

Cardiology

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Clinical examination of the cardiovascular system

6 Face, mouth and eyes

Pallor
Central cyanosis
Dental caries
Fundí (retinopathy)
Stigmata of hyperlipidaemia and thyroid disease



▲ Malar flush



▲ Poor oral hygiene in a patient with infective endocarditis



▲ Xanthelasma

5 Jugular venous pulse (see opposite)

Height
Waveform



▲ Jugular venous pulse

4 Carotid pulses

Volume
Character
Bruits
(see opposite)

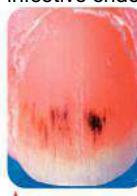
3 Blood pressure

2 Radial pulse

Rate
Rhythm

1 Hands

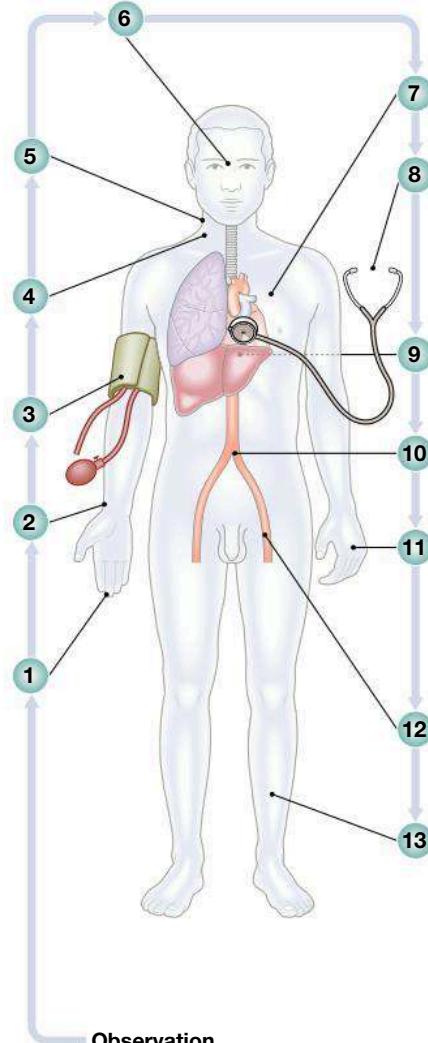
Clubbing
Splinter haemorrhages and other stigmata of infective endocarditis



▲ Splinter haemorrhage



▲ Cyanosis and clubbing in a patient with complex cyanotic congenital heart disease



Observation

Symptoms and well-being

- Breathlessness
- Distress etc.

Body habitus

- Body mass (obesity, cachexia)
- Marfan and other syndromes

Tissue perfusion

- Skin temperature
- Sweating
- Urine output

7 Precordium

Inspect
Palpate
(see opposite)

8 Auscultation

(see opposite)

9 Back

Lung crepitations
Sacral oedema

10 Abdomen

Hepatomegaly
Ascites
Aortic aneurysm
Bruits

11 Tendon xanthomas

(hyperlipidaemia)



12 Femoral pulses

Radio-femoral delay
Bruits

13 Legs

Peripheral pulses
Oedema



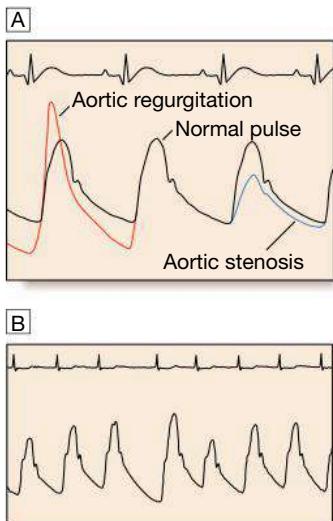
▲ Vasculitis in a patient with infective endocarditis



▲ Peripheral oedema in a patient with congestive cardiac failure

4 Examination of the arterial pulse

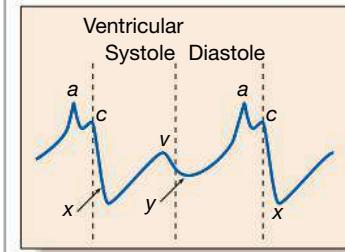
- The character of the pulse is determined by stroke volume and arterial compliance, and is best assessed by palpating a major artery, such as the carotid or brachial artery.
- Aortic regurgitation, anaemia, sepsis and other causes of a large stroke volume typically produce a bounding pulse with a high amplitude and wide pulse pressure (panel A).
- Aortic stenosis impedes ventricular emptying. If severe, it causes a slow-rising, weak and delayed pulse (panel A).
- Sinus rhythm produces a pulse that is regular in time and volume. Arrhythmias may cause irregularity. Atrial fibrillation produces a pulse that is irregular in time and volume (panel B).



5 Examination of the jugular venous pulse

The internal jugular vein, superior vena cava and right atrium are in continuity, so the height of the jugular venous pulsation reflects right atrial pressure. When the patient is placed at 45°, with the head supported and turned to the left, the jugular venous pulse is visible along the line of the sternocleidomastoid muscle (see opposite). In health it is normally just visible above the clavicle.

- The height of the jugular venous pulse is determined by right atrial pressure and is therefore elevated in right heart failure and reduced in hypovolaemia.
- If the jugular venous pulse is not easily seen, it may be exposed by applying firm pressure over the abdomen.
- In sinus rhythm, the two venous peaks, the *a* and *v* waves, approximate to atrial and ventricular systole, respectively.
- The *x* descent reflects atrial relaxation and apical displacement of the tricuspid valve ring. The *y* descent reflects atrial emptying early in diastole. These signs are subtle.
- Tricuspid regurgitation produces giant *v* waves that coincide with ventricular systole.



i Distinguishing venous/arterial pulsation in the neck

- The venous pulse has two peaks in each cardiac cycle; the arterial pulse has one peak.
- The height of the venous pulse varies with respiration (falls on inspiration) and position.
- Abdominal compression causes the venous pulse to rise.
- The venous pulse is not easily palpable and can be occluded with light pressure.

7 Palpation of the precordium

Technique

- Place fingertips over apex (1) to assess for position and character. Place heel of hand over left sternal border (2) for a parasternal heave or 'lift'. Assess for thrills in all areas, including the aortic and pulmonary areas (3). Normal position is the 5th or 6th intercostal space, at the mid-clavicular line.

Common abnormalities of the apex beat

- Volume overload, such as mitral or aortic regurgitation: displaced, thrusting
- Pressure overload, such as aortic stenosis, hypertension: discrete, heaving
- Dyskinetic, such as left ventricular aneurysm: displaced, incoordinate

Other abnormalities

- Palpable S1 (tapping apex beat: mitral stenosis)
- Palpable P2 (severe pulmonary hypertension)
- Left parasternal heave or 'lift' felt by heel of hand (right ventricular hypertrophy)
- Palpable thrill (aortic stenosis)



8 Auscultation of the heart

- Use the diaphragm to examine at the apex, lower left sternal border (tricuspid area) and upper left (pulmonary area) and right (aortic area) sternal borders.
- Use the bell to examine low-pitched noises, particularly at the apex for the mid-diastolic murmur of mitral stenosis.
- Time the sounds and murmurs by feeling the carotid pulse; the first heart sound (S1) just precedes the upstroke of the pulse and the

second heart sound (S2) is out of step with it. If present, a third heart sound (S3) immediately follows S2, and a fourth heart sound (S4) just precedes S1. Systolic murmurs are synchronous with the pulse.

- Listen for radiation of systolic murmurs, over the base of the neck (aortic stenosis) and in the axilla (mitral incompetence).
- Listen over the left sternal border with the patient sitting forward (aortic incompetence), then at the apex with the patient rolled on to the left side (mitral stenosis).

Cardiovascular disease is the commonest cause of death worldwide. The World Health Organization estimates that more people have died from cardiovascular disease since 1990 than any other category of illness, including infectious diseases. Strategies for the treatment and prevention of heart disease can be highly effective and have been subjected to rigorous evaluation by randomised trials. The evidence base for the treatment of cardiovascular disease is stronger than for almost any other disease group.

Coronary heart disease is the leading cause of death, with 3.8 million men and 3.4 million women dying each year. Although the incidence has been falling in some countries, it is rising in lower-income countries, where it accounts for more than 60% of the global burden of coronary heart disease. Valvular heart disease is also common but the aetiology varies in different parts of the world. In South Asia and in Africa it is predominantly due to rheumatic fever, whereas calcific aortic valve disease is the commonest problem in high-income countries.

