanisms of action of drugs used to treat hyperlipidaemias



All cells require **lipids** (fats) to synthesize membranes and provide energy. Lipids are transported in the blood as **lipoproteins**. These small particles consist of a core of **triglycerides** and **cholesteryl esters**, surrounded by a coat of **phospholipids**, **cholesterol** and proteins termed **apolipoproteins** or **apoproteins**. Apoproteins stabilize the lipoprotein particles and help target specific types of lipoproteins to various tissues. **Hyperlipidaemias** are abnormalities of lipoprotein levels which promote the development of **atherosclerosis** (see Chapter 37) and coronary heart disease (CHD; see Chapters 40–42, 44, 45).

Lipoproteins and lipid transport

Figure 36.1 illustrates pathways of lipid transport in the body. The **exogenous** pathway (left side of Figure 36.1) delivers ingested lipids to the body tissues and liver. Ingested triglycerides and cholesterol are transported by the protein Niemann–Pick C1-like 1 (NPC1L1) into the mucosal cells lining the intestinal lumen, which combine them with apoprotein **apo B-48,** forming **nascent chylomicrons** which are secreted into the lymph, pass into the bloodstream, and combine with apo E and apo C-II to become **chylomicrons**. These bind to the capillary endothelium in muscle and adipose tissue, where apo CII activates the endothelium-bound enzyme **lipoprotein lipase** (LPL). LPL hydrolyses the triglycerides to fatty acids which enter the tissues. The liver takes up the residual **chylomicron remnants**. These are broken down to yield cholesterol, which the liver also synthesizes. The rate-limiting enzyme in cholesterol synthesis is **hydroxy-methylglutaryl coenzyme A reductase** (HMG-CoA reductase). The liver uses cholesterol to make **bile acids.** These pass into the intestine and act to solubilize dietary cholesterol so it can be absorbed via NPC1L1. Bile acids are almost entirely reabsorbed and returned to the liver, although about 0.5 g/day is lost in the faeces, providing a path by which the body excretes cholesterol.

The **endogenous** pathway (right side of Figure 36.1) cycles lipids between the liver and peripheral tissues. The liver forms and secretes nascent **very low-density lipoproteins** (VLDLs), consisting mainly of triglycerides with some cholesterol and apo B-100, into the lacteal

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vessels. These acquire apo E and apo C-II from HDL in the plasma to become VLDL. As with chylomicrons, apo C-II activates LPL causing VLDL triglyceride hydrolysis and provision of fatty acids to body tissues. As it is progressively drained of triglycerides, VLDL becomes **intermediate density lipoprotein** (IDL) and then **low-density lipoprotein** (LDL), losing all of its apoproteins (to HDL) except for **apo B-100** in the process. Most LDL, which contains mainly cholesteryl esters (CE), is taken up by the liver; the rest serves to distribute cholesterol to the peripheral tissues. Cells regulate their cholesterol uptake by expressing more LDL receptors (which bind to apo B-100) when their cholesterol requirement increases.

Cholesterol is removed from tissues by **high-density lipoprotein** (HDL). HDL is initially assembled in the plasma from lipids and apoproteins (mainly **apo A1,** but also apo C-II and apo E) lost by other lipoproteins, and then progressively accumulates cholesterol (which it stores as CE) from body tissues. **Cholesteryl ester transfer protein** (CETP), which is in the plasma, transfers these from HDL to VLDL, IDL and LDL, which return them to the liver. This process by which HDL transports cholesterol to the liver from the rest of the body is termed **reverse cholesterol transport** and may explain why plasma HDL levels are inversely proportional to the risk of developing CHD.

Hyperlipidaemias: types and treatments

Primary hyperlipidaemias are caused by genetic abnormalities affecting apoproteins, apoprotein receptors or enzymes involved in lipoprotein metabolism, and occur in about 1 in 500 people. **Secondary hyperlipidaemias** are caused by conditions or drugs (e.g. diabetes, renal disease, alcohol abuse, thiazide diuretics) affecting lipoprotein metabolism. However, hypercholesterolaemia is most commonly caused by consumption of a diet high in saturated fats, probably because this decreases hepatic lipoprotein clearance. Although hyperlipidaemia often involves simply an excess of LDL cholesterol (LDL-C), many people, especially those with *metabolic syndrome* (see Chapter 34) have a combination of high LDL-C, high triglycerides (high VLDL), and low HDL cholesterol (HDL-C) levels in their plasma. This pattern is thought to confer a particularly large risk of developing CHD.

The treatment of hyperlipidaemias aims to slow or reverse the progression of atherosclerotic lesions by lowering LDL-C and/or triglycerides and to raise HDL-C. Although the US has abandoned formal cholesterol target levels, current European guidelines state that plasma LDL-C should be <115 mg/dL (3 mmol/L) for those who are at moderate risk of developing CHD, <100 mg/dL (2.5mmol/L) for high-risk patients, and <70 mg/dL (1.8 mmol/L) for very high-risk patients. Treatment often begins with a low fat, high carbohydrate diet. If this fails to normalize hyperlipidaemia adequately after 3 months, therapy with a lipid-lowering drug is considered. The vast majority of those with high LDL-C receive 'statins', which have been consistently shown to reduce CHD and the mortality it causes. Those with high triglycerides and low HDL-C may also be given 'fibrates' or niacin.

HMG-CoA reductase inhibitors or '**statins**' include **simvastatin, lovastatin, pravastatin, fluvastatin, mevastatin, atorvastatin** and **rosuvastatin**. The landmark **Scandinavian Simvastatin Survival Study** (4S) reported in 1994 that simvastatin reduced cardiovascular mortality by 42% over a 6-year period in CHD patients with high LDL-C. Statins act by reducing hepatic synthesis of cholesterol, causing an upregulation of hepatic receptors for B and E apoproteins. This increases the clearance of LDL, IDL and VLDL from the plasma. Statins also modestly increase plasma HDL-C levels by an unknown mechanism. Although the main benefits of statins result from their lipid-lowering effects, they also probably reduce CHD through additional mechanisms. These include an enhancement of nitric oxide release, possibly due to activation of the PI3K–Akt pathway (see Chapter 24), and also anti-inflammatory and antithrombotic effects. Some of these effects occur because the inhibition of HMG-CoA reduces cellular concentrations of lipids required for the functioning of the monomeric G proteins Rho (Rho acts to suppress eNOS expression) and Ras (Ras stimulates NFκB, which is involved in the expression of many pro-inflammatory genes).

Serious statin-associated adverse effects are rare. They include hepatoxicity and rhabdomyolysis (destruction of skeletal muscle), the risk of which is increased with concomitant use of nicotinic acid or a fibric acid derivative. Statin use also increases the chances of developing type 2 DM, especially in those already at risk of developing this disease, although the both the magnitude of this effect and its clinical relevance remain hotly debated.

Niacin (nicotinic acid) or **fibrates (fibric acid derivatives)** are used in patients who are receiving statins but whose triglyceride levels are too high and HDL-C levels are too low. Niacin is a B vitamin that inhibits the synthesis and release of VLDL by the liver. Because VLDL gives rise to IDL and LDL, plasma levels of these lipoproteins also fall. Conversely, HDL levels rise significantly as a result of decreased breakdown. Most patients experience flushing with niacin therapy due to vasodilatation caused by prostaglandin release from the endothelium; this can be prevented by non-steroidal anti-inflammatory drugs. Other adverse effects include hepatotoxicity, palpitations, impaired glucose tolerance, hyperuricaemia, hypotension and amblyopia.

Fibrates include **gemfibrozil**, **clofibrate**, **bezafibrate**, **ciprofibrate** and **fenofibrate**. Fibrates bind to peroxisome proliferator-activated receptor alpha (PPARα) to stimulate the expression and activity of LPL, thereby reducing VLDL triglycerides by increasing their hydrolysis. They also promote changes in LDL composition, which render it less atherogenic, and enhance fibrolysis. They cause mild gastrointestinal disorders in 5–10% of patients and can potentially cause muscle toxicity and renal failure if combined with HMG-CoA reductase inhibitors or excessive alcohol use.

Bile acid sequestrants: bile acids are synthesized from cholesterol in the liver, and cycle between the liver and intestine (enterohepatic recirculation). **Cholestyramine** and **colestipol** bind and trap bile acids in the intestine, increasing their excretion. This enhances hepatic bile acid synthesis and cholesterol utilization. The resulting depletion of hepatic cholesterol upregulates LDL receptors, increasing the clearance of LDL-C from the plasma. These drugs must be taken in large amounts (up to 30 g/day) and cause gastrointestinal side effects such as emesis, diarrhoea and reflux oesophagitis, so are rarely used.

Ezetimibe reduces absorption of dietary cholesterol by inhibiting **NPC1L1**. This reduces the plasma concentration and hepatic uptake of chylomicrons. The liver responds to this by expressing more LDL receptors to maintain its cholesterol uptake, and plasma LDL-C levels fall by ~15%. The IMPROVE-IT (2015) study showed that adding ezetimibe to simvastatin treatment in patients recently hospitalized with an acute coronary syndrome further lowered cholesterol by 23% and reduced the occurrence of subsequent major cardiovascular events by 6% over 7 years.

Alirocumab and **evolocumab** are antibodies which inhibit **proprotein convertase subtilisin/kexin type 9** (PCSK9), a protein in liver cells which ferries LDL receptors (LDL-R) to lysosomes, where they are destroyed. PCS9K inhibitors thus increase the number of LDL receptors in the hepatocyte membrane, enhancing the clearance of LDL-C from the plasma. The FOURIER (2017) trial reported that evolocumab reduced plasma LDL-C by a remarkable 59% in patients already receiving statins and decreased the incidence of myocardial infarction and ischaemic stroke by ~25% over 2 years.

37 Atherosclerosis

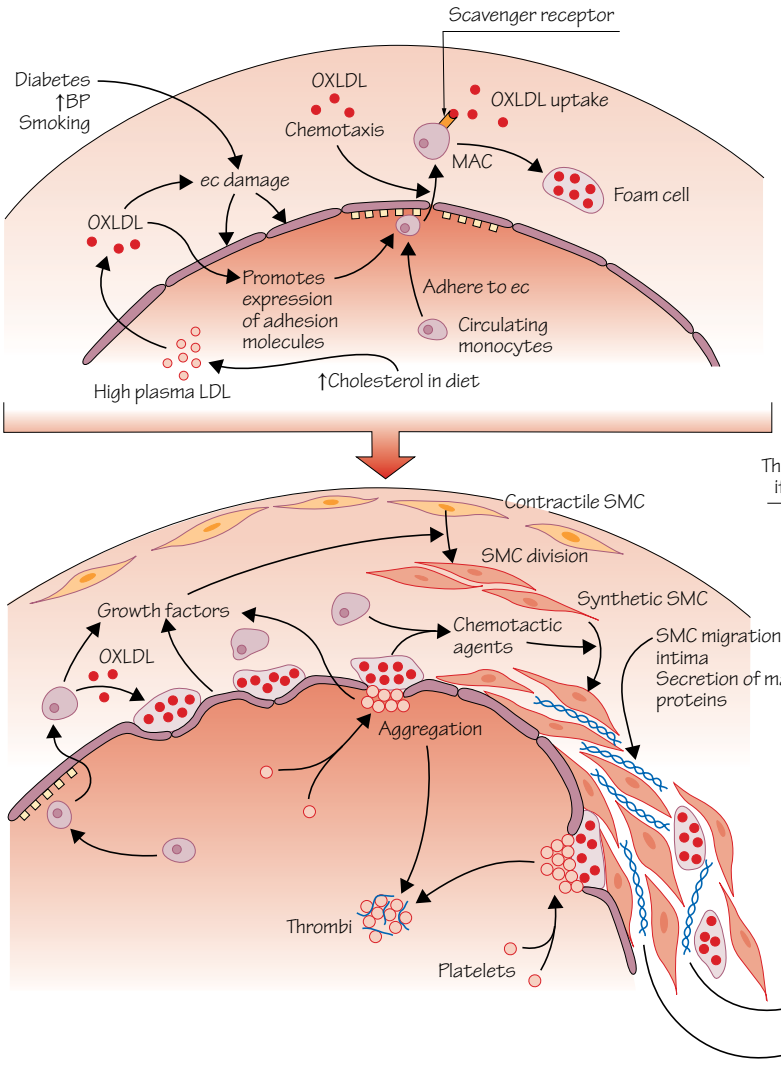

Figure 37.1 Initiation of atherosclerotic lesion

Figure 37.2 Development of lesion

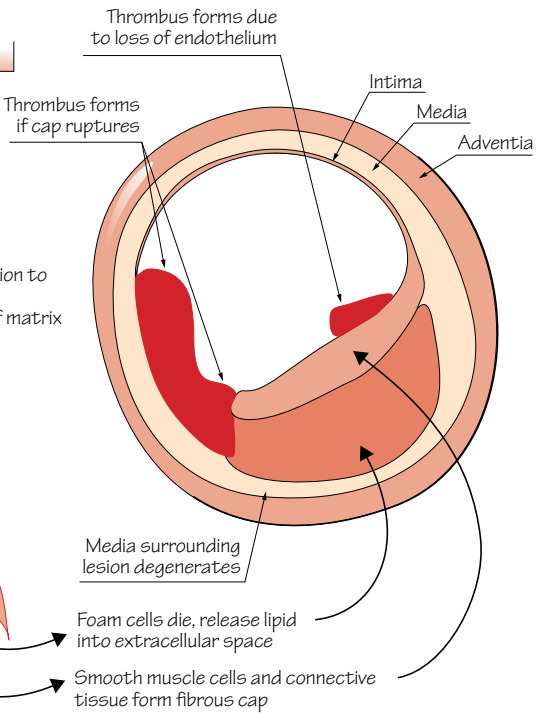

Figure 37.3 Advanced lesion

Atherosclerosis is a disease of the larger arteries. It begins in childhood with localized accumulations of lipid within the arterial intima, termed **fatty streaks**. By middle age some of these develop into **atherosclerotic plaques**, focal lesions where the arterial wall is grossly abnormal. Plaques may be several centimetres across and are most common in the *aorta*, the *coronary* and *internal carotid arteries*, and the *circle of Willis*. An advanced atherosclerotic plaque demonstrates several features.

1 The arterial wall is focally thickened by intimal smooth muscle cell proliferation and the deposition of fibrous connective tissue, forming a hard **fibrous cap**. This projects into the vascular lumen, restricting the flow of blood and often causes ischaemia in the tissue region served by the artery.
2 A soft pool of extracellular lipid and cell debris accumulates beneath the fibrous cap (*athera* is Greek for 'gruel' or 'porridge'). This weakens the arterial wall, so that the fibrous cap may fissure or tear away. As a result, blood enters the lesions and **thrombi** (blood clots) are formed. These thrombi, or the material leaking from the ruptured lesion, may be carried to the upstream vascular bed to *embolize* (plug) smaller vessels. A larger thrombus may totally occlude (block) the artery at the site of the lesion. This causes myocardial infarction or stroke if it occurs in a coronary or cerebral artery, respectively.
3 The endothelium over the lesion is partially or completely lost. This can lead to ongoing formation of thrombi, causing intermittent flow occlusion as in unstable angina.

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4 The medial smooth muscle layer under the lesion degenerates. This weakens the vascular wall, which may distend and eventually rupture (an **aneurysm**). Aneurysms are especially common in the abdominal aorta.

Atherosclerotic arteries may also demonstrate spasms or reduced vasodilatation. This worsens the restriction of the blood flow and promotes thrombus formation (see Chapter 40).

Pathogenesis of atherosclerosis

The risk of developing atherosclerosis is in part genetically determined. The incidence of clinical consequences of atherosclerosis such as ischaemic heart disease rises with age, especially after age 40. Atherosclerosis is much more common in men than in women. This difference is probably due to a protective effect of oestrogen and progressively disappears after menopause. Important risk factors that predispose towards atherosclerosis include smoking, hypertension, diabetes and high serum cholesterol.

The most widely accepted hypothesis for the pathogenesis of atherosclerosis proposes that it is initiated by *endothelial injury or dysfunction*. Plaques tend to develop in areas of low or variable haemodynamic shear stress (e.g. where arteries branch or bifurcate). The endothelium is especially vulnerable to damage at such sites, as evidenced by increased endothelial cell turnover and permeability. Endothelial dysfunction promotes the adhesion of **monocytes**, white blood cells which burrow beneath the endothelial monolayer and become **macrophages**. Macrophages normally have an important role during inflammation, the body's response to injury and infection. They do so by acting as scavenger cells to remove dead cells and foreign material and also by subsequently releasing *cytokines* and *growth factors* to promote healing. As described below, however, macrophages in the arterial wall can be abnormally activated, causing a type of slow inflammatory reaction, which eventually results in advanced and clinically dangerous plaques.

Oxidized low-density lipoprotein, macrophages and atherogenesis

Lipoproteins transport cholesterol and other lipids in the bloodstream (see Chapter 36). Elevated levels of one type of lipoprotein, low-density lipoprotein (LDL), are associated with atherosclerosis. Native LDL is not atherogenic. However, oxidative modification of LDL by oxidants derived from macrophages and endothelial and smooth muscle cells can lead to the generation of highly atherogenic **oxidized LDL** within the vascular wall.

Oxidized LDL is thought to promote atherogenesis through several mechanisms (Figure 37.1). Oxidized LDL is chemotactic for (i.e. attracts) circulating monocytes and increases the expression of endothelial cell adhesion molecules to which monocytes attach. The monocytes then penetrate the endothelial monolayer, lodge beneath it and mature into macrophages. Cellular uptake of native LDL is normally highly regulated. However, certain cells, including macrophages, are unable to control their uptake of oxidized LDL, which occurs via **scavenger receptors**. Once within the vascular wall, macrophages therefore accumulate large quantities of oxidized LDL, eventually becoming the cholesterol-laden **foam cells** forming the fatty streak.

As shown in Figure 37.2, stimulation of macrophages and endothelial cells by oxidized LDL causes these cells to release cytokines. T lymphocytes may also enter the vascular wall and release cytokines. Additional cytokines are released by platelets aggregating on the endothelium at the site at which it has been damaged by oxidized LDL and other toxic substances released by the foam cells. The cytokines act on the vascular smooth muscle cells of the media, causing them to *migrate into the intima*, to *proliferate* and to transform into a **synthetic phenotype** (in contrast to the contractile phenotype which normally characterizes smooth muscle cells) in which they *secrete abundant amounts of type 1 collagen and other connective tissue proteins*. Over time, the intimal accumulation of smooth muscle cells and connective tissue forms the fibrous cap on the inner arterial wall. Underneath this, ongoing foam cell formation and **apoptosis** (programmed cell death) form a layer of extracellular lipid (largely cholesterol and cholesteryl esters) and cellular debris referred to as the **necrotic core**. Still-viable foam cells often localize at the edges or shoulders of the lesion. Underneath the lipid, the medial layer of smooth muscle cells is weakened and atrophied.

Advanced atherosclerotic lesions, illustrated in Figure 37.3, commonly contain abundant deposits of calcium. These begin as microscopic granules which form around debris in the necrotic core and grow to form larger lumps. This process of **calcification** may ultimately encompass most of the plaque.

Clinical consequences of advanced atherosclerosis

Atherosclerotic lesions are of most clinical consequence when they occur in the coronary arteries. However atherosclerosis of cerebral arteries ultimately causes the vast majority of **strokes** (see Chapter 59) and atherosclerotic stenosis of the renal arteries causes about two-thirds of cases of **renovascular hypertension**.

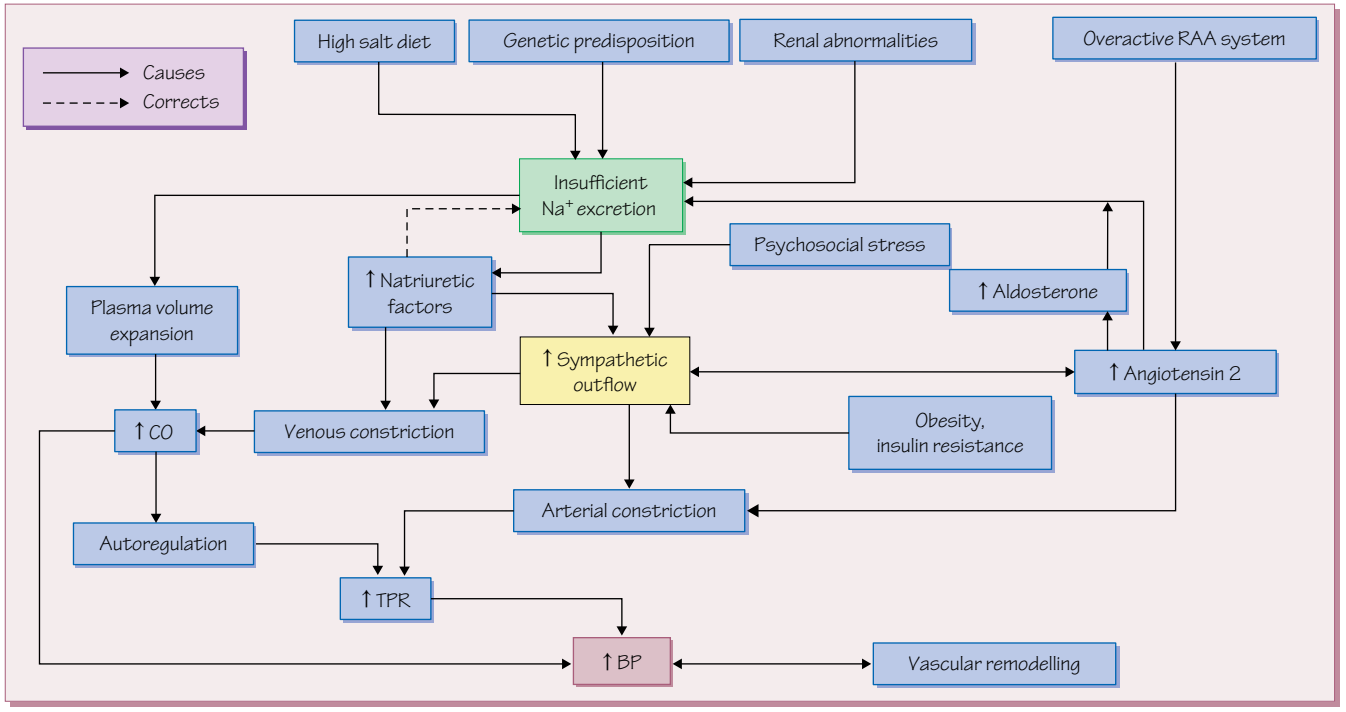
Lesions in which the fibrous cap becomes thick tend to cause a significant **stenosis**, or narrowing of the vascular lumen, which gradually comes to cause cardiac ischaemia, especially when myocardial oxygen demand rises. This leads to **stable** or **exertional angina** (see Chapter 40). Conversely, other lesions, referred to as **vulnerable plaques**, are unstable and prone to rupturing because the fibrous cap has lost most of its smooth muscle cells and is very thin. This type of plaque, also referred to as **thin-cap fibroatheroma**, typically has a large necrotic core, shows relatively little calcification, and causes minimal narrowing of the artery. Such lesions are also highly infiltrated by macrophages, which produce proteases that degrade the connective tissue matrix, and by T lymphocytes, which produce interferon-γ that inhibits matrix formation. These processes weaken the fibrous cap, rendering it apt to tear.

Rupture of vulnerable plaque allows blood to enter the lesion, causing thrombi to form on the surface and/or within the lesion, often resulting in an **acute coronary syndrome** such as unstable angina (see Chapter 42) or myocardial infarction (see Chapter 44). Thrombi may also form in the absence of plaque rupture. This often occurs at sites where the vascular endothelium has been lost (referred to as **plaque erosion**).

Following rupture, plaques may heal, and thrombi may gradually be replaced by connective tissue and incorporated into the lesion, a process termed **organization**. This may occur several times within a plaque and tends to form a highly occlusive stenosis.

38 Mechanisms of primary hypertension

Figure 38.1 Summary of mechanisms proposed to cause primary hypertension



In most people with **hypertension** (high arterial blood pressure; ABP), the condition is idiopathic (i.e. of unknown or uncertain cause) and is referred to as **essential** or **primary hypertension** (PH). S**econdary hypertension**, which is less common, arises due to an identifiable cause (e.g. hyperaldosteronism, renal disease, monogenic hypertension).

Population studies show that average systolic blood pressure (SBP) increases progressively throughout adulthood, whereas diastolic blood pressure (DBP) increases until midlife (40–59 years) and then declines. Thus, the majority of those beyond middle age suffer from **isolated systolic hypertension** (see Chapters 19 and 39). Often, however, PH develops earlier in life and is associated with increases in both SBP and DBP. This type of PH is a **complex genetic disease** in which an interaction between genetic variability and certain lifestyle and environmental factors (e.g. a high salt diet, psychosocial stress) results in the dysfunction of control systems regulating BP, causing it to rise. Genetic variability occurs because genes can exist in alternative forms (alleles), which have arisen as a result of mutation and become widespread in the population. There appear to be hundreds of genes which have commonly occurring alleles that cause tiny increases in ABP, such that inheriting enough of these would predispose to hypertension. Large genome-wide association scans have begun to identify many such genes. These include *ATP2B1*, which codes for the plasma membrane Ca^{2+} ATPase (see Chapter 15), and *UMOD*, which codes for uromodulin, a protein expressed in the thick ascending loop of Henle that is thought to regulate Na^+ reabsorption. This type of polygenetic inheritance can be contrasted with **monogenic** or **Mendelian** hypertension, in which a mutation affecting only one protein raises ABP because that protein plays a very important role in controlling ABP. One example of monogenic hypertension is **Liddle syndrome**, in which mutation of the mineralocorticoid-sensitive Na^+ channel (ENaC) impairs renal Na^+ excretion.

Although the precise details of how genetic and other factors interact to cause PH are unknown and doubtless differ between individuals, extensive research over more than a century has given rise to a number of models designed to explain how ABP regulation may go awry. A simplified integration of some of these ideas is shown in Figure 38.1.

Guyton's model of hypertension: The kidneys regulate long-term ABP by controlling the body's Na^+ content (see Chapter 29). Guyton and colleagues proposed in the 1970s that hypertension is initiated by renal dysfunction leading to impaired or inadequate Na^+ excretion, which manifests as a rightward shift of the pressure-natriuresis curve (see Figure 29.4). The resulting Na^+ retention increases blood volume and therefore CO and ABP. The increased ABP then promotes Na^+ excretion by causing pressure natriuresis and reducing the activity of the RAA system. Whole body Na^+ balance is therefore restored, but at the cost of an increased ABP. Subsequently, the rise in ABP and blood volume sets in train autoregulatory processes resulting in long-term vasoconstriction

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and/or vascular structural remodelling. This would reduce blood volume to normal levels, but by raising total peripheral resistance (TPR) would maintain the high ABP needed for Na^+ balance.

Two key findings supporting the concept that dysfunctional renal Na^+ handling is of paramount importance in causing hypertension are that (i) the ABP of hypertensive patients falls when they receive a kidney transplanted from a normotensive individual, and (ii) monogenic hypertension syndromes almost always involve abnormal renal Na^+ excretion. Moreover, a considerable body of evidence indicates that in many people an overactivity of the RAA system, which has a crucial role in regulating renal Na^+ excretion, may be responsible for the defect in renal Na^+ excretion proposed by Guyton. Interestingly, the kidney has its own renin–angiotensin system which is regulated independently of the RAA system in the rest of the body. Studies with mice in which the AT_1 receptor was knocked out only in the kidney suggest that it is this 'intra-renal' RAA system which may be of predominant importance in causing hypertension, although whether this is also true in humans is unknown.

In essence, this 'renocentric' model of PH pathogenesis depends on a very tight coupling between ABP and Na^+ excretion. Although it is accepted by many, it is coming under increasing attack in light of recent evidence that changes in ABP can occur independently of Na^+ excretion and vice versa.

Neurohormonal models of PH are based around the concept that long-term perturbations in ABP are due to abnormalities in neurological and hormonal control systems that have widespread actions on both the cardiovascular system and the kidneys. For example, some believe that PH in many patients is primarily due to dysfunction of the sympathetic nervous system (SNS). This view is supported by evidence that the SNS is overactive in ~50% of hypertensives. Recent clinical trials also show that decreasing sympathetic outflow chronically using **barostimulation** (electrical stimulation of the carotid sinus baroreceptors via implanted electrodes), causes a sustained fall in ABP in many PH patients. Similarly, imidazoline receptor agonists such as moxonidine, which act in the brain to reduce sympathetic outflow, effectively lower ABP (see Chapter 39). Overactivity of the SNS could potentially be caused by chronic stress and/or a variety of factors that have been shown to stimulate areas of the brainstem that control sympathetic outflow; these include angiotensin 2, inflammation, hypoxia, elevated reactive oxygen species, and endogenous ouabain (see below).

There are a variety of mechanisms by which overactivity of the SNS could raise ABP, since sympathetic nerves innervate not only the heart and the vasculature, but also the kidneys, in which sympathetic stimulation activates the RAA system and causes Na^+ retention. There is evidence in some animal models of hypertension (e.g. obese dogs) that it is the renal effects of the SNS overactivity that raise ABP. However in other animal models of hypertension (e.g. rats infused with angiotensin 2 and fed a high salt diet) the increase in ABP persists if the renal sympathetic nerve supply is cut but is prevented by denervation of the sympathetic supply to the splanchnic vascular bed (the blood vessels in the GI tract, liver and spleen). This has led to the proposal by Osborne and colleagues that the body counters increases in ABP by reducing sympathetically-mediated constriction of splanchnic arteries (thus decreasing TPR) and veins (thus decreasing central venous pressure and therefore CO). The suggestion is that these responses, which would successfully stabilize ABP in normotensives, are deficient in those with PH, thereby rendering the body unable to control the ABP properly.

The natriuretic factor hypothesis De Wardener and others have proposed that the body responds to inadequate renal salt excretion by producing one or more **natriuretic factors** (not to be confused with **atrial natriuretic peptide**; see Chapter 29) which promote salt excretion by inhibiting the Na^+–K^+-ATPase in the nephron. Although this effect would be expected to reduce ABP, the Na^+–K^+-ATPase is also indirectly involved in lowering intracellular Ca^{2+}, via regulation of both the membrane potential and Na^+–Ca^{2+} exchange, in smooth muscle cells and neurons. By blocking these effects of the Na^+–K^+-ATPase, natriuretic factors would cause additional responses such as vasoconstriction and increased norepinephrine release which would increase TPR, thereby causing hypertension. There is evidence that one such factor, **endogenous ouabain**, is synthesized in the adrenal glands and also in the hypothalamus, where it acts to increase sympathetic drive. Plasma levels of endogenous ouabain and **marinobufagenin**, another natriuretic factor that inhibits the Na^+–K^+-ATPase, are elevated in plasma taken from many hypertensives.

Insulin resistance is a condition in which the body becomes less responsive to the actions of the hormone *insulin*, leading to a compensatory rise in plasma insulin levels. Both insulin resistance and obesity, with which it is often associated, are very common in hypertensives. There is evidence that excessive insulin can cause multiple effects on the body which could promote hypertension, including activation of the sympathetic nervous system, increased renal Na^+ reabsorption and reduced endothelium-dependent vasodilatation. Obesity has also been shown to have a leptin-induced effect on the hypothalamus which stimulates the SNS.

Vascular remodelling

Established hypertension is associated with the *structural alteration* of small arteries and larger arterioles. This process, termed **remodelling**, results in the narrowing of these vessels and an increase in the ratio of wall thickness to luminal radius. Remodelling is proposed to be an adaptive mechanism which would reduce vascular wall stress (see the Laplace/Frank law; Chapter 18) and protect the microcirculation from increased ABP. However, it would also 'lock in' vascular narrowing and the resulting increase in TPR. Remodelling may also be enhanced by overactivation of the RAA and sympathetic nervous systems, which is known to promote smooth muscle cell growth.

Remodelling will increase basal TPR and also exaggerate any increase in TPR caused by vasoconstriction. In addition, studies in *spontaneously hypertensive rats* indicate that remodelling of renal afferent arterioles may contribute to hypertension by interfering with renal Na^+ excretion.

Secondary hypertension

In those with secondary hypertension, high ABP is caused by an identifiable condition or factor. Common causes include:

1. *Endocrine disturbances*, often of the adrenal cortex, and associated with oversecretion of aldosterone, cortisol and/or catecholamines,
2. *Renal parenchymal* and *renovascular diseases*, which impair volume regulation and/or activate the RAA system,
3. *Oral contraceptives*, which may raise ABP via RAA activation and hyperinsulinaemia.

It has been argued that hypertension associated with obesity should also be viewed as secondary, as the link between these two conditions are now very well established.

Malignant or accelerated hypertension is an uncommon condition that develops quickly, involves large elevations in pressure, is often secondary to other conditions, rapidly damages the kidneys, retina, brain and heart, and if untreated causes death within 1–2 years.

39 Treatment of hypertension

Figure 39.1 Mechanisms of antihypertensive treatments. Dashed lines indicate inhibition of processes/systems by treatments

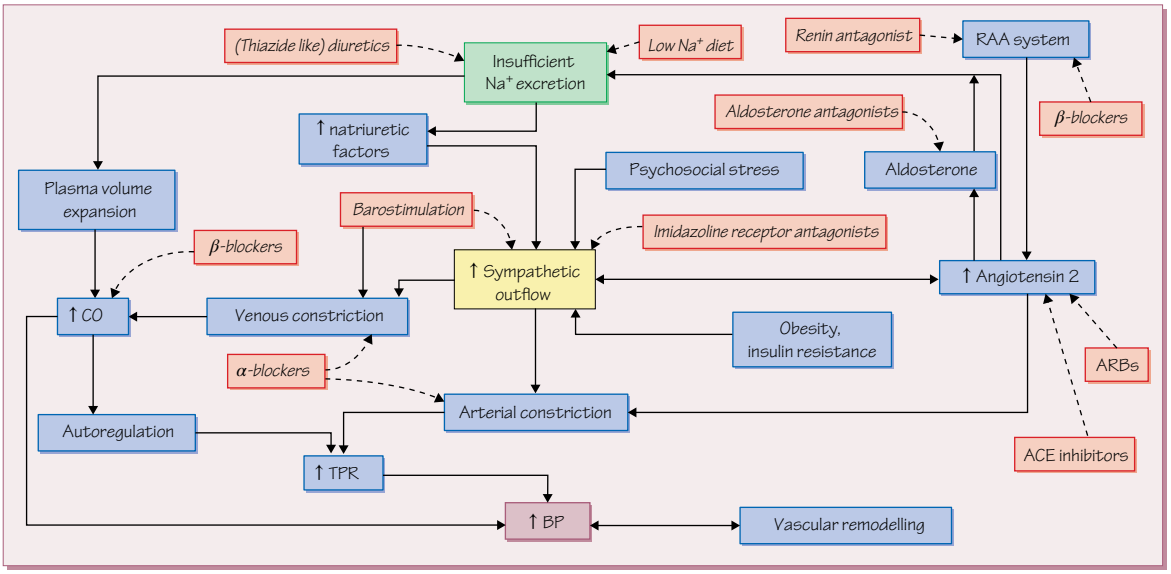

Table 39.1 Hypertension stages as defined by the UK National Institute for Clinical Excellence

Stage 1 Clinic ABP ≥ 140/90 mmHg and subsequent ambulatory ABP monitoring (ABPM) or home ABP monitoring (HBPM) shows average ABP of ≥ 135/85 mmHg
Stage 2 Clinic ABP ≥ 160/100 mmHg and subsequent ambulatory ABP monitoring (ABPM) or home ABP monitoring (HBPM) shows average ABP of ≥ 150/95 mmHg
Severe Clinic systolic ABP ≥ 180 mmHg or clinical diastolic ABP ≥ 110 mmHg

Definition and implications of hypertension

Hypertension is defined pragmatically as the level of arterial blood pressure (ABP) above which therapeutic intervention can be shown to reduce the risk of developing cardiovascular disease. Chronic hypertension causes changes in the arteries similar to those due to ageing, which include endothelial damage and **arteriosclerosis**, a thickening and increased connective tissue content of the arterial wall that reduces arterial compliance. These effects on vascular structure combine with elevated ABP pressure to promote atherosclerosis, coronary heart disease, left ventricular hypertrophy and renal damage. Hypertension is therefore an important risk factor for *myocardial infarction*, *congestive heart failure*, *stroke* and *renal failure*. Risk increases progressively with *both* systolic and diastolic ABP levels. Epidemiological studies predict that a long-term 5–6 mmHg diminution of diastolic arterial blood pressure (DBP) should reduce the incidence of stroke and CHD by about 40 and 25%, respectively. **Isolated systolic hypertension** (see Chapters 19 and 38) is particularly harmful to the brain and kidney since these organs have a relatively low vascular resistance; thus the increased blood pressure pulsatility which characterizes this type of hypertension penetrates deeply into their microcirculations, damaging them.