Prompt recognition of the development of heart disease is limited by two key factors. First, it is often clinically silent for prolonged periods and coronary heart disease can proceed to an advanced stage before the patient notices any symptoms. Second, the diversity of symptoms attributable to heart disease is limited, so different pathologies may frequently present with the same symptoms.

Functional anatomy and physiology

Anatomy

The heart acts as two serial pumps that share several electrical and mechanical components. The right heart circulates blood to the lungs where it is oxygenated, and the left heart circulates it to the rest of the body (Fig. 16.1). The atria are thin-walled structures that act as priming pumps for the ventricles which provide most of the energy required to maintain the circulation. The atria are situated posteriorly within the mediastinum where the left atrium (LA) sits anterior to the oesophagus and descending aorta. The right atrium (RA) receives blood from the superior and inferior venae cavae and the coronary sinus. The LA receives blood from four pulmonary veins, two from each of the left and right lungs. The ventricles are thick-walled structures that pump blood through large

vascular beds under pressure. The atria and ventricles are separated by the annulus fibrosus, which forms the skeleton for the atrioventricular (AV) valves and electrically insulates the atria from the ventricles. The right ventricle (RV) is about 2–3 mm thick and triangular in shape. It extends from the annulus fibrosus to near the cardiac apex and sits anterior and to the right of the left ventricle (LV). The anterosuperior surface of the RV is rounded and convex, and its posterior extent is bounded by the interventricular septum, which bulges into the chamber. Its upper extent forms the conus arteriosus or outflow tract, from which the pulmonary artery arises. The LV is more conical in shape and in cross-section is nearly circular. It extends from the LA to the apex of the heart. The LV myocardium is approximately 10 mm thick because it pumps blood at a higher pressure than the RV.

Normally, the heart occupies less than 50% of the transthoracic diameter in the frontal plane, as seen on a chest X-ray. On the patient's left, the cardiac silhouette is formed by the aortic arch, the pulmonary trunk, the left atrial appendage and the LV. On the right, the silhouette is formed by the RA and the superior and inferior venae cavae, and the lower right border is formed by the RV (Fig. 16.2). In disease states or congenital cardiac abnormalities, the silhouette may change as a result of hypertrophy or dilatation.

Coronary circulation

The left main and right coronary arteries arise from the left and right sinuses of the aortic root, distal to the aortic valve (Fig. 16.3). Within 2.5 cm of its origin, the left main coronary artery divides into the left anterior descending artery (LAD), which runs in the anterior interventricular groove, and the left circumflex artery (CX), which runs posteriorly in the atrioventricular groove. The LAD gives branches to supply the anterior part of the septum (septal perforators) and the anterior, lateral and apical walls of the LV. The CX gives marginal branches that supply the lateral, posterior and inferior segments of the LV. The right coronary artery (RCA) runs in the right atrioventricular groove, giving branches that supply the RA, RV and inferoposterior aspects of the LV. The posterior descending artery runs in the posterior interventricular groove and supplies the inferior part of the interventricular septum. This vessel is a branch of the RCA in approximately 90% of people (dominant right system) and is supplied by the CX in the remainder (dominant left system). The coronary anatomy varies greatly from person to person and there are many normal variants.

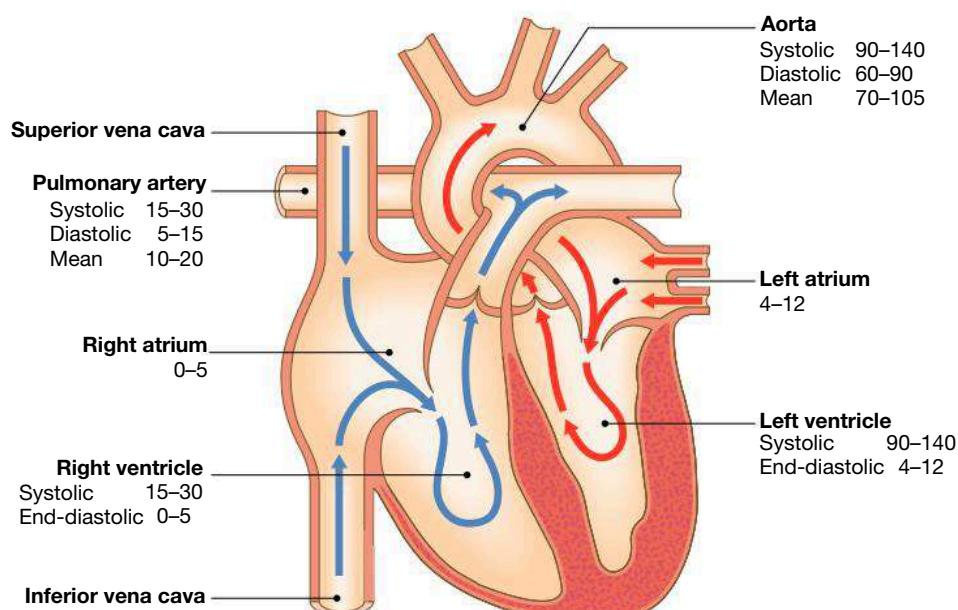


Fig. 16.1 Direction of blood flow through the heart. The blue arrows show deoxygenated blood moving through the right heart to the lungs. The red arrows show oxygenated blood moving from the lungs to the systemic circulation. The normal pressures are shown for each chamber in mmHg.

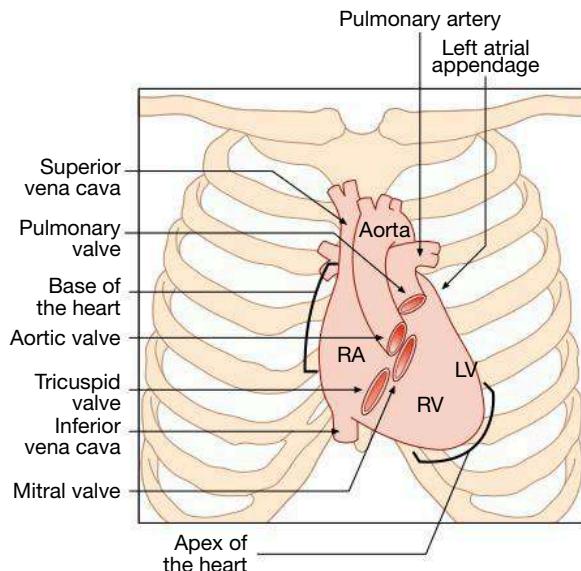


Fig. 16.2 Surface anatomy of the heart. The positions of the major cardiac chambers and heart valves are shown. (LV = left ventricle; RA = right atrium; RV = right ventricle)

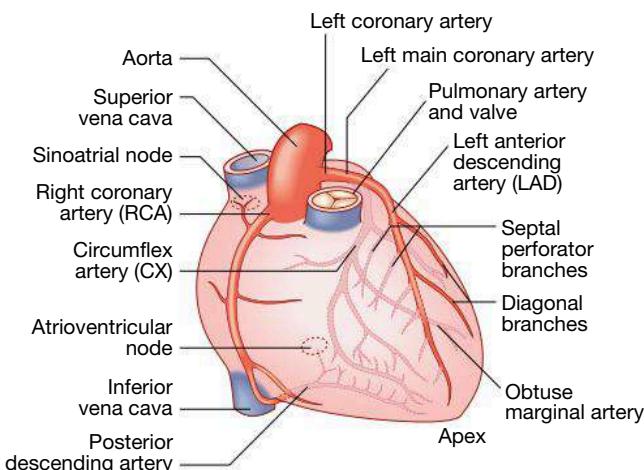


Fig. 16.3 The coronary arteries: anterior view.

The RCA supplies the sinoatrial (SA) node in about 60% of individuals and the AV node in about 90%. Proximal occlusion of the RCA therefore often results in sinus bradycardia and may also cause AV nodal block. Abrupt occlusion of the RCA, due to coronary thrombosis, results in infarction of the inferior part of the LV and often the RV. Abrupt occlusion of the LAD or CX causes infarction in the corresponding territory of the LV, and occlusion of the left main coronary artery is usually fatal.