Diagnosis and general management of hypertension

ABP measurements taken using sphygmomanometry can vary significantly, and current guidelines state that, unless severe (>180/110 mmHg with signs of retinal or optic nerve damage), hypertension (ABP >140/90 mmHg) initially detected in the clinic should be confirmed by measuring ambulatory ABP or using a home monitor which records ABP over a 24-hour period. Tests for damage to target organs vulnerable to hypertension (e.g. eyes, kidneys) and assessment of other cardiovascular risk factors should also be carried out. Treatment depends on hypertension stage (see Table 39.1) and other factors. Those with *stage 1* hypertension who are <80 years of age should be treated if they have overt cardiovascular disease, diabetes, target organ damage, renal disease or an overall cardiovascular risk of >20% per 10 years (as estimated using risk algorithms; see Chapter 34). Even if they lack additional risk factors, stage 1 hypertensives under 40 years of age may warrant investigation for secondary hypertension and target organ damage. Those of any age with *stage 2* or *severe* hypertension should be treated. The goal of antihypertensive therapy is to reduce the blood pressure to below 135/85 mmHg for those under 80, 145/85 mmHg for those over 80, and 130/80 mmHg in diabetics and those with renal disease.

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Lifestyle modifications such as *weight reduction*, *regular aerobic exercise* and *limitation of dietary sodium* and *alcohol intake* can often normalize pressure in mild hypertension. They are also useful adjuncts to pharmacological therapy of more severe disease, and have the important added bonus of reducing overall cardiovascular risk.

However, adequate ABP control usually requires the lifelong use of **antihypertensive drugs.** These ultimately act to reduce cardiac output (CO) and/or total peripheral resistance (TPR) (Figure 39.1).

Stepped treatment: Treatment of hypertension is typically initiated with a single drug, but combinations of several drugs are usually needed to achieve adequate blood pressure control. The renin–angiotensin–aldosterone axis is more likely to be a contributing factor in causing hypertension in younger white patients, and so *step 1* is to offer an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) to white patients <55 of age. A calcium-channel blocker (CCB) should be offered to black and older white hypertensives; if a CCB is contraindicated a thiazide-like diuretic should be offered instead. If this fails to control ABP, *step 2* in all patients is to try a combination of a CCB (or diuretic) with an ACEI or ARB. If ABP is still not adequately controlled, *step 3* is to offer an (ACEI or ARB)/CCB/diuretic combination. Low dose spironolactone or a higher dose of thiazide-like diuretic can be added to this combination as *step 4,* and if ABP is still too high an α- or β-blocker can be tried. Drug selection is also influenced by whether coexisting considerations render a certain type of antihypertensive more or less appropriate in that individual (e.g. β-blockers can be used in younger patients in whom ACEI/ARB are contraindicated; ACEI are also useful for treating heart failure and diabetic nephropathy but should not be used in pregnant women; Ca^{2+} channel blockers are used to control angina).

When hypertension is secondary to a known condition or factor (e.g. renal stenosis, oral contraceptives), removal of this cause is often sufficient to normalize the ABP.

Drugs used to treat hypertension

Thiazide-like diuretics such as indapamide and chlortalidone increase renal Na^+ excretion by inhibiting Na^+/Cl^- symport in the cortical part of the ascending loop of Henle and the distal tubule. This leads to a fall in blood volume and CO. These drugs may also have vasodilating properties which contribute to their antihypertensive effects. Thiazide-like diuretics can cause hypokalaemia by promoting Na^+–K^+ exchange in the collecting tubule. This can be prevented by giving K^+ supplements or also by combining thiazide diuretics with K^+-sparing diuretics (e.g. amiloride) to reduce Na^+ reabsorption and therefore K^+ secretion by blocking Na^+ channels (EnaC) in the collecting duct. Additional side effects include increases in plasma insulin, glucose or cholesterol, as well as hypersensitivity reactions and impotence.

Angiotensin-converting enzyme inhibitors such as **ramipril**, **enalipril** and **lisinopril** block the conversion of angiotensin 1 into angiotensin 2. This reduces TPR because angiotensin 2 stimulates the sympathetic system centrally, promotes release of noradrenaline from sympathetic nerves, and vasoconstricts directly. The fall in plasma angiotensin 2, and consequently in aldosterone, also promotes diuresis/natriuresis because both hormones cause renal Na^+ and water retention (see Chapter 29). ACE also metabolizes the vasodilators bradykinin and substance P and increases in the concentrations of these substance in the lung associated with ACEI treatment are thought to sensitize sensory nerves in the airways, leading to the chronic cough that is the most common adverse effect of ACEI. This effect does not occur with **angiotensin 2 receptor (AT_1) blockers** (ARB) such as **losartan** and **valsartan**, which selectively inhibit the effects of angiotensin 2 on its AT_1 subtype without affecting bradykinin levels. Both ACEI and ARB have few side effects. However, they are contraindicated in pregnancy, renovascular disease and aortic stenosis. Aldosterone receptor antagonists (e.g. **spironolactone**; see Chapter 47), are also used to treat hypertension, as is **aliskiren**, an antagonist of renin which prevents it from producing angiotensin 1. As described in Chapter 35, aliskiren has theoretical advantages over ACEI and ARB with regard to less waning of its efficacy with time. Although there is some evidence that it may be more beneficial than ACEI or ARBs in hypertensives who are also diabetic, obese or suffer from metabolic syndrome, unlike these drugs aliskiren is not currently recommended for first-line use.

Calcium-channel blockers such as **nifedipine**, **verapamil** and **diltiazem** are commonly used to treat hypertension due to their vasodilating properties, as described in Chapter 35. The dihydropyridine CCBs, which are selective for vascular smooth muscle over the heart and are used most widely, also have a beneficial diuretic effect. Dihydropyridines have been shown to be especially effective in the elderly, and are safe in pregnancy.

β-adrenergic receptor blockers antagonize sympathetic nervous system stimulation of cardiac β-receptors (mainly β_1), thereby reducing cardiac output through negative inotropic and chronotropic effects. They also block β-receptors on juxtaglomerular granule cells in the kidney, thus inhibiting renin release and reducing plasma levels of angiotensin 2 and aldosterone. During treatment, TPR rises initially and then returns to the predrug level via an unknown mechanism, while CO remains depressed. All β-blockers used to treat hypertension antagonize the β_1 subtype, but some have additional effects on other adrenergic receptors which may contribute to their ABP-lowering actions and side effects (Chapter 35). β-blockers are contraindicated in moderate/severe asthma due to their potential effects on bronchiolar β_2-receptors. Adverse effects of these drugs include fatigue, negative inotropy, CNS disturbances in some (e.g. nightmares), and worsening and masking of the signs of hypoglycaemia.

α_1-adrenergic receptor blockers cause vasodilatation by inhibiting the constriction of arteries by the sympathetic neurotransmitter noradrenaline. Like β-blockers, these drugs are used at a late stage of stepped treatment if combinations of other drugs have failed to adequately control the blood pressure.

The drugs **rilmenidine** and **moxonidine** reduce sympathetic outflow by activating central **imidazoline** (I_1) receptors in the rostral ventrolateral medulla (RVLM). This lowers blood pressure with few side effects, but the use of these drugs is limited due to lack of evidence from clinical trials that they have beneficial effects on survival.

In ~25% of patients, ABP cannot be adequately lowered with drugs. Recent clinical trials suggest that combining pharmacological therapy with **barostimulation** (Chapter 27) can significantly improve ABP control in such patients.

Renal effects of vasodilators

In a recent paper, Dorrington and colleagues have pointed out that an implication of a strictly renocentric mechanism of hypertension pathogenesis (Chapter 38) is that vasodilator-induced reduction of TPR cannot by itself reverse hypertension, since any fall in ABP it causes will then diminish natriuresis/diuresis, thereby causing fluid retention and a rise in CO which will restore the high blood pressure. They propose that all vasodilators which lower TPR also have a natriuretic/diuretic effect (by lowering renal vascular resistance and/or inhibiting tubular solute reabsorption) and that it is the latter effect which lowers ABP. An alternative interpretation is that arterial and/or venous constriction also contributes to long term control of ABP and that a wholly renocentric view of ABP control is incorrect.

40 Stable, microvascular, and vasospastic angina

Figure 40.1 Balance of O_2 supply and demand in the myocardium

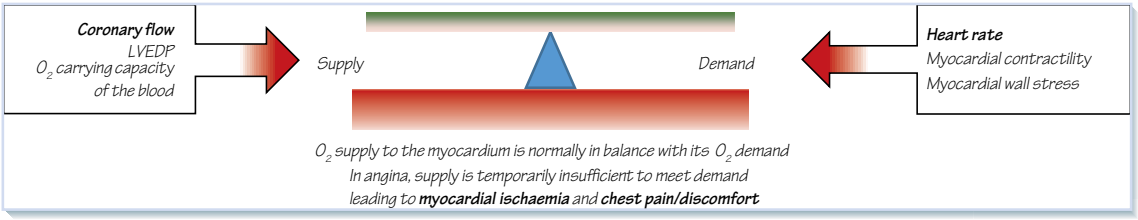


Figure 40.2 Stable angina

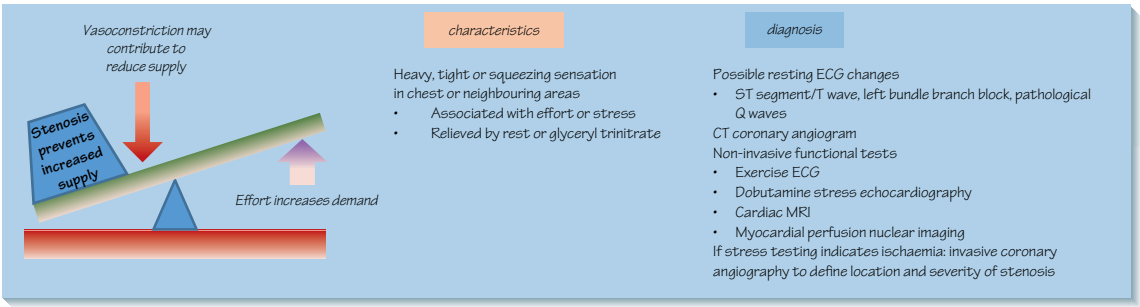


Figure 40.3 Microvascular angina

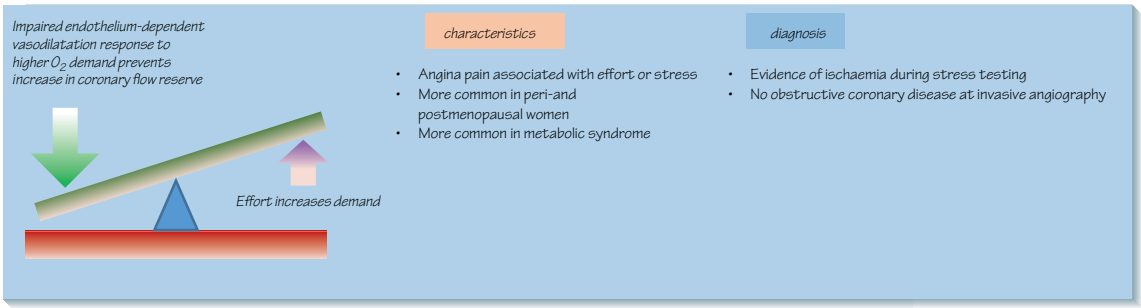
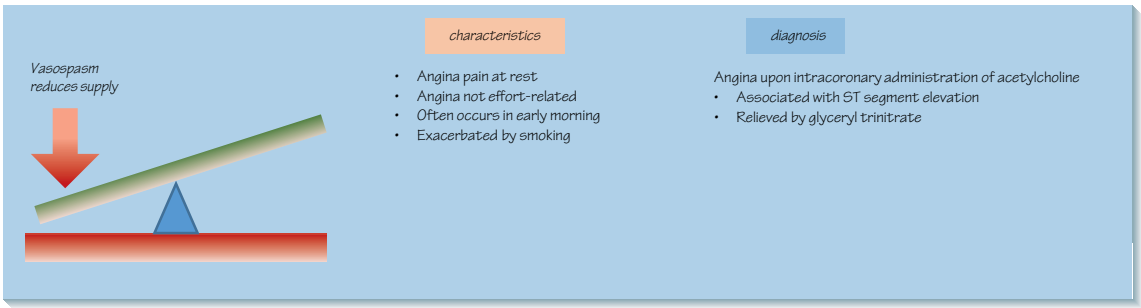


Figure 40.4 Vasospastic angina



Angina pectoris is pain or discomfort in the chest caused by myocardial ischaemia. Adjectives used to describe it include squeezing, crushing, tight, or heavy. The discomfort may radiate to the neck, jaw, arms or back. Epigastric discomfort may occur alone or in association with angina and may be mistaken for indigestion.

Angina is described as either typical or atypical. Typical angina meets all three of the following characteristics: (i) substernal chest discomfort of characteristic quality and duration; (ii) provoked by exertion or emotional stress; and (iii) relieved by rest and/or nitrates within minutes. Atypical angina meets two of these characteristics and non-cardiac chest pain meets only one if any of them.

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Angina is caused by myocardial ischaemia due to an imbalance between myocardial O_2 supply and demand (Figure 40.1). O_2 demand is determined by **heart rate**, **left ventricular contractility** and **systolic wall stress** and increases with **exercise**, **hypertension** and **left ventricular dilatation** (e.g. during chronic heart failure). Myocardial O_2 supply is primarily determined by coronary blood flow and coronary vascular resistance, mainly occurring at the level of the intramyocardial arterioles. With exercise coronary blood flow can increase to four to six times baseline, which is the normal coronary flow reserve (see Chapter 26).

Stable angina (Figure 40.2)

Stable angina is a consequence of stable coronary artery disease (CAD). In 2019, the European Society of Cardiology (ESC) introduced the term **chronic coronary syndromes** to describe stable CAD. This change emphasises that the underlying pathophysiology of CAD is a dynamic process of atherosclerotic plaque accumulation that can have long, stable periods but can also become unstable at any time, due to plaque rupture causing an **acute coronary syndrome** (Chapters 42 and 45). Stable angina arises when the flow reserve of one or more coronary arteries is limited by a significant structural stenosis resulting from atherosclerosis. At rest, cardiac O_2 demand is low enough to be satisfied even by a diminished coronary flow. However, when exertion increases myocardial O_2 demand, flow reserve is limited because of the stenosis, which presents a fixed obstruction. The resulting imbalance between myocardial O_2 demand and supply causes myocardial ischaemia manifesting as angina. Ischaemia develops mainly in the **subendocardium**, the inner part of the myocardial wall. This is because the blood flow to the left ventricular wall occurs mainly during diastole as a result of arteriolar compression during systole. The arterioles of the subendocardium are compressed more than those of the mid- or subepicardial layers; thus the subendocardium is most vulnerable to a relative lack of O_2.

In addition to causing pain, ischaemia causes a decline in high-energy phosphates (creatine phosphate and ATP). As a result, both ventricular contractility and diastolic relaxation in the territory of affected arteries are impaired. This can cause a fall in cardiac output, pulmonary congestion and activation of the sympathetic nervous system. Stable angina is usually relieved within minutes by rest or by glyceryl trinitrate (GTN) spray.

Some patients with stable angina may have excellent effort tolerance one day but develop angina with minimal activity on another day. Contributing to this phenomenon of *variable threshold angina* is a dynamic endothelial dysfunction which often occurs in patients with coronary artery disease. The endothelium normally acts via nitric oxide to dilate coronary arteries during exercise. If this endothelium-dependent vasodilatation is periodically impaired, exercise may result in paradoxical vasoconstriction due to the unopposed vasoconstricting effect of the sympathetic nervous system on coronary α-receptors.

Diagnosis of stable angina If coronary artery disease is suspected based on the symptom and risk factor profile, a 12 lead ECG and an echocardiogram are performed. Ischaemia or previous myocardial infarction can be indicated on the resting ECG by ST segment/T wave changes, left bundle branch block or pathological Q waves. If clinical assessment indicates typical or atypical angina, the patient is offered a CT coronary angiogram. For those in whom coronary artery disease is confirmed (e.g. previous MI, revascularisation), a non-invasive functional test is offered. Examples of functional testing include exercise ECG, dobutamine stress echocardiography, cardiac magnetic resonance imaging, and myocardial perfusion nuclear imaging. If stress testing demonstrates ischaemia, then invasive coronary angiography is used to provide direct radiographic visualisation of the extent and severity of disease. A decision is then taken whether to intervene on any lesion (see Chapter 43).

Prognosis Uncomplicated stable CAD has a similar mortality rate to that of the general population but as noted in the 2019 ESC guidelines the disease can become unstable at any time. Studies show that cardiovascular mortality in patients with stable angina is 1.2–2.4% per year. Mortality increases with the number of diseased arteries. Patients with previous myocardial infarction, poor left ventricular function or diabetes are at an increased risk of mortality of up to 3.8% per year.

Microvascular angina (Figure 40.3)

Patients with **microvascular angina** have ischaemic symptoms with objective evidence of ischaemia such as a positive stress test but no obstructive coronary disease at invasive angiography. This condition is more common in peri- and postmenopausal women and in those with features of the metabolic syndrome (hypertension, dyslipidaemia and insulin resistance). In a large study, 40% of women with chest pain and evidence of ischaemia undergoing invasive angiography were found to have nonobstructive coronary disease, compared to only 8% of men.

Pathophysiology Myocardial ischaemia is due to coronary microvascular dysfunction. This is caused by an impaired endothelial response to increased myocardial O_2 demand, which is believed to be an imbalance between endothelium-derived vasodilators and vasoconstrictors, and may be an early marker of vascular disease. This results in lower coronary flow reserve, which is associated with increased risk for major adverse outcomes. Increased pain nociception has been proposed as a pathogenic mechanism underlying cases of microvascular angina refractory to standard therapy.

Prognosis The Women's Ischemia Syndrome Evaluation study found that women with angina and either normal coronary arteries or non-obstructive coronary artery disease had significantly higher rates of adverse cardiovascular outcomes compared to asymptomatic age- and race-matched controls even after adjusting for cardiac risk factors.

Vasospastic angina (Figure 40.4)

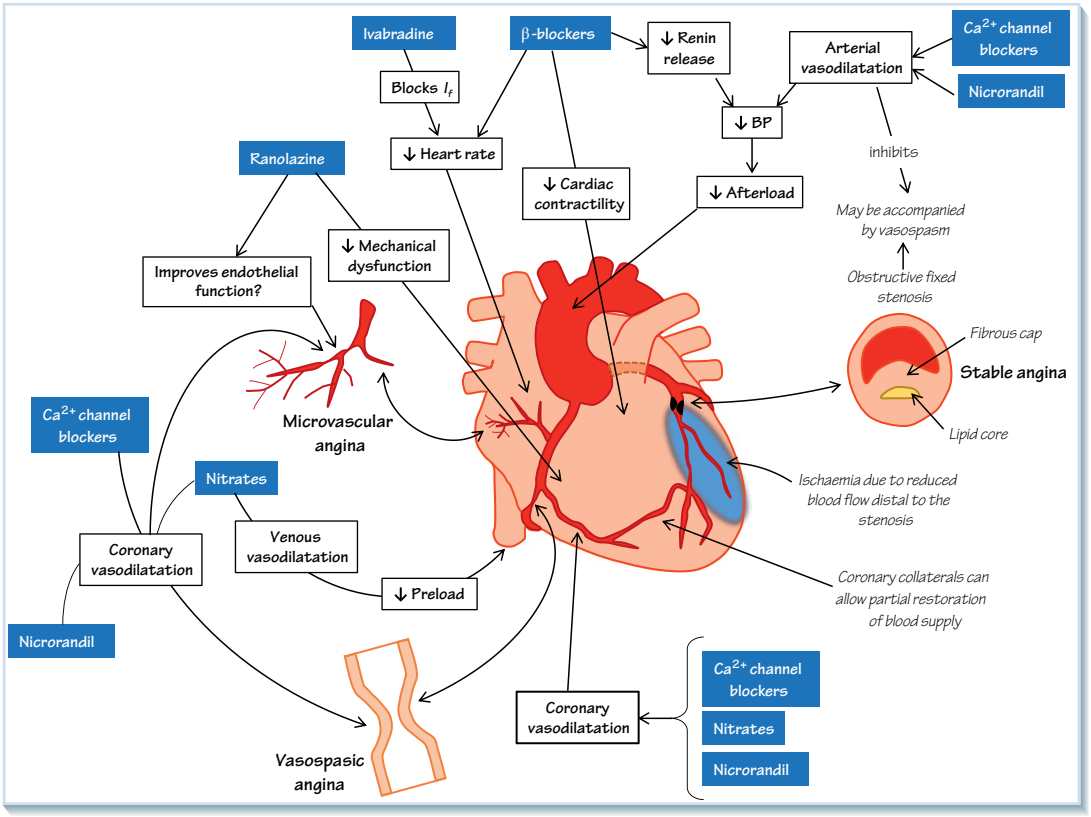
Vasospastic angina, previously termed **variant** or **Prinzmetal** angina, is an uncommon condition in which myocardial ischaemia and pain are caused by a severe transient occlusive spasm of one or more epicardial coronary arteries. Patients with vasospastic angina may or may not have coronary atherosclerosis, and in the former case, vasospasm often occurs in the vicinity of plaques. Vasospastic angina occurs at rest or on exertion and may be intensely painful. It is exacerbated by smoking and can be precipitated by alcohol or cocaine use. Cardiac ischaemia caused by vasospastic angina can result in ventricular arrhythmias, syncope, myocardial infarction and cardiac arrest during prolonged attacks. Vasospasm is thought to occur because a segment of artery becomes abnormally overreactive to vasoconstricting agents (e.g. noradrenaline, serotonin). There is also evidence that flow-mediated vasodilatation, a function of the endothelium, is impaired in the coronary arteries of patients with vasospastic angina and that this endothelial dysfunction may be due to oxidative stress (see Chapter 24).

Diagnosis The hallmark of vasospastic angina is nitrate-responsive angina associated with transient ST segment elevation on the ECG. It can be induced and directly visualised angiographically in the cardiac catheter laboratory by intracoronary administration of acetylcholine.

Prognosis The major adverse cardiac event rate (including death and myocardial infarction) from vasospastic angina is 1% or less. Whilst this event rate is low, it is concerning that adverse events tend to occur within the first three months, often before the diagnosis has been made. Consequently, vasospastic angina should be considered in patients presenting with an acute coronary syndrome in the absence of a culprit lesion, unexplained syncope, or in aborted sudden cardiac death.

41 Pharmacological management of stable, microvascular and vasospastic angina

Figure 41.1 Pharmacological management of angina



The aim of treatment of **stable** and **microvascular angina** is twofold: to control symptoms and to halt the progression of underlying coronary disease. Antianginals control symptoms and work by restoring the balance between myocardial O_2 demand and supply. Patients with stable angina whose symptoms are refractory to guideline-directed **optimal medical therapy** should be considered for revascularisation with angioplasty or bypass grafting. The treatment of **vasospastic angina** is primarily directed at preventing or reversing coronary vasospasm (Figure 41.1).

Antianginal agents

First-line treatment for stable angina consists of either a β-adrenergic receptor blocker (**β-blocker**), or a **calcium-channel blocker** (CCB) together with the short-acting nitrate glyceryl trinitrate. The initial choice between a β-blocker or a CCB depends on coexisting conditions and contraindications. For example, a CCB is preferable if the patient has moderate or severe asthma or hypertension, and a β-blocker may be appropriate if heart rate control is also required (i.e. if atrial fibrillation is present). If the patient cannot tolerate either a β-blocker or CCB, then monotherapy with either of the following should be used: isosorbide mononitrate, nicorandil, ivabradine, or ranolazine. If the patient is taking a β-blocker or a CCB and their symptoms remain poorly controlled, then both agents are used together. If the other agent is not tolerated or is contraindicated then isosorbide mononitrate, nicorandil, ivabradine, or ranolazine can be added. If the patient remains symptomatic on the maximum tolerated doses of two drugs then they should be referred to a cardiologist for consideration of revascularisation (Chapter 43).

β-Adrenergic receptor blockers

(see also Chapter 35)

β-blockers decrease cardiac O_2 demand by causing a fall in the resting and exercising heart rate and also by decreasing myocardial contractility and wall stress. The fall in the heart rate increases the fraction of time the heart spends in diastole. This enhances perfusion of the left ventricle, which occurs predominantly during diastole (Chapter 26). The main therapeutic action of these drugs is on cardiac β_1-receptors, but both β_1-selective and (β_1/β_2) non-selective blockers are used.

Potential adverse effects of β-blockers include fatigue, reduced left ventricular function and bradycardia. Impotence may be a concern in men. β-blockers can precipitate asthma by blocking β_2-receptors in the airways, and therefore even β_1-selective agents are contraindicated in this condition. Lipid-soluble β-blockers (e.g. propranolol) can enter the central nervous system and cause depression or nightmares. β-blockers can also worsen insulin-induced hypoglycaemia in people with diabetes.

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Ca^{2+}-channel blockers (see also Chapter 35)

CCBs act by blocking the L-type voltage-gated Ca^{2+} channels that allow depolarisation-mediated influx of Ca^{2+} into smooth muscle cells and also cardiac myocytes (see Chapters 11, 12 and 35). As described in Chapter 35, *dihydropyridine* CCBs such as **amlodipine**, **nifedipine** and **felodipine** act selectively on vascular smooth muscle L-type Ca^{2+} channels, while the *non-dihydropyridines* **verapamil** and **diltiazem** block these channels in cardiac myocytes as well. The non-dihydropyridine CCBs therefore reduce the heart rate and are referred to as *rate-limiting calcium channel blockers*.

CCBs prevent angina mainly by causing systemic arteriolar vasodilatation and decreasing afterload. They also prevent coronary vasospasm, making them particularly useful in vasospastic angina. The negative inotropic and chronotropic effects of verapamil and diltiazem also contribute to their usefulness by reducing myocardial O_2 demand.

The vasodilatation caused by CCBs can cause hypotension, headache and peripheral oedema (mainly dihydropyridines). The non-dihydropyridines verapamil and diltiazem should not be combined with β-blockers as severe bradycardia and heart failure can ensue.

Nitrovasodilators

Nitrovasodilators include **glyceryl trinitrate** (GTN), **isosorbide mononitrate**, and **isosorbide dinitrate**. The rapidly acting nitrovasodilator GTN is used to terminate acute attacks of angina, while longer-acting preparations provide long-term reduction in angina symptoms.

Nitrovasodilators are metabolised to release nitric oxide (NO), thus acting as a 'pharmacological endothelium'. GTN is thought to be metabolised mainly by the enzyme mitochondrial aldehyde dehydrogenase, whereas longer acting nitrovasodilators may be metabolised by cytochrome P450. NO stimulates guanylate cyclase to elevate cGMP, thereby causing vasodilatation (see Chapter 24). At therapeutic doses, nitrovasodilators act primarily to dilate veins, thus reducing central venous pressure (preload) and as a consequent ventricular end-diastolic volume. This lowers myocardial contraction, wall stress and O_2 demand. Some arterial dilatation also occurs, diminishing total peripheral resistance (afterload). This allows the left ventricle to maintain cardiac output with less energy expenditure, again decreasing O_2 demand.

Nitrovasodilators can also increase the perfusion of ischaemic myocardium. They dilate larger coronary arteries (those >100 μm in diameter). These give rise to **collateral vessels** (see Chapter 2) which can bypass stenotic arteries. Collaterals increase in number and diameter in the presence of a significant stenosis, providing an alternative perfusion of ischaemic tissue which is then enhanced by the nitrovasodilators. Nitrovasodilators also relieve coronary vasospasm and may diminish plaque-related platelet aggregation and thrombosis by elevating platelet cGMP.

GTN taken sublingually relieves angina within minutes; this route of administration avoids the extensive first-pass metabolism of these drugs associated with oral dosing. Nitrovasodilators can also be given in slowly absorbed oral, transdermal and buccal forms for sustained effect.

Continuous exposure to nitrovasodilators causes **tolerance**. This is caused in part by increased production within blood vessels of reactive oxygen species, which may inactivate NO and also interfere with nitrovasodilator bioconversion. Reflex activation of the renin–angiotensin–aldosterone system by nitrovasodilator-induced vasodilatation may also contribute to tolerance. Tolerance is irrelevant with short-acting nitrovasodilators, but long-acting preparations become ineffective within hours. Tolerance can be minimized by 'eccentric' dosing schedules that allow blood concentrations to become low overnight. The most common adverse effect of nitrovasodilators is headache. Reflex tachycardia and orthostatic hypotension may also occur.

Other antianginals

Nicorandil is a vasodilator with a dual mechanism. It increases the intracellular concentration of cGMP and thereby has nitrate-like effects and also causes smooth muscle cell hyperpolarisation by opening potassium (K_{ATP}) channels. **Ivabradine** reduces cardiac ischaemia by inhibiting the cardiac pacemaker current I_f (see Chapter 11) with a resultant reduction in heart rate. **Ranolazine** is thought to work by inhibiting the late Na^+ current in cardiac myocytes leading to a reduction in the intracellular calcium concentration. Unlike other antianginals, ranolazine has no clinically significant effect on heart rate or blood pressure. An important potential adverse effect of ranolazine is prolongation of the QT interval due to its action on the outward potassium delayed rectifier current I_{Kr} during phase 3 of the cardiac action potential. It is therefore contraindicated in individuals with a corrected prolonged QT interval on the ECG.

Management of microvascular angina

Some patients, but not all, respond to drugs given for stable angina. β-blockers have been shown to be more effective than CCBs or nitrates in the treatment of microvascular angina. Based on evidence from several small recent clinical trials, ranolazine should be considered in those refractory to traditional antianginal agents. The mechanisms by which it can improve symptoms in some patients with microvascular angina are unclear. However, it has been suggested that ranolazine has anti-inflammatory or antioxidant actions that improve coronary endothelial function. In addition, its effect on cardiac cells ameliorates myocardial mechanical dysfunction and may thereby diminish compression of the coronary microvasculature, resulting in a reduction of its resistance. Drugs which modify microvascular function, that is, statins and angiotensin converting enzyme inhibitors (ACEI) have a role in therapy as these increase coronary flow reserve and exert anti-inflammatory effects on endothelial cells. In patients whose microvascular angina is believed to involve abnormal pain nociception, the serotonin and noradrenaline uptake inhibitor imipramine may be helpful. It has been shown in studies to improve the symptoms of chest pain in patients with unobstructed coronary arteries at angiography.

Management of vasospastic angina

CCBs and nitrovasodilators are used to treat vasospastic angina but *β-blockers are not*, as they may worsen coronary vasospasm by blocking the β_2-mediated (vasodilating) but not α_1-mediated (vasoconstricting) effects of sympathetic stimulation.

Drugs for secondary prevention of cardiovascular disease

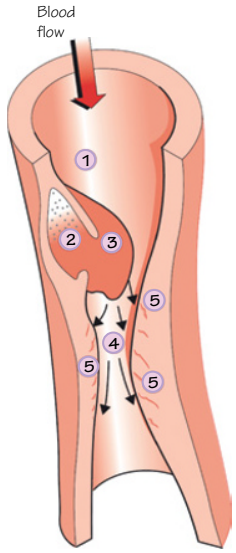
The reduction of risk factors that contribute to the further progression of coronary artery disease is a key aim of the management of all types of angina. Patients should be treated with 75 mg/day aspirin, which suppresses platelet aggregation and greatly reduces the risk of myocardial infarction and death. They should be offered a statin to reduce their plasma LDL levels. The 2001 HOPE trial showed that the ACEI ramipril reduced the progression of atherosclerosis and enhanced survival over a period of 5 years, in a group with coronary artery disease or diabetes, and ACEI are recommended for patients with stable angina with concomitant conditions (e.g. hypertension or heart failure) for which these drugs are also indicated.

42 Non-ST segment elevation acute coronary syndromes (NSTE-ACS)

Figure 42.1 Acute coronary syndromes

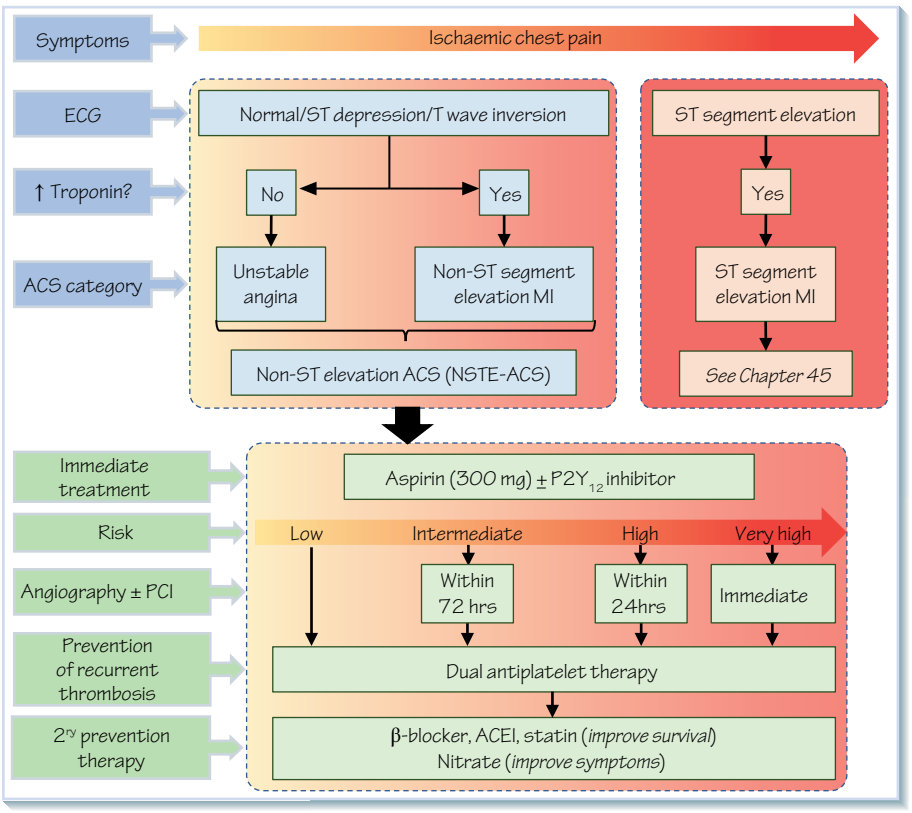
Acute cardiac ischaemia caused by coronary thrombosis and vasoconstriction
Unstable angina: coronary occlusion insufficient duration and/or extent to cause cardiac necrosis
NSTEMI: coronary occlusion sufficient to cause mainly subendocardial necrosis
STEMI: coronary occlusion sufficient to cause transmural cardiac necrosis

Figure 42.2 Pathophysiology



① Plaque rupture initiates platelet aggregation and thrombosis; ②Intraplaque thrombus: expands lesion, may occlude artery; ③Intraluminal thrombus: partial and/or transient occlusion of artery; ④Release of vasoconstricting factors associated with platelet aggregation, contributes to occlusion; ⑤ Endothelial damage associated with plaque promotes vasoconstriction

Figure 42.3 Management of acute coronary syndromes



The **acute coronary syndromes (ACS,** Figure 42.1), including in ascending order of severity, **unstable angina (UA)**, **non-ST segment elevation myocardial infarction (NSTEMI)** and **ST segment elevation myocardial infarction (STEMI)**, represent a spectrum of dangerous conditions in which myocardial ischaemia results from *a sudden decrease in the flow of blood through a coronary artery*. This decrease is almost always initiated by the rupture of an unstable atherosclerotic plaque, resulting in the formation of an intracoronary thrombus that diminishes or abolishes the flow of blood.