The venous system follows the coronary arteries but drains into the coronary sinus in the atrioventricular groove, and then to the RA. An extensive lymphatic system drains into vessels that travel with the coronary vessels and then into the thoracic duct.

Conduction system

The SA node is situated at the junction of the superior vena cava and RA (Fig. 16.4). It comprises specialised atrial cells that depolarise at a rate influenced by the autonomic nervous system and by circulating catecholamines. During normal (sinus) rhythm, this depolarisation wave propagates through the atria via sheets of atrial myocytes. The annulus fibrosus

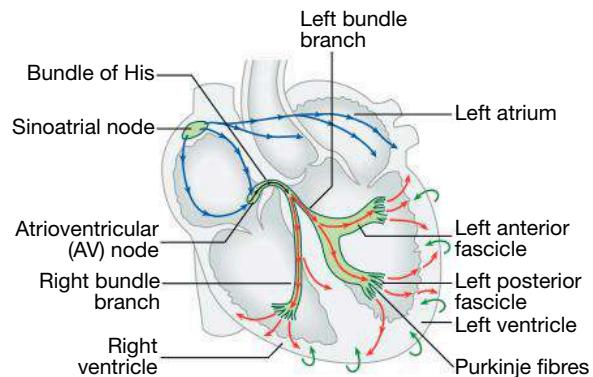


Fig. 16.4 The cardiac conduction system. Depolarisation starts in the sinoatrial node and spreads through the atria (blue arrows), and then through the atrioventricular node (black arrows). Depolarisation then spreads through the bundle of His and the bundle branches to reach the ventricular muscle (red arrows). Repolarisation spreads from epicardium to endocardium (green arrows).

forms a conduction barrier between atria and ventricles, preventing transmission of conduction except through the AV node. The AV node is a midline structure, extending from the right side of the interatrial septum, penetrating the annulus fibrosus anteriorly. It conducts relatively slowly, producing a necessary time delay between atrial and ventricular contraction. The His–Purkinje system is composed of the bundle of His extending from the AV node into the interventricular septum, the right and left bundle branches passing along the ventricular septum and into the respective ventricles, the anterior and posterior fascicles of the left bundle branch, and the smaller Purkinje fibres that ramify through the ventricular myocardium. The tissues of the His–Purkinje system conduct very rapidly and allow near-simultaneous depolarisation of the entire ventricular myocardium.

Nerve supply of the heart

The heart is innervated by both sympathetic and parasympathetic fibres. Adrenergic nerves from the cervical sympathetic chain supply muscle fibres in the atria and ventricles, and the electrical conducting system. Activation of β_1 -adrenoceptors in the heart results in positive inotropic and chronotropic effects, whereas activation of β_2 -adrenoceptors in vascular smooth muscle causes vasodilatation. Parasympathetic pre-ganglionic fibres and sensory fibres reach the heart through the vagus nerves. Cholinergic nerves supply the AV and SA nodes via muscarinic (M2) receptors. Under resting conditions, vagal inhibitory activity predominates and the heart rate is slow. Adrenergic stimulation, associated with exercise, emotional stress, fever and so on, causes the heart rate to increase. In disease states, the nerve supply to the heart may be affected. For example, in heart failure the sympathetic system may be up-regulated, and in diabetes mellitus the nerves themselves may be damaged by autonomic neuropathy so that there is little variation in heart rate.

Physiology

Myocardial contraction

Myocardial cells (myocytes) are about 50–100 μm long; each cell branches and interdigitates with adjacent cells. An intercalated disc permits electrical conduction via gap junctions, and mechanical conduction via the fascia adherens, to adjacent cells (Fig. 16.5A). The basic unit of contraction is the sarcomere (2 μm long), which is aligned to those of adjacent myofibrils, giving a striated appearance due to the Z-lines (Fig. 16.5B and C). Actin filaments are attached at right angles to the Z-lines and interdigitate with thicker parallel myosin filaments. The cross-links between actin

and myosin molecules contain myofibrillar adenosine triphosphatase (ATPase), which breaks down adenosine triphosphate (ATP) to provide the energy for contraction (Fig. 16.5E). Two chains of actin molecules form a helical structure, with a second molecule, tropomyosin, in the grooves of the actin helix, and a further molecule complex, troponin, attached to every seventh actin molecule (Fig. 16.5D).

During the plateau phase of the action potential, calcium ions enter the cell and are mobilised from the sarcoplasmic reticulum. They bind to troponin and thereby precipitate contraction by shortening of the sarcomere through the interdigititation of the actin and myosin molecules. The force of cardiac muscle contraction, or inotropic state, is regulated by the influx of calcium ions through 'slow calcium channels'. The extent to which the sarcomere can shorten determines stroke volume of the ventricle. It is maximally shortened in response to powerful inotropic drugs or marked exercise. However, the enlargement of the heart seen in heart failure is due to slippage of the myofibrils and adjacent cells rather than lengthening of the sarcomere.

Cardiac peptides

Cardiomyocytes secrete peptides that have humoral effects on the vasculature and kidneys. Atrial natriuretic peptide (ANP) is a 28-amino acid peptide that acts as a vasodilator, reducing blood pressure (BP), and as a diuretic, promoting renal excretion of water and sodium. It is released by atrial myocytes in response to stretch. Brain natriuretic peptide (BNP; originally identified in extracts of porcine brain) is a 32-amino acid peptide produced by ventricular cardiomyocytes in response to

stretch, as occurs in heart failure. Like ANP, it has diuretic properties. Neprilysin, an enzyme produced by the kidney and other tissues, breaks down ANP, BNP and other proteins and, in so doing, acts as a vasoconstrictor. It forms a therapeutic target in patients with heart failure.

Circulation

The RA receives deoxygenated blood from the superior and inferior venae cavae and discharges blood to the RV, which in turn pumps it into the pulmonary artery. Blood is oxygenated as it passes through the pulmonary arterial and alveolar capillary bed before draining into the pulmonary veins and LA. Blood then passes into the LV which pumps it into the aorta (see Fig. 16.1). During ventricular contraction (systole), the tricuspid valve in the right heart and the mitral valve in the left heart close, and the pulmonary and aortic valves open. In diastole, the pulmonary and aortic valves close, and the two AV valves open. Collectively, these atrial and ventricular events constitute the cardiac cycle of filling and ejection of blood from one heart beat to the next. Blood passes from the heart through the large central elastic arteries into muscular arteries before encountering the resistance vessels, and ultimately the capillary bed, where there is exchange of nutrients, oxygen and waste products of metabolism. The central arteries, such as the aorta, are predominantly composed of elastic tissue with little or no vascular smooth muscle cells. When blood is ejected from the heart, the compliant aorta expands to accommodate the volume of blood before the elastic recoil sustains BP and blood flow following cessation of cardiac contraction. This 'Windkessel' effect prevents excessive rises in systolic