The ACS are divided into those with sustained (>20 mins) ST-segment elevation in two or more contiguous ECG leads (ST-segment myocardial infarction; STEMI) and those without (UA, NSTEMI). STEMI is discussed in Chapters 44 and 45. As UA and NSTEMI are indistinguishable at initial presentation, they are grouped together as non-ST elevation ACS (NSTE-ACS).

In order to differentiate between UA and NSTEMI, the cardiac biomarker troponin T is measured. This is a protein integral to muscle contraction in cardiac muscle and is released into the blood by the death of cardiac cells. In NSTEMI there is a troponin rise, indicating myocyte necrosis, but in UA there is not. Both NSTEMI and UA may be associated with ECG changes other than ST elevation, for example ST segment depression and T-wave inversion. Symptoms of NSTE-ACS resemble those of stable angina, but they are generally more severe and persistent. Typical presentations include:

1 Angina of recent onset at rest or on minimal exertion or that which awakens the patient from sleep and lasts >10 mins.

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2 An accelerating pattern of angina attacks, which are progressively more severe, prolonged and frequent.
3 Post-MI angina (ischaemic pain 24 h to 2 weeks after MI).

Pathophysiology of NSTE-ACS

Episodes of unstable angina are preceded by a fall in coronary blood flow, thought to result from the periodic development of coronary **thrombosis** and **vasoconstriction**, which are triggered by coronary artery disease (Figure 42.2).

Thrombosis is promoted by the endothelial damage and turbulent blood flow associated with atherosclerotic plaques. Compared with the lesions of stable angina, plaques found in patients with ACS tend to have a thinner fibrous cap and a larger lipid core and are generally more widespread and severe. These stenoses are often *eccentric* – the plaque does not surround the entire circumference of the artery. Such lesions are especially vulnerable to being ruptured by haemodynamic stress. This exposes the plaque interior, which powerfully stimulates platelet aggregation and thrombosis. The thrombus propagates out into the coronary lumen, occluding the artery. Rupture may also cause haemorrhage into the lesion itself, expanding it out into the lumen and worsening stenosis.

These events may be exacerbated by impaired coronary vasodilatation, and vasospasm due to plaque-associated endothelial damage, which reduces the local release of endothelium-dependent relaxing factors, such as nitric oxide. Platelet aggregation and thrombosis also cause the local generation of vasoconstrictors such as thromboxane A_2 and serotonin.

Management of NSTE-ACS (Figure 42.3)

The management of NSTE-ACS involves acute stabilisation of the patient, treatment of the culprit lesion and long-term management aimed at preventing disease progression and future plaque rupture/erosion events (secondary prevention). According to the European Society of Cardiology guidelines, those with **very high risk** NSTE-ACS (haemodynamic instability, refractory symptoms, ventricular arrhythmias, acute heart failure, dynamic ST/T wave changes) require *immediate* invasive angiography and percutaneous coronary intervention (PCI) if indicated. Patients with a **high risk** profile (elevated troponin, dynamic ECG changes) benefit from an **early invasive strategy**, that is, angiography and PCI if indicated *within 24 hours*. Patients at **intermediate risk** (diabetes, chronic kidney disease, impaired LV function, prior PCI or coronary artery bypass grafting (CABG)) should undergo angiography and PCI if indicated *within 72 hours*. Not all patients with NSTE-ACS are suitable for angiography; in the very elderly and frail population, or in those with high bleeding risk, medical therapy is appropriate.

Long-term **optimal medical therapy** aims to prevent future acute coronary events and slow the progression of atherosclerosis.

Antiplatelet therapy (Chapter 8) Patients with NSTE-ACS are immediately treated with **300 mg aspirin**. This is then reduced to 75 mg/day, lifelong. Aspirin suppresses platelet aggregation. A meta-analysis of randomised controlled trials showed that aspirin is associated with a highly significant reduction in major vascular events.

The **$P2Y_{12}$ inhibitor clopidogrel** is an inactive prodrug which requires activation by the cytochrome P450 system to generate its active metabolite. Its onset time is 2–6 hours. It inhibits ADP-stimulated platelet aggregation and was shown in the 2000 CURE trial to reduce cardiovascular morbidity and mortality by ~20% in patients with NSTE-ACS.

Ticagrelor is a reversibly binding $P2Y_{12}$ inhibitor with a 30 min onset time. The PLATO trial in 2009 demonstrated that in ACS patients, ticagrelor compared to clopidogrel reduced the primary endpoint of cardiovascular death, MI and stroke. The bleeding risk was higher with ticagrelor but the incidence of life-threatening or fatal bleeds was the same. Therefore ticagrelor has superseded clopidogrel in the ACS setting apart from in older patients with a higher bleeding risk.

Prasugrel is a prodrug which irreversibly blocks platelet $P2Y_{12}$ receptors with a rapid onset time of 30 mins. It was compared to clopidogrel in ACS patients in the TRITON-TIMI 38 trial and reduced cardiovascular events but was associated with more severe bleeding complications and is contraindicated in patients with prior stroke or transient ischaemic attack.

Cangrelor is an intravenous adenosine triphosphate analogue with a very rapid onset time (2 min) that reversibly binds to the $P2Y_{12}$ receptor. A meta-analysis showed that cangrelor resulted in a 19% relative risk reduction of periprocedural death, MI, ischaemia-driven revascularisation and stent thrombosis when compared to clopidogrel. As with prasugrel, the bleeding risk was increased. Cangrelor is currently licensed for patients undergoing PCI in whom oral therapy with a $P2Y_{12}$ inhibitor is not feasible, for example, in those who are unconscious.

Intravenous **glycoprotein IIb/IIIa inhibitors** (abciximab, tirofiban) block fibrinogen-mediated cross-linkage of platelets. These drugs are generally used in patients undergoing PCI. In patients treated with ticagrelor or prasugrel, glycoprotein IIb/IIIa inhibitors should be restricted to periprocedural thrombotic complications as the bleeding risk of giving both drugs has not been prospectively addressed.

Anticoagulant therapy Anticoagulants inhibit thrombin generation and/or activity. The combination of antiplatelet and anticoagulant drugs is more effective at reducing ischaemic events in NSTE-ACS than either treatment alone. **Unfractionated heparin** is routinely given to patients during elective and emergency angiography done via the radial route to prevent radial artery occlusion. If PCI is undertaken, higher doses of unfractionated heparin are given to prevent thrombus formation at the site of balloon injury and on angioplasty equipment. The **low molecular weight heparin (LMWH) enoxaparin** was associated with a marginally lower incidence of death or MI in ACS compared to unfractionated heparin according to a meta-analysis. **The factor Xa inhibitor fondaparinux** binds reversibly to antithrombin, thereby preventing thrombin generation. The OASIS-5 trial found that in NSTE-ACS, fondaparinux resulted in less bleeding and less mortality than enoxaparin.

Antianginal drugs **β-Blockers** are beneficial in MI for several reasons. They diminish O_2 demand by lowering the heart rate and decrease ventricular wall stress by lowering afterload. They therefore reduce ischaemia and infarct size when given acutely. They also decrease recurrent ischaemia and free wall rupture, and suppress arrhythmias (see Chapter 48). They should be given unless contraindicated (e.g. acute left ventricular failure since they are negatively inotropic, high grade atrioventricular block, severe asthma).

Nitrates can be given for symptom control, but do not reduce mortality.

In terms of long term management, **statins** and **angiotensin-converting enzyme inhibitors (ACEI)** improve survival in NSTE-ACS and are used routinely for secondary prevention. **ACEI** (e.g. enalapril, ramipril) reduce afterload and ventricular wall stress and improve ejection fraction. Inhibition of ACE raises bradykinin levels, which may improve endothelial function and limit coronary vasospasm. ACEI also limit ventricular remodelling and infarct expansion (see Chapter 47), thereby reducing mortality and the incidence of congestive heart failure and recurrent MI. Therapy should be instituted within 24 h in patients with STEMI, especially if there is evidence of heart failure or left ventricular dysfunction, and should continue long term if LV dysfunction remains evident.

43 Coronary revascularisation

Figure 43.1 Percutaneous coronary intervention (PCI)

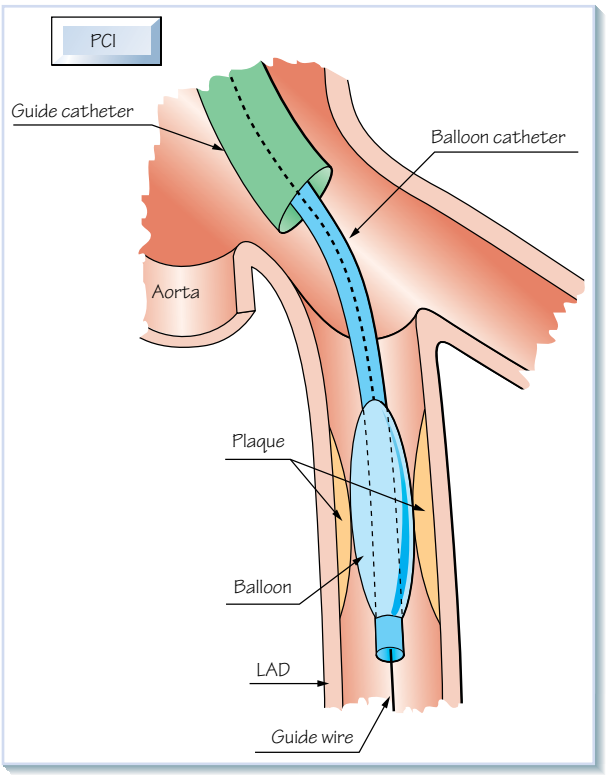
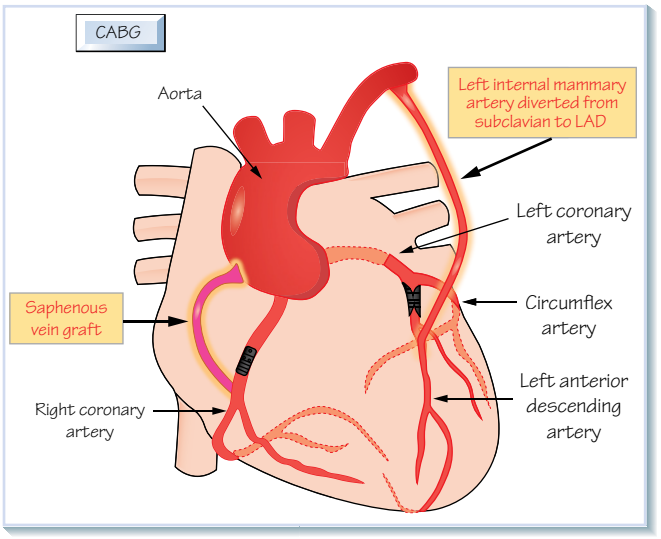


Figure 43.2 Coronary artery bypass grafting (CABG)



Revascularisation is the restoration of perfusion to ischaemic myocardium. **Percutaneous coronary intervention (PCI)** and **coronary artery bypass grafting (CABG)** are revascularisation techniques used to treat patients with both acute coronary syndromes and stable coronary artery disease (CAD). The choice of technique is determined by several factors including extent of disease and patient choice.

Percutaneous coronary intervention

(Figure 43.1)

PCI was first performed in 1977 by Andreas Gruentzig and the field has expanded enormously over the past 4 decades. In a typical procedure, an angiogram is taken to demonstrate the coronary anatomy and pattern of disease. If the decision is made to proceed to revascularisation, a **guide catheter** is introduced via the radial or femoral artery and is positioned in the right or left main coronary ostium. A **guide wire** is then advanced through the guide catheter down the lumen of the coronary artery distal to the lesion. A **balloon catheter** is advanced over the guide wire and inflated at the site of the stenosis in what is termed **pre-dilation** (Figure 43.1). A **stent** is then deployed at the site of the lesion to act as a tubular scaffold maintaining vessel patency. Another balloon catheter is advanced and inflated at the site of the stent to improve its expansion against the vessel wall (**post-dilation**). PCI is deemed a success if blood flow is restored to a normal level.

Primary PCI refers to the emergency revascularisation of a patient who has suffered an ST segment elevation myocardial infarction (STEMI). These patients are typically brought directly to a cardiac catheterisation laboratory ('**cath lab**') where an emergency team is waiting. In the UK, primary PCI accounts for more than a quarter of all PCI activity, the remainder being for non-ST segment elevation MI and stable angina.

Complications of PCI include **stent thrombosis**, which is the acute occlusion of the stent with a thrombus, and **in-stent restenosis**, which is a gradual narrowing of the stented vessel lumen due to neointimal proliferation which occurs as part of the immune response to a foreign body. Stent thrombosis usually results in an acute coronary syndrome and in-stent restenosis often results in a return of angina. **Drug-eluting stents (DES)** were developed to overcome in-stent restenosis, a particular problem with bare metal stents in which restenosis rates can be up to 25%. DES elute antiproliferative medications (e.g. zotarolimus, everolimus) up to 180 days after implantation, which reduces inflammation and excessive neointimal growth. Restenosis rates with current second generation DES are in the single digits.

DES require **dual antiplatelet therapy** (DAPT) due to the increased risk of late stent thrombosis. Despite advances in stent

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technology, stent thrombosis and in-stent restenosis remain complications of PCI. The continued use of bare metal stents is controversial. Proponents argue that they are safer in those with a higher bleeding risk owing to the much shorter duration of DAPT required. However the 2017 SENIOR trial showed that in elderly patients undergoing PCI, a DES and shorter duration of DAPT was preferred to a bare metal stent and similar duration of DAPT in terms of all-cause mortality.

Recent innovations in the field of interventional cardiology include **drug-coated balloons**, which deliver an antiproliferative medication (paclitaxel) to the vessel wall and were shown in the 2017 DARE trial to be noninferior to everolimus-eluting stents in the treatment of in-stent restenosis.

Bioresorbable vascular scaffolds are a new technology in which the implant degrades over time. The aim is to overcome the late complications of stenting. However early trials have been disappointing with a higher incidence of adverse cardiac events compared to drug-eluting stents.

The role of PCI in stable coronary artery disease

Whilst the role of PCI in acute coronary syndromes is indisputable in terms of improving survival, its role in stable CAD is less clear. One of the most important trials in the management of stable CAD was COURAGE. It compared optimal medical therapy (OMT) to OMT + PCI in more than 2000 patients with stable CAD. It showed that while OMT + PCI did not lead to a reduction in mortality compared to OMT alone at 4.6 years' follow-up, it did reduce anginal symptoms. However, the rates of angina equalised within 5 years.

The groundbreaking 2017 ORBITA trial was the first placebo-controlled trial of PCI in stable CAD. It compared OMT + PCI to OMT + placebo PCI, that is, a sham procedure in patients with single vessel coronary disease and angina. It found that there was no difference between treadmill exercise time after 6 weeks but there was a significant change in dobutamine stress echocardiography wall motion score index favouring the OMT + PCI group.

The ISCHEMIA trial is currently enrolling 8000 patients with moderate ischaemia on stress testing and will randomise patients to PCI + OMT or OMT alone. It aims to define the role of PCI in stable CAD in the modern era.

Coronary artery bypass grafting (CABG)

(Figure 43.2)

CABG was introduced in the 1960s. In a typical triple bypass operation, the left internal mammary artery (LIMA; a branch of the subclavian artery) is grafted onto the left anterior descending artery (LAD), and segments of harvested saphenous vein are grafted from the aorta onto the left circumflex artery (LCx) or its branches. The saphenous vein is also used to graft from the aorta onto the right coronary artery (RCA). Vein grafts have limited long-term patency due to early thrombosis, intimal hyperplasia with smooth muscle proliferation within the first year, and the development of atherosclerosis after approximately 5–7 years. Most arterial grafts remain patent after 10 years and are associated with improved survival compared with vein grafts alone. The use of both left and right internal mammary arteries (**bilateral internal mammary artery**) for grafting has become more common, especially in younger patients. For example, the right internal mammary artery (RIMA) may be grafted to the LAD while the LIMA is anastomosed onto the circumflex system. The radial artery is also used as a graft in CABG. The operation is usually performed with the patient on *cardiopulmonary bypass*, with the heart stopped (cardioplegia). Blood is removed from the right atrium, drained into a reservoir, and then pumped through an oxygenator, then a filter and back into the aorta to perfuse the systemic circulation. The main complications are a systemic inflammatory response, atrial fibrillation and stroke. The latter is thought to be caused by emboli, either formed in the bypass circuit or produced by disturbance of aortic plaques during cannulation, which lodge in the cerebral vasculature. These complications can be avoided by *off-pump CABG*, which does not involve stopping the heart. In this case, the region of the cardiac wall encompassing the target coronary segment is immobilised to allow grafting. Randomised trials show that both types of CABG offer similar outcomes. The mortality rate associated with CABG is ~2%. Advances in surgical technique mean it is possible to perform minimally invasive bypass grafting which does not require a sternotomy. This approach is called **minimally invasive direct CABG** or MIDCAB. Typically, the LIMA is harvested under direct visualisation through a small thoracotomy incision or endoscopically and is anastomosed onto the LAD.

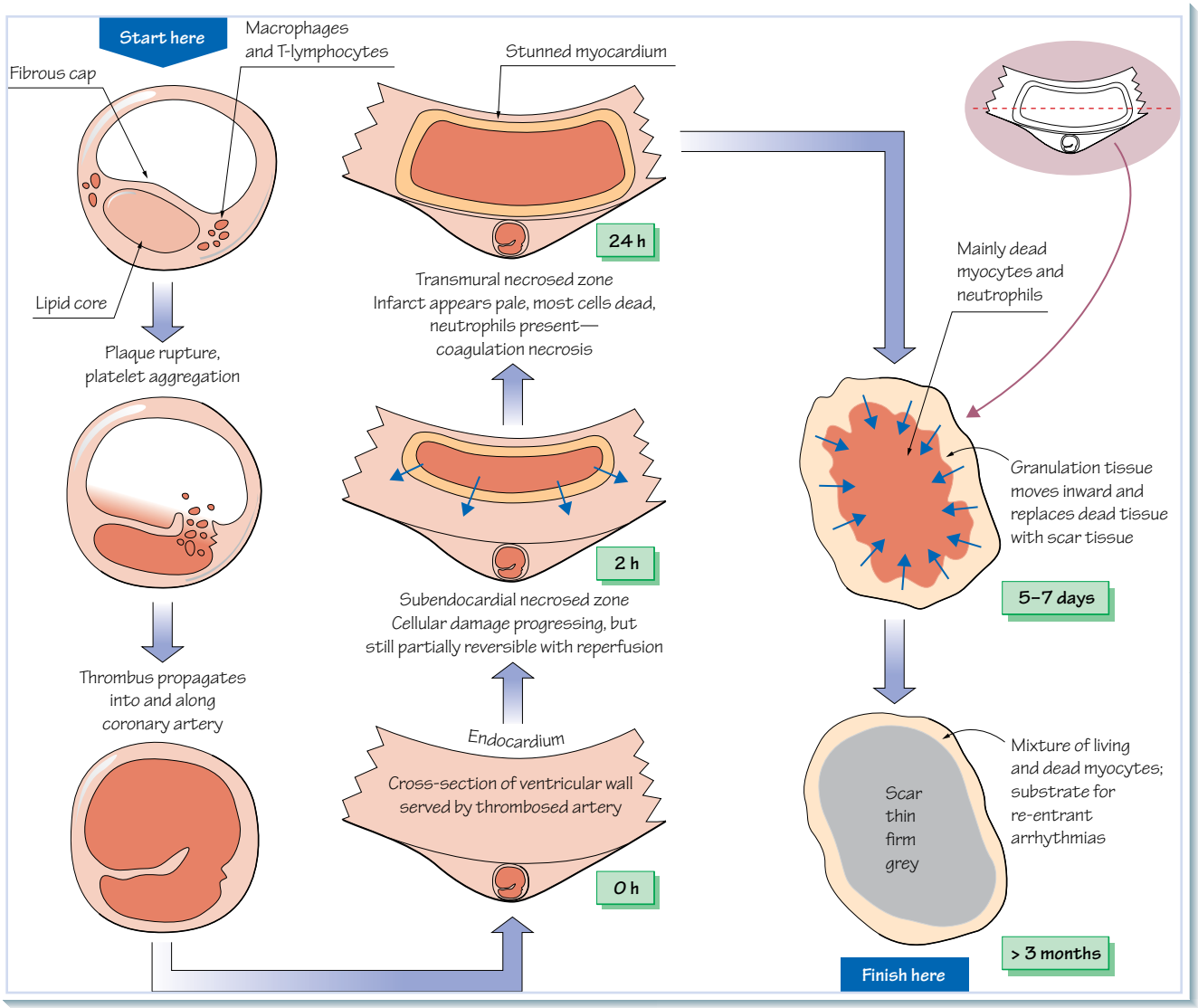
PCI vs CABG in stable coronary artery disease

PCI outcomes are similar to CABG in stable CAD if there is one- or two-vessel disease not involving the proximal LAD, or if there is three-vessel disease with simple lesions amenable to PCI. CABG is preferred if there is distal left main stem disease and two- or three-vessel disease or in diabetic patients with multivessel disease.

The SYNTAX trial compared PCI to CABG in stable CAD and showed that in complex multivessel CAD, CABG is superior to PCI in terms of rates of death, MI, stroke or repeat revascularisation. Follow-on analysis of the FREEDOM trial at 7.5 years showed that in diabetic patients, CABG retains a mortality benefit over PCI in patients with multivessel CAD.

44 Pathophysiology of acute myocardial infarction

Figure 44.1 Pathophysiology of acute MI



Infarction refers to the death of any tissue by ischaemia. Acute **myocardial infarction** (MI) refers to the death of myocardial tissue due to acute ischaemia. Ischaemia may be due to coronary thrombosis or other factors which cause an imbalance between O_2 supply and demand to the myocardium. The **Fourth Universal Definition of Myocardial Infarction (2018)** categorises five types of MI, only the first of which is caused by occlusive or non-occlusive thrombus and leads to STEMI/NSTEMI respectively.

Type 1 MI: spontaneous MI is related to atherosclerotic plaque rupture, ulceration, fissuring, erosion or dissection with resulting intraluminal thrombosis in one or more coronary arteries leading to decreased myocardial blood flow, or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe coronary artery disease (CAD), but on occasion non-obstructive or no CAD.

Type 2 MI: MI secondary to ischaemic imbalance *not* due to acute plaque rupture and consequent occlusive or non-occlusive coronary thrombosis. Rather, the myocardial injury is caused by the following conditions: fixed atherosclerosis, coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/bradyarrhythmias, anaemia, respiratory failure, hypotension and hypertension. The management of type 2 MI is to treat the underlying cause of the myocardial injury.

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Type 3 MI: patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia but die before blood samples for cardiac biomarkers can be obtained.

Type 4 and type 5 MI are due to myocardial injury secondary to percutaneous coronary intervention and coronary artery bypass grafting respectively.

Role of thrombosis in MI

Pivotal studies by DeWood and colleagues showed that *coronary thrombosis* is the critical event resulting in type 1 MI. Of patients presenting within 4 h of symptom onset with ECG evidence of transmural MI, coronary angiography showed that 87% had complete thrombotic occlusion of the infarct-related artery. The incidence of total occlusion fell to 65% 12–24 h after symptom onset due to spontaneous fibrinolysis. Fresh thrombi on top of ruptured plaques have also been demonstrated in the infarct-related arteries in patients dying of MI.

Mechanisms and consequences of plaque rupture (Figure 44.1)

Coronary plaques that are prone to rupture are typically small and non-obstructive, with a large lipid-rich core covered by a thin fibrous cap. These 'high-risk' plaques typically contain abundant **macrophages** and **T lymphocytes** which are thought to release **metalloproteases** and **cytokines** that weaken the fibrous cap, rendering it liable to tear or erode due to the shear stress exerted by the blood flow.

Plaque rupture reveals subendothelial collagen, which serves as a site of platelet adhesion, activation and aggregation. This results in:

1. The release of substances such as *thromboxane A_2 (TXA_2)*, *fibrinogen*, *5-hydroxytryptamine (5-HT)*, *platelet activating factor* and *adenosine diphosphate (ADP)*, which further promote platelet aggregation.
2. Activation of the clotting cascade, leading to fibrin formation and propagation and stabilization of the occlusive thrombus.

The endothelium is often damaged around areas of coronary artery disease. The resulting deficit of antithrombotic factors such as *thrombomodulin* and *prostacyclin* enhances thrombus formation. In addition, the tendency of several platelet-derived factors (e.g. TXA_2, 5-HT) to cause vasoconstriction is increased in the absence of endothelial-derived relaxing factors. This may promote the development of local vasospasm, which worsens coronary occlusion.

Sudden death and acute coronary syndrome onset show a **circadian variation** (daily cycle), peaking at around 9 a.m. with a trough at around 11 p.m. Levels of catecholamines peak about an hour after awakening in the morning, resulting in maximal levels of platelet aggregability, vascular tone, heart rate and blood pressure, which may trigger plaque rupture and thrombosis. Increased physical and mental stress can also cause MI and sudden death, supporting a role for increases in catecholamines in MI pathophysiology. Furthermore, chronic β-adrenergic receptor blockade abolishes the circadian rhythm of MI.

Autopsies of young people killed in road traffic accidents often show small plaque ruptures in susceptible arteries, suggesting that plaque rupture does not always have pathological consequences. The degree of coronary occlusion and myocardial damage caused by plaque rupture probably depends on systemic catecholamine levels, as well as local factors such as plaque location and morphology, the depth of plaque rupture and the extent to which coronary vasoconstriction occurs.

Severe and prolonged ischaemia produces a region of necrosis spanning the entire thickness of the myocardial wall. Such a *transmural* infarct usually causes ST segment elevation (i.e. STEMI; see Chapter 45). Less severe and protracted ischaemia can arise when:

1. Coronary occlusion is followed by spontaneous reperfusion
2. The infarct-related artery is not completely occluded
3. Occlusion is complete, but an existing collateral blood supply prevents complete ischaemia
4. The oxygen demand in the affected zone of myocardium is smaller.

Under these conditions, the necrotic zone may be mainly limited to the subendocardium, typically causing non-ST segment elevation MI.

Evolution of the infarct (Figure 44.1)

Both infarcted and unaffected myocardial regions undergo progressive changes over the hours, days and weeks following coronary thrombosis. This process of postinfarct myocardial evolution leads to the occurrence of characteristic complications at predictable times after the initial event (see Chapter 45).

Ischaemia causes an immediate loss of contractility in the affected myocardium, a condition termed **hypokinesis**. Necrosis starts to develop in the subendocardium (which is most prone to ischaemia; see Chapter 26), about 15–30 min after coronary occlusion. The necrotic region grows outward towards the epicardium over the next 3–6 h, eventually spanning the entire ventricular wall. In some areas (generally at the edges of the infarct) the myocardium is **stunned** (reversibly damaged) but will eventually recover if blood flow is restored. Contractility in the remaining viable myocardium increases, a process termed **hyperkinesis**.

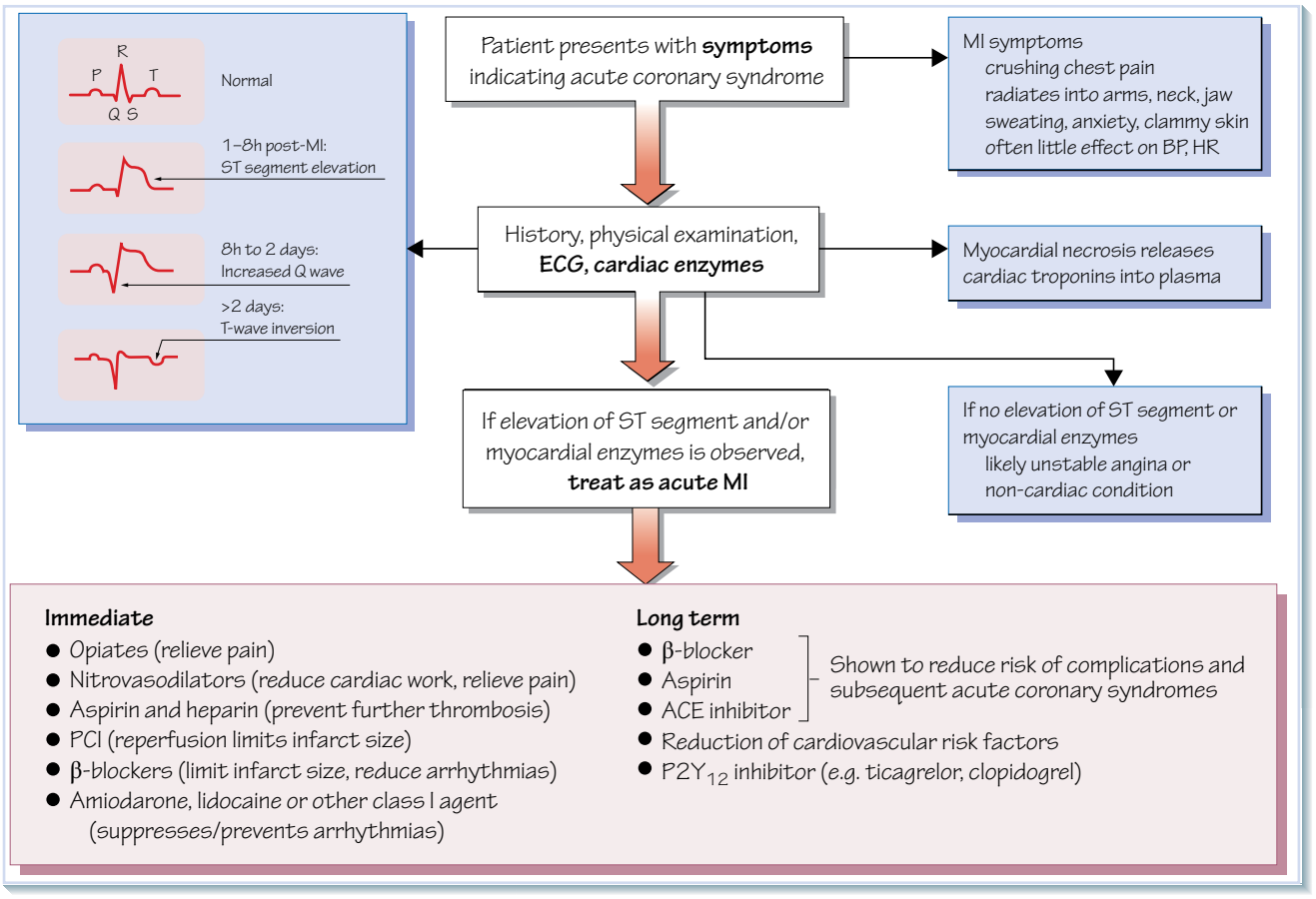
A progression of cellular, histological and gross changes develop within the infarct. Although alterations in the gross appearance of infarcted tissue are not apparent for at least 6 h after the onset of cell death, cell biochemistry and ultrastructure begin to show abnormalities within 20 min. Cell damage is progressive, becomingly increasingly irreversible over about 12 h. This period therefore provides a window of opportunity during which percutaneous coronary intervention (PCI) or thrombolysis leading to reperfusion may salvage some of the infarct (see Chapter 43).

Between 4 and 12 h after cell death starts, the infarcted myocardium begins to undergo **coagulation necrosis**, a process characterized by cell swelling, organelle breakdown and protein denaturation. After about 18 h, **neutrophils** (phagocytic lymphocytes) enter the infarct. Their numbers reach a peak after about 5 days and then decline. After 3–4 days, **granulation tissue** appears at the edges of the infarct zone. This consists of **macrophages**, **fibroblasts**, which lay down scar tissue, and **new capillaries**. The infarcted myocardium is especially soft between 4 and 7 days and is therefore maximally prone to **rupturing**. This event is usually fatal, may occur at any time during the first 2 weeks, and is responsible for about 10% of MI mortality. As the granulation tissue migrates inward toward the centre of the infarct over several weeks, the necrotic tissue is engulfed and digested by the macrophages. The granulation tissue then progressively matures, with an increase in connective (scar) tissue and loss of capillaries. After 2–3 months, the infarct has healed, leaving a non-contracting region of the ventricular wall that is thinned, firm and pale grey.

Infarct expansion, the stretching and thinning of the infarcted wall, may occur within the first day or so after an MI, especially if the infarction is large or transmural, or has an anterior location. Over the course of several months, there is progressive dilatation, not only of the infarct zone, but also of healthy myocardium. This process of **ventricular remodelling** is caused by an increase in end diastolic wall stress. Infarct expansion puts patients at a substantial risk for the development of congestive heart failure, ventricular arrhythmias and free wall rupture.

45 ST segment elevation myocardial infarction (STEMI)

Figure 45.1 Management of acute MI



ST segment elevation myocardial infarction (STEMI) is the most severe of the acute coronary syndromes (ACS). It is defined by characteristic symptoms of myocardial ischaemia in association with persistent electrocardiographic ST segment elevation and release of biomarkers of myocardial necrosis. It usually indicates complete blockage of a coronary artery with thrombus following acute plaque rupture.

Symptoms and signs (Figure 45.1)

The typical presentation of STEMI is with sudden onset central or retrosternal chest pain, which may radiate down the left arm or to the neck or jaw. There may be associated breathlessness, nausea or vomiting. The pain occurs at rest or with minimal exertion and typically lasts longer than 20 min and is not relieved by glyceryl trinitrate (GTN) spray.

The patient will appear anxious and in distress. The heart rate may be normal or demonstrate a tachycardia or bradycardia. The blood pressure is usually normal but if the infarct is severe enough to cause cardiogenic shock, the systolic BP will be by definition below 90 mmHg. The rest of the cardiovascular examination may be unremarkable, but there may be a third or fourth heart sound on auscultation as well as a new and/or worsening murmur and bibasal crackles indicating pulmonary oedema. Patients can also present in cardiac arrest.