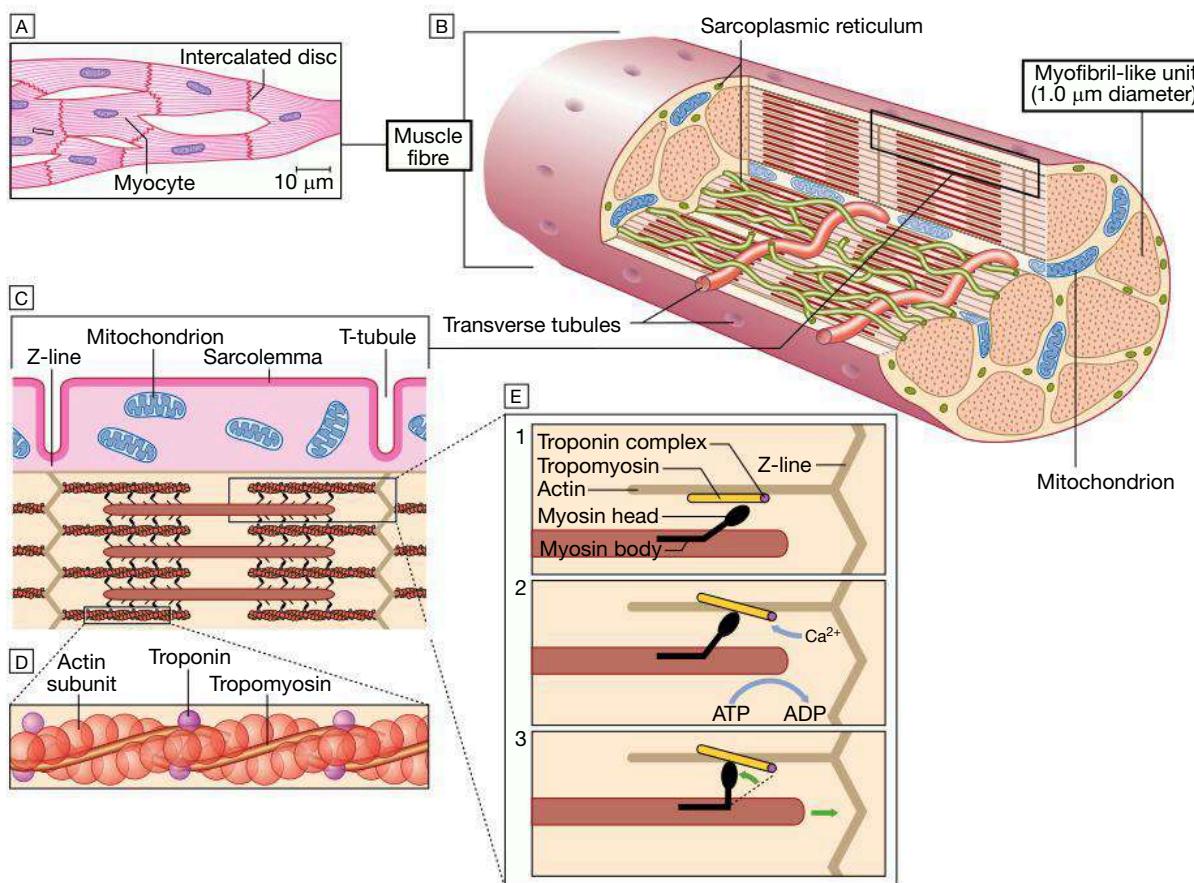


Fig. 16.5 Schematic of myocytes and the contraction process within a muscle fibre. **A** Myocytes are joined together through intercalated discs. **B** Within the myocytes, myofibrils are composed of longitudinal and transverse tubules extending from the sarcoplasmic reticulum. **C** The expanded section shows a schematic of an individual sarcomere with thick filaments composed of myosin and thin filaments composed primarily of actin. **D** Actin filaments are composed of troponin, tropomyosin and actin subunits. **E** The three stages of contraction, resulting in shortening of the sarcomere. (1) The actin-binding site is blocked by tropomyosin. (2) ATP-dependent release of calcium ions, which bind to troponin, displacing tropomyosin. The binding site is exposed. (3) Tilting of the angle of attachment of the myosin head, resulting in fibre shortening. (ADP = adenosine diphosphate; ATP = adenosine triphosphate)

BP while sustaining diastolic BP, thereby reducing cardiac afterload and maintaining coronary perfusion. These benefits are lost with progressive arterial stiffening, which occurs with ageing and advanced renal disease. Passing down the arterial tree, vascular smooth muscle cells progressively play a greater role until the resistance arterioles are encountered. Although all vessels contribute, the resistance vessels (diameter 50–200 µm) provide the greatest contribution to systemic vascular resistance, with small changes in radius having a marked influence on blood flow; resistance is inversely proportional to the fourth power of the radius (Poiseuille's Law). The tone of these resistance vessels is tightly regulated by humoral, neuronal and mechanical factors. Neurogenic constriction operates via α -adrenoceptors on vascular smooth muscle, and dilatation via muscarinic and β_2 -adrenoceptors. In addition, systemic and locally released vasoactive substances influence tone; vasoconstrictors include noradrenaline (norepinephrine), angiotensin II and endothelin-1, whereas adenosine, bradykinin, prostaglandins and nitric oxide are vasodilators. Resistance to blood flow rises with viscosity and is mainly influenced by the haematocrit.

Coronary blood vessels receive sympathetic and parasympathetic innervation. While stimulation of α -adrenoceptors causes vasoconstriction and stimulation of β_2 -adrenoceptors causes vasodilatation, the predominant effect of sympathetic stimulation in coronary arteries is vasodilatation. Parasympathetic stimulation also causes modest dilatation of normal coronary arteries. Because of these homeostatic mechanisms that regulate vessel tone, narrowing or stenosis in a coronary artery does not limit flow, even during exercise, until the cross-sectional area of the vessel is reduced by at least 70%.

Endothelium

The endothelium plays a vital role in the control of vascular homeostasis. It synthesises and releases many vasoactive mediators that cause vasodilatation, including nitric oxide, prostacyclin and endothelium-derived hyperpolarising factor, and vasoconstriction, including endothelin-1 and angiotensin II. A balance exists whereby the release of such factors contributes to the maintenance and regulation of vascular tone and BP. Damage to the endothelium may disrupt this balance and lead to vascular dysfunction, tissue ischaemia and hypertension.

The endothelium has a major influence on key regulatory steps in the recruitment of inflammatory cells and on the formation and dissolution of thrombus. Once activated, the endothelium expresses surface receptors such as E-selectin, intercellular adhesion molecule type 1 (ICAM-1) and platelet–endothelial cell adhesion molecule type 1 (PECAM-1), which mediate rolling, adhesion and migration of inflammatory leucocytes into the subintima. The endothelium also stores and releases the multimeric glycoprotein von Willebrand factor, which promotes thrombus formation by linking platelet adhesion to denuded surfaces, especially in the arterial vasculature. In contrast, once intravascular thrombus forms, tissue plasminogen activator is rapidly released from a dynamic storage pool within the endothelium to induce fibrinolysis and thrombus dissolution. These processes are critically involved in the development and progression of atherosclerosis, and endothelial function and injury are seen as central to the pathogenesis of many cardiovascular disease states.

Respiration

Cardiac output, BP and pulse rate change with respiration as the result of changes in blood flow to the right and left heart, as summarised in Box 16.1. During inspiration, the fall in intrathoracic pressure causes increased return of venous blood into the chest and right side of the heart, which increases cardiac output from the RV. However, blood is sequestered in the lungs due to the increased capacitance of the pulmonary vascular bed, leading to a reduction in blood flow to the LV and a slight fall in BP. With expiration the opposite sequence of events occurs; there is a fall in venous return to the right heart with a reduction in RV output, and a rise in the venous return to the left side of the heart with an increase in LV output. As the result of these changes, BP normally falls

	16.1 Haemodynamic effects of respiration	
	Inhalation	Exhalation
Jugular venous pressure	Falls	Rises
Blood pressure	Falls (up to 10 mmHg)	Rises
Heart rate	Accelerates	Slows
Second heart sound	Splits*	Fuses*

*Inspiration prolongs right ventricular ejection, delaying P₂, and shortens left ventricular ejection, bringing forward A₂; expiration produces the opposite effects.

during inhalation but rises during exhalation. These changes are exaggerated in patients with severe airways obstruction secondary to asthma or chronic obstructive pulmonary disease (COPD) leading to pulsus paradoxus, which describes an exaggerated fall in BP during inhalation. As well as being found in airways obstruction, pulsus paradoxus is also characteristic of cardiac tamponade. Here, cardiac filling is constrained by external pressure, and on inhalation, compression of the RV impedes the normal increase in flow during inhalation. The interventricular septum then moves to the left, impeding left ventricular filling and cardiac output. This produces an exaggerated fall in BP (>10 mmHg fall during inhalation).

Investigation of cardiovascular disease

16

Several investigations may be required in the diagnosis of cardiac disease and assessment of its severity. Basic tests, such as electrocardiography, chest X-ray and echocardiography, can be performed in an outpatient clinic or at the bedside, whereas more complex procedures such as cardiac catheterisation, radionuclide imaging, computed tomography (CT) and magnetic resonance imaging (MRI) require specialised facilities.

Electrocardiogram

The electrocardiogram (ECG) is used to assess cardiac rhythm and conduction as well as the diagnosis of myocardial ischaemia and infarction.