Investigations

- **ECG** (Figure 45.1): ECG changes associated with myocardial infarction (MI) indicate the area of the heart which has infarcted. In STEMI there is ST segment elevation of at least 2.5 mm in men aged under 40 years; at least 2 mm ST segment elevation in men aged 40 years and older or at least 1.5 mm in women in leads V2–V3 and/or at least 1 mm in the other leads. A posterior STEMI resulting from an acutely occluded circumflex artery is indicated by ST segment depression in leads V1–V3. New left

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bundle branch block in the context of an appropriate clinical presentation should be treated as a STEMI equivalent.
- **Cardiac biomarkers:** STEMI is unique in the acute coronary syndromes in that it is diagnosed on clinical presentation and ECG alone without the need to wait for the serum troponin result.

Immediate management (Figure 45.1)

At the point of first medical contact the patient is assessed by brief history and clinical examination, and is connected to an ECG monitor with defibrillation capacity. A 12 lead ECG is recorded. To prevent further platelet aggregation300 mg chewable **aspirin** and 180 mg **ticagrelor** are given. **GTN** is sprayed underneath the tongue. Oxygen is given if the peripheral saturations are less than 90%. **Morphine**, which has vasodilator properties, together with an antiemetic (e.g. metoclopramide) is administered to relieve pain and anxiety, thus reducing the tachycardia that these cause. The gold standard treatment of STEMI is emergent **revascularisation** with **primary percutaneous coronary intervention** (PPCI; see Chapter 43) of the culprit vessel within 2 h of symptom onset. Revascularisation allows reperfusion, which limits infarct size and reduces the risk of complications such as arrhythmias and heart failure.

Not every acute hospital is a PCI centre. Those that are not are affiliated with centres that are and protocols exist to enable the rapid transfer of patients. If the anticipated time from diagnosis of STEMI to PCI-mediated reperfusion is greater than 120 minutes, the alternative treatment is immediate **thrombolysis**. This is pharmacological dissolution of the clot with **thrombolytic agents** (e.g alteplase and tenecteplase) within 12 h of presentation unless contraindicated (see below). Thrombolytic agents induce **fibrinolysis**, which is the fragmentation of the fibrin strands holding the clot together. The main risk of thrombolysis is bleeding, particularly intracerebral haemorrhage, which occurs in ~1% of cases. Contraindications to thrombolysis therefore include recent haemorrhagic stroke, recent surgery or trauma, and severe hypertension. If thrombolysis fails to restore perfusion, the patient must be sent for rescue PCI to be performed as soon as possible.

Subsequent management (Figure 45.1)

Following treatment with PCI, the patient is admitted to the **coronary care unit** where they are closely monitored. An echocardiogram is performed to assess left ventricular systolic function, which may be moderately or severely impaired in the case of a large territory infarct. The patient has already been started on **dual antiplatelet therapy** (aspirin and ticagrelor) and further **secondary prevention** medications are added to reduce the risk of reinfarction. These are the same medications that are given in cases of non-ST segment elevation ACS (Chapter 42). They are a **β-blocker** such as bisoprolol, an **angiotensin-converting enzyme inhibitor** (ACEI) such as ramipril, plus the **mineralocorticoid antagonist** eplerenone if the left ventricle (LV) ejection fraction is equal to or less than 40%, and **high dose statin**. The EPHESUS study in 2003 demonstrated that in patients with acute myocardial infarction complicated by left ventricular dysfunction, the addition of eplerenone to standard medical therapy reduced mortality. Cardiac risk factors such as smoking, diabetes and hypertension are addressed. The patient is referred to cardiac rehabilitation after discharge from hospital. This is a programme of exercise and education sessions that permit patients to get back to everyday life as successfully as possible.

Complications of acute myocardial infarction

Complications of acute MI are either mechanical or arrhythmic.

With large infarcts, depression of pump function is sufficient to cause **cardiac failure**. An infarct involving more than 40% of the LV causes **cardiogenic shock**. It is heralded by a large fall in cardiac output, pulmonary congestion and hypotension. The mortality is extremely high. Treatment involves O_2 to prevent hypoxaemia and positive inotropes (e.g. the β_1-agonist dobutamine) to aid myocardial contractility. Revascularization is crucial. An **intra-aortic balloon pump (IABP)** can be used temporarily to support the circulation. A catheter-mounted balloon is inserted via the femoral artery and positioned in the descending thoracic aorta. The balloon is inflated during diastole, increasing the pressure in the aortic arch and thereby improving perfusion of the coronary and cerebral arteries. During systole, deflation of the balloon creates a suction effect that reduces ventricular afterload and promotes systemic perfusion.

Rupture of the LV free wall is almost always fatal. Rupture of the ventricular septum creates a **ventricular septal defect** (VSD) and may result in leakage of blood between the ventricles. Rupture of the myocardium underlying a papillary muscle, or more rarely of the papillary muscle itself, may cause **mitral regurgitation**, detected clinically as a pansystolic murmur radiating to the axilla. **Dressler's syndrome** is the triad of pericarditis, pericardial effusion and fever. It is believed to be an autoimmune-mediated reaction to myocardial antigens produced after an MI.

Arrhythmias in the acute phase include the potentially life-threatening broad complex (QRS duration >0.12 s) tachycardias, ventricular tachycardia (VT) or ventricular fibrillation (VF). Supraventricular arrhythmias include atrial flutter and atrial fibrillation. Bradyarrhythmias are also common, especially in inferior infarcts, as the right coronary artery supplies the sinoatrial and atrioventricular nodes. **Infarct expansion** (see Chapter 44) is a dangerous late complication.

46 Heart failure

Figure 46.1 Underlying causes of heart failure

Primary defect	Examples
Myocardial dysfunction	Ischaemic heart disease, Diabetes mellitus Pregnancy, congenital cardiomyopathies Myocardial disease e.g. amyloidosis
Volume overload	Aortic or mitral valve regurgitation
Pressure overload	Aortic stenosis, hypertension

Primary defect	Examples
Impaired filling	Reduced ventricular compliance: hypertension, hypertrophy, fibrosis Constrictive pericarditis: rheumatic heart disease Cardiac tamponade: excess fluid pressure in pericardial space
Arrhythmias	Atrial fibrillation
High output	Thyrotoxicosis, arteriovenous shunts, anaemia

Figure 46.2 Cardiac function curve

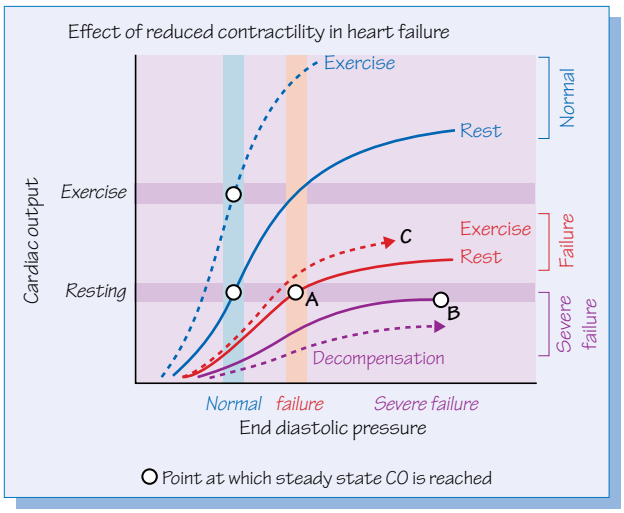


Figure 46.4 Role of neurohumoral mechanisms in progression of heart failure

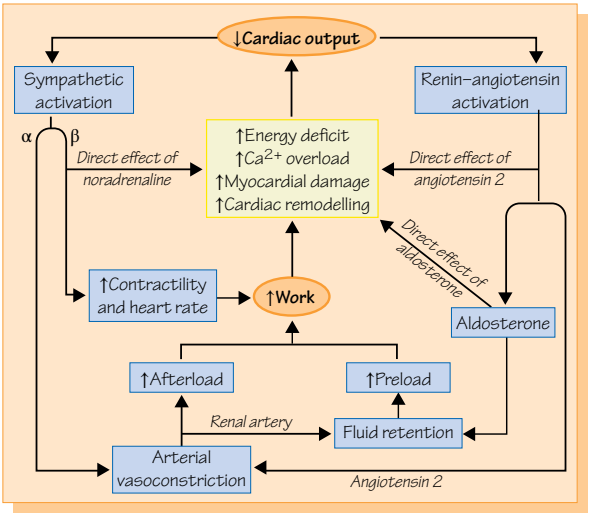
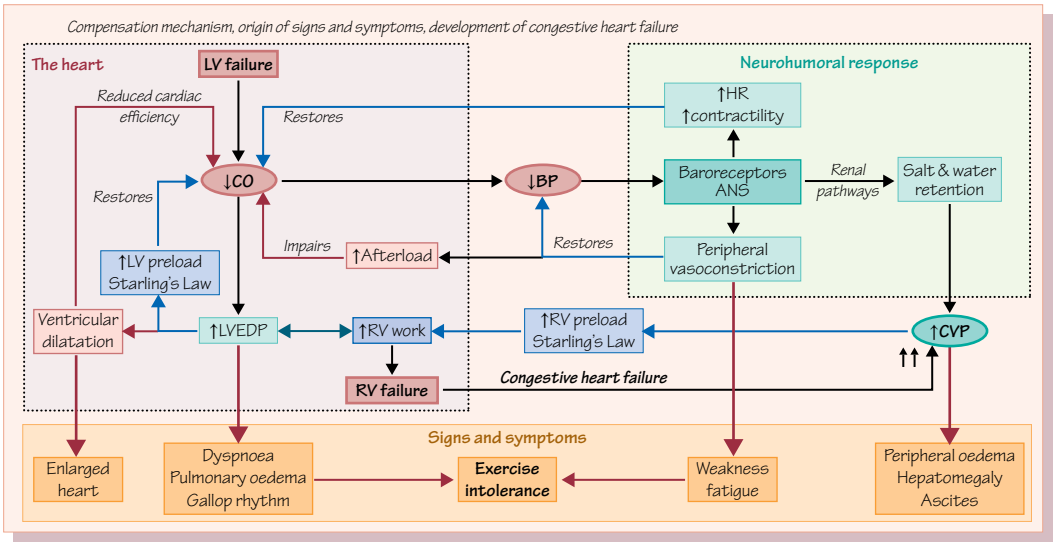


Figure 46.3 Consequences of left ventricular failure due to ischaemic heart disease (dependent on severity)



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Heart failure is a complex syndrome in which the heart is incapable of generating sufficient cardiac output (CO) to meet the demands of the body. Initially, compensatory mechanisms may allow adequate CO to be maintained at rest but not during exercise (**exercise intolerance**). Eventually CO cannot be maintained at rest (**decompensation**); this can be precipitated by infection (e.g. influenza), stress, arrhythmias, acute coronary syndrome, or drugs causing water or salt retention (e.g. NSAIDs) or that are cardiotoxic (e.g. alcohol). Heart failure is predominantly a disease of older people. It occurs in ~2% of patients under 50 years, but in 10–20% over 70; 5-year survival is poor (<50%). There are many underlying causes (Figure 46.1).

Types of heart failure

Heart failure with a reduced ejection fraction (HFrEF) (systolic failure): Most common (~70% cases), due to impaired left ventricular function with an **ejection fraction** <45% (Figure 46.2); most often a consequence of ischaemic heart disease (IHD).

Heart failure with preserved ejection fraction (HFpEF) (diastolic failure): Heart failure presents with a normal or mildly reduced ejection fraction, due to **impaired ventricular relaxation** and **ventricular filling**; caused by increased ventricular stiffness due to fibrosis, hypertrophy, or cardiac restriction (e.g. pericarditis). Most common in hypertension, obesity and diabetes.

Left heart failure refers to a clinical picture dominated by **pulmonary congestion** and thus **dyspnoea** (breathlessness), whereas in *right heart failure* the dominant features are a **raised central venous pressure (CVP)** and **peripheral oedema**. Right heart failure may result from chronic lung disease (**cor pulmonale**), pulmonary hypertension (Chapter 58) or pulmonary embolism. It most commonly occurs secondary to left heart failure; in *biventricular (or* **congestive***) heart failure* the clinical picture includes signs and symptoms of both left and right heart failure.

High output failure occurs when a healthy heart is unable to meet grossly elevated demands for output due to anaemia or a drastically reduced peripheral resistance (e.g. septic shock).

Acute heart failure describes a sudden loss of cardiac function, for example **acute coronary syndrome** (Chapter 44), resulting in sudden onset pulmonary congestion and cardiogenic shock (Chapter 31).

Pathophysiology

The pathophysiology of chronic heart failure is largely a consequence of mechanisms that compensate for reduced cardiac function. Impaired cardiac function causes accumulation of venous blood and thus raised filling pressures, so CO increases as a consequence of **Starling's law** (Figures 46.2, 46.3; Chapter 17). **Neurohumoral** mechanisms are activated by the **baroreceptor reflex** (Figure 46.4; Chapter 28), and the autonomic nervous system and circulating catecholamines stimulate increases in heart rate and contractility, arterial vasoconstriction (raises total peripheral resistance [TPR]) and venoconstriction (raises CVP) (Chapters 12 and 17). Sympathetic stimulation of renal granular cells and reduced renal perfusion cause release of **renin**, and consequently **angiotensin 2** and **aldosterone; vasopressin** (antidiuretic hormone, ADH) also increases. These cause renal sodium and water retention and so elevate blood volume and CVP (and thus CO through Starling's law) (Chapter 29). Angiotensin 2 and vasopressin also increase TPR. In mild disease these mechanisms can maintain CO and blood pressure without overt symptoms. However, end-diastolic pressure (EDP) and volume (EDV) are always elevated (Figure 46.2, A) so **ejection fraction** is reduced, an early sign of heart failure.

As cardiac function declines, CO can be maintained only by an ever-increasing CVP and heart rate (Figure 46.2, B), fostering further **myocardial damage** (see below). This vicious circle drives a relentless decay towards decompensation and death. Although adequate CO may be maintained at rest even in quite severe failure, this is at the expense of greatly increased venous pressures as the function curve flattens and Starling's law becomes less effective (Figure 46.2, A,B; Chapter 17). High venous pressures underlie most signs and symptoms of heart failure.

Consequences of compensation (Figure 46.3)

Initially, symptoms only appear during exertion, which exacerbates the rise in venous pressures (Figure 46.2, C); this limits the ability to exercise (**exercise intolerance**). Any increase in contractility and heart rate during exercise is small because they are already strongly stimulated at rest, and in late disease β-adrenoceptor density and sensitivity are reduced. **Dyspnoea** on exertion is often the first symptom of left heart failure. It is caused by **pulmonary congestion** due to the raised pulmonary venous pressure, making the lungs stiffer and so promoting the sensation of breathlessness. Redistribution of blood to the lungs on lying down or during sleep can instigate dyspnoea (**orthopnoea**; **paroxysmal nocturnal dyspnoea**), and in severe failure and decompensation **pulmonary oedema**, when fluid enters the alveoli. This is a life-threatening condition causing extreme dyspnoea and hypoxaemia.

A high CVP similarly causes **peripheral oedema** (Chapter 21), **hepatomegaly** and **ascites**, common features of **right** and **congestive heart failure**. High EDP eventually leads to **cardiac dilation** and a greatly enlarged heart (see below) and is associated with an **S_3/S_4 gallop rhythm** (Chapter 16). In more severe disease diversion of blood flow from skeletal muscle and non-essential tissues leads to **weakness** and **fatigue** and contributes to exercise intolerance.

Myocardial dysfunction and remodelling

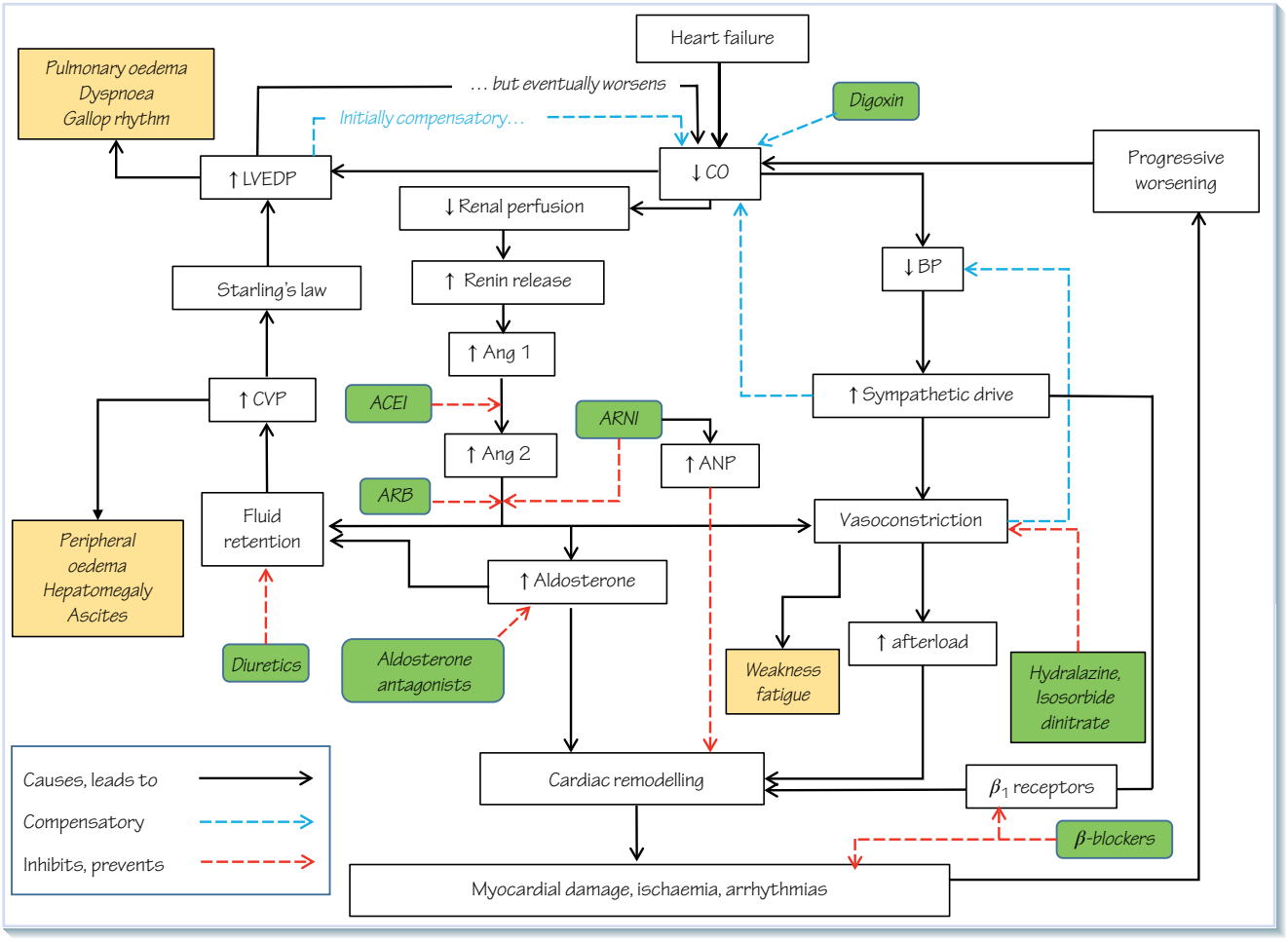
Chronic heart failure is characterized by progressive cardiac dysfunction, accompanied by **myocardial remodelling**. Compensation forces an already compromised heart to work harder. This leads to **energy deficit**, dysfunction of ATP-dependent transporters (e.g. Ca^{2+}-ATPases and Na^+ pump) (Chapters 10 and 12), and consequent **Ca^{2+} overload** (Figure 46.4). This impairs relaxation and fosters lengthening of the action potential (e.g. *acquired long QT syndrome*; Chapter 57) and generation of **arrhythmias**, a major cause of sudden death. Mitochondrial dysfunction worsens the energy deficit. **Oxidative stress** and cytokines promote further damage, structural alterations and **apoptosis** (programmed cell death). Myocardial remodelling is potentiated by direct action of noradrenaline, angiotensin 2 and aldosterone (Figure 46.4).

Dilatation reduces cardiac *efficiency*, as pressure in a sphere is proportional to wall tension (i.e. myocardial force) divided by radius (Law of Laplace). Large dilated hearts therefore have to contract harder in order to develop the same pressure as smaller hearts.

Cardiac dilatation must not be confused with **hypertrophy**, where cardiac myocytes grow larger and ventricular wall thickness increases in response to a sustained increase in afterload (e.g. hypertension, aortic stenosis). Hypertrophy is not usually associated with IHD. Although force is increased, the thicker ventricle is less **compliant**, which impedes filling and contributes to *diastolic failure*. **Capillary density** is reduced, lowering **coronary reserve** (difference between maximum and resting coronary flow), so myocardial perfusion may be limited. Changes in **contractile protein isoforms** (myosin, tropomyosin) decrease contraction velocity and contractility. Gross hypertrophy may physically impair valve operation.

47 Treatment of chronic heart failure

Figure 47.1 Mechanisms of drugs used to treat chronic heart failure



Treatment of chronic heart failure (CHF) is designed to (i) improve the quality of life by reducing symptoms, (ii) lengthen survival, and (iii) slow the progression of cardiac deterioration.

The **sympathetic** and **renin–angiotensin–aldosterone** (RAA) systems activated in response to reduced pump function initially help to maintain cardiac output but also drive the progression of cardiac deterioration (Chapter 46). Therapy mainly involves inhibiting these systems (Figure 47.1) using an **angiotensin-converting enzyme inhibitor (ACEI)** and a **β-blocker**, which together slow CHF progression, lengthen survival time and improve haemodynamics. **Angiotensin receptor blockers (ARBs)** are used as an alternative in ACEI-intolerant patients, and an ACEI–ARB combination can be used in β-blocker intolerant patients. **Sacubitril/valsartan**, a combination of an ARB and a neprilysin inhibitor, can be given in place of an ACEI or ARB (or their combination).

Diuretics are used to control fluid accumulation and the positive inotrope **digoxin** may be used to support cardiac function. In severe or refractory CHF, or when existing therapy fails to control symptoms adequately, an **aldosterone antagonist** such as spironolactone is recommended. In intensive care settings, positive inotropes such as **dobutamine**, **dopamine** or **milrinone** may be used temporarily if decompensation (an acute worsening of heart failure) occurs, as can **intra-aortic balloon counterpulsation** (Chapter 45).

ACEI and other vasodilators

Clinical trials in the 1980s showed that although vasodilation per se did not lengthen survival in CHF, certain vasodilating drugs did have this effect. The most effective of these was the ACEI captopril. It later emerged that ACEI were improving survival because the stimulation of angiotensin 2 production which occurs in CHF is an important cause of the cardiac hypertrophy and fibrosis which drive the progression of this condition. However, the vasodilating and diuretic properties of ACEI are also beneficial because they

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help to reduce symptoms. Angiotensin 2 causes vasoconstriction and promotes fluid retention via multiple mechanisms (Chapter 29). ACEI, which inhibit the conversion of angiotensin 1 to angiotensin 2, therefore dilate arteries and veins, and reduce blood volume. Arterial vasodilatation decreases afterload and cardiac work and improves tissue perfusion by increasing stroke volume and cardiac output. Venous dilatation and reduction of fluid retention diminish pulmonary congestion, oedema and central venous pressure (CVP) (preload). Reduction of preload lowers ventricular filling pressure, therefore lowering cardiac wall stress, workload and ischaemia.

Angiotensin (AT_1) receptor blockers such as **valsartan** are used in patients unable to tolerate ACEI due to dry cough or angioedema. The 2003 VALIANT study showed that valsartan was as effective as captopril in providing a morbidity and mortality benefit in people who had suffered a recent MI and showed signs of developing heart failure.

In 2014, the PARADIGM-HF trial reported that combining valsartan with **sacubitril**, a **neprilysin inhibitor**, prolonged survival of CHF patients and caused less renal dysfunction and hyperkalaemia compared to the ACEI enalapril. Neprilysin, a neutral endopeptidase which is highly expressed in the kidneys, breaks down natriuretic peptides, bradykinin and substance P. By increasing the bioavailability of these peptides, its inhibition causes natriuresis, vasodilation and a reduction in ventricular remodelling. Approved in 2015, this angiotensin receptor/neprilysin inhibitor (ARNI) can be used instead of an ARB or ACEI in patients with mild-moderate CHF and a ventricular ejection fraction of ≤40%.

The combination of the vasodilators **isosorbide dinitrate** (Chapter 41) and **hydralazine** can be used instead of an ACEI or ARB for patients in whom these drugs are not tolerated or in patients of Afro-Caribbean descent. The 2004 A-HeFT trial showed that in black patients, compared to placebo, isosorbide dinitrate plus hydralazine caused a 43% relative risk reduction in all-cause mortality. The survival benefit of this drug combination probably arises due to nitric oxide release by isosorbide dinitrate.

β-receptor blockers

β-blockers have a strong evidence base in CHF and all patients with LVEF <40% should receive a β-blocker. The 1999 CIBIS-II trial showed that the addition of the β_1-cardioselective agent **bisoprolol** to standard therapy (ACEI/other vasodilator plus diuretic) improved mortality. **Carvedilol,** a non-selective β-blocker that also has α-antagonist and antioxidant properties, was shown in the 2003 COMET trial to extend survival in patients already being treated with ACEI and diuretics

Long-term treatment with β-blockers increases ejection fraction, reduces systolic and diastolic volume, and eventually causes regression of left ventricular hypertrophy. Other beneficial effects of β-blockers in CHF probably include reduced ischaemia and a reduction in heart rate, thus improving myocardial perfusion, inhibition of the deleterious effects of excess catecholamines on myocardial structure and metabolism, and reduction of cytokine release. β-blockers appear to be particularly effective in reducing sudden death in those with CHF, suggesting that the prevention of ventricular fibrillation (Chapters 48, 51 and 52) constitutes an important part of their action.

The negative inotropic effect of β-blockers is potentially hazardous in some patients with CHF, because cardiac function is already compromised. Therapy is therefore initiated with low doses which are carefully uptitrated over several weeks or months.

Aldosterone antagonists

Aldosterone levels initially fall during ACEI treatment but often rise again ('escape') during prolonged treatment. Aldosterone has a number of effects that worsen CHF and its consequences: inducing cardiac fibrosis and remodelling, reducing nitric oxide release, increasing Na^+ retention, and promoting arrhythmias by decreasing plasma K^+ and cardiac noradrenaline release.

The aldosterone antagonist **spironolactone** was shown in the 1999 RALES trial to reduce mortality when added to ACEI in severe CHF. Its use is recommended in patients with more severe heart failure and good renal function. As it can cause hyperkalaemia, careful monitoring of plasma K^+ levels is important. Spironolactone also causes antiandrogenic side effects such as gynaecomastia. The more selective aldosterone antagonist **eplerenone** is also available and has fewer side effects.

Ivabradine dose-dependently reduces the heart rate by selectively blocking the I_f ("funny") current that controls spontaneous depolarisation in the sinus node. The 2010 SHIFT study showed that adding ivabradine to standard therapy significantly reduced mortality.

Diuretics

Diuretics reduce fluid accumulation by increasing renal salt and water excretion. Preload, pulmonary congestion and systemic oedema are thereby relieved. **Loop diuretics** inhibit the Na^+–K^+–$2Cl^-$ symport in the ascending loop of Henle. Na^+ and Cl^- reabsorption is thereby inhibited, and the retention of these ions in the tubule promotes fluid loss in the urine. Diuretics commonly used in heart failure include **furosemide** and **bumetanide**. Thiazide and thiazide-like diuretics (Chapter 38), particularly **metolazone**, are sometimes combined with a loop diuretic.

Both loop and thiazide diuretics can cause hypokalaemia (low plasma K^+) and metabolic alkalosis because some of the Na^+ they cause to be retained in the tubular fluid is reabsorbed in exchange for K^+ and H^+ in the distal nephron. This process is stimulated by aldosterone (see Chapter 29), and diuretic-induced hypokalaemia can therefore be prevented by an ACEI or an aldosterone antagonist. Hypokalaemia can also be treated with K^+ supplements, or by using **K^+-sparing diuretics** such as **amiloride** or **triamterene** which inhibit Na^+ reabsorption and K^+ secretion in the collecting duct. Long-term use of loop diuretics can result in hypovolaemia, reduced plasma Mg^{2+}, Ca^{2+} and Na^+, and hyperuricaemia and hyperglycaemia. This is more common in the elderly, who may require high doses of diuretics to overcome **diuretic resistance**.

Cardiac glycosides

Cardiac glycosides such as digoxin improve symptoms but do not prolong life. They work by inhibiting the Na^+ pump in cardiac muscle, thereby increasing intracellular [Na^+]. This reduces Ca^{2+} extrusion by the Na^+–Ca^{2+} antiport (Chapter 12) and thus increases intracellular [Ca^{2+}]. The rise in Ca^{2+} enhances cardiac contractility and shortens action potential duration and refractory period in atrial and ventricular cells by stimulating K^+ channels. Digoxin also increases baroreceptor responsiveness, thereby reducing sympathetic tone.

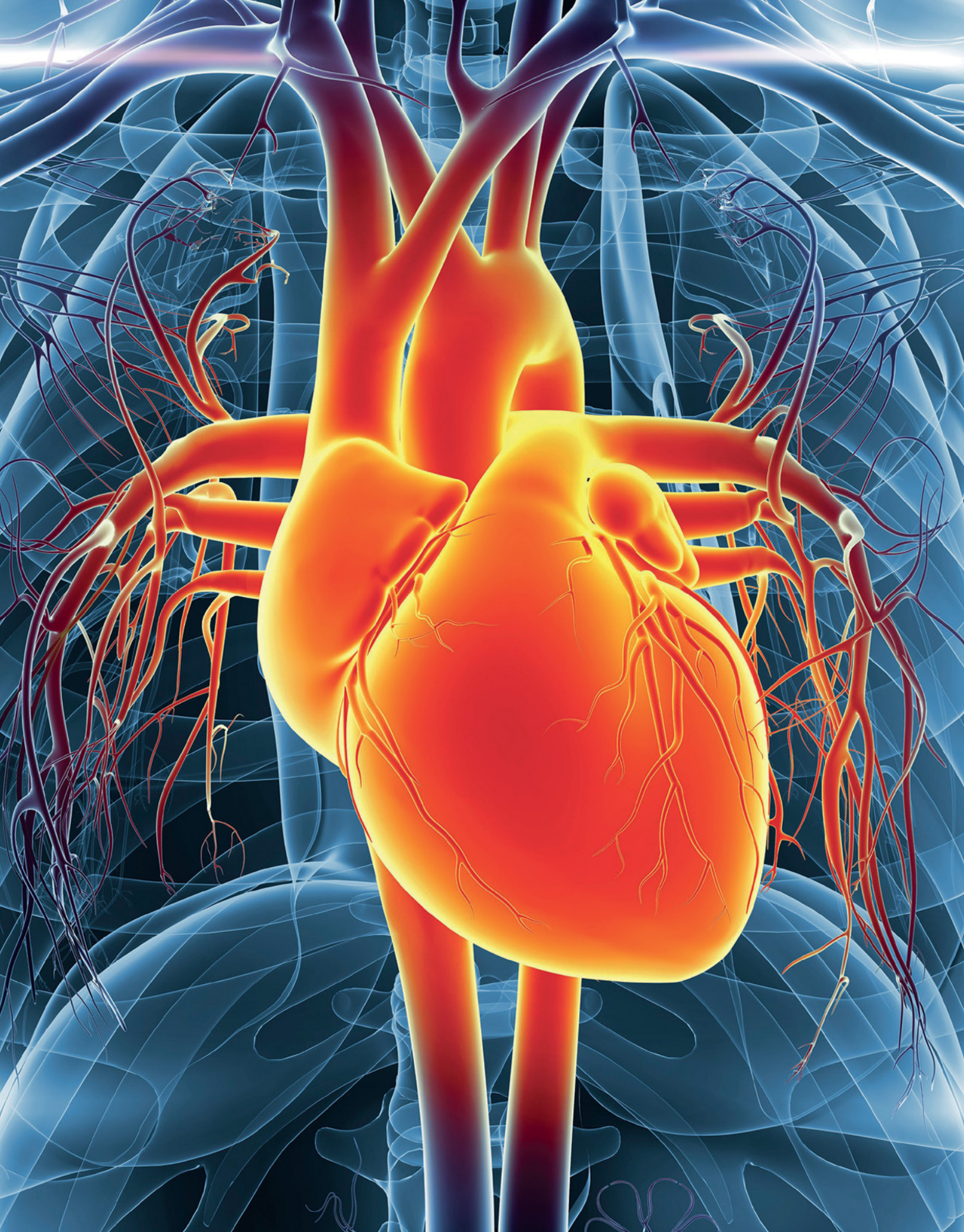
Digoxin also acts on the nervous system to increase vagal tone. This slows sinoatrial node (SAN) activity and reduces atrioventricular node (AVN) conduction and can be useful in treating atrial arrhythmias (Chapters 49 and 52). It is therefore mainly used in patients with both CHF and atrial fibrillation.

Even a small (two- to threefold) excess of digoxin over the optimal therapeutic concentration can cause arrhythmias. This occurs because an excessive rise in $[Ca^{2+}]_i$ causes oscillations in membrane potential after action potentials. These **delayed afterdepolarizations** (Chapter 48) can trigger ectopic beats and at higher doses can cause ventricular tachycardia. Inhibition of the Na^+ pump also decreases intracellular K^+, causing depolarization and facilitating arrhythmias. In addition, excess digoxin can increase vagal tone enough to block conduction at the AVN and can also raise sympathetic tone, again favouring arrhythmias. Digoxin toxicity is enhanced by hypokalaemia, because K^+ decreases the affinity of digoxin for the Na^+ pump. Digoxin causes toxic gastrointestinal effects, including anorexia, nausea and vomiting. Acute toxicity can be treated with intravenous K^+, antiarrhythmics (e.g. lidocaine) and digoxin-specific antibodies (Digibind).

Device therapy in CHF

Implantable cardiac defibrillators are indicated in patients with poor LV ejection fraction (<35%) who are at increased risk of sudden cardiac death due to ventricular arrythmias (Chapter 50). **Cardiac resynchronization therapy,** involving implantation of a pacemaker that stimulates both ventricles to contract simultaneously, is also used in patients with moderate to severe CHF and evidence of asynchronous ventricular contraction.

A **left ventricular assist device (LVAD)** (a pump that takes over part or all of the heart's pumping action) can serve as a bridge for patients awaiting cardiac transplant or as a destination device to lengthen survival if transplant is not possible.