The ECG is recorded by electrodes on the body surface which detect the electrical depolarisation of myocardial tissue produced from a small dipole current. These signals are amplified and either printed or displayed on a monitor (Fig. 16.6). During sinus rhythm, the SA node triggers atrial depolarisation, producing a P wave. Depolarisation proceeds slowly

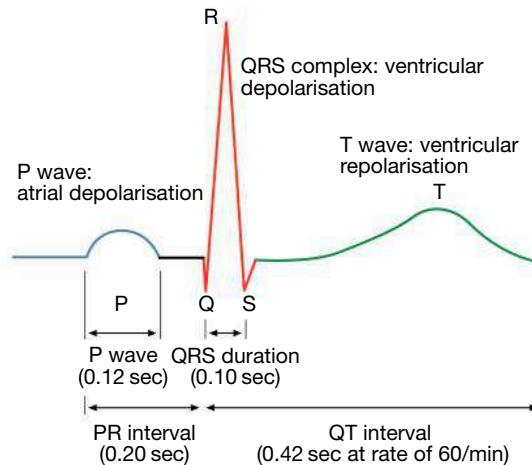


Fig. 16.6 The electrocardiogram. The components correspond to depolarisation and repolarisation, as depicted in Fig. 16.4. The upper limit of the normal range for each interval is given in brackets.

16.2 How to read a 12-lead electrocardiogram: examination sequence	
Rhythm strip (lead II)	To determine heart rate and rhythm
Cardiac axis	Normal if QRS complexes +ve in leads I and II
P-wave shape	Tall P waves denote right atrial enlargement (P pulmonale) and notched P waves denote left atrial enlargement (P mitrale)
PR interval	Normal = 0.12–0.20 sec. Prolongation denotes impaired atrioventricular nodal conduction. A short PR interval occurs in Wolff–Parkinson–White syndrome
QRS duration	If > 0.12 sec, ventricular conduction is abnormal (left or right bundle branch block)
QRS amplitude	Large QRS complexes occur in slim young patients and in patients with left ventricular hypertrophy
Q waves	May signify previous myocardial infarction
ST segment	ST elevation may signify myocardial infarction, pericarditis or left ventricular aneurysm; ST depression may signify ischaemia or infarction
T waves	T-wave inversion has many causes, including myocardial ischaemia or infarction, and electrolyte disturbances
QT interval	Normal < 0.44 sec (male), 0.46 sec (female) corrected for heart rate. QT prolongation may occur with congenital long QT syndrome, low K ⁺ , Mg ²⁺ or Ca ²⁺ , and some drugs (see Box 16.28)
ECG conventions	Depolarisation towards electrode: +ve deflection Depolarisation away from electrode: -ve deflection Sensitivity: 10 mm = 1 mV Paper speed: 25 mm per sec Each large (5 mm) square = 0.2 sec Each small (1 mm) square = 0.04 sec Heart rate = 1500/RR interval (mm) (i.e. 300 ÷ number of large squares between beats)

through the AV node, which is too small to produce a depolarisation wave detectable from the body surface. The bundle of His, bundle branches and Purkinje system are then activated, initiating ventricular myocardial depolarisation, which produces the QRS complex. The muscle mass of the ventricles is much larger than that of the atria, so the QRS complex is larger than the P wave. The interval between the onset of the P wave and the onset of the QRS complex is termed the 'PR interval' and largely reflects the duration of AV nodal conduction. Injury to the left or right bundle branch delays ventricular depolarisation, widening the QRS complex. Selective injury of one of the left fascicles (hemiblock) affects the electrical axis. Repolarisation is slower and spreads from the epicardium to the endocardium. Atrial repolarisation does not cause a detectable signal but ventricular repolarisation produces the T wave. The QT interval represents the total duration of ventricular depolarisation and repolarisation.

The 12-lead ECG

The 12-lead ECG (Box 16.2) is generated from 10 electrodes that are attached to the skin. One electrode is attached to each limb and six electrodes are attached to the chest. In addition, the left arm, right arm and left leg electrodes are attached to a central terminal acting as an additional virtual electrode in the centre of the chest (the right leg electrode acts as an earthing electrode). The 12 'leads' of the ECG refer to recordings made from pairs or sets of these electrodes. They comprise three

groups: three dipole limb leads, three augmented voltage limb leads and six unipole chest leads.

Leads I, II and III are the dipole limb leads and refer to recordings obtained from pairs of limb electrodes. Lead I records the signal between the right (negative) and left (positive) arms. Lead II records the signal between the right arm (negative) and left leg (positive). Lead III records the signal between the left arm (negative) and left leg (positive). These three leads thus record electrical activity along three different axes in the frontal plane. Leads aVR, aVL and aVF are the augmented voltage limb leads. These record electrical activity between a limb electrode and a modified central terminal. For example, lead aVL records the signal between the left arm (positive) and a central (negative) terminal, formed by connecting the right arm and left leg electrodes (Fig. 16.7). Similarly augmented signals are obtained from the right arm (aVR) and left leg (aVF). These leads also record electrical activity in the frontal plane, with each lead 120° apart. Lead aVF thus examines activity along the axis +90°, and lead aVL along the axis –30°, and so on.

When depolarisation moves towards a positive electrode, it produces a positive deflection in the ECG; depolarisation in the opposite direction produces a negative deflection. The average vector of ventricular depolarisation is known as the frontal cardiac axis. When the vector is at right

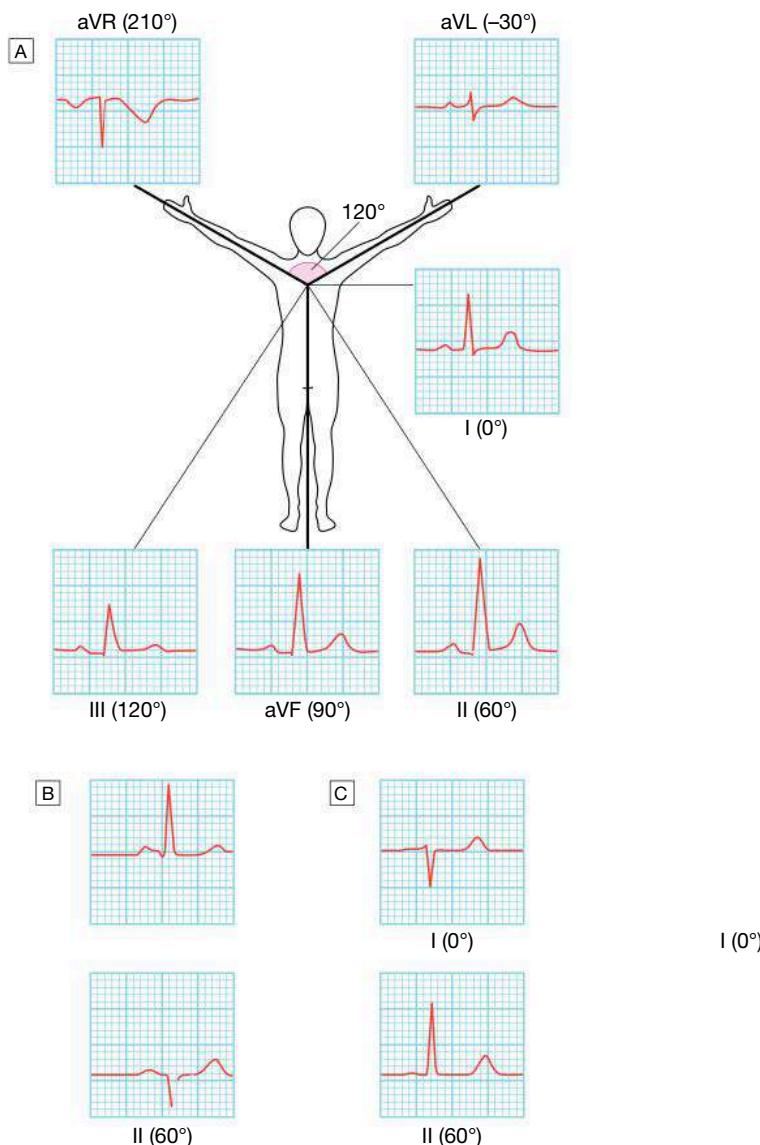


Fig. 16.7 The appearance of the ECG from different leads in the frontal plane.

[A] Normal. [B] Left axis deviation, with negative deflection in lead II and positive in lead I. [C] Right axis deviation, with negative deflection in lead I and positive in lead II.