48 Mechanisms of tachyarrhythmia

Figure 48.1 Mechanisms of early and delayed afterdepolarisations

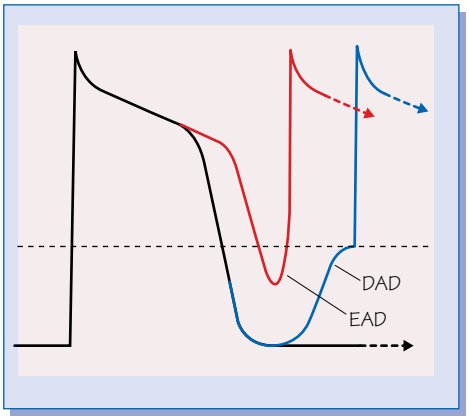


Figure 48.2 Mechanism of Wolff-Parkinson-White syndrome

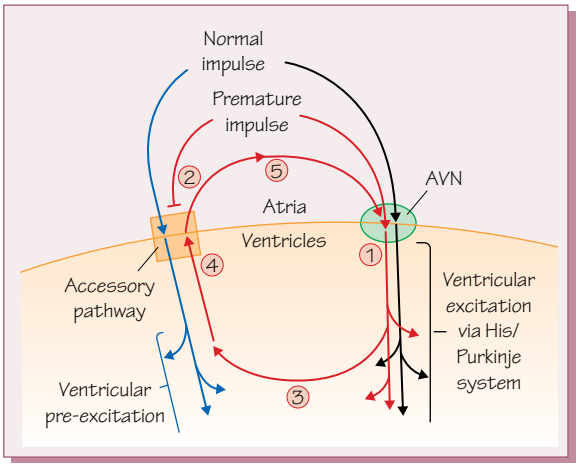


Figure 48.3 Mechanism of re-entry in myocardial scar border zone

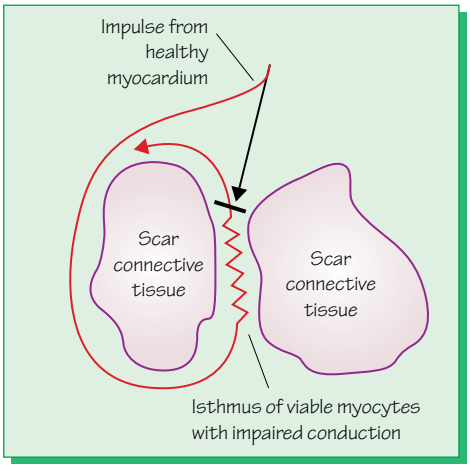
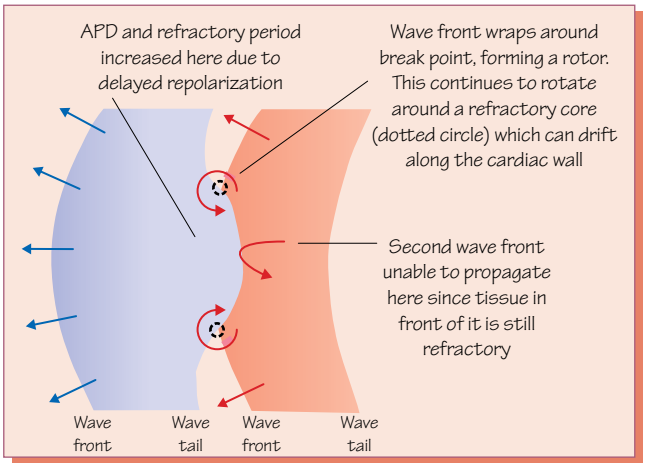


Figure 48.4 Mechanism of functional re-entry



Arrhythmias are abnormalities of the heart rate or rhythm caused by disorders of impulse generation or conduction.

Disorders of impulse generation: latent pacemakers and triggered automaticity

All parts of the cardiac conduction system demonstrate a spontaneous phase 4 depolarization (**automaticity**), and are therefore potential or **latent pacemakers**. Because sinoatrial node (SAN) pacemaking is of the highest frequency (70–80 beats/min), it causes **overdrive suppression** of pacemaking by the atrioventricular node (AVN) (50–60 beats/min) or Purkinje fibres (30–40 beats/min). However, ischaemia, hypokalaemia, fibre stretch or local catecholamine release may increase automaticity in latent pacemakers, which can then 'escape' from SAN dominance to cause arrhythmias.

Triggered automaticity is caused by **afterdepolarizations**. These are oscillations in the membrane potential that occur during or after repolarization. Oscillations large enough to reach threshold initiate premature action potentials and thus heartbeats (Figure 48.1). This may occur repeatedly, initiating a sustained arrhythmia either directly or by triggering re-entry (see below). Afterdepolarization magnitude is influenced by changes in heart rate, catecholamines and parasympathetic withdrawal.

Early afterdepolarizations (EADs) occur during the terminal plateau or repolarization phases of the action potential. They develop more readily in Purkinje fibres than in ventricular or atrial myocytes. EADs can be induced by agents that prolong action potential duration and increase the inward current. For example, drugs such as sotalol which block K^+ currents can cause EADs and triggered activity by delaying repolarization, especially when the

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heart rate is slow. The abnormal rhythms induced by such drugs resemble **torsade de pointes**, a type of congenital arrhythmia.

Delayed afterdepolarizations (DADs) occur after repolarization is complete and are caused by excessive increases in cellular $[Ca^{2+}]$. DADs can be caused by catecholamines, which increase Ca^{2+} influx through the L-type Ca^{2+} channel, and by digitalis glycosides, which increase $[Ca^{2+}]_i$ (see Chapter 47). They can also occur in heart failure, in which myocyte Ca^{2+} regulation is impaired. The oscillation of membrane potential following the increase in $[Ca^{2+}]_i$ is caused by a **transient inward current** involving Na^+ influx, and the occurrence and magnitude of DADs and the likelihood that they will cause arrhythmias are increased by conditions that enhance this current. These include increased Ca^{2+} release from the sarcoplasmic reticulum and longer action potentials, which cause larger increases in $[Ca^{2+}]_i$. Therefore, drugs prolonging action potential duration may trigger DADs, whereas drugs shortening the action potential have the opposite effect. The magnitude of the transient inward current is also influenced by the resting membrane potential, and is maximal when this is approximately −60 mV.

Abnormal impulse conduction: re-entry

Re-entry occurs when an impulse that is delayed in one region of the myocardium re-excites adjacent areas of the myocardium more than once. The initiating impulse is often premature, for example having resulted from triggered automaticity. One type of re-entry, termed **anatomical**, requires the presence of three conditions:

1. There must exist an anatomical circuit around which the impulse can circulate (a process termed **circus movement**). This circuit can utilize parallel conduction pathways such as two Purkinje fibre branches or the AVN and an accessory atrioventricular conduction pathway.
2. Impulse conduction at some point in the circuit should be slow enough to allow the region in front of the impulse to recover from refractoriness. This region is termed the **excitable gap**.
3. The circuit must also include a zone of unidirectional block where conduction is blocked in one direction while remaining possible in the other.

Wolff–Parkinson–White (WPW) syndrome (see Chapter 50) is an uncommon supraventricular arrhythmia (population incidence 0.1–0.2%) which provides a prototypical example of anatomical re-entry. People with WPW have a congenital accessory (extra) conduction pathway (formerly termed the **bundle of Kent**) between an atrium and ventricle, which is often situated on the left free wall of the heart. Thus, as shown in Figure 48.2, normal atrial depolarization (black arrows) is conducted to the ventricles through both the AVN and the accessory pathway (blue arrows). The accessory pathway has properties differing from that of the AVN. First, it *conducts more rapidly* than the AVN, so the part of the ventricle to which the pathway connects depolarizes before the rest (**pre-excitation**), resulting in a widened QRS complex. Second, the accessory pathway has a *longer refractory period* than the AVN. Thus, if a premature impulse arises in an atrium (red arrows), it may be conducted normally to the ventricles via the AVN (**1** in Figure 48.2), but may not be conducted forwards through the accessory pathway, which is still refractory from the previous impulse (**2**). However, when the impulse through the AVN is distributed to the ventricles (**3**), it will encounter the distal end of the accessory pathway (**4**) which has now had time to recover its excitability, and will be conducted backwards through this pathway into the atrium (**5**). It can then traverse the AVN again and continue to cycle though the anatomical circuit encompassing the AVN, His–Purkinje system, ventricles, accessory pathway and atrium (**1**–**3**–**4**–**5**). The ventricles are excited with each circuit, which causes a tachycardia because the impulse cycles more quickly than the SAN spontaneously depolarizes.

It is noteworthy that the 'border zone' between healthy myocardium and the scar resulting from the healing of a myocardial infarct (see Chapter 44) typically contains a mixture of living muscle cells and connective tissue. In some cases, a narrow band ('isthmus') of still-viable muscle cells spans an area of non-conducting scar, thereby connecting two regions of healthy myocardium (Figure 48.3). Conduction of the impulse by the isthmus may be slowed or even demonstrate effective unidirectional block because this tissue takes so long to recover its excitability between action potentials. This arrangement provides conditions analogous to those that WPW (think of the isthmus as playing the part of the accessory pathway and the healthy myocardium to the side of the non-conducting scar as mimicking the AVN) and is thought to cause many ventricular arrhythmias arising in patients following myocardial infarct healing.

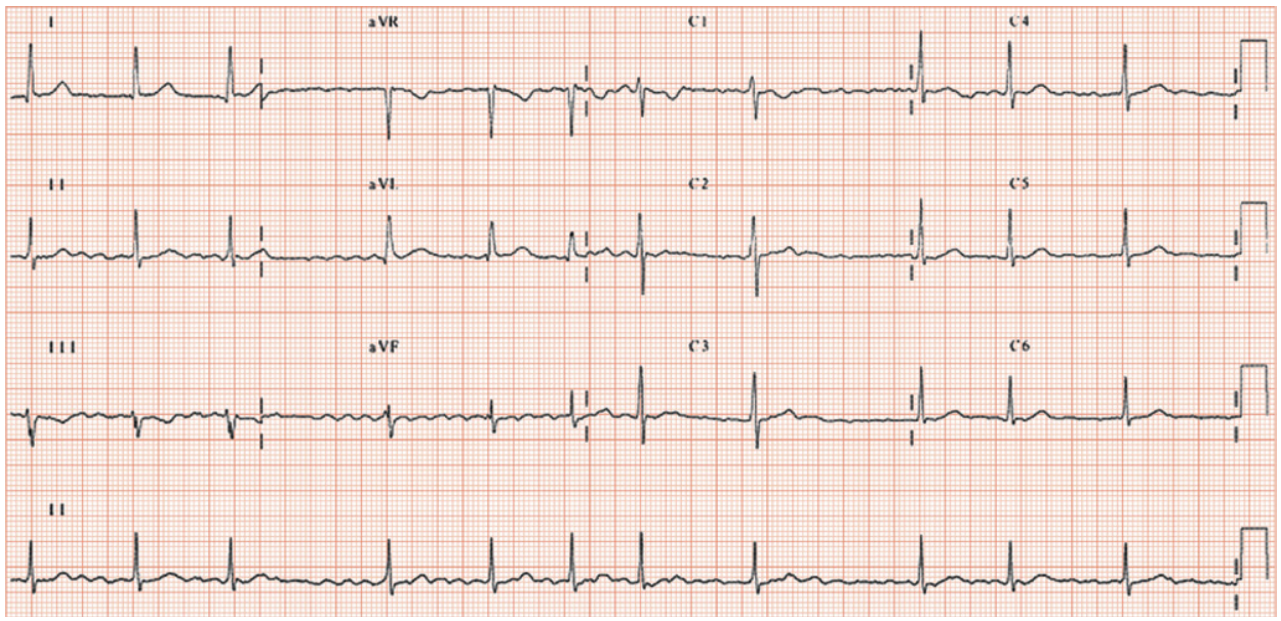
Functional re-entry does not require an anatomically defined circuit and tends to arise when conduction is impaired or repolarization is delayed in a region of myocardium, usually as a result of ongoing ischaemia or damage from a previous myocardial infarction. Under these conditions, the firing of frequent or premature impulses can cause the front of one wave of depolarization to collide with the tail of the preceding wave where it has been slowed (Figure 48.4). The second wave is unable to proceed into the region of the myocardium that is still refractory, but at the edges of this region it curls into itself, forming twin 'whirlpools' of depolarization, termed **rotors**. Rotors can similarly form under some conditions if an impulse collides with a structural obstacle such as a scar. Once formed, rotors may persist and continue to emit spiral waves of depolarization with a frequency determined by the rotation period of the spiral; these excite the heart and cause tachycardia. The formation of such spiral waves, and the further fragmentation of the waves of depolarization they generate, is thought to underlie the genesis of the chaotic electrical activity that results in the total loss of atrial or ventricular coordinated contraction termed **fibrillation** (see Chapters 49 and 51).

The sympathetic nervous system and arrhythmias

Sympathetic stimulation of the heart results in results in a variety of β-receptor mediated effects enabling positive chronotropy and inotropy (see Chapters 12 and 13). These include the acceleration of impulse generation and conduction by the SA and AV nodes, respectively. In cardiac muscle cells Ca^{2+} influx and release are facilitated leading to an increased rise in $[Ca^{2+}]_i$ during the action potential, and the activities of multiple ion channels are modulated in such a way as to enhance conduction and decrease refractoriness. These effects are crucial for the normal tuning of cardiac function, but excessive sympathetic stimulation of the heart during myocardial infarction, or in the context of cardiac scarring, ischemia, chronic heart failure or cardiomyopathy, can be arrhythmogenic. The reasons for this are not well understood but may relate to observations that the myocardium is innervated more densely in some areas than in others and that ion channel expression also varies between different parts of the ventricles. Thus, sympathetic activation may exaggerate intrinsic regional inhomogeneities in conduction velocity and refractoriness. These effects are likely to promote triggered automaticity and functional re-entry and therefore tachycardia and fibrillation.

49 Atrial fibrillation

Figure 49.1 12 lead ECG showing rate-controlled atrial fibrillation



12 lead ECG showing rate-controlled atrial fibrillation. The patient is likely taking β-blockers to achieve a resting ventricular rate of ~70 bpm. P waves are absent because there is loss of co-ordinated atrial contraction. The ventricular rate is irregularly irregular. The fibrillatory F waves are best seen in leads II and aVF.

Atrial fibrillation (AF) is a supraventricular arrhythmia characterised by low amplitude baseline oscillations called fibrillatory waves with a rate of 300–600 beats per minute and an irregularly irregular ventricular rhythm. Atrial depolarisation occurs in rapid waves with constantly changing pathways, resulting in loss of coordinated atrial contraction so that on the 12 lead ECG, P waves are absent. The ventricular rate is typically less than 200 bpm because the AVN is unable to conduct most of the atrial impulses impinging upon it (Figure 49.1). *The only time the ventricular rate is regular in AF is when complete heart block is also present*. In this case a regular ventricular escape rhythm is responsible for the QRS complexes seen on the ECG.

Classification of atrial fibrillation

AF, the most common arrhythmia, occurs in ~10% of people over the age of 75 and can be caused by both cardiac and non-cardiac factors (see Figure 49.2). AF is classified into three types, based on duration. AF terminating within 7 days is called **paroxysmal AF**. AF present for more than 7 days is termed **persistent AF**. Longstanding AF refractory to attempts to cardiovert to sinus rhythm is called **permanent AF**. Paroxysmal AF is usually driven by an ectopic focus or reentrant pathway in the cardiac muscle surrounding pulmonary veins where they enter the left atrium. As AF progresses, it causes changes in the electrical and structural properties of the atrial myocardium, promoting further and more complex forms of reentry, thus rendering it more persistent and refractory to treatment. Palpitations, dyspnoea, dizziness, chest pain or syncope may occur as a result of an increased ventricular rate or the absence of atrial systolic filling, which reduces ventricular stroke volume by ~20%.

The ventricular rate in atrial fibrillation

The ventricular rate in AF is either normal (60–100 bpm), fast (>100 bpm; **AF with a fast ventricular response**) or slow (<60 bpm; **AF with a slow ventricular response**). In the presence of bundle branch block, AF with a fast ventricular response is termed **AF with aberrant conduction**. Importantly, this may be difficult to distinguish from ventricular tachycardia (VT) on the 12 lead ECG, and *if there is any doubt regarding the diagnosis of a broad complex tachycardia, the safest approach is to treat as VT*. The ventricular rate in AF can be dangerously high in patients with Wolff-Parkinson-White syndrome. This condition, **pre-excited AF**, occurs because an accessory pathway permits 1:1 conduction of the atrial rate to the ventricles, bypassing the AVN and resulting in a ventricular rate of up to 300 bpm (see Chapter 50). If untreated, this will rapidly degenerate to ventricular fibrillation and cardiac arrest.

If the ventricular rate is slow, any rate-limiting drugs should be stopped and if the slow ventricular rate persists, implantation of a

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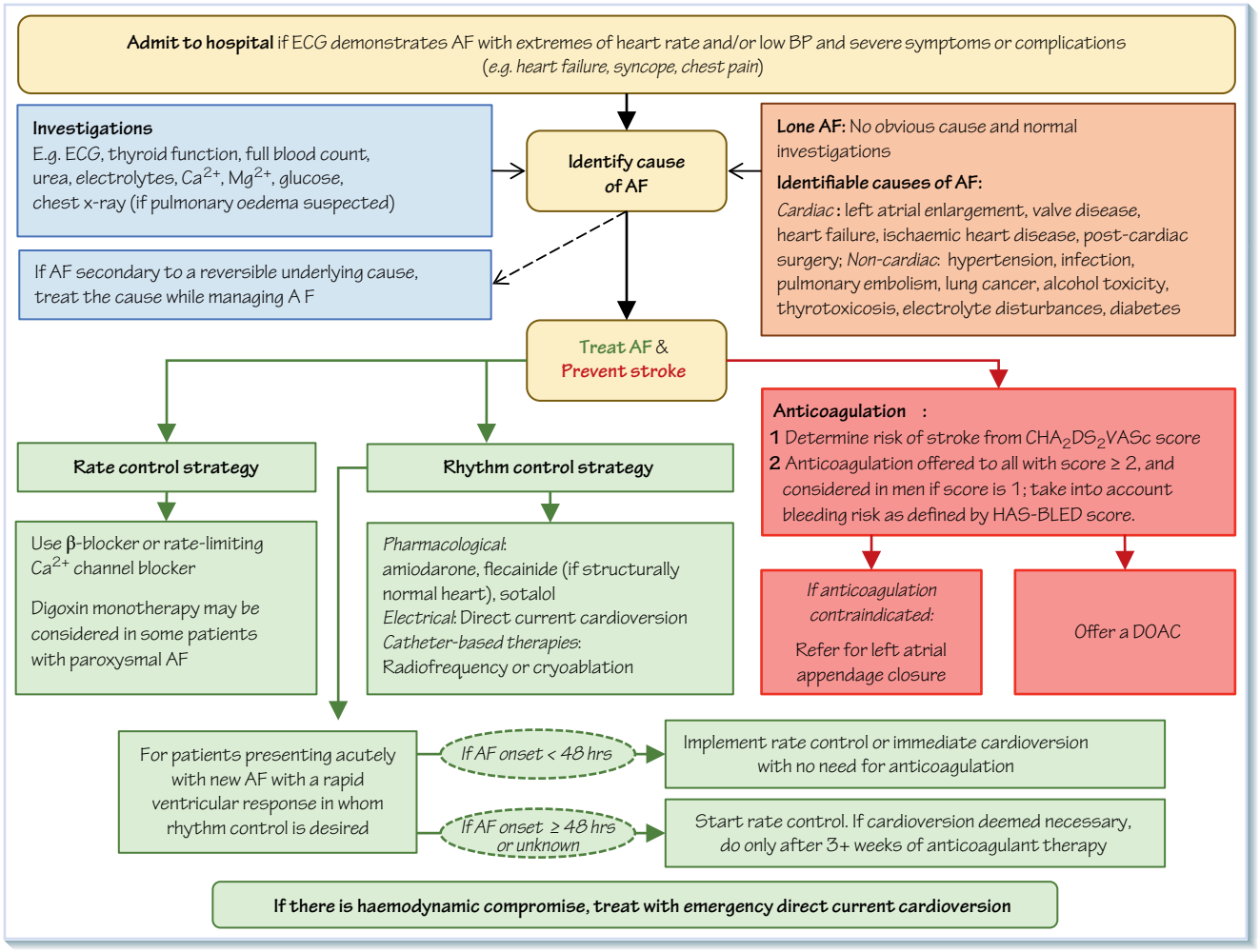
Figure 49.2 Management of atrial fibrillation



permanent pacemaker should be considered. Slow AF may occur in **tachy-brady syndrome**. In this type of SAN disease, the patient alternates between high and low ventricular rates and requires implantation of a permanent pacemaker for management of the slow rate and concomitant use of AV nodal blocking agents such as bisoprolol to protect against ventricular high rates.

Atrial fibrillation and stroke

AF accounts for ~20% of overall stroke incidence and up to 30% in those older than 80. Thrombi may form in the left atrium or in the **left atrial appendage** because the lack of coordinated atrial contraction leads to stasis of blood and clots which can then embolise to the systemic circulation. Stroke can be the first manifestation of AF in asymptomatic individuals.

Management of atrial fibrillation

Management The management of AF (Figure 49.2) is threefold: control of the ventricular rate (rate control, Chapter 52), control of the atrial rhythm (rhythm control, used if the patient is not in permanent AF, Chapter 52) and prevention of thromboembolic complications such as stroke. Any underlying structural heart disease or other potential cause should also be investigated and treated.

Rate control is used in most patients to reduce the ventricular rate if it is >100 bpm. This is a common reason for presentation to emergency departments. β-blockers (bisoprolol, metoprolol), calcium channel blockers (verapamil, diltiazem) and digoxin are the rate-limiting (AV nodal blocking) agents commonly used.

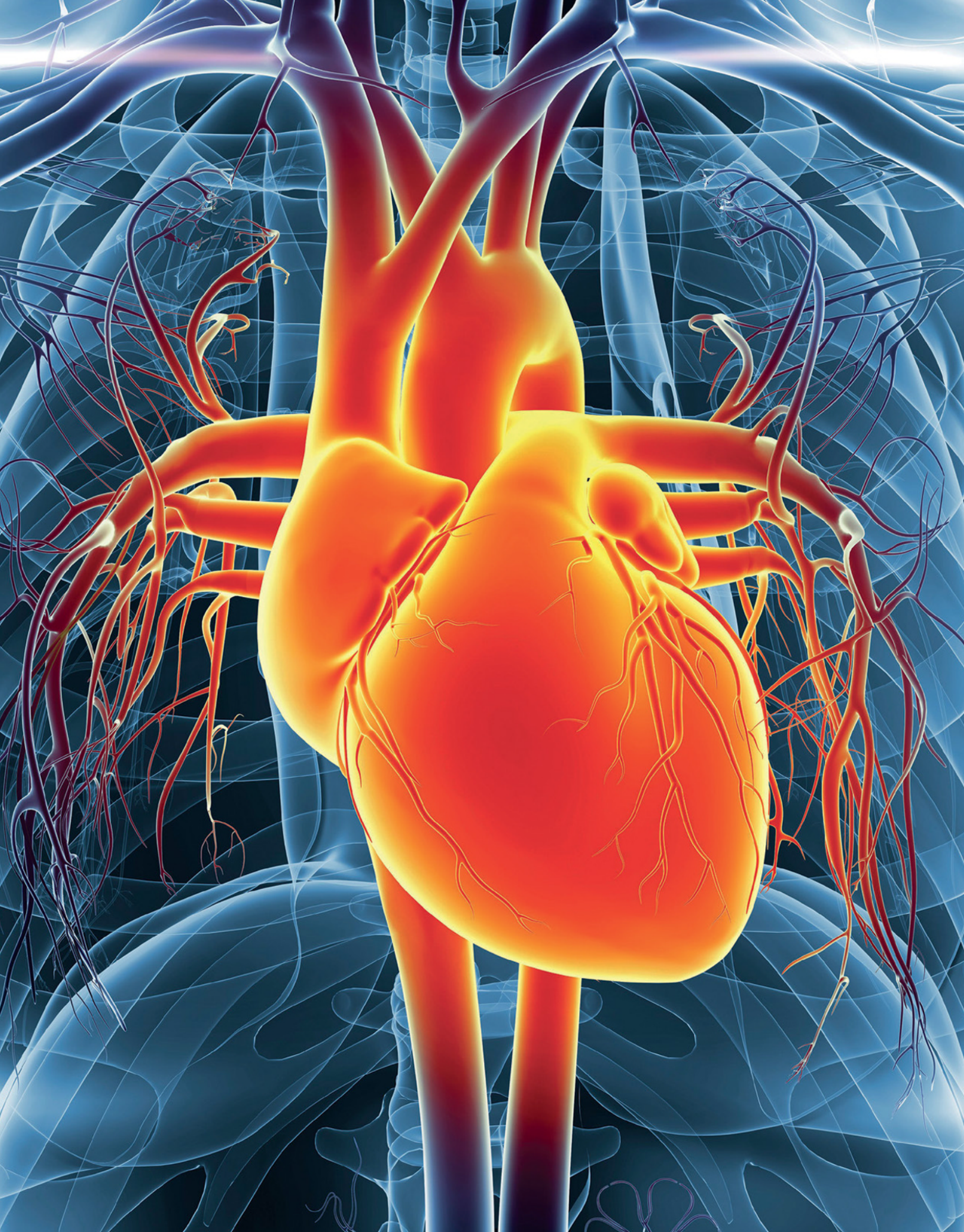
Rhythm control is the preferred strategy under certain circumstances including new onset AF and in those with an identifiable reversible cause, for example, infection. Strategies for rhythm control depend on whether the patient is haemodynamically unstable. If this is the case, or if the patient has significant cardiac ischaemia or pulmonary oedema, then emergency **direct current cardioversion (DCCV**; see Chapter 51) is required. Shocks are delivered in synchrony with the R wave of the QRS complex to the heavily sedated patient via defibrillator pads placed below the right clavicle and over the apex of the heart. *This strategy is used for the treatment of all unstable arrhythmias*. DCCV can be used electively as a rhythm control strategy in patients who have been therapeutically anticoagulated for at least 3 weeks, or in those in whom a transoesophageal echocardiogram has confirmed no intracardiac thrombus. If the patient is not haemodynamically compromised, a pharmacological rhythm control strategy can be attempted with the class III antiarrhythmic amiodarone or the β-blocker sotalol which also has class III properties. If there is no structural heart disease on echocardiography then the class IC agent flecainide can be used.

Ablation has assumed a central role in treating many arrhythmias and is curative in >90% of certain supraventricular arrhythmias. It is also used to treat VT when an appropriate target (e.g. a slowly conducting 'isthmus' in a myocardial scar) can be identified. The pathways or focally automatic sites causing or maintaining certain arrhythmias are ablated (destroyed) by focal heating or freezing delivered via a catheter. The catheter is inserted through the femoral vein and its tip is located at the surface of the endocardium at desired site. The tip temperature is raised to 55–70°C, creating a lesion 8–10 mm in diameter and of similar depth. Although seldom causing complications, catheter ablation of sites very close to the AVN can potentially damage it, causing complete heart block which necessitates pacemaker implantation. This can be avoided using **cryoablation,** in which the catheter tip is cooled rather than heated. Cooling the tip briefly to −30°C causes a focal block of electrical activity that is reversible and so cannot cause permanent damage. If this stops the arrhythmia without causing undesirable effects the tip is then further cooled to −60°C, causing a permanent lesion and ablating the abnormal rhythm.

To treat AF, multiple ablation lesions are created to effect electrical isolation of the four pulmonary veins at their insertion points into the left atrium. Recurrent AF after catheter ablation occurs in 20-40% of patients, most commonly due to resumption of conduction between previously isolated pulmonary veins and the left atrium ('pulmonary vein reconnection'), and it is not uncommon for patients to undergo two or even three ablations to ensure durable pulmonary vein isolation.

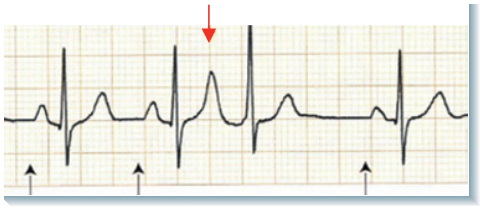
A palliative rhythm control strategy 'pace and ablate' is reserved for those who have derived no benefit from drugs and/or ablation, and still experience symptomatic AF that has a significant impact upon quality of life. This involves implantation of a dual chamber permanent pacemaker and subsequent catheter ablation of the AVN. This renders the patient 'pacing dependent', that is, they are now in complete heart block and the dual chamber pacemaker takes over the electrical activity of the heart.

Prevention of thromboembolic complications AF confers a fivefold increased risk of stroke in patients who are not anticoagulated, and AF may in fact present with stroke. The annual risk of stroke is calculated using the CHA_2DS_2VASC score, which stands for congestive cardiac failure, hypertension, age, diabetes, stroke, vascular disease, and female sex. Each risk factor scores one point except for age greater than 75 years and stroke, which score two points each. Patients scoring ≥2 have at least a 2.2% risk of stroke per annum and should be anticoagulated. Direct acting oral anticoagultants (DOACs) such as apixaban, rivaroxaban, edoxaban, and dabigatran are preferred to warfarin, although in some patients warfarin may be more suitable, for example, those with metallic heart valves. In patients unable to take anticoagulation, for example, those with a history of major haemorrhage or a high bleeding risk, the left atrial appendage, which is the primary site of thrombus formation, can be closed with a specialised device.



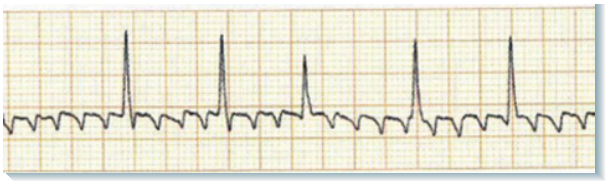
50 Other supraventricular arrhythmias

Figure 50.1 Lead II of the 12 lead ECG showing atrial ectopy



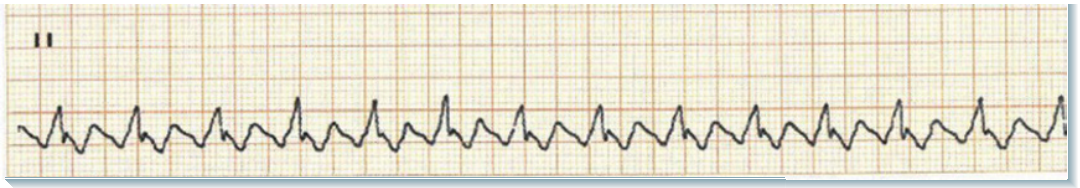
The first two and final complexes originate in the sino-atrial node (SAN) as they are preceded by a P wave. The 3rd complex is a PAC originating at a site other than the SAN, as shown by the abnormal P wave, which is buried within the T wave of the preceding beat (red arrow).

Figure 50.2 Lead II of the 12 lead ECG showing atrial tachycardia



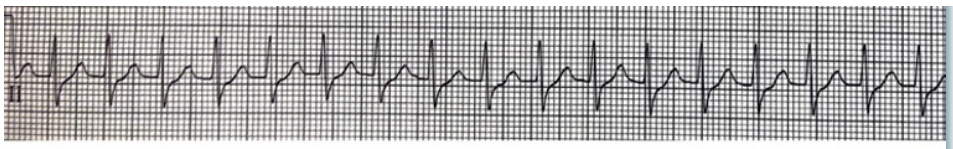
AT accounts for 5—10% of cases of supraventricular tachycardia. The impulse originates in atrial tissue separate to the sinoatrial node and can be either left atrial or right atrial in origin. It does not require the atrioventricular node for its initiation and maintenance.

Figure 50.3 Lead II of the 12 lead ECG showing atrial flutter



There are characteristic flutter waves present as a "saw tooth" baseline. In typical atrial flutter these are best seen in the inferior leads (II, III, aVF). In this example, every other flutter wave is triggering a QRS complex (flutter with 2:1 AV block). Flutter waves are generated by a macro reentrant rhythm in the right atrium in an anticlockwise pattern involving the cavo-tricuspid isthmus.

Figure 50.4 Atrioventricular nodal re-entrant tachycardia



Atrioventricular nodal re-entrant tachycardia. AVNRT is characterised by a heart rate of 150—250 (in this case ~160 bpm), with normal QRS complexes. The atria are activated retrogradely since the impulse originates from the AV node. The P wave may be obscured by the QRS complex, or, as shown in Figure 50.4.1 (left), may occur as a small R wave in Lead I (termed an rSR' pattern) which is not present in the normal ECG (Figure 50.4.2, right).

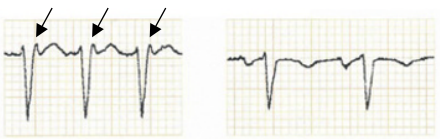
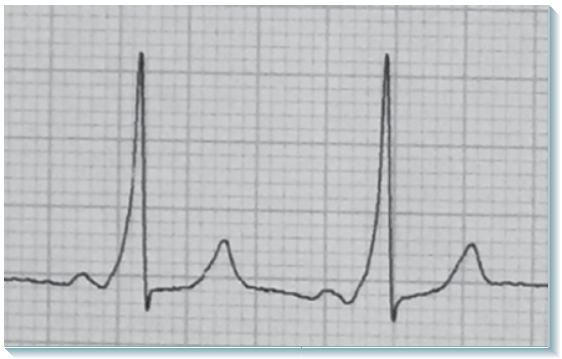
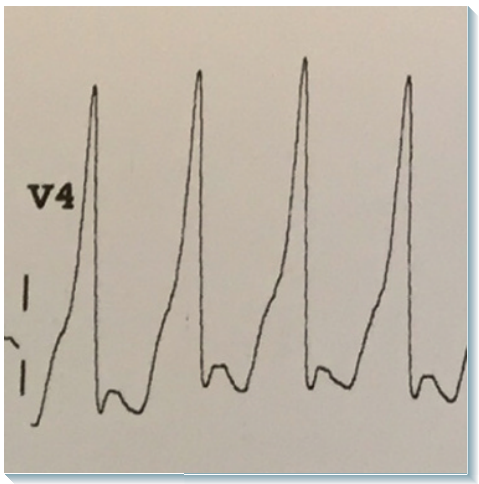


Figure 50.5 Lead II of the 12 lead ECG showing two complexes with ventricular pre-excitation



The PR interval is short and there is a characteristic slurred upstroke to the QRS complex, termed a delta wave. These are present because the atrial impulse is conducted early to the ventricles via an accessory pathway. This ECG pattern occurring with palpitations is termed the Wolff-Parkinson-White syndrome.

Figure 50.6 Lead V4 of the 12 lead ECG showing pre-exited atrial fibrillation (AF)



In this case, AF has conducted to the ventricles down the accessory pathway resulting in an extraordinarily rapid ventricular rate which can degenerate to ventricular fibrillation.

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Tachyarrhythmias are abnormalities in the origin, timing or sequence of cardiac depolarization that result in a heart rate of >100 beats/min, respectively. They may be **supraventricular**, in which case they arise in either the atria or the atrioventricular node (AVN) or **ventricular** in origin (see Chapter 51).

Supraventricular tachycardia (SVT) is an umbrella term describing all tachycardias which originate above the His-Purkinje system. The differential diagnosis for SVT is broad and includes sinus tachycardia, atrial fibrillation (AF), atrial flutter, AV node re-entry tachycardia (AVNRT), AV re-entry tachycardia (AVRT), and atrial tachycardia. SVTs are rarely life threatening, but they can cause serious haemodynamic compromise and cardiac sequelae (e.g. tachycardiomyopathy, heart failure) if not treated.

Premature atrial complexes (PACs; Figure 50.1) are caused by **ectopic** (i.e. originating from a site other than the SAN) depolarizations. The commonest sites of origination are in and around the pulmonary veins where they insert into the left atrium. They are typically conducted to the ventricles to cause a premature beat, which is generally followed by a pause. The P wave is abnormally shaped because atrial contraction is not generated in the SAN.

Atrial tachycardia (Figure 50.2), characterized by a heart rate of 120–240 beats/min, is frequently caused by an ectopic pacemaker, and can arise in either atrium (e.g. often close to the pulmonary veins in the left atrium). Other atrial tachycardias are re-entrant in nature, frequently following surgery that involves incision into the atrium. The tachycardia may start and stop suddenly or gradually. As with atrial ectopics, the P wave is abnormally shaped.

Atrial flutter results from re-entry in an atrium (usually the right), often with an area of slowed conduction near the orifice of the inferior vena cava and a circuit involving the whole atrium. The atrial rate is typically ~300 beats/min. The ECG has a 'sawtooth' appearance due to the presence of rapid regular **F waves** representing atrial depolarization; these become more obvious if AVN conduction and the QRS complex are suppressed, for example, by adenosine. As shown in Figure 50.3, the AVN is often able to conduct only every other atrial impulse (2:1 AV block) to the ventricles because it is still refractory from the previous impulse so that the ventricular rate is typically ~150 beats/min. Less commonly, 3:1 or 4:1 block can occur, leading to correspondingly slower rates of ventricular contraction. Atrial flutter is typically seen in patients with underlying cardiac disease, often associated with atrial dilatation. It is particularly common in older hypertensive patients and may also be caused by acute pulmonary thromboembolism or thyrotoxicosis, but can also develop paroxysmally in patients without underlying heart disease (e.g. secondary to infection or alcohol excess). Attempts to **cardiovert** (restore normal sinus rhythm) atrial flutter with class IA drugs (see Chapter 52) may cause severe ventricular tachycardia and sudden death by establishing 1:1 AVN conduction. This occurs because these drugs suppress vagal firing, thereby increasing AVN conduction. This hazard is avoided by pre-administering a drug that suppresses AVN conduction (e.g. a β-blocker).

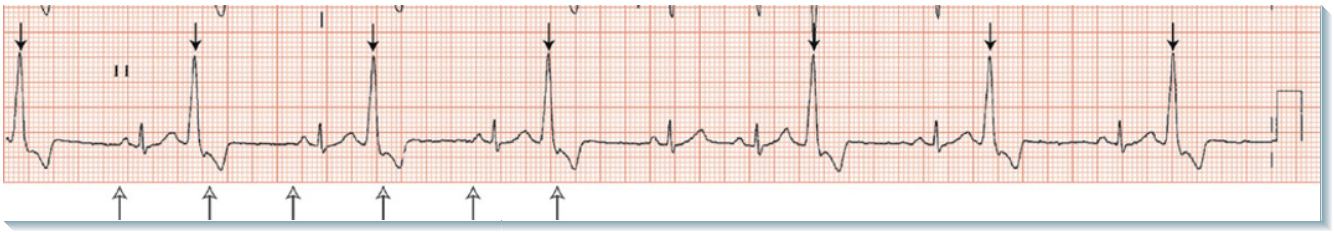
Atrioventricular nodal re-entrant tachycardia (AVNRT) (Figure 50.4) and **atrioventricular re-entrant tachycardia (AVRT)** result in periodic episodes during which the heart rate abruptly increases to 150–250 beats/min, and they are therefore referred to as **paroxysmal supraventricular tachycardias**. Individuals with AVNRT have an additional or accessory conduction pathway between the atrium and the AVN. In most cases, the normal AV pathway (termed α) conducts rapidly and has a long refractory period, whereas the accessory (β) pathway conducts slowly and has a short refractory period. In these individuals, AVNRT can be initiated by a premature impulse arising in an atrium. This impulse will not be conducted by the α pathway if it is still refractory from the preceding impulse. However, the impulse may travel slowly down the β pathway (which has recovered from the preceding impulse) and then encounter the distal end of the α pathway. Sufficient time has now elapsed for this pathway to be no longer refractory, and the impulse is able to ascend the α pathway in a *retrograde* (backwards) direction, allowing it to return to the atrium. From here it can continue to cycle through the α and β pathways, exciting the ventricles to cause a heartbeat with each circuit. An abnormal P wave is also generated each time the impulse cycles through the atrium. This immediately follows the QRS complex because the re-entrant circuit, and thus the cycle time, is very short (compare Figures 50.4.1 and 50.4.2).

An accessory pathway allowing impulse conduction between an atrium and ventricle also exists in AVRT, but in this case it is not located within the AVN. Those in whom this pathway can conduct impulses in both directions may develop **Wolff–Parkinson–White (WPW)** or **pre-excitation syndrome,** the mechanism of which is described in Chapter 48. When the individual is in normal sinus rhythm, the atrial impulse is conducted in an *anterograde* (forward) direction through both the accessory pathway and the AVN. Because it is conducted more quickly through the accessory pathway, excitation of part of one ventricle occurs more quickly than normal (i.e. pre-excitation occurs), resulting in a shortened PR interval and an initial widening of the QRS complex referred to as a *delta wave* (Figure 50.5). During the tachycardia, however, the accessory pathway conducts in the *retrograde* direction (see Chapter 48) and so pre-excitation does not occur. Instead, premature P waves (often superimposed on the T wave) caused by rapid excitation of the atria by the retrograde impulse are observed. This type of accessory pathway is particularly dangerous in people with atrial fibrillation, because it is often better at conducting rapid impulses than the AVN because of its shorter refractory period. Thus, the AVN 'filter' which protects the ventricles from high-frequency atrial activity is bypassed, and the ventricular rate becomes very fast. In this condition, termed **pre-excited AF** (see Chapter 49), the ECG shows rapid and irregular QRS complexes, the majority of which are widened by pre-excitation (Figure 50.6).

Less common forms of AVRT also exist. In *antidromic* AVRT, the accessory pathway conducts in an anterograde direction during the tachycardia. In other cases, the accessory pathway is capable of conducting only in the retrograde direction. Thus, pre-excitation does not occur, and the bypass pathway is said to be *concealed*.

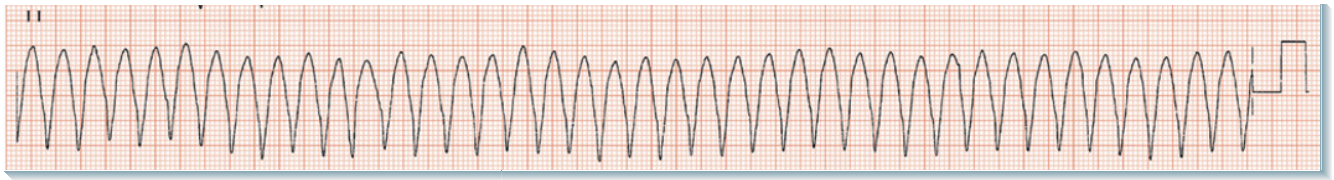
51 Ventricular tachyarrhythmias and their non-pharmacological management

Figure 51.1 Ventricular ectopics



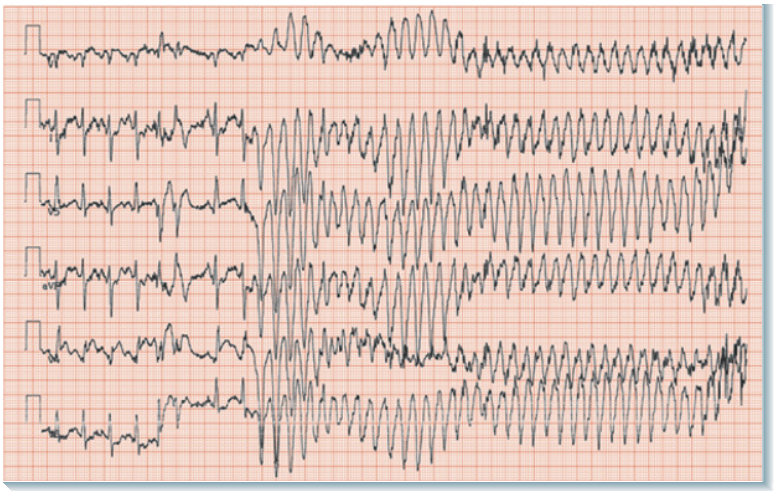
Lead II of the 12 lead ECG showing premature ventricular complexes (PVCs). PVCs are wide QRS complexes not preceded by a P wave which arise from the right or left ventricle rather than the sinoatrial node (black arrows). They can occasionally cause symptoms such as a skipped beat or palpitations. The first three PVCs occur in a bigeminal pattern (every other beat is a PVC) and the fourth PVC occurs in a trigeminal pattern (every third beat is a PVC). The QRS complexes triggered normally by P waves are indicated by red arrows.

Figure 51.2 Monomorphic ventricular tachycardia



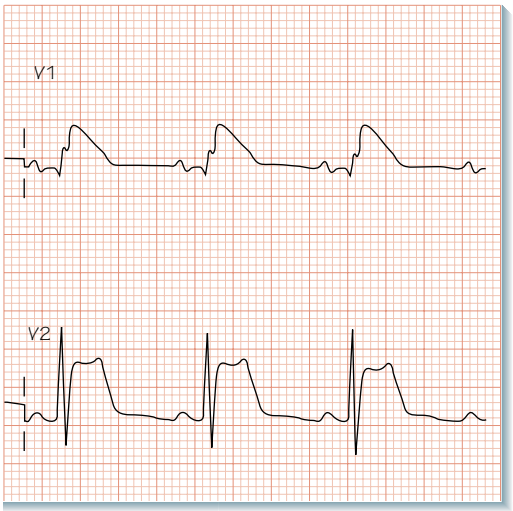
Lead II of the 12 lead ECG showing monomorphic ventricular tachycardia. Monomorphic refers to there being only one type of QRS morphology, originating from a single focus in the ventricle, such as a scar. In this rhythm strip, the QRS complexes are wide (>120 ms) and the rate is close to 300 beats per minute.

Figure 51.3 Polymorphic ventricular tachycardia



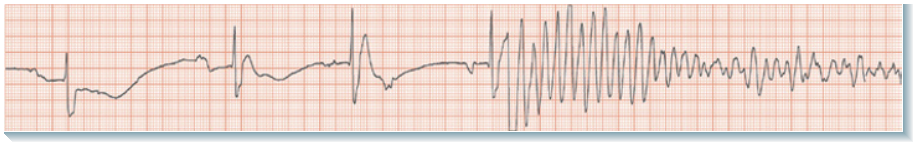
12 lead ECG showing polymorphic ventricular tachycardia. Polymorphic means there are multiple QRS morphologies. Polymorphic VT is either associated with a prolonged QT interval in which case it is called Torsades de Pointes, or with a normal QT interval, which is likely due to ischaemia. In Torsades de Pointes, there are rapid irregular QRS complexes which appear to twist around the isoelectric line. It can rapidly degenerate into ventricular fibrillation.

Figure 51.4 Brugada



ECG showing the type 1 Brugada pattern. Note the characteristic coved (i.e. rounded) ST segment elevation in Lead V1. Brugada syndrome is a genetic disorder in which the most commonly involved gene is SCN5A which encodes the cardiac sodium channel.

Figure 51.5 Ventricular fibrillation



Lead II of the 12 lead ECG showing sinus bradycardia degenerating into VF. VF is very rarely captured on the 12 lead ECG. It is usually seen on a defibrillator monitor in the context of cardiac arrest and is characterised by irregular QRS complexes without any P waves. It is due to disorganised electrical activity in the ventricles.

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Tachyarrhythmias originating in the ventricles are most often associated with ischaemic heart disease. They are common during and up to 24 h after acute myocardial infarction (MI), when increases in sympathetic activity and extracellular [K^+] as well as slowed conduction favour their initiation. Such arrhythmias may be immediately life threatening, and indeed the vast majority of deaths associated with MI are caused by ventricular fibrillation occurring before the individual reaches hospital. Subsequently, however, the border zone of the healed infarct scar may serve as a substrate for the development of dangerous re-entrant ventricular tachycardia (VT) which can recur or become incessant weeks to years after the MI. These late arrhythmias themselves confer an additional risk of death and must be treated with drugs and an **implantable cardioverter defibrillator** (ICD; see below). Ventricular tachyarrhythmias can also be associated with cardiomyopathy and valvular and congenital heart disease, and idiopathic varieties may occur in structurally normal hearts (e.g. focal VT).

Ventricular rhythm disturbances

Premature ventricular complexes (PVCs) are caused by a ventricular ectopic focus and can occur randomly or following every (*bigeminy*) or every second (*trigeminy*) sinus beat (Figure 51.1). Because depolarisation is initiated within and conducts through the ventricle, it spreads more slowly than sinus beats which are distributed rapidly by the His–Purkinje conduction system. Thus the resultant QRS complex is broad and abnormally shaped. PVCs may be associated with a 'compensatory pause'. PVCs may be of no prognostic significance but can predispose to more serious arrhythmias if they develop during or after MI, and/or occur during the T wave of the preceding beat. Studies have shown that a daily PVC burden of >20% can induce cardiomyopathy. Such patients should be offered investigation of the underlying cause (e.g. ischaemia) and catheter ablation.

Ventricular tachycardia originates in the ventricles and is defined as four or more successive ventricular ectopic beats occurring at a rate of >100 beats/min. VT is described as *non-sustained* or *sustained* based on whether it lasts for >30 s. VT can cause symptoms such as syncope, angina and shortness of breath, and if sustained can compromise cardiac pumping, leading to heart failure and death. VT can also deteriorate into ventricular fibrillation (see below), particularly with a rate of >200 beats/min.

ECG criteria for VT include broad QRS complexes (>120 ms), atrioventricular dissociation (P waves and QRS complexes occur at different rates), extreme axis deviation (QRS positive in lead aVR and negative in leads I and aVF), and positive or negative concordance in leads V1–.V6 (i.e. these leads show entirely positive or negative complexes). Normal atrial activation may continue to be driven by the SAN, or the abnormal ventricular pacemaker may cause atrial tachycardia via retrograde impulses through the AVN. The configuration of the QRS complex can be used to classify VT into two broad categories. In *monomorphic* VT (Figure 51.2), the QRS complexes all have a similar morphology and the heart rate is generally constant, whereas in *polymorphic* VT both the QRS morphology and the rate vary continually. Monomorphic VT generally indicates the presence of a stable re-entrant pathway, the substrate for which is typically ischaemic scar (see Chapter 48). Polymorphic VT is thought to be caused by multiple ectopic foci or re-entry in which the circuit pathway is continually varying and most often occurs during or soon after an MI.

Torsade de pointes is a type of polymorphic VT in which episodes of tachycardia, which may give rise to fibrillation and sudden death, are superimposed upon intervals of bradycardia, during which the QT interval (indicative of the ventricular action potential duration) is prolonged. During the tachycardia, the ECG has a distinctive appearance in which the amplitude of the QRS complexes alternately waxes and wanes (Figure 51.3). Torsade de pointes may be caused by drugs or conditions that delay ventricular repolarisation (e.g. class IA and III antiarrhythmics, hypokalaemia, hypomagnesaemia). It is also associated with **congenital long QT (LQT) syndrome**, which can be caused by mutations in *KvLQT1* or *hERG*, genes coding for cardiac K^+ channels mediating repolarisation, or *SCN5A*, the gene coding for the cardiac Na^+ channel. In congenital LQT syndrome, torsades de pointes is often triggered by sympathetic activity (e.g. caused by stress), which may give rise to early or delayed afterdepolarisations and may also involve functional re-entry mediated by spiral waves of depolarisation (see Chapter 48).

Ventricular fibrillation (VF) is a chaotic ventricular rhythm (Figure 51.4) incompatible with a cardiac output. The patient is therefore in cardiac arrest. VF may follow episodes of VT or acute ischaemia and frequently occurs during MI. It is the main cause of sudden cardiac death, which is responsible for ~10% of all mortality. VF is generally associated with severe underlying heart disease, including ischaemic heart disease and cardiomyopathy.

VF occasionally occurs idiopathically, for example in people with LQT syndrome or **Brugada syndrome** (Figure 51.5). This latter condition is associated with ion channel mutations (e.g. in *SCN5A*) which shorten the action potential in epicardial but not endocardial cells of the right ventricle, a situation favouring re-entry.

Focal VT and **fascicular tachycardia** are forms of idiopathic VT; that is, they can occur in structurally normal hearts. Focal VT most commonly originates in the **right ventricular outflow tract** (RVOT tachycardia) and is associated with increases in sympathetic activity. This is thought to raise intracellular [cyclic AMP] and therefore $[Ca^{2+}]_i$, initiating delayed afterdepolarisations. Fascicular tachycardia may in some cases be caused by a re-entrant circuit involving the Purkinje system. Idiopathic VTs generally have a good prognosis and can usually be successfully treated with radiofrequency catheter ablation (see Chapter 49).

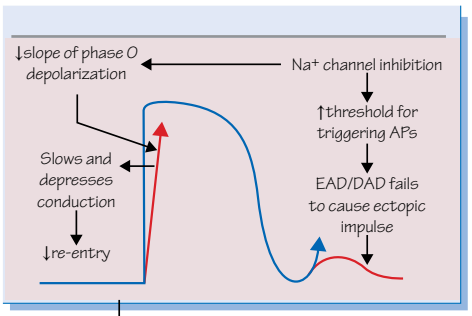
Direct current cardioversion (DCCV) allows rapid **cardioversion** (reversion to sinus rhythm) of any haemodynamically unstable arrhythmia in an emergency setting. An electrical shock synchronised with the peak of the R wave is delivered from a defibrillator to the heart via electrodes applied to the chest and back of the heavily sedated patient. If the shock is not synchronised, it is given as soon as the button on the defibrillator is pressed and so may occur during the T wave (ventricular repolarisation). If this is the case, there is a high chance that ventricular fibrillation will follow. DCCV is believed to prolong refractoriness in myocardial tissue, allowing for the termination of ventricular arrhythmias.

Implantable cardioverter defibrillators consist of a generator connected to electrodes placed transvenously in the heart and superior vena cava. A sensing circuit detects arrhythmias, which are classified as tachycardia or fibrillation on the basis of rate. The treatment algorithm is either as burst pacing, which can terminate VT with a high degree of success, or by the delivery of a shock at up to 40 J, which can cardiovert VT and VF. Shock delivery is between an electrode in the right ventricle and another in the superior vena cava or to the body of the generator. Refinements in detection allow the distinction of supraventricular and ventricular arrhythmias, so that several tiers of progressively more aggressive therapy can be deployed. The AVID study reported that, in patients with malignant ventricular arrhythmia, this approach improved survival by 31% over 3 years compared with antiarrhythmic drug therapy (mainly amiodarone).

52 Pharmacological treatment of tachyarrhythmias

Figure 52.1 Antiarrhythmic drugs

Figure 52.1.1 Class I: Na^+ channel blockers



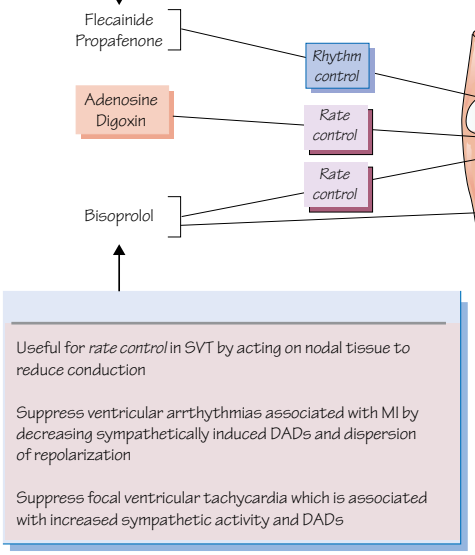
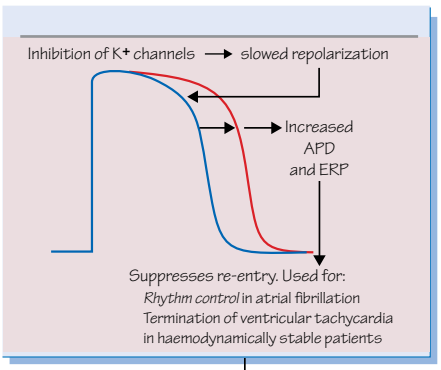


Figure 52.1.2 Class II: β-blockers

Figure 52.1.3 Class III: K^+ channel blockers



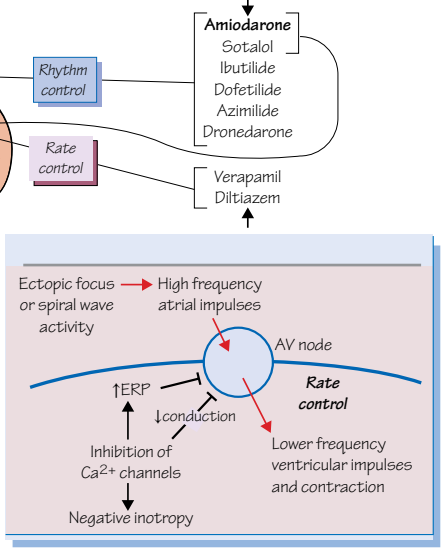


Figure 52.1.4 Class IV: Ca^{2+} channel blockers

Table 52.1 Action site-based classification of antiarrhythmic drugs

Atrial fibrillation rate control	Classes II, IV, digoxin
Atrial fibrillation rhythm control	Classes IC, III
Pre-excited atrial fibrillation)	Classes 1A, IC
Atrioventricular re-entrant tachycardia	Adenosine, Class IV
Ventricular tachycardia	Classes 1A, 1B, IC, II, III, magnesium sulphate

Most antiarrhythmic drugs (AADs) have two actions that reduce abnormal electrical activity but cause tolerably small effects on normal myocardium:

1 They suppress abnormal (ectopic) pacemakers more than they do the sinoatrial node.
2 They increase the ratio of the effective refractory period to action potential duration (ERP : APD).

AADs are divided into four classes, based on their mechanisms (Figure 52.1). However, most AADs have properties of more than one class, often because drug metabolites have their own separate antiarrhythmic effects or because the drugs exist as 50/50 mixtures of two stereoisomers with different actions. This classification system, introduced by Vaughan Williams and Singh, also excludes several drugs and is not useful for matching specific drugs to particular arrhythmias. A more clinically relevant classification scheme is shown in Table 52.1.

Clinical trials have shown that class I agents do not enhance survival and in fact are deleterious if used for some purposes (e.g.

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prevention of premature ventricular complexes). Conversely, the class III agent amiodarone modestly increases survival, and class II agents (β-blockers) can suppress a wide spectrum of arrhythmias and increase survival in conditions such as chronic heart failure and ischaemic heart disease which may lead to lethal arrhythmias. However, because catheter ablation can effectively cure many supraventricular tachyarrhythmias and implantable defibrillators are more effective than drugs at treating ventricular arrhythmias, the emphasis of arrhythmia management has shifted towards device-based therapy.

Class I drugs (Figure 52.1.1)

Class I drugs act mainly by blocking Na^+ channels, thus depressing impulse conduction. This suppresses re-entrant circuits which depend on an area of impaired conduction, as further Na^+ channel blockade here may block conduction completely, which terminates the arrhythmia. Class I drugs can also suppress automaticity by raising the membrane potential threshold required for delayed afterpolarizations to trigger action potentials (APs).

Because they have a higher affinity for Na^+ channels when they are open or inactivated, these drugs bind to Na^+ channels during each AP and then progressively dissociate following repolarization. Dissociation is slowed in cells in which the resting potential is decreased, and this deepens channel blockade in tissue that is depolarized due to ischaemia.

Three subclasses of class I drugs are designated based on their differential effects on the AP in canine Purkinje fibres. Once bound, each subclass of drug dissociates from the Na^+ channel at different rates. Class IB drugs (**lidocaine**, **mexiletine**) dissociate from the channel very rapidly and almost completely between APs. They therefore have little effect in normal myocardium because the steady-state level of drug bound to the channel is minimal. However, in tissue that is depolarized or firing at a high frequency, dissociation between impulses is decreased, promoting channel blockade and depression of conduction. These drugs have therefore been used to treating ventricular tachycardia (VT) associated with MI, which mainly originates in myocardium depolarized by ischaemia. Conversely, class IC drugs (**flecainide**, **propafenone**) dissociate very slowly, remaining bound to channels between APs even at low frequencies of stimulation. This strongly depresses conduction in both normal and depolarized myocardium, thus reducing cardiac contractility. The intermediate dissociation rate of class IA drugs (**procainamide**, **disopyramide**) causes a lengthening of the ERP, which gives them class III activity (see below).

Class I drugs cause many side effects, not the least of which are several types of arrhythmia. This **proarrhythmic** effect is unsurprising, given that depression of conduction and prolongation of the AP can induce arrhythmia development (Chapter 48).

Whereas class 1A drugs are seldom used, class 1B lidocaine and procainamide are sometimes employed to terminate episodes of VT. Class 1C drugs (e.g. flecainide, propafenone) are used in the prophylaxis of certain supraventricular tachycardias, particularly AF, and act by suppressing the arrhythmia at its source. This approach to treating supraventricular tachycardia (SVT) is termed **rhythm control**. An alternative strategy, **rate control**, uses drugs that slow or block the conduction of impulses through the AVN, thereby slowing the ventricles and unmasking the underlying atrial rhythm. Drugs used for this purpose include class II and IV agents, as well as adenosine and digoxin.

Class II drugs (Figure 52.1.2)

β-blockers such as **bisoprolol** and **metoprolol** form the second class of antiarrhythmics. They are used for rate control in SVT and work by reducing the conduction of the atrial impulse through the AVN, because this is promoted by sympathetic stimulation. They can also be useful in ameliorating VT because sympathetic drive to the heart is arrhythmogenic, particularly if there is ischaemia or structural heart disease (Chapter 48).

Class III drugs (Figure 52.1.3)

Class III drugs are K^+ channel blockers that increase APD and therefore prolong ERP. Re-entry occurs when an impulse is locally delayed, and then re-enters and re-excites adjacent myocardium (see Chapter 48). Drugs that prolong ERP can prevent this re-excitation because the adjacent myocardium is still refractory (inexcitable) at the time when the delayed impulse reaches it.

The class III agent amiodarone is effective against both SVT and VT, probably because it also has class IA, II and IV actions. Although amiodarone modestly reduces mortality after MI and in congestive heart failure, its long-term use is recommended only if other AADs fail, because it has many cumulative adverse effects and must be discontinued in about one-third of patients. Hazards include pulmonary fibrosis, hypo- and hyperthyroidism, liver dysfunction, photosensitivity, and peripheral neuropathy. Amiodarone also has a very unpredictable and long (4–15 weeks) plasma half-life, which complicates its oral administration. **Dronedarone** is another class III drug, used to prevent recurrence of AF, which is structurally similar to amiodarone and also has class I and IV activity. It is not licenced in the UK. Compared with amiodarone, it has fewer side effects and a much better pharmacokinetic profile ($t_{1/2}$ of 1 day) but is less effective. It cannot be used in patients with severe heart failure and may in rare cases cause liver failure. **Sotalol** is a mixed class II and III drug used for both VT and SVT. Although it causes far fewer extracardiac side effects than amiodarone, it is more likely to cause torsades de pointes (see Chapter 51). **Dofetilide**, **ibutilide** and **azimilide** are drugs that are seen as 'pure' class III agents in that they are relatively selective for the voltage-gated K^+ channels involved in repolarization. These drugs are used to terminate atrial flutter and fibrillation. Ibutilide is used to premedicate patients due for cardioversion because it enhances myocardial sensitivity. These agents can also cause torsades de pointes, although azimilide is less apt to do so. **Vernakalant** is a class III drug used to terminate episodes of AF. It acts selectively on the atria and seems to cause torsades de pointes less often than other class III drugs.

Class IV drugs, adenosine and digoxin (Figure 52.1.4)

Class IV drugs (**verapamil**, **diltiazem**) are used to treat SVT and exert their antiarrhythmic effects on the AVN by blocking L-type Ca^{2+} channels, which mediate the AVN action potential. Their blockade therefore slows AVN depolarization and conduction and also increases its refractory period. These effects suppress AVN re-entrant rhythms and can slow the ventricular rate in atrial flutter and fibrillation by preventing a proportion of atrial impulses from being conducted through the AVN. Negative inotropy can occur due to L-type channel inhibition, especially if left ventricular function is impaired. Negative inotropic and chronotropic effects are exacerbated by coadministration of β-blockers. These drugs are also sometimes effective in treating focal ventricular tachycardias, because these may be triggered by delayed afterdepolarizations (see Chapter 48).

Adenosine, an endogenous nucleoside (see Chapter 23), acts on A_1-receptors in the AVN, suppressing the Ca^{2+} current and enhancing K^+ currents. This depresses AVN conduction enough to break the circuit causing the tachyarrhythmia. Adenosine, given as a bolus injection, is the drug of choice for rapidly terminating SVT. It commonly causes transient facial flushing, bronchospasm and a sense of impending doom. **Digoxin** slows AV conduction by stimulating the vagus and is used to treat AF and other SVTs, especially in patients with heart failure (see Chapter 47).

53 Conduction system abnormalities and pacing

Figure 53.1 Complete heart block – ventricular escape

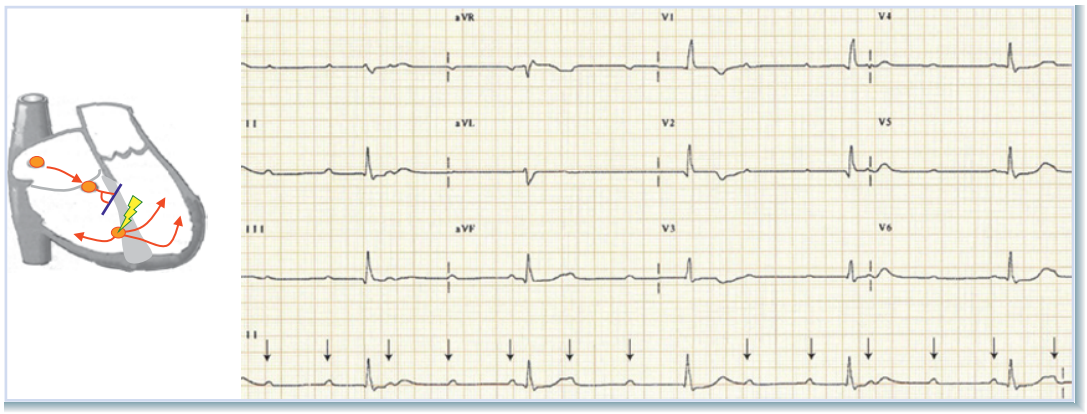


Figure 53.2 Left bundle branch block

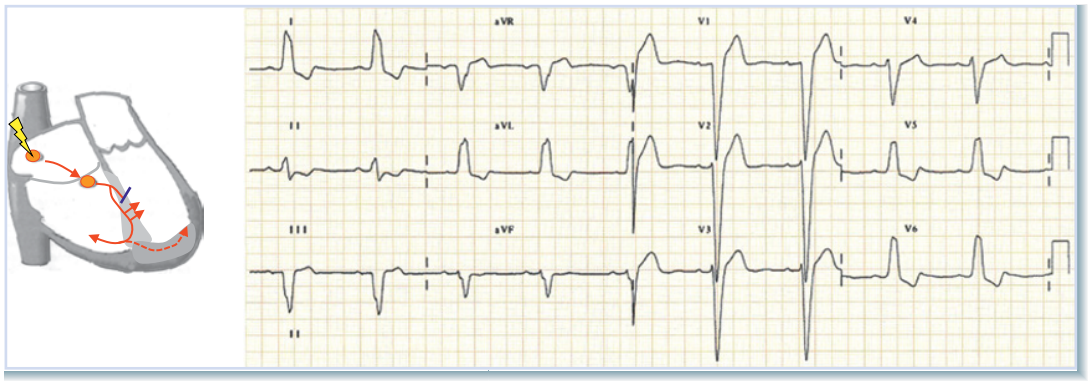
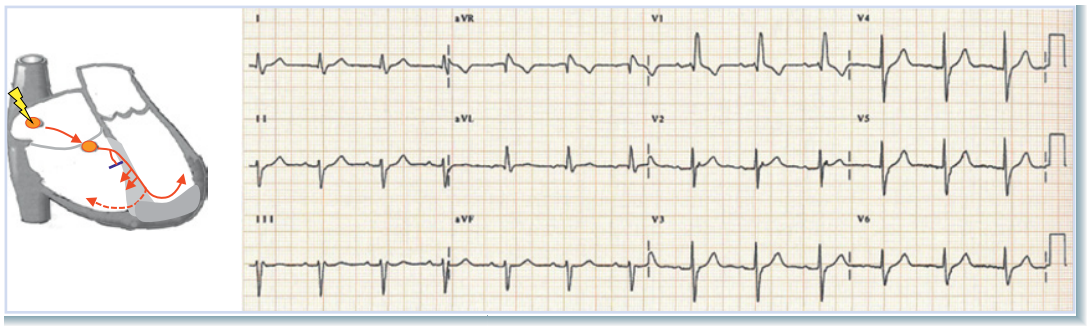


Figure 53.3 Right bundle branch block



Block of the cardiac conduction system, which can occur at various levels, is the cause of a number of important arrhythmias (see also Chapter 13).

Atrioventricular block

Atrioventricular (AV) block occurs when an atrial impulse is not conducted to the ventricle or is conducted with delay; there are three types (illustrated in Chapter 13).

First-degree AV block: delayed conduction from the atria to the ventricles; all atrial impulses are conducted but with a PR interval longer than 0.2 seconds (Figure 13.3.3). Causes include intrinsic disease of the AV node and/or His-Purkinje system, high vagal tone (slows AV conduction), and drugs which slow AV node conduction, that is, calcium channel blockers, β-blockers or digoxin. May occur in aortic stenosis or in aortic root abscess because the aortic valve is in close proximity to the AV node. ***Treatment:*** None required unless the PR interval is particularly prolonged (>300

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ms), which may result in lightheadedness and dizziness. In these cases a pacemaker is indicated.

Second-degree AV block: some but not all atrial impulses are conducted to the ventricle; it is subdivided into Mobitz types I and II.

Mobitz type I (or **Wenckebach**) is characterised by progressive lengthening of the PR interval until there is a non-conducted P wave (Figure 13.3.5). The defect is almost always located within the AV node. This is a common and usually benign variant but can be caused by intrinsic disease of AV node, AV nodal blocking drugs, Lyme disease and myocarditis, and rarely by radiofrequency catheter ablation of AV nodal re-entrant pathways. ***Treatment***: None if asymptomatic, as there is a very low chance of progression to higher grades of AV block. However, if the associated QRS complex is broad, indicating that the block is located in the His-Purkinje system, the likelihood of progressing to higher degrees of AV block is greater. In these instances, implantation of a permanent pacemaker is indicated.

Mobitz type II is characterised by intermittent conduction of P waves but with fixed P-P and PR intervals. The block is located within the His-Purkinje system and has a high likelihood of progression to complete heart block. The QRS complex is usually broad. Causes include intrinsic disease of the His-Purkinje system, drugs which slow conduction through this system (e.g. flecainide, quinidine, propafenone), coronary artery disease, and infiltrative conditions such as sarcoid, amyloid and Lyme disease. ***Treatment:*** as risk is high, implantation of a permanent pacemaker is indicated.

Second-degree AV block with 2:1 conduction (Figure 13.3.4) occurs when alternate P waves are conducted to the ventricles, potentially making diagnosis of Mobitz type I or II difficult. If the QRS is narrow, the block is most likely within the AV node. ***Treatment:*** If the block is located in the His-Purkinje system then a permanent pacemaker is indicated.

Third-degree AV block (complete heart block; CHB): no P waves are conducted to the ventricles. There is complete dissociation of atrial (P waves) and ventricular (QRS complex) activity (**AV dissociation**), with atrial rhythm faster than ventricular rhythm. The latter now originates in either the AV nodal junction (**junctional escape rhythm**, narrow QRS; Figure 13.3.6) or ventricles (**ventricular escape rhythm**, broad QRS; Figure 53.1). The latter is slower than junctional escape rhythm at typically <40 bpm. CHB can occur with atrial sinus rhythm or atrial fibrillation. Causes of CHB include ischaemia, electrolyte abnormalities and antiarrhythmic drugs. ***Treatment***: potentially reversible causes must be treated before considering permanent pacing, which is normally indicated unless the block persists for less than 1–2 weeks after myocardial infarction and the patient is asymptomatic.