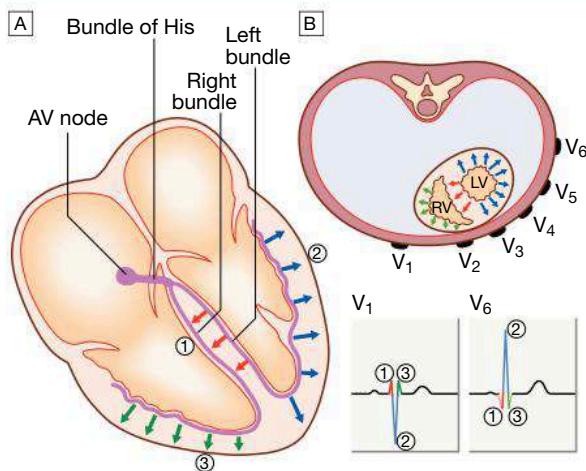


Fig. 16.8 The sequence of activation of the ventricles. **A** Activation of the septum occurs first (red arrows), followed by spreading of the impulse through the left ventricle (LV; blue arrows) and then the right ventricle (RV; green arrows). **B** Normal electrocardiographic complexes from leads V_1 and V_6 . (AV = atrioventricular)

angles to a lead, the depolarisation in that lead is equally negative and positive (isoelectric). In Fig. 16.7A, the QRS complex is isoelectric in aVL, negative in aVR and most strongly positive in lead II; the main vector or axis of depolarisation is therefore 60° . The normal cardiac axis lies between -30° and $+90^\circ$. Examples of left and right axis deviation are shown in Fig. 16.7B and C.

There are six chest leads, V_1 – V_6 , derived from electrodes placed on the anterior and lateral left side of the chest, over the heart. Each lead records the signal between the corresponding chest electrode (positive) and the central terminal (negative). Leads V_1 and V_2 lie approximately over the RV, V_3 and V_4 over the interventricular septum, and V_5 and V_6 over the LV (Fig. 16.8). The LV has the greater muscle mass and contributes the major component of the QRS complex.

The shape of the QRS complex varies across the chest leads. Depolarisation of the interventricular septum occurs first and moves from left to right; this generates a small initial negative deflection in lead V_6 (Q wave) and an initial positive deflection in lead V_1 (R wave). The second phase of depolarisation is activation of the body of the LV, which creates a large positive deflection or R wave in V_6 (with reciprocal changes in V_1). The third and final phase involves the RV and produces a small negative deflection or S wave in V_6 .

Exercise ECG

In exercise or stress electrocardiography, a 12-lead ECG is recorded during exercise on a treadmill or bicycle ergometer. It is similar to a resting ECG, except that the limb electrodes are placed on the shoulders and hips rather than the wrists and ankles. The Bruce Protocol is the most commonly used. During an exercise ECG, BP is recorded and symptoms are assessed. Common indications for exercise testing are shown in Box 16.3. The test is considered positive if angina occurs, BP falls or fails to increase, or if there are ST segment shifts of more than 1 mm (see Fig. 16.57). Exercise testing is useful in confirming the diagnosis of coronary artery disease in patients with suspected angina, and under these circumstances has reasonable sensitivity and excellent specificity (see Box 16.3). False-negative results can occur in patients with coronary artery disease, and not all patients with a positive test have coronary disease. This is especially true in low-risk individuals, such as asymptomatic young or middle-aged women, in whom an abnormal response is more likely to represent a false-positive than a true-positive test. Stress testing is contraindicated in the presence of acute coronary syndrome, decompensated heart failure and severe hypertension.

16.3 Exercise testing

Indications

- To confirm the diagnosis of angina
- To evaluate stable angina
- To assess prognosis following myocardial infarction
- To assess outcome after coronary revascularisation, e.g. coronary angioplasty
- To diagnose and evaluate the treatment of exercise-induced arrhythmias

High-risk findings

- Low threshold for ischaemia (within stage 1 or 2 of the Bruce Protocol)
- Fall in blood pressure on exercise
- Widespread, marked or prolonged ischaemic ECG changes
- Exercise-induced arrhythmia

Ambulatory ECG

Ambulatory ECG recordings can be obtained using a portable digital recorder. These devices usually provide limb lead ECG recordings only, on a continuous basis for periods of between 1 and 7 days. The main indication for ambulatory ECG is in the investigation of patients with suspected arrhythmia, such as those with intermittent palpitation, dizziness or syncope. In this situation, a standard ECG provides only a snapshot of the cardiac rhythm and is unlikely to detect an intermittent arrhythmia, so a longer period of recording is required (see Fig. 16.30). Ambulatory ECG can also be used to assess rate control in patients with atrial fibrillation, and to detect transient myocardial ischaemia using ST segment analysis. If symptoms are infrequent, special recorders can be issued that can be activated by the patient when a symptom episode occurs and placed on the chest wall to record the cardiac rhythm at that point in time. With some devices, the recording can be transmitted to hospital electronically. If the symptoms are very infrequent but potentially serious, such as syncope, implantable 'loop recorders' resembling a leadless pacemaker can be used and implanted subcutaneously to record cardiac rhythm for prolonged periods of between 1 and 3 years (see Fig. 16.51).

Cardiac biomarkers

Several biomarkers are available that can be measured in peripheral blood to assess myocardial dysfunction and ischaemia.

Brain natriuretic peptide

Brain natriuretic peptide (BNP) is a peptide hormone of 32 amino acids with diuretic properties. It is secreted by the LV as a 108-amino acid prohormone, which is cleaved to produce active BNP, and an inactive 76-amino acid N-terminal fragment (NT-proBNP). Serum concentrations are elevated in conditions associated with LV systolic dysfunction. Generally, NT-proBNP is measured in preference to BNP since it is more stable. Measurements of NT-proBNP are indicated for the diagnosis of LV dysfunction and to assess prognosis and response to therapy in patients with heart failure.

Cardiac troponins

Troponin I and troponin T are structural cardiac muscle proteins (see Fig. 16.5) that are released during myocyte damage and necrosis, and represent the cornerstone of the diagnosis of acute myocardial infarction (MI, see Box 16.47). Modern assays are extremely sensitive and can detect minor degrees of myocardial damage, so that elevated plasma troponin concentrations may be observed in conditions other than acute MI, such as pulmonary embolus, septic shock and pulmonary oedema.

Chest X-ray

This is useful for determining the size and shape of the heart, and the state of the pulmonary blood vessels and lung fields. Most information is given by a postero-anterior (PA) projection taken in full inspiration. Anteroposterior (AP) projections can be performed when patient movement is restricted but result in magnification of the cardiac silhouette.

An estimate of overall heart size can be made by comparing the maximum width of the cardiac outline with the maximum internal transverse diameter of the thoracic cavity. The term cardiomegaly is used to describe an enlarged cardiac silhouette when the ratio of cardiac width to the width of the lung fields is greater than 0.5. Cardiomegaly can be caused by chamber dilatation, especially left ventricular dilatation, or by a pericardial effusion, but may also be due to a mediastinal mass or pectus excavatum. Cardiomegaly is not a sensitive indicator of left ventricular systolic dysfunction since the cardiothoracic ratio is normal in many patients with poor left ventricular function and is not specific, since many patients with cardiomegaly on chest X-ray have normal echocardiograms.

Dilatation of individual cardiac chambers can be recognised by the characteristic alterations to the cardiac silhouette (Fig. 16.9):

- Left atrial dilatation results in prominence of the left atrial appendage, creating the appearance of a straight left heart border, a double cardiac shadow to the right of the sternum, and widening of the angle of the carina (bifurcation of the trachea) as the left main bronchus is pushed upwards.
- Right atrial enlargement projects from the right heart border towards the right lower lung field.
- Left ventricular dilatation causes prominence of the left heart border and enlargement of the cardiac silhouette. Left ventricular hypertrophy produces rounding of the left heart border (Fig. 16.10).
- Right ventricular dilatation increases heart size, displaces the apex upwards and straightens the left heart border.

Lateral or oblique projections may be useful for detecting pericardial calcification in patients with constrictive pericarditis or a calcified thoracic aortic aneurysm, as these abnormalities may be obscured by the spine on the PA view.

The lung fields on the chest X-ray may show congestion and oedema in patients with heart failure (see Fig. 16.25), and an increase in pulmonary blood flow ('pulmonary plethora') in those with left-to-right shunt. Pleural effusions may also occur in heart failure.