Bundle branch block

Left bundle branch block (LBBB) means that the left ventricle has to be activated by impulses transmitted via the myocardium (i.e. slow conduction) from the right bundle branch of His. It is associated with typical changes in the 12 lead ECG, with a wide, negative QRS in lead V1 and prominent R waves in leads I, aVL and V6 (Figure 53.2). Activation of the left ventricle is delayed, causing it to contract later than the right ventricle; as a result the aortic valve closes later than the pulmonary valve. Causes: most often underlying heart disease (e.g. coronary heart disease, cardiomyopathy) but also ageing of the conduction pathways. ***Treatment*:** a pacemaker may be indicated by a history of syncope; LBBB results in ventricular dysynchrony in patients with significant LV dysfunction and may contribute to heart failure; such patients may be treated with a **cardiac resynchronisation device** (see below).

Right bundle branch block (RBBB) means that the right ventricle has to be activated via the left bundle branch and its fascicles. It is associated with a distinctive pattern on the ECG, with a wide QRS of >120 ms duration and an rSR' pattern in lead V1, with wide S waves in leads I, aVL and V5-V6 (Figure 53.3). Causes: RBBB can occur in healthy hearts with the incidence increasing with age. It is associated with structural heart disease and can occur following myocardial infarction, pulmonary embolism and myocarditis. **Treatment:** Usually none.

Bifascicular block involves conduction delay due to RBBB plus block of left anterior (most common) or left posterior fascicles. The ECG demonstrates RBBB plus left or right axis deviation. Causes include ischaemic heart disease, hypertension and aortic stenosis. ***Treatment:*** requires implantation of a pacemaker only if symptoms are present due to progression to second- or third-degree AV block.

Trifascicular block is a term widely used in clinical practice to describe bifascicular block in combination with first-degree AV block. This is technically incorrect, since first-degree AV block occurs not in a fascicle but in the AV node. Trifascicular block is associated with underlying structural heart disease, such as coronary artery disease or degenerative disease of the conduction system and can progress to complete heart block. ***Treatment:*** Trifascicular block in association with syncope is an indication for a permanent pacemaker.

Pacing systems

Pacing systems can be used either temporarily or permanently to initiate the heartbeat by imposing repeated cardiac depolarisations. **Temporary pacing** is generally accomplished using a catheter-tipped electrode introduced via a large vein and provides for the rapid treatment of life-threatening bradycardias. A temporary pacemaker can also be used to terminate a persistent arrhythmia by pacing the heart at a rate faster than that of the arrhythmia; sinus rhythm is often restored when this **overdrive pacing** is stopped. **Permanent pacemakers** are usually implanted to treat bradyarrhythmias. The pacemaker generator is implanted under the subcutaneous tissue above the pectoral muscle inferior to the clavicle and stimulates the heart through leads introduced into the heart via the cephalic, axillary or subclavian vein. Pacemakers are able to pace both the atria and ventricles to maintain AV synchronisation and to adjust the pacemaking frequency to respond to changes in physical activity by sensing parameters such as respiration and the interval between the stimulated depolarisation and the T wave, a measure of sympathetic nervous system activity.

Pacemakers may be single or dual chamber. A **single chamber pacemaker** has one lead to carry impulses to and from either the right atrium or the right ventricle. These devices are usually implanted in people whose underlying rhythm is atrial fibrillation. A **dual chamber pacemaker** has two leads, one to the right atrium and one to the right ventricle. This allows the pacemaker to create a rhythm that more closely resembles the natural conduction activity of the heart. **Biventricular pacemakers** have three leads: one to the right atrium and one to each ventricle. These are called **cardiac resynchronisation devices** and they aim to restore ventricular synchrony to enable more efficient cardiac contraction and improvement in heart failure symptoms.

54 Diseases of the aortic valve

Figure 54.1 Aortic stenosis

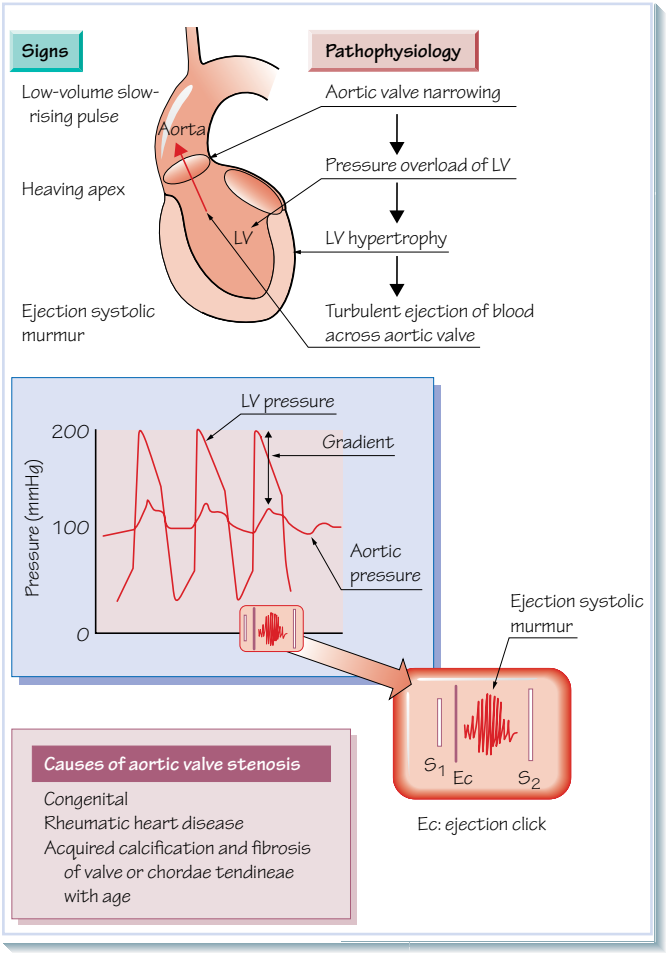
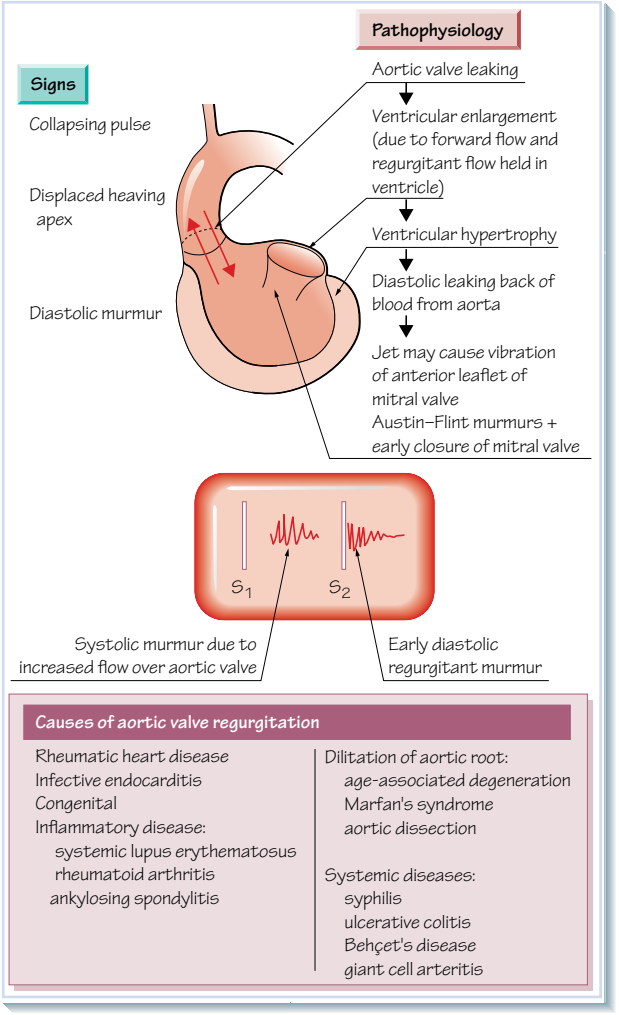


Figure 54.2 Aortic regurgitation



The **aortic valve** is a tricuspid valve that permits the flow of blood during systole from the left ventricle (LV) into the LV outflow tract and ascending aorta. Impaired aortic valve opening, due to its narrowing, is known as **aortic stenosis** (AS). It impedes outflow of blood from the LV into the aorta and imposes a **pressure load** on the LV. Deficient valve closure (**aortic regurgitation**, AR) allows blood to flow back into the LV and thus imposes a **volume load** on the LV.

Aortic stenosis

Causes

Calcific aortic valve disease, where calcium is deposited at the base of the cusps, is the most common cause of AS. The disease process likely represents proliferative and inflammatory processes involving lipid accumulation, upregulated angiotensin converting enzyme activity, oxidative stress and T-cell and macrophage infiltration. Calcific AS is more common in people with congenital bicuspid valves and the onset is about 20 years earlier.

Rheumatic AS as a result of rheumatic heart disease is unusual without coexisting mitral valve disease. Inflammation and scarring of the aortic valve occur secondary to an autoimmune reaction to group A haemolytic Streptococci.

Congenital A **unicuspid aortic valve** is usually fatal within 1 year of birth. **Bicuspid** aortic valves develop progressive fusion of the commissures, and symptoms usually present after 40 years.

Pathophysiology

A slow reduction in aortic valve area requires the LV to work harder to expel blood into the aorta, which causes **left ventricular**

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hypertrophy and eventual myocardial dysfunction, arrhythmias and **heart failure** (see Chapter 46). **Severe AS** is present when the aortic valve area is <1 cm^2, and the peak gradient across the valve is >40 mmHg with a normal cardiac output. With worsening AS, cardiac output cannot increase adequately during exercise and eventually becomes insufficient at rest. As AS progresses the left ventricle dilates, and LV end-diastolic pressure (EDP) increases to the point where overt LV failure ensues.

Clinical features

The classical symptom triad of AS is angina, syncope and breathlessness. Patients present usually between the ages of 50 and 70 years, most commonly with **angina** either due to reduced cardiac output secondary to AS reducing coronary artery perfusion relative to myocardial demand or concurrent coronary artery disease, which is the case in 50%. In AS the hypertrophied LV mass has a higher oxygen demand and inadequate cardiac output for this demand occurs during exercise. Exercise tolerance is decreased, and if cerebral blood flow is insufficient patients may develop **syncope**. Once patients with AS develop angina, syncope or LV failure, their median survival is less than 3 years. Patients with mild AS have a normal blood pressure and pulse. In moderate to severe AS the pulse is slow rising and has a narrow pulse pressure. There may be a demonstrable **thrill** (vibration) felt on palpation over the precordium. The apex beat is **heaving** due to LV hypertrophy. Initially, the apex is non-displaced; however, once the LV starts dilating in late-stage AS then it will displace. Auscultation reveals a normal S1, **a quiet S2** and an **ejection systolic murmur** (Figure 54.1; see Chapter 32), heard best in the second intercostal space to the right of the sternum and which classically radiates to the carotids. It is louder with squatting and softer with standing or during the **Valsalva manoeuvre** (forced expiration against a closed glottis). With worsening AS and a fall in cardiac output, the murmur may become softer (**silent AS**).

Investigations

Echocardiography is the key imaging modality. Echocardiography shows reduced valve opening and calcification of cusps and permits calculation of valve area. Doppler imaging allows calculation of the pressure gradient across the valve.

Management

No medical therapy has been proven to delay the progression of AS. **Aortic valve replacement** surgery is the treatment of choice for symptomatic AS in patients who are suitable. When valve intervention is planned it is important that it is done before the LV starts to dilate. **Coronary angiography** is performed as part of the pre-operative workup, and coronary artery bypass performed during the same operation if significant disease is present. Mechanical valves require **anticoagulation** (see Chapter 8). Bovine or porcine valves do not; hence these can be used in women of childbearing age, because warfarin is teratogenic. In those who are not surgical candidates, **transcatheter aortic valve implantation (TAVI)** can be offered. This procedure involves using a balloon catheter to dilate the stenosed valve and deliver a new valve which sits inside the diseased one. An option for the frailest patients is **balloon valvuloplasty**, which dilates the stenosed valve.

Aortic regurgitation

AR occurs when the valve cannot close firmly at the end of ventricular systole and as a result blood flows back into the ventricle from the aorta at the start of diastole.

Causes

Causes of AR include **rheumatic disease**, where fibrous retraction of the valve cusps prevents apposition, **infective endocarditis** causing valve damage and **congenital malformations** (e.g. bicuspid valve) (Figure 54.2).

Pathophysiology

AR imposes a volume load on the LV because of flow back into the ventricle. **Acute AR** (trauma, infective endocarditis, aortic dissection) is usually catastrophic. Here the LV cannot accommodate the acute increase in volume and LV EDP rises. The early increase in LV EDP causes premature closure of the mitral valve and inadequate forward LV filling, resulting in cardiovascular collapse and acute respiratory failure.

In **chronic AR**, volume load and LV EDP increase gradually, and **LV hypertrophy** allows adequate output to be maintained. As the aortic valve never completely closes, there is no LV isovolumetric relaxation phase (see Chapter 16) and the pulse pressure is wide.

Clinical features

Patients usually do not present with symptoms until LV failure develops. Signs include a wide pulse pressure (caused by reduction in diastolic pressure) and a **collapsing pulse** (see Chapter 16). The LV apex is displaced laterally and is hyperdynamic. Auscultation reveals a high-pitched **early diastolic murmur** at the left sternal edge and often a **systolic flow murmur** across the aortic valve. AR is associated with several eponymous signs. While these are rare in clinical practice, they are favoured by some finals examiners. **Quincke's sign** is visible nail bed pulsation; **Corrigan's sign** denotes visible pulsations in the carotids; **de Musset's sign** is pulsatile head bobbing; **Traube's sign** is a 'pistol shot' heard on auscultation of the femoral arteries; the **Austin Flint murmur** is a **rumbling late diastolic murmur** caused by premature closure of the mitral valve; it denotes **severe AR**.

Investigations

Echocardiography can determine the aetiology and severity of AR by imaging the valve leaflets and LV dimensions, aortic root diameter and diastolic closure or fluttering of the mitral valve. Doppler imaging quantifies the amount of regurgitation.

Management

Acute severe AR requires urgent valve replacement. Chronic AR has a generally good prognosis until symptoms develop. Patients with moderate AR should undergo echocardiography every 6–12 months. Valve replacement should be considered in symptomatic patients, or in asymptomatic patients with worsening LV dimensions, LV function or aortic root diameter. Valve replacement is similar to that for AS, except that replacement of the aortic root may also be required in patients with a severely dilated ascending aorta.

55 Diseases of the mitral valve

Figure 55.1 Mitral stenosis

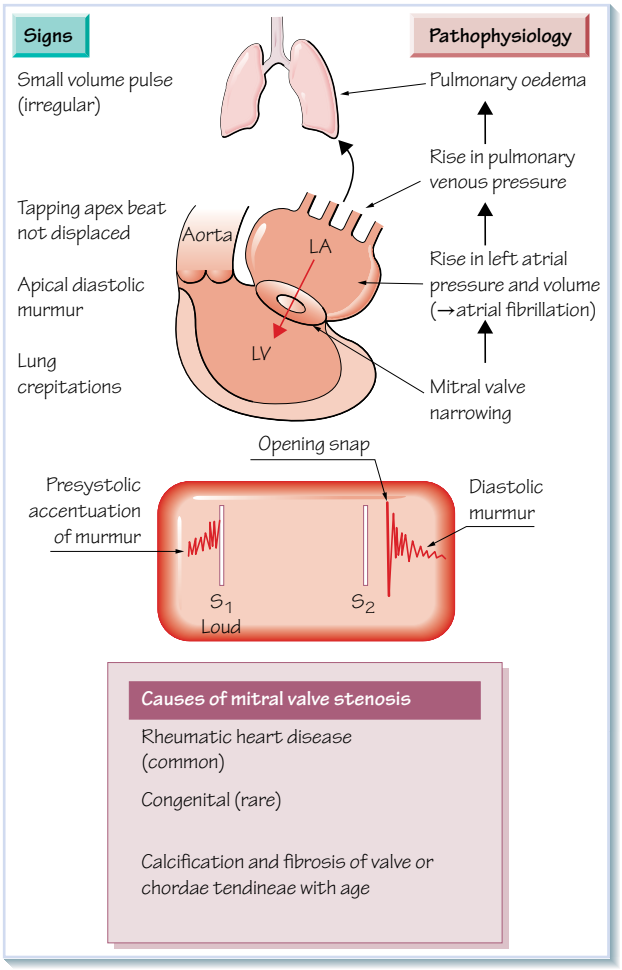
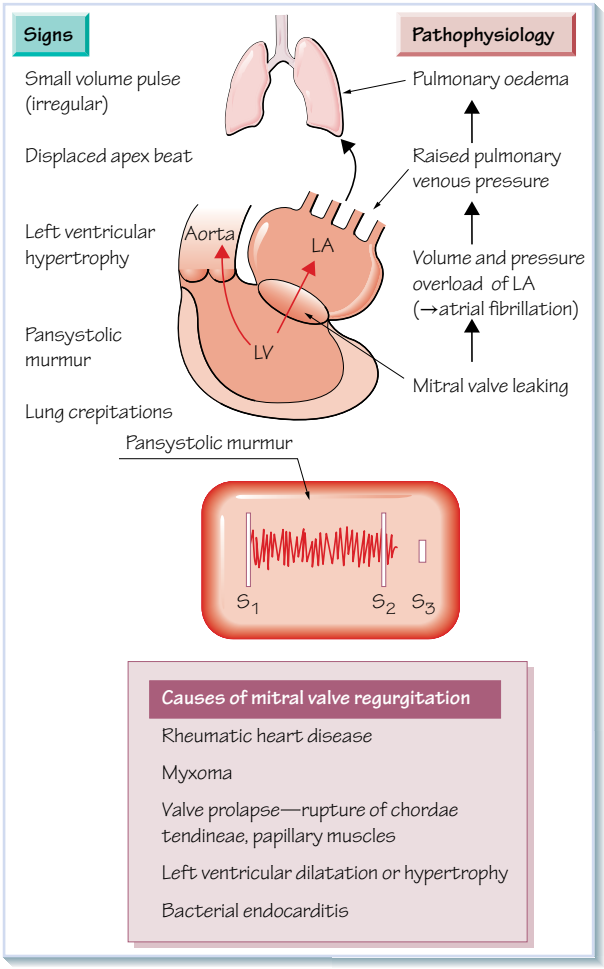


Figure 55.2 Mitral regurgitation



The **mitral valve** is normally bicuspid and separates the left atrium (LA) and left ventricle (LV). The valve may narrow (**mitral stenosis**) or leak (**mitral regurgitation**).

Mitral stenosis (Figure 55.1)

Causes

Mitral stenosis (MS) is usually caused by prior episodes, often during childhood, of acute **rheumatic fever**. This causes thickening and fusion of the mitral **commissures**, **cusps** or **chordae tendineae**, making the cusps less flexible and narrowing the orifice. Symptoms from MS usually develop more than 10 years after the acute attack of rheumatic fever, which patients may not recall. The normal area of a mitral valve is 6 cm^2; critical MS occurs when this area falls to 1 cm^2. Other less common causes include congenital mitral stenosis and carcinoid tumours, which are very rare.

Pathophysiology

MS prevents the free flow of blood from the LA to the LV, and slows ventricular filling during diastole. The left atrial pressure rises to maintain cardiac output, and there is **atrial hypertrophy** and **dilatation**. The elevated left atrial pressure causes pulmonary congestion and can result in **pulmonary hypertension** and **oedema**, and **right heart failure** (see Chapter 46). Patients with MS rely on atrial systole (the so-called 'atrial kick') for ventricular filling, and **atrial fibrillation** (caused by atrial enlargement) significantly reduces cardiac output. The LV is usually normal in MS, but may be abnormal due to either chronic underfeeding of the LV or rheumatic scarring.

Clinical features

Patients present in their thirties to forties with **dyspnoea**, either on exertion or during situations that raise cardiac output (e.g. fever, anaemia, pregnancy). This is a result of **pulmonary congestion**,

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which causes the lungs to become stiffer. Patients may present with **palpitations, chest pain, stroke** (via embolization of thrombi) or **haemoptysis** (coughing up of blood). Hoarseness may be present as a result of the enlarged LA compressing the left recurrent laryngeal nerve. Symptoms may be precipitated by atrial fibrillation. The patient's cheeks may appear pinkish – '**malar flush**' or '**mitral facies**', due to slight arterial hypoxia resulting from the reduced cardiac output. The **apex beat** is described as **tapping** and the first heart sound is loud. Auscultation reveals an **opening snap** soon after S_2 that is best heard at the apex, and by a **rumbling mid-diastolic murmur** leading to a loud S_1. The duration of the murmur is related to the severity of the MS. It is brief in mild MS and **pandiastolic** (i.e. lasts for the whole of diastole) in severe MS. When auscultating for the diastolic murmur of MS, ask the patient to lean towards their left side and to hold their breath in expiration. This manoeuvre helps accentuate the murmur as it brings the heart against the thoracic wall and briefly increases left-sided cardiac output. Patients in sinus rhythm may have **presystolic accentuation** of the murmur due to atrial contraction and a large venous 'a' wave (see Chapter 16). If the mitral valve is completely immobile there may be no opening snap or a loud S_1. As MS becomes more severe, the pulse becomes less prominent, **crackles** are heard on auscultation of the lung bases because of developing pulmonary oedema, and the **jugular venous pressure** becomes elevated.

The ECG may show signs consistent with LA enlargement only, although many patients are in atrial fibrillation. The chest X-ray may show left atrial enlargement with normal left ventricular size, but with increasing severity of MS there may be pulmonary venous congestion, enlarged pulmonary arteries, denoting pulmonary hypertension, and right ventricular enlargement.

Management

Mild MS may require little treatment, although management should include measures to avoid **anaemia** and **tachyarrhythmias** as these may precipitate decompensation and cardiac failure (see Chapter 46). If the patient is in atrial fibrillation, **rate control** with a β-blocker or rate-limiting Ca^{2+} channel blocker is crucial. Anticoagulation must be given to prevent stroke resulting from an embolus arising from the fibrillating atrium. Patients with MS can remain minimally symptomatic for many years but deteriorate quickly once symptoms worsen. Therefore, **valve replacement** with a mechanical valve, **valvotomy** (surgical separation of commissures) or **balloon valvuloplasty** (the use of a balloon catheter to force cusps open) should be performed in moderately symptomatic patients.

Mitral regurgitation (Figure 55.2)

Causes

Acute mitral regurgitation (MR) is usually a result of **infective endocarditis**, **ruptured chordae tendineae** or ischaemic **papillary muscle rupture**. Chronic MR arises from **myxomatous degeneration** of the mitral leaflets, **mitral valve prolapse** (reversal into atrium) and chronic MR may also develop in any disease causing LV dilatation, so preventing apposition (coming together) of the mitral leaflets, or because of ischaemic dysfunction of the papillary muscles. As MR causes LV dilatation, mitral regurgitation begets further mitral regurgitation.

Pathophysiology

In **acute MR** the LV ejects blood back into the LA, imposing a sudden volume load on the LA during ventricular systole. Left atrial pressure rises suddenly and this is rapidly followed by a rise in pulmonary venous pressure and capillary pressure. This leads to fluid entering the lung interstitium, causing stiffness and dyspnoea, or into the alveoli, causing **pulmonary oedema**.

Chronic MR is characterized by LV dilatation and hypertrophy, and dilatation of the LA. The latter protects the pulmonary circulation from the effects of the regurgitant volume. This form of MR is called *chronic compensated*. However, LA dilatation leads to atrial fibrillation. The fibrillating atrium is liable to develop **thrombi** that may be **embolized** (dislodge and move freely in the blood) causing stroke (see Chapter 8).

MR imposes a diastolic volume load on the LV that causes dilatation, because each systolic stroke volume is composed of a portion that enters the aorta (LV output) and an ineffective portion that re-enters the LA (LV regurgitant volume) and adds to the venous return. The regurgitant volume increases when LV emptying is impaired, such as with aortic stenosis or hypertension.

Clinical features

Patients with mild chronic MR are usually asymptomatic. As MR worsens, patients develop **fatigue, dyspnoea on exertion, orthopnoea** and **pulmonary oedema** as a result of progressive LV failure and elevation of pulmonary capillary pressure (see Chapter 46). The development of atrial fibrillation is common because of dilatation of the LA. Chronic MR is associated with a **pansystolic** murmur, which is heard best at the apex, and which radiates classically to the axilla. S_1 is soft and S_2 is widely split because of an early aortic component. Echocardiography can detect a prolapsing or rheumatic valve and determine LV size and function. Doppler imaging of the regurgitant jet can assess the severity of MR.

Management

Management is focused on promoting LV emptying into the aorta. Reduction of afterload with **angiotensin-converting enzyme inhibitors** is beneficial (see Chapter 47). Patients with atrial fibrillation receive **anticoagulants** to prevent stroke. A prolapsing valve may sometimes be repaired. Dilatation of the mitral valve ring may be corrected by implantation of an artificial ring. Rheumatic valves and those damaged by endocarditis often need replacement with an artificial valve. Valve replacement is best performed prior to the development of LV dysfunction or pulmonary hypertension and should always be performed in patients with symptomatic MR despite medical therapy. The risks of surgery are higher in acute MR; however, valve replacement should be performed in patients with uncontrollable heart failure or end-organ failure, even in cases of acute infective endocarditis.

56 Congenital heart disease

Figure 56.1 Normal

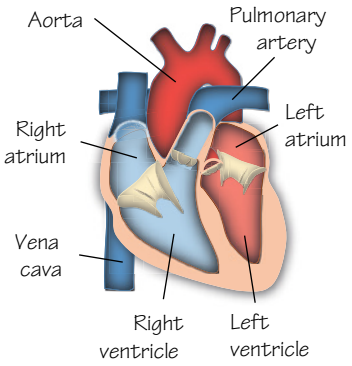


Figure 56.2 VSD – low PVR

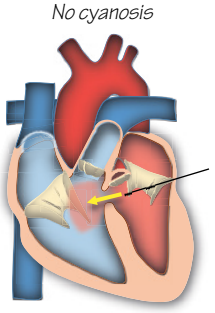
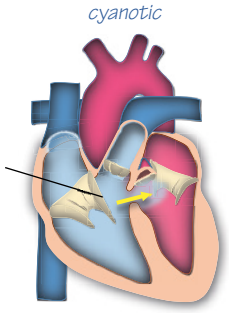
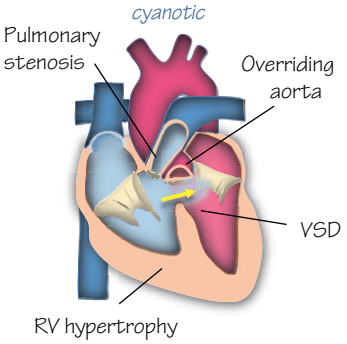


Figure 56.3 VSD – high PVR



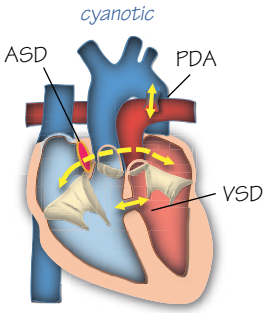
Initially left to right shunt because PVR and RV pressure are low. But if persistent, pulmonary hypertension and vascular remodelling may increase PVR and RV pressure sufficiently to cause right to left shunt and thus cyanosis

Figure 56.4 Fallot's tetralogy



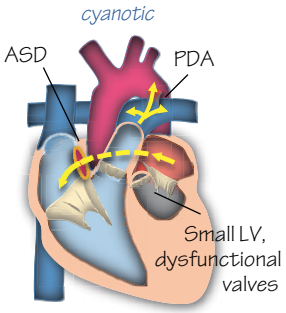
The 4 features of Fallot'stetralogy
Degree of pulmonary stenosis determines size of right to left shunt and therefore cyanosis.

Figure 56.5 d-TGA



Fatal after birth if no VSD, ASD or PDA to allow mixing of blood. Degree of cyanosis depends of extent of circulatory mixing

Figure 56.6 HLHS



Fatal after birth if no ASD *and* PDA. Not correctable; right ventricle performs entire work of heart, even after surgery

Figure 56.7 Incidence of most common congenital heart diseases and valve/vascular disorders

	per 10,000 births
Mitral valve prolapse – *but often acquired*	200
Bicuspid aortic valve	140
VSD – *ventricular septal defect*	35
ASD – *atrial septal defect*	10
PDA – *patent ductus arteriosus*	8
Pulmonary stenosis	7
Fallot's Tetralogy	5
Coarctation of aorta–*usually at region of ductus*	4
Aortic stenosis	4
AVSD –*atrioventricular septal defects*	4
d-TGA–*d-transposition of great arteries*	4
HLHS–*hypoplastic left heart syndrome*	2.5

Congenital heart diseases (**CHDs**) are abnormalities of cardiac structure that are present at birth, caused by abnormal development between 3 and 8 weeks' gestation. The incidence of CHD is ~1% of live births, excluding common valve disorders such as bicuspid aortic valve and mitral valve prolapse (Chapters 54, 55, Figure 56.7). Many spontaneously aborted or stillborn fetuses have cardiac malformations, which are also common in Down's syndrome and other genetic disorders of development. Maternal circumstances during gestation significantly increase the risk of CHD. These include later maternal age, **diabetes** (but not gestational), **rubella** infection, **alcohol abuse** and medications such as acne treatments containing **isotretinoin**, or **ibuprofen** taken in the first trimester.

CHDs often present in infancy with **congestive heart failure** or **central cyanosis**, although some only become a problem later. Heart failure in an infant is usually caused by a **left to right shunt**, such as **ventricular septal defect** (VSD) or **patent ductus arteriosus** (PDA), or as a result of aortic obstruction. **Central cyanosis** may be caused by severe pulmonary disease or **right to left shunt**. It is characteristic of **transposition of the great vessels** and **tetralogy of Fallot**.

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Ventricular septal defects (**VSD**) are the most common CHDs and may occur with other abnormalities. In utero, pulmonary vascular resistance (PVR) exceeds systemic vascular resistance (SVR), so most blood exits the left ventricle via the aorta. However, after birth PVR < SVR, and blood is shunted from the left to right ventricle via the VSD, and into the pulmonary artery (Figure 56.2). The magnitude of shunt is related to the size of defect and relative size of PVR and SVR. In young children, moderate VSD may limit exercise or cause fatigue, an enlarged heart and hypertrophy. Shunting of blood into the pulmonary circulation leads to pulmonary hypertension, and if persistent irreversible **pulmonary vascular remodelling**. PVR may then exceed SVR, reversing the shunt and causing cyanosis (Figure 56.3; **Eisenmenger's syndrome**). Surgical correction is then not possible, so infants with significant VSD benefit from early surgery. Half of smaller VSDs close spontaneously within ~4 years.

Atrial septal defects (**ASD**) generally involve the midseptum in the ostium secundum and are distinct from a **patent foramen ovale** (PFO;), which are generally smaller and of little consequence, though very common (Chapter 25). They are often initially asymptomatic and if small may close spontaneously, though patients with small to moderate ASDs may develop symptoms when adult. With larger ASDs the left to right shunt may eventually lead to pulmonary hypertension, Eisenmenger's syndrome (see above) or left ventricular failure. There is also a risk of atrial arrhythmias, and as the child gets older stroke due to passage of thrombi. Due to the risk of complications in later life ASDs are normally repaired in childhood even if asymptomatic. Repair is rarely performed after 25 years of age, especially if there is pulmonary hypertension.

Patent ductus arteriosus (see Chapter 25) arises when the ductus does not close properly, often due to malformations and possibly related to maternal rubella. It is more common in females. The duct may not close in premature babies due to immaturity. Frequently PDA is not diagnosed at birth but only after development of heart failure or infective endocarditis. Treatment is initiated as soon as possible to prevent development of full heart failure. Ligation of the ductus arteriosus must be performed within 5 years of birth. A cyclooxygenase inhibitor (e.g. indomethacin) to reduce PGE_1 is sometimes sufficient to promote closure.

Fallot's tetralogy is the most common **cyanotic CHD** in children surviving to 1 year (Figure 56.4). It consists of a VSD, pulmonary stenosis, an overriding aorta (positioning of aorta over VSD) and right ventricular hypertrophy. There is a high right ventricular pressure and right to left shunt. The degree of cyanosis depends on the degree of pulmonary stenosis. Infants with Fallot's tetralogy develop slowly and may present with dyspnoea, fatigue and hypoxic episodes (**Fallot's, tetralogy** or **"Tet" spells**), characterized by rapidly worsening cyanosis, progressing to limpness, stroke and loss of consciousness. There is a 50% mortality rate by 6 years if untreated. Surgical correction of the VSD and pulmonary obstruction is performed preferably around 12 months and has <5% mortality.

Complete **transposition of the great arteries** (**d-TGA**; *dextropositioning of RV*) is the second most common **cyanotic** CHD, where the left ventricle empties into the pulmonary artery and the right ventricle into the aorta (Figure 56.5). This results in two separate circulations, one through the body and one through the lungs, so tissues have no access to oxygenated blood. Life can be supported only if there is mixing of oxygenated and deoxygenated blood, via either a VSD (present in 50%), PDA and/or ASD. Without an VSD severe cyanosis occurs rapidly after closure of the ductus arteriosus. This can be delayed by administrating PGE_1 or creation of an ASD (balloon septostomy). Surgical correction involves reconnection of the great arteries to their appropriate ventricles in first week of life. Without correction, d-TGA is fatal within 2 weeks for ~30% and a year for 90%, depending on extent of VSD/ASD. **L-TGA** (or *congenitally corrected* TGA) is rare. Here the right and left ventricles rather than great arteries are transposed, so blood follows a normal route through the lungs. However, as the right ventricle now serves the systemic circulation, it may hypertrophy and eventually fail.

Atrioventricular septal defects (**AVSD**) occur due to failure of the embryonic endocardial cushions to develop into the lower part of atrial septum and upper part of the ventricular septum, and to separate the mitral and tricuspid valves. It is common in Down's syndrome. In **complete AVSD** there is effectively a large hole in the centre of the heart where the atrial and ventricular septa would normally meet, and the upper and lower chambers are separated by a single common inflow valve. In **partial AVSD** the ventricular septum (but not atrial) is complete and there are distinct tricuspid and mitral valves, though the latter is generally defective and leaks. There are also transitional forms. AVSDs generally lead to congestive heart failure and pulmonary hypertension if untreated. Surgical correction is performed at 3–6 months (complete AVSD) or 6–18 months (partial) depending on severity. Medical treatment prior to surgery is as for heart failure (Chapter 47).

Hypoplastic left heart syndrome (**HLHS**) is one of the most challenging CHDs, characterized by a poorly developed left ventricle, small or blocked mitral and aortic valves, and small aorta (Figure 56.6). It is more common in males. As the ductus arteriosus starts to close after birth, symptoms including tissue hypoxia develop rapidly, and without treatment survival is a few days at most. HLHS is not correctable, but life can be extended by surgery to divert right ventricular output to the systemic circulation whilst maintaining pulmonary blood flow (a complex procedure), or in some cases heart transplant. The neonatal death rate is nevertheless close to 25%, and barely 70% survive to their teens. **Hypoplastic right heart syndrome** is similar but less common and involves the right ventricle, tricuspid and pulmonary valves.

57 Cardiomyopathies and channelopathies

Figure 57.1 Cardiomyopathies

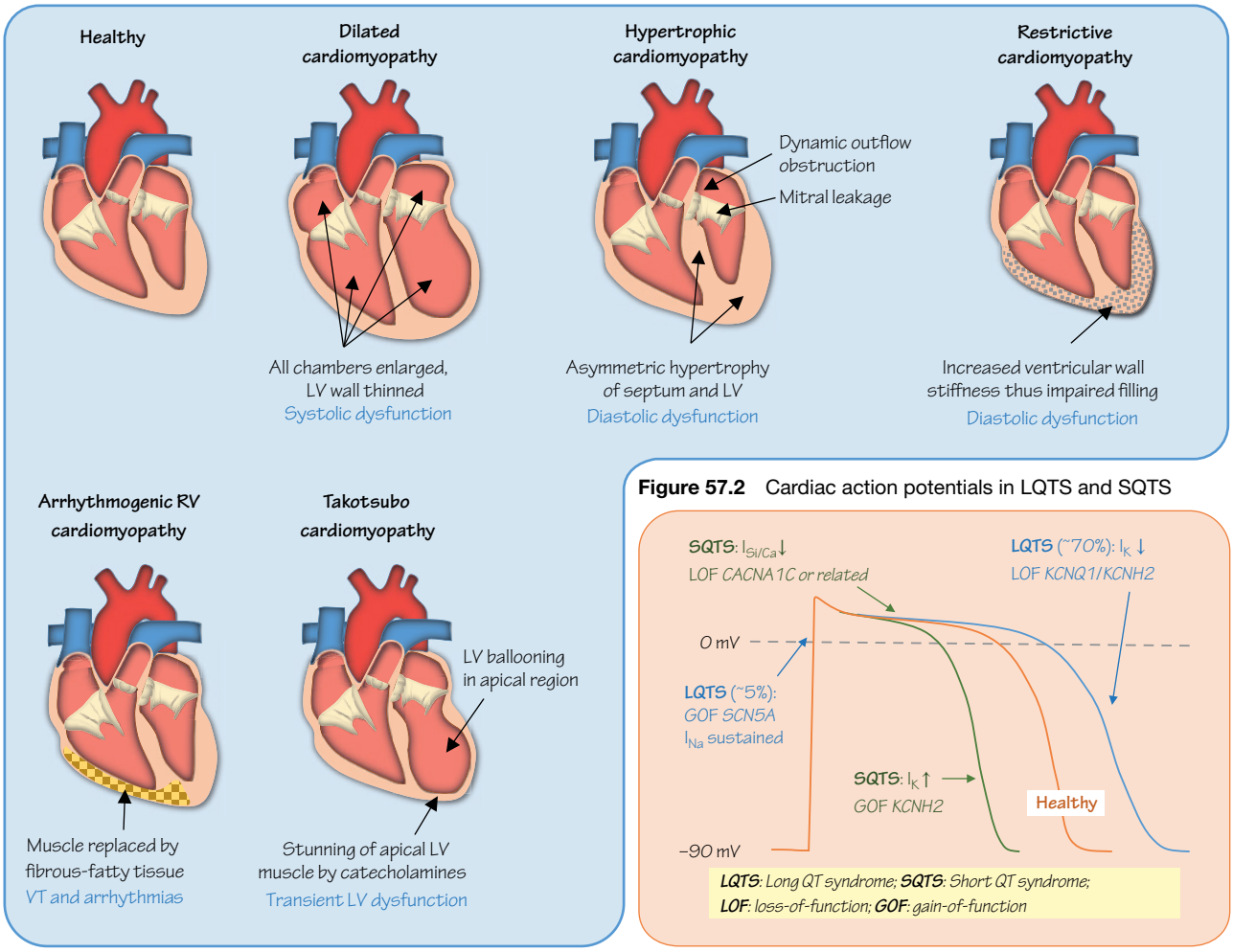

Figure 57.2 Cardiac action potentials in LQTS and SQTS

Cardiomyopathies are diseases of cardiac muscle and, along with channelopathies, the most common medical cause of sudden cardiac death in people under 35.

Cardiomyopathies (Figure 57.1)

Dilated cardiomyopathy (DCM) is relatively common, with highest incidence in males and middle age. It is characterised by ventricular and atrial dilation and impaired systolic function and is the **third most common cause of heart failure** and most **frequent reason for heart transplants**. Symptoms may be absent or slow in onset and are similar to those for heart failure (Chapter 46) including dyspnoea, oedema and arrhythmias. Most cases are idiopathic (unknown aetiology), though ~35% show **autosomal dominant** inheritance; genes encoding sarcomere and cytoskeletal proteins have been implicated, including β myosin heavy chain, troponin and dystrophin. DCM can also be **acquired** in **myocarditis** (inflammation of cardiac muscle), for example, viral infections, systemic lupus erythematosus (SLE), chronic alcohol or cocaine abuse. One in 4000 women develop DCM just before or after childbirth (**peripartum cardiomyopathy**), attributed to inflammatory cytokines. Management is similar to that for heart failure (Chapter 47) and aimed at controlling symptoms and life-threatening arrhythmias.

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac disease, with a prevalence of 1 in 500. Although generally asymptomatic, it is the leading cause of **sudden cardiac death** in young athletes and a significant cause in the general population. HCM is associated with septal and left ventricular hypertrophy, often **asymmetric,** caused by disordered myocardial growth. This is frequently coupled to **left ventricular outflow tract obstruction** and valve dysfunction, conduction defects and arrhythmias. Inheritance is **autosomal dominant**. Mutations in sarcomere-related genes are present in 60% of cases, most commonly β myosin heavy chain

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(~45%) and cardiac myosin binding protein C (~35%). Clinical features are variable, ranging from asymptomatic to dyspnoea, angina, palpitations and syncope and, in a minority, heart failure, stroke and sudden cardiac death. Moderate symptoms are treated with β-blockers and/or verapamil, severe cases require surgery for outflow tract obstruction, and high-risk patients benefit from an **implantable cardioverter defibrillator** (ICD).

Restrictive cardiomyopathy (RCM) is rare and characterised by abnormal diastolic function due to reduced ventricular wall compliance and impaired filling. It invariably progresses to heart failure (Chapter 46). Symptoms include dyspnoea on exertion and syncope. It is often idiopathic though 30% of cases have a family history; it may involve similar genetic abnormalities as HCM. RCM can be secondary to infiltrative disorders including amyloidosis, sarcoidosis, some metabolic conditions and haemochromatosis (iron overload), and also fibrosis following radiation treatment.

Arrhythmogenic right ventricular cardiomyopathy (or **dysplasia**) (ARVC) is a rare, (1 in 5000) autosomal dominant inherited condition which can cause sudden cardiac death, particularly in the young. Right (and sometimes left) ventricular muscle is replaced with fibrous-fatty tissue, with disorganised electrical conduction leading to re-entrant ventricular tachycardias and arrhythmias. Genes linked to ARVC encode for desmosome proteins (Chapters 2, 13), suggesting a role for gap junctions. Presentation varies widely; management is focused on antiarrhythmic therapy and ICDs.

Stress (Takotsubo) cardiomyopathy (TCM; aka *broken heart syndrome*) is characterized by acute but rapidly reversible left ventricular systolic dysfunction, often localised to the apical region causing ballooning (like a Japanese octopus pot: *takotsubo*). It occurs after **severe emotional or psychological stress**, for example, intense grief or anger, serious accidents, although sometimes there is no obvious trigger. Clinical presentation is indistinguishable from acute coronary syndrome, with chest pain, dyspnoea and ST-segment elevation (Chapter 42), but there is no coronary artery obstruction, and in ~95% of cases there is full recovery after a month. TCM has been diagnosed in ~2% of admissions for acute coronary syndrome; ~90% of cases involve postmenopausal women aged between 58 and 75. TCM may be caused by "stunning" of cardiac muscle by stress-induced catecholamines. Oestrogen may protect premenopausal women.

Channelopathies

Channelopathies are inherited diseases caused by mutations in genes for ion channels and predispose to arrhythmias, syncope and sudden cardiac death, most commonly in young, otherwise healthy adults with structurally normal hearts.

Long QT syndrome (LQTS) is characterized by a prolonged QT interval (QT_C >0.44 s; see Chapter 14). This is normally of no consequence and patients are otherwise healthy, but rarely acute emotion or exertion triggers the polymorphic ventricular tachyarrhythmia **torsade de pointes** (Chapter 51), causing syncope (most common), seizures or sudden cardiac death. The trigger is increased sympathetic activity (see also CPVT below). LQTS is autosomal dominant inherited, with a prevalence of ~1 in 6000; ~4% suffer sudden cardiac death, largely children and young adults, but 30% remain asymptomatic lifelong. About 75% of cases involve three genes (Figure 57.2): **loss-of-function** mutations in *KCNQ1* (~30%) or *KCNH2* (*hERG*) (~40%), which encode **delayed rectifier K^+ channels**, reduce I_K and so prolong repolarization (Chapter 12), whilst **gain-of-function** mutations in *SCN5A* (~5%; encodes the **Na^+ channel**) slow channel inactivation so I_{Na} is sustained, prolonging the action potential. Treatment with β-blockers to suppress sympathetic stimulation is effective, but an ICD may be required. Functional LQTS can be **acquired** in heart failure (Chapter 46). **Drug-induced** LQTS is common, not only with class IA and III antiarrhythmics (as expected; Chapter 52), but also antimalarial, antihistamine, antibiotic, psychiatric and recreational drugs (e.g. cocaine) because the *hERG* protein is promiscuous in its interactions. Such drugs dangerously increase risk for genetic LQTS.

Short QT syndrome (SQTS) has only recently been described. In contrast to LQTS repolarisation is abnormally shortened, predisposing to atrial and ventricular fibrillation. It has a high lethality; in ~30% sudden cardiac arrest was the first presentation, most often in young adults. Others experience syncope and palpitations. Most cases exhibit **gain-of-function** mutations in *KCNH2* (the opposite of LQTS), others have **loss-of-function** mutations in *CACNA1C* or related genes encoding the L-type Ca^{2+} channel (Figure 57.2). Inheritance is autosomal dominant, and there is high penetrance in affected families. ICD is the mainstream and often prophylactic therapy, though quinidine may be effective.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) has similar symptoms to LQTS and is also triggered by acute emotion, exercise and increased sympathetic activity; however, the resting ECG is normal. Symptoms generally become apparent in the first decade of life, and 60% will have had symptoms by the age of 20. Prevalence is 1 in 10 000. Most cases (50–70%) are associated with mutations in *RYR2*, which encodes the **SR Ca^{2+} release channel** and has autosomal dominant inheritance. A minority (~8%) have mutations in *CASQ2*, which encodes **calsequestrin** and is recessive (Chapter 12). Treatment is the same as for LQT syndrome.

Brugada syndrome is characterized by a Brugada pattern ECG (ST elevation in leads V_1–V_3; Chapters 11, 14, 51); there is an increased risk of sudden cardiac death due to **ventricular fibrillation**, often during rest or sleep. Inheritance is autosomal dominant, though it is ~9-fold more common in males. Prevalence may be 1 in 2000, particularly in Southeast Asia where it is the leading cause of sudden death in young men. About 20% of cases are associated with **loss-of-function** mutations in *SCN5A* encoding **Na^+ channels**, which may favour re-entry arrhythmias due to electrical differences between subepicardial and subendocardial cells (Chapter 51), though numerous other genes have also been implicated. The only known effective treatment is an ICD.

58 Pulmonary hypertension

Figure 58.1 Nice (2013) classification of pulmonary hypertension

Group 1. Pulmonary arterial hypertension
- 1.1 Idiopathic PAH (iPAH)
- 1.2 Heritable PAH (hPAH)
- 1.2.1 BMPR2 mutations
- 1.2.2 ALK-1, ENG,SMAD9,CAV1,KCNK3 mutations
- 1.2.3 Unknown
- 1.3 Drug and toxin induced
- 1.4 Associated with (aPAH):
- 1.4.1 Connective tissue disease
- 1.4.2 HIV infection
- 1.4.3 Portal hypertension
- 1.4.4 Congenital heart diseases
- 1.4.5 Schistosomiasis

Group 1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

Group 1". Persistent PH of the newborn (PPHN)

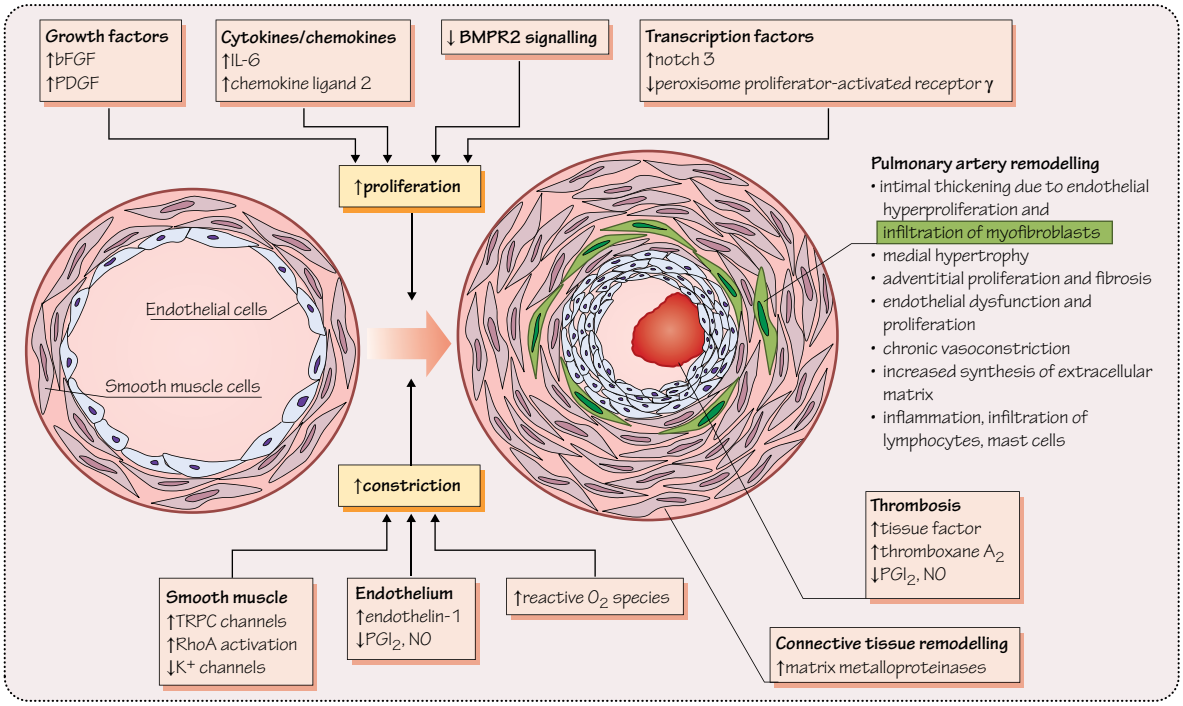
Group 2 Pulmonary hypertension due to left heart disease
- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

Group 3. PH due to lung diseases and/or hypoxia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases

Group 4. Chronic thromboembolic PH (CTEPH)

Group 5. PH with unclear multifactorial mechanisms
- 5.1 Haematologic disorders: (e.g. chronic haemolytic anaemia)
- 5.2 Systemic disorders: (e.g. sarcoidosis)
- 5.3 Metabolic disorders: (glycogen storage disease, thyroid disorders
- 5.4 Others: obstruction of PA by a tumour, chronic renal failure)

Figure 58.2 Pathogenesis of PAH – putative mechanisms



The mean pressure in the pulmonary artery (mPAP) in a normal resting adult is ~16 mmHg. Pulmonary hypertension (PH) is defined as an mPAP exceeding 25 mmHg at rest. The increased PAP can be due to a rise in pulmonary vascular resistance (PVR), increased pulmonary blood flow due to a systemic to pulmonary shunt (Eisenmenger's syndrome; see Chapter 56) or back pressure from the left heart. PH increases right ventricular afterload, eventually leading to right heart failure.

Types of pulmonary hypertension

PH was initially (in 1973) classified as **primary** if it was idiopathic or **secondary** if a cause could be identified. Progressively more complex classification schemes which grouped the various manifestations of PH according to their pathological and/or clinical features and management options were then created, with the most recent emerging from the 5th World Symposium on PH held in

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Nice in 2013 (Figure 58.1). Together, the various forms of PH affect ~100 million people worldwide.

Group 1 PH, also termed **pulmonary arterial hypertension** (PAH) comprises heritable (hPAH), idiopathic PAH (iPAH) and also PH associated with a number of other conditions (aPAH). Patients demonstrate a clinical syndrome indicative of severe PH and an increased PVR associated with a unique set of pulmonary vascular abnormalities (see below). Both hPAH and iPAH are characterized by a decreased expression of **bone morphogenetic protein receptor type 2** (BMPR2) which, usually in hPAH and sometimes in iPAH, is associated with mutations in *BMPR2*, its cognate gene. **Groups 1′ and 1′′ PH** have features resembling those of PAH but are separate clinical entities. Groups 2–5 are forms of secondary PH. **Group 2 PH** is due to left heart disease, chiefly ventricular failure or mitral and/or aortic valve disease, which results in increased left atrial pressure that backs up into the pulmonary arteries. **Group 3 PH** is associated with lung diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, and other conditions such as sleep-disturbed breathing, the common factor being the presence of alveolar hypoxia. **Group 4 PH** is associated with chronic thromboembolic disease causing a persistent blockage of pulmonary arteries due to venous thromboembolism. **Group 5** represents PH associated with a heterogeneous set of conditions such as chronic myeloid leukaemia, sarcoidosis, Gaucher's disease, and thyroid disease. Secondary PH is generally managed by treating the cause. Group 2 PH is often controlled as a consequence of addressing the underlying left heart disease, whereas Group 3 PH patients with COPD may benefit from O_2 therapy. Group 4 PH is treated with anticoagulation and surgical removal of the embolus (thromboembolectomy).

Pulmonary arterial hypertension

PAH includes hPAH and iPAH, as well as severe PH which for unknown reasons often arises in association with certain conditions (aPAH). iPAH and hPAH together affect only ~15 people per million, whereas aPAH is much more common. PAH prognosis is poor, with a 15% mortality rate after 1 year; the only cure is lung transplant. Right ventricular function is an important determinant of prognosis, as patients usually die from progressive right heart failure, and individuals vary with regard to the ability of the right ventricle to compensate for the increased afterload generated as a result of the increased PVR.

Pathophysiology

Although excessive pulmonary vasoconstriction is an important factor in ~20% of PAH cases, the main cause of the increased PVR in PAH is **pulmonary remodelling** characterized by excessive pulmonary artery (PA) smooth muscle cell proliferation. PA remodelling typically results in hyperplasia of the intimal layer due to the invasion of myofibroblasts (cells with properties of fibroblasts and smooth muscle), as well as hypertrophy of the medial layer, and adventitial proliferation. These processes cause the muscularization of very small PA, which normally contain little smooth muscle. Thrombosis *in situ*, inflammation, and the presence of complex vascular lesions (often termed **plexiform lesions**) comprising endothelial cells, lymphocytes and mast cells, are additional features that contribute to raised PVR and blood flow restriction. The causes of remodelling remain controversial, but some of the mechanisms currently thought to contribute to this process are shown in Figure 58.2.

Clinical findings and diagnosis

Often the first clinical manifestation of pulmonary hypertension is gradually increasing breathlessness upon exertion and fatigue. As the condition progresses, these symptoms may be present at rest. Other symptoms include chest pain and peripheral oedema.

Physical examination Signs in severe PH include an increased intensity of the pulmonary component of the second heart sound due to the elevated pulmonary pressure that increases the force of closure of the pulmonary valve and a midsystolic ejection murmur indicating turbulent pulmonary outflow.

Diagnosis Definitive diagnosis of PH requires measurement of mPAP. A Swan–Ganz catheter is inserted via the femoral vein and advanced into the vena cava and then into the right atrium, right ventricle and finally the main PA, where the mPAP is measured.

Management

Management of PAH includes treatment of symptoms and newer specific therapies which slow disease progression but do not afford a cure. Symptomatic therapy includes diuretics to reduce peripheral oedema, anticoagulants to prevent clots, inhaled O_2 to increase blood oxygenation and digoxin to provide positive inotropy. Calcium-channel blockers can lower PAP in a small subset of patients. Specific therapies include **prostacyclin (PGI_2) analogues**, **endothelin receptor antagonists, phosphodiesterase-5 inhibitors** and **riociguat**.

Production by PA of PGI_2, an endothelium-derived vasodilator and inhibitor of platelet aggregation, is thought to be deficient in PAH, and stable PGI_2 analogues have become a mainstay of its treatment. **Epoprostenol**, the first to be introduced, is used for the intravenous treatment of advanced PAH and is the only drug that has been shown to lengthen survival in PAH. **Iloprost** and **beraprost** are synthetic analogues of PGI_2 which are administered by inhalation and orally, respectively; **selexipag**, an agonist of the prostaglandin IP receptor which is structurally dissimilar to PGI_2, is also administered orally.

Endothelin-1 (see Chapter 24) is a potent vasoconstrictor and pro-proliferative agent that may contribute to the development of PAH. **Bosentan** is an antagonist of ET_A and ET_B receptors which was shown in the BREATHE-1 trial to significantly improve exercise tolerance. **Ambrisentan**, a selective blocker of the ET_A receptor, is also used and was shown in the ARIES-1 and ARIES-2 trials to improve the 6-minute walk distance (a test often used to gauge the severity of PAH) after 12 weeks. **Macicentan**, a newer ET_A/ET_B antagonist, is also used.

Production by PA of the potent endothelium-derived vasodilator nitric oxide (NO), which acts by stimulating smooth muscle cell soluble guanylate cyclase, thereby increasing cyclic guanosine monophosphate (cGMP) levels (see Chapters 15 and 24), is thought to be deficient in PAH. cGMP is broken down by various phosphodiesterases (PDEs), so that PDE inhibition enhances and prolongs the vasodilating effect of NO. PDE-5 is the most important phosphodiesterase in the pulmonary circulation, and PDE-5 inhibitors (**sildenafil, vardenafil, tadalafil**) have accordingly emerged as an important pillar of therapy. The SUPER-1 study showed that patients taking sildenafil were more likely to show an improvement in symptoms than those taking placebo. **Riociguat**, released in 2013 for use in PAH, acts to raise cGMP levels by directly stimulating guanylate cyclase.

59 Stroke

Figure 59.1 Arterial blood supply to the brain

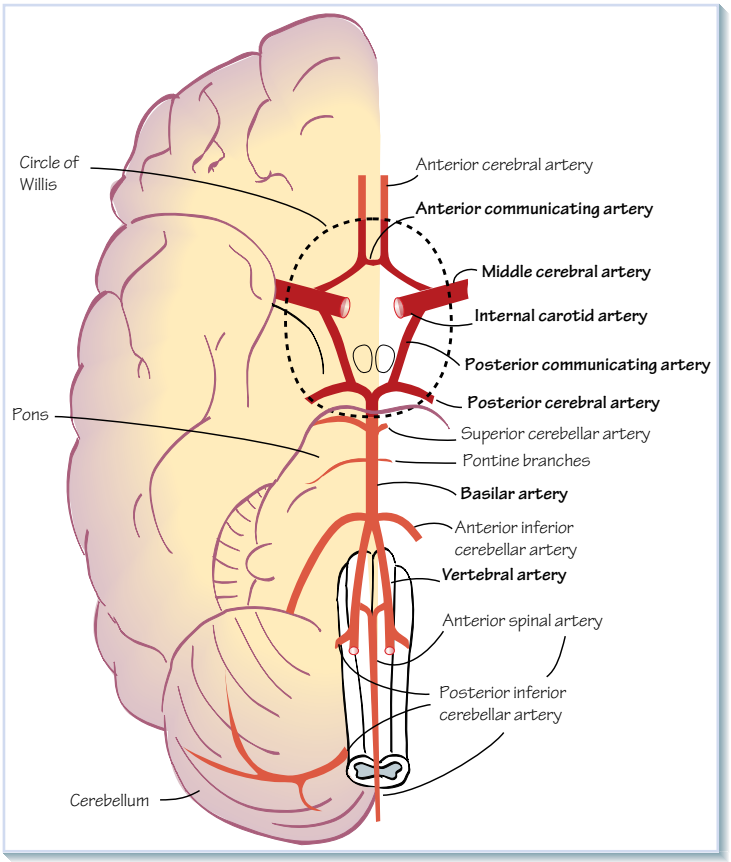

Figure 59.2 Lateral aspect of the cerebral hemisphere showing blood supply

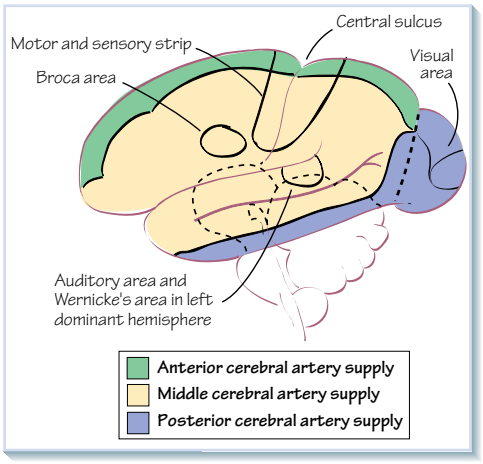

Figure 59.3 Coronal section of brain showing blood supply

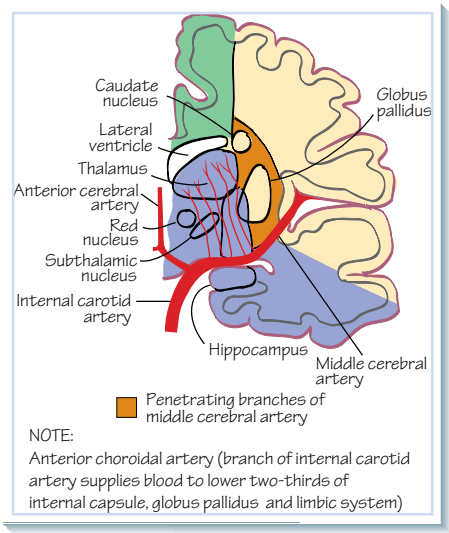

Figure 59.4 Stroke symptoms due to arterial occlusion at different sites

Middle cerebral artery: supplies the largest part of the cerebral cortex and is most common site of strokes
- Occlusion here causes contralateral paralysis (hemiplegia) or weakness (hemiparesis), also hemisensory loss in head/arm (e.g. homonymous hemianopia – blindness over one half of visual field of both eyes).
- With dominant hemisphere stroke: speech/language dysfunction (aphasia) and dyspraxia (inability to carry out complex movements)
- With non-dominant hemisphere stroke: hemispatial neglect (deficient awareness of stimuli on one side of the head/arm)

Anterior cerebral artery - distal to the anterior communicating artery (which provides an alternative circulation):
- Occlusion here causes contralateral hemiplegia/hemiparesis, hemisensory loss in leg/foot; incontinence.

Posterior cerebral artery
- Occlusion here causes homonymous hemianopia, visual agnosia (objects can be seen but not recognised), memory deficit

Internal carotid artery:
- Occlusion here is often fatal since so much of the cerebrum is supplied by branches of this artery; symptoms resemble those of middle cerebral artery occlusion

Vertebrobasilar arteries:
- An extensive stroke here is usually fatal.
- Occlusion of smaller arteries can cause a wide variety of symptoms depending on which region is affected. These may include coma, quadriplegia, ataxia (loss of coordination), visual deficits, dysphagia (difficulty in swallowing), dysarthria (difficulty in speaking), nausea, vertigo, Horner syndrome

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Stroke (cerebrovascular infarct), the second leading cause of death and the largest source of disability worldwide, is defined as a sudden onset neurological deficit which is of cerebrovascular cause, is associated with a central nervous system infarct, and persists for more than 24 hours. **Ischaemic** stroke (~85% of cases) is usually due to a focal reduction of blood flow within the CNS caused by arterial thrombosis or embolism (e.g. due to atrial fibrillation), intracranial venous thrombosis, or is of undetermined cause. **Haemorrhagic** stroke (~15% of cases) is due to **intracerebral haemorrhage** (ICH, bleeding in the brain) or **subarachnoid haemorrhage** (bleeding between the arachnoid membrane and the pia mater). A stroke is said to be *completed* when symptoms have reached a stable maximum. **Transient ischaemic attack (TIA)** is neurological dysfunction associated with focal cerebral, spinal cord or retinal ischaemia that lasts <24 hours (typically <15 minutes). TIA is not associated with infarct but indicates a high risk of future stroke.

Blood supply to the brain As shown in Figures 59.1–59.3, most of the cerebrum is supplied with blood through the middle and anterior cerebral arteries (yellow and green regions, respectively, in Figures 59.2–59.3), which are branches of the internal carotid arteries (the **anterior circulation**). However, parts of the temporal and occipital lobes (blue regions, Figures 59.2–59.3) receive their blood from the posterior cerebral arteries. These arise from the basilar artery, which is formed by the anastomosis of the vertebral arteries. The vertebrobasilar arteries (the **posterior circulation**) also give rise to arteries supplying blood to the medulla, pons, cerebellum, thalamus, and the midbrain. The **Circle of Willis** (Figure 59.1), which is formed from the anastomosis of arteries of the anterior and posterior circulations and their communicating branches, allows blood from either the posterior or anterior circulations to reach any part of the cerebrum. This redundancy of supply can potentially ameliorate the effects of a slowly developing vascular occlusion in the internal carotid or vertebral arteries, although the extent to which this occurs is variable since the calibre of the communicating arteries differs between individuals.

Stroke signs, symptoms and risk factors

Signs and symptoms of stroke depend on the site of the infarct, as shown in Figure 59.4. **Stroke prognosis** also depends on the site and size of the infarct, with infarct in the territory of the middle cerebral artery being particularly dangerous. **Stroke risk** doubles every 10 years after age 55, such that in the UK approximately 18% of the population will have had a stroke by age 75. The largest modifiable risk factor for stroke is hypertension (increases risk fivefold). Diabetes, atherosclerosis, atrial fibrillation, smoking, hyperlipidaemia, high alcohol consumption and sickle cell disease are other important risk factors.

Pathogenesis

The developing lesion in stroke consists of an **ischaemic core** where blood flow has fallen drastically due to occlusion of a cerebral artery, surrounded by a **penumbra** in which blood flow is less markedly reduced because of the existence of collateral circulation from other arteries. Cells in the ischaemic core die within minutes, whereas those in the penumbra have a depressed electrical activity and will die over a period of hours but have the potential to recover if blood flow is restored quickly enough (e.g. by thrombolysis).

As described in Chapter 26, brain cells require a very high blood flow to maintain cellular ATP stores. These are therefore depleted within minutes in the ischaemic core, causing failure of the Na^+, K^+ ATPase and a consequent rundown of the neuronal transmembrane Na^+ and K^+ gradients which causes cell depolarization. This opens voltage-gated Ca^{2+} channels, leading to a rise in cell [Ca^{2+}] which is exaggerated by failure of the ATP-driven Ca^{2+} pump which extrudes Ca^{2+} from cells. Neuronal depolarization also causes a greatly increased release of **glutamate**, the most abundant neurotransmitter in the CNS. Glutamate acts on a variety of receptors, one of which, the *N*-methyl-D-aspartate receptor (NMDAR), is a Na^+ and Ca^{2+} permeable ion channel that is particularly sensitive to depolarization. Astrocytic uptake of glutamate, which normally controls its extracellular concentration, also fails due to ischaemia, further promoting the rise in extracellular [glutamate]. This leads to **excitotoxicity**, a vicious cycle of increasing Na^+ and Ca^{2+} influx and glutamate release which results in activation of destructive enzymes, production of reactive oxygen species, cell swelling, membrane rupture, and necrosis in the ischaemic core.

Cell death in the penumbra is more gradual and occurs mainly by **apoptosis** (programmed cell death), a process which can be initiated by multiple stimuli including NMDAR -induced rises in cell [Ca^{2+}] and the binding of ligands to cellular death receptors. Activation of NMDAR in the penumbra is associated with **spreading depolarizations**. These are long-lasting waves of depolarization which are initiated by the breakdown of the membrane potential in the ischaemic core and spread out through the penumbra as slow-moving waves, causing vasoconstriction and glutamate release as they spread. Apoptosis is also promoted by inflammation, which is driven both by activation of **microglial cells** (resident macrophages in the brain) and by the entry of leukocytes and lymphocytes from the circulation which occurs due to local disruption of the blood–brain barrier and results in the release of TNFα and other death receptor ligands.

Investigations

Speed is critical in the diagnosis and treatment of stroke, as irreversible brain damage progresses rapidly. In those with a sudden onset of neurological symptoms, the FAST (Face Arm Speech Test) can be used anywhere to screen for possible stroke; once in hospital the ROSIER (Rule Out Stroke In the Emergency Room) or National Institutes of Health Health Stroke Scale questionnaires can be used for more definitive diagnosis. Patients should receive an immediate brain scan using magnetic resonance imaging (MRI) or computed tomography (CT) to identify the site of the infarct and distinguish between ischaemic and haemorrhagic stroke, as the treatments for these differ. Blood tests are done to rule out hypoglycaemia (symptoms can mimic those of stroke) and check for polycythaemia (since increases in blood viscosity and can cause stroke). An ECG is taken because emboli resulting from atrial fibrillation or MI are common causes of ischaemic stroke.

Acute management

Stroke patients should be treated in a **specialist stroke care unit,** as this improves prognosis. Supportive treatment for ischaemic stroke includes maintaining a stable arterial O_2 saturation (> 93%), temperature (< 37.5°C), and blood glucose (< 180 mg/dl), as high temperature and hyperglycaemia worsen the infarct. Antihypertensive treatment should be used in patients with SBP >180 mmHg who are thrombolysed. Continual cardiac monitoring is necessary for several days.

Ischaemic stroke can be treated with **tissue plasminogen activator** (tPA, alteplase), the aim being to dissolve the blood clot in the affected cerebral artery, restore blood flow, and thereby promote recovery of tissue in the ischaemic penumbra. tPA does not affect survival but improves the chances of functional recovery. Its effectiveness decreases rapidly as treatment is delayed, so it is given *only* if symptoms are known to have been present for less than 4.5 hours. tPA is used only if a brain scan has ruled out ICH and is absolutely contraindicated by concurrent anticoagulant treatment, recent GI bleeding or surgery/major trauma/head injury, and severe hypertension. 0.9 mg/kg of tPA is given intravenously, with 10% injected as a bolus and the rest infused over an hour. 300 mg aspirin should also be administered immediately to limit further thrombosis and continued for a lower dose for 2 weeks or until discharge from hospital, after which long-term antithrombotic treatment should be started.

In strokes due to thrombosis of the proximal middle cerebral or internal carotid arteries, mechanical removal of the thrombus (**thrombectomy**) is a relatively new treatment which can improve functional outcome. Thrombectomy can be combined with thrombolysis or can be used as an alternative to thrombolysis in patients who are on anticoagulants.

Haemorrhagic stroke

There are no specific treatments for ICH, and management revolves around 'active care', in which patients are monitored to allow rapid intervention to prevent neurological worsening and the occurrence of further complications. For example, hypertension, hyperglycaemia and fever all worsen outcome and should be controlled. Antithrombotic treatment is an important predisposing factor for haemorrhagic stroke and worsens outcome; patients on warfarin can be given IV vitamin K and prothrombin complex concentrate (PCC), whereas those on a direct acting oral anticoagulant (DOAC; see Chapter 8) can be given PCC or a specific antidote (e.g. idarucizumab for dabigatran).

Long-term management, rehabilitation and secondary prevention

Secondary prevention for ischaemic stroke includes careful control of vascular risk factors such as smoking, diabetes, hypertension and high cholesterol. Patients with atrial fibrillation should be treated with a DOAC or warfarin. Secondary prevention for ICH focuses on strict control of hypertension.

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