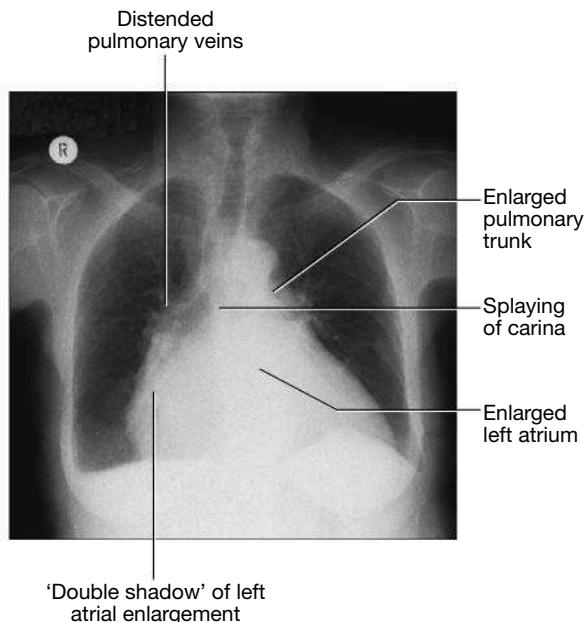


Fig. 16.9 Chest X-ray of a patient with mitral stenosis and regurgitation indicating enlargement of the LA and prominence of the pulmonary artery trunk.

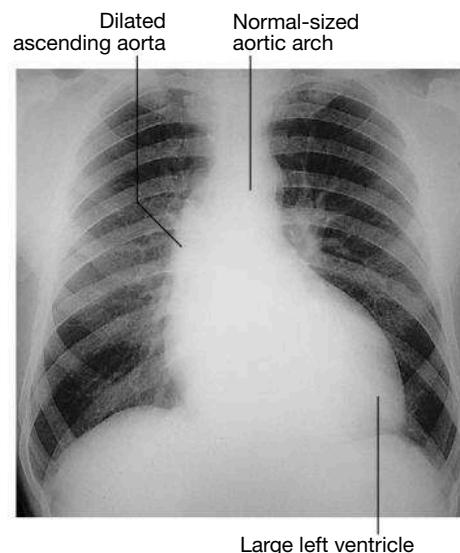


Fig. 16.10 Chest X-ray of a patient with aortic regurgitation, left ventricular enlargement and dilatation of the ascending aorta.

Echocardiography

Transthoracic echocardiography

Transthoracic echocardiography, commonly referred to as 'echo', is obtained by placing an ultrasound transducer on the chest wall to image the heart structures as a real-time two-dimensional 'slice'. This can be used for rapid evaluation of various aspects of cardiac structure and function (Box 16.4).

Doppler echocardiography

Doppler echocardiography provides information on blood flow within the heart and the great vessels. It is based on the Doppler principle that sound waves reflected from moving objects, such as red blood cells, undergo a frequency shift. Doppler echocardiography can therefore detect the speed and direction of blood flow in the heart chambers and great vessels. The information can be presented either as a plot of blood velocity against time for a particular point in the heart (Fig. 16.11) or as a colour overlay on a two-dimensional real-time echo picture (colour-flow Doppler, Fig. 16.12). Doppler echocardiography is useful in the detection



16.4 Common indications for echocardiography

- Assessment of left ventricular function
- Diagnosis and quantification of severity of valve disease
- Identification of vegetations in endocarditis
- Identification of structural heart disease in atrial fibrillation, cardiomyopathies or congenital heart disease
- Detection of pericardial effusion
- Identification of structural heart disease or intracardiac thrombus in systemic embolism

of valvular regurgitation, where the direction of blood flow is reversed and turbulence is seen, and is also used to detect pressure gradients across stenosed valves. For example, the normal resting systolic flow velocity across the aortic valve is approximately 1 m/sec; in the presence of aortic

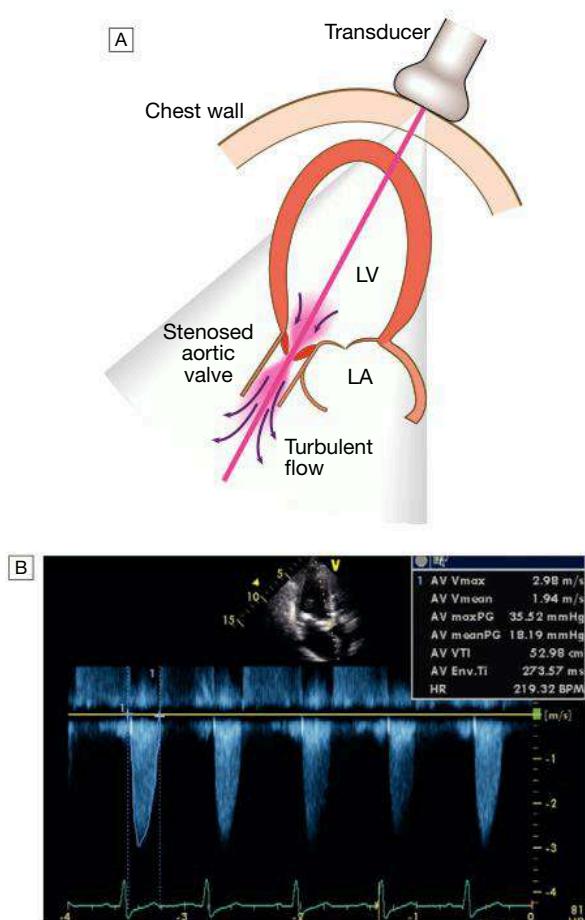


Fig. 16.11 Doppler echocardiography in aortic stenosis. **A** The aortic valve is imaged and a Doppler beam passed directly through the left ventricular outflow tract and the aorta into the turbulent flow beyond the stenosed valve. **B** The velocity of the blood cells is recorded to determine the maximum velocity and hence the pressure gradient across the valve. In this example, the peak velocity is approximately 450 cm/sec (4.5 m/sec), indicating severe aortic stenosis (peak gradient of 81 mmHg). (LA = left atrium; LV = left ventricle)

stenosis, this is increased as blood accelerates through the narrow orifice. In severe aortic stenosis, the peak aortic velocity may be increased to 5 m/sec (see Fig. 16.11). An estimate of the pressure gradient across a valve or lesion is given by the modified Bernoulli equation:

$$\text{Pressure gradient (mmHg)} = 4 \times (\text{peak velocity (m/sec)})^2$$

Advanced techniques include three-dimensional echocardiography, intravascular ultrasound (defines vessel wall abnormalities and guides coronary intervention), intracardiac ultrasound (provides high-resolution images), tissue Doppler imaging (quantifies myocardial contractility and diastolic function) and speckle tracking (assesses myocardial motion and strain).

Transoesophageal echocardiography

Transoesophageal echocardiography (TOE) involves passing an endoscope-like ultrasound probe into the oesophagus and upper stomach under light sedation and positioning it behind the LA. It is particularly useful for imaging structures such as the left atrial appendage, pulmonary veins, thoracic aorta and interatrial septum, which may be poorly visualised by transthoracic echocardiography, especially if the patient is overweight or has obstructive airways disease. The high-resolution

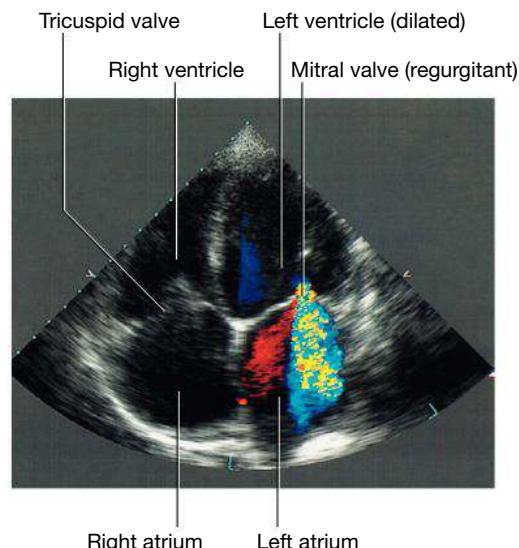


Fig. 16.12 Echocardiographic illustration of the principal cardiac structures in the 'four-chamber' view. Colour-flow Doppler has been used to demonstrate mitral regurgitation: a flame-shaped (yellow/blue) turbulent jet into the left atrium.

images that can be obtained makes TOE particularly valuable for investigating patients with prosthetic (especially mitral) valve dysfunction, congenital abnormalities such as atrial septal defects, aortic dissection, infective endocarditis (vegetations that are too small to be detected by transthoracic echocardiography) and systemic embolism (intracardiac thrombus or masses).

Stress echocardiography

Stress echocardiography is used to investigate patients with suspected coronary artery disease who are unsuitable for exercise stress testing, such as those with mobility problems or pre-existing bundle branch block. A two-dimensional echo is performed before and during infusion of a moderate to high dose of an inotropic, such as dobutamine. Myocardial segments with poor perfusion become ischaemic and contract poorly under stress, manifesting as a wall motion abnormality on the scan. Stress echocardiography is sometimes used to examine myocardial viability in patients with impaired left ventricular function. Low-dose dobutamine can induce contraction in 'hibernating' myocardium; such patients may benefit from bypass surgery or percutaneous coronary intervention.

Computed tomography

Computed tomography (CT) is useful for imaging the cardiac chambers, great vessels, pericardium, and mediastinal structures and masses. Multidetector scanners can acquire up to 320 slices per rotation, allowing very high-resolution imaging in a single heartbeat. CT is often performed using a timed injection of X-ray contrast to produce clear images of blood vessels and associated pathologies. Contrast scans are very useful for imaging the aorta in suspected aortic dissection (see Fig. 16.73), and the pulmonary arteries and branches in suspected pulmonary embolism.

Some centres use cardiac CT scans for quantification of coronary artery calcification, which may serve as an index of cardiovascular risk. However, modern multidetector scanning allows non-invasive coronary angiography (Fig. 16.13) with a spatial resolution approaching that of conventional coronary arteriography and at a lower radiation dose. CT coronary angiography is particularly useful in the initial assessment of patients with chest pain and a low or intermediate likelihood of disease, since it has a high negative predictive value in excluding coronary artery

disease. Modern volume scanners are also able to assess myocardial perfusion, often at the same sitting.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) can be used to generate cross-sectional images of the heart, lungs and mediastinal structures. It provides better differentiation of soft tissue structures than CT but is poor at demonstrating calcification. MRI scans need to be 'gated' to the ECG, allowing the scanner to produce moving images of the heart and mediastinal structures throughout the cardiac cycle. MRI is very useful for imaging the aorta, including suspected dissection (see Fig. 16.72), and can define the anatomy of the heart and great vessels in patients with congenital heart disease. It is also useful for detecting infiltrative conditions affecting the heart and for evaluation of the RV that is difficult to image by echocardiography.

Physiological data can be obtained from the signal returned from moving blood, which allows quantification of blood flow across regurgitant or stenotic valves. It is also possible to analyse regional wall motion in patients with suspected coronary disease or cardiomyopathy.

Myocardial perfusion and viability can also be readily assessed by MRI. When enhanced by gadolinium-based contrast media, areas of myocardial hypoperfusion can be identified with better spatial resolution than nuclear medicine techniques. Later redistribution of this contrast, so-called delayed enhancement, can be used to identify

myocardial scarring and fibrosis: this is a particular strength of cardiac MRI (Fig. 16.14). This can help in selecting patients for revascularisation procedures, or in identifying those with myocardial infiltration, such as that seen with sarcoid heart disease and arrhythmogenic right ventricular cardiomyopathy.

Cardiac catheterisation

This involves passing a specialised catheter through a peripheral vein or artery into the heart under X-ray guidance. Cardiac catheterisation allows BP and oxygen saturation to be measured in the cardiac chambers and great vessels, and is used to perform angiograms by injecting contrast media into a chamber or blood vessel.

Left heart catheterisation involves accessing the arterial circulation, usually through the radial artery, to allow catheterisation of the aorta, LV and coronary arteries. Coronary angiography is the most widely performed procedure, in which the left and right coronary arteries are selectively imaged, providing information about the extent and severity of coronary stenoses, thrombus and calcification (Fig. 16.15). Additional anatomical (intravascular ultrasound, optical coherence tomography) or functional (pressure wire) assessments are sometimes used to define plaque characteristics and severity more precisely. This permits planning of percutaneous coronary intervention and coronary artery bypass graft surgery. Left ventriculography can be performed during the procedure to determine the size and function of the LV (Fig. 16.16) and to demonstrate mitral regurgitation. Aortography defines the size of the aortic root and thoracic aorta, and can help quantify aortic regurgitation. Left heart catheterisation is a day-case procedure and is relatively safe, with serious complications occurring in only approximately 1 in 1000 cases.

Right heart catheterisation is used to assess right heart and pulmonary artery pressures, and to detect intracardiac shunts by measuring oxygen saturations in different chambers. For example, a step up in oxygen saturation from 65% in the RA to 80% in the pulmonary artery is indicative of a large left-to-right shunt that might be due to a ventricular septal defect. Cardiac output can also be measured using thermodilution techniques. Left atrial pressure can be measured directly by puncturing the interatrial septum from the RA with a special catheter. For most purposes, a satisfactory approximation to left atrial pressure can be obtained by 'wedging' an end-hole or balloon catheter in a branch of the pulmonary artery. Swan-Ganz balloon catheters are often used to monitor pulmonary 'wedge' pressure as a guide to left heart filling pressure in critically ill patients (see Fig. 9.25).

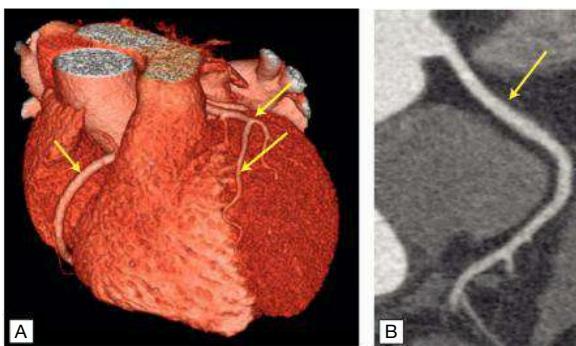


Fig. 16.13 Computed tomography coronary angiography, demonstrating normal coronary arteries (arrows). **A** Three-dimensional image. **B** Two-dimensional image.

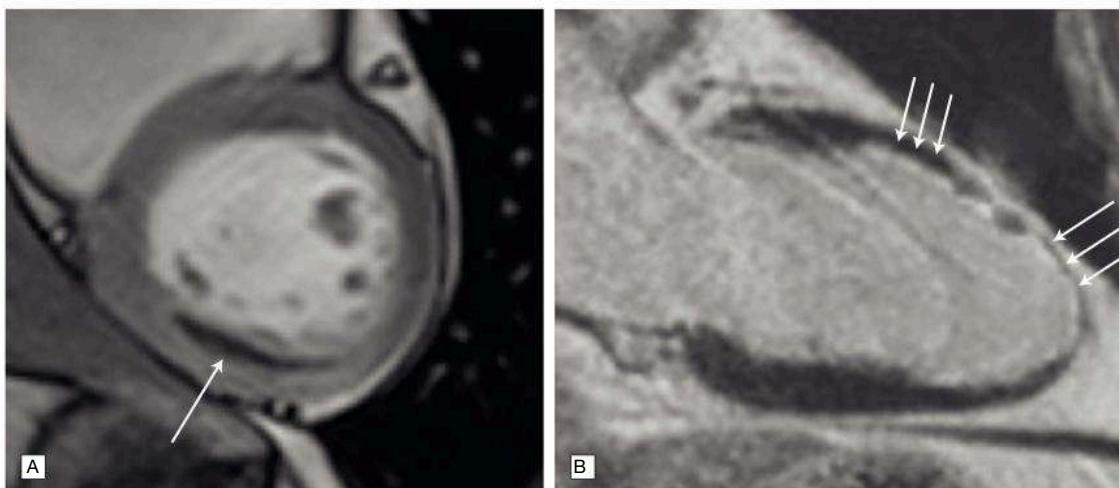


Fig. 16.14 Cardiac magnetic resonance imaging. **A** Recent inferior myocardial infarction with black area of microvascular obstruction (arrow). **B** Old anterior myocardial infarction with large area of subendocardial delayed gadolinium enhancement (white area, arrows).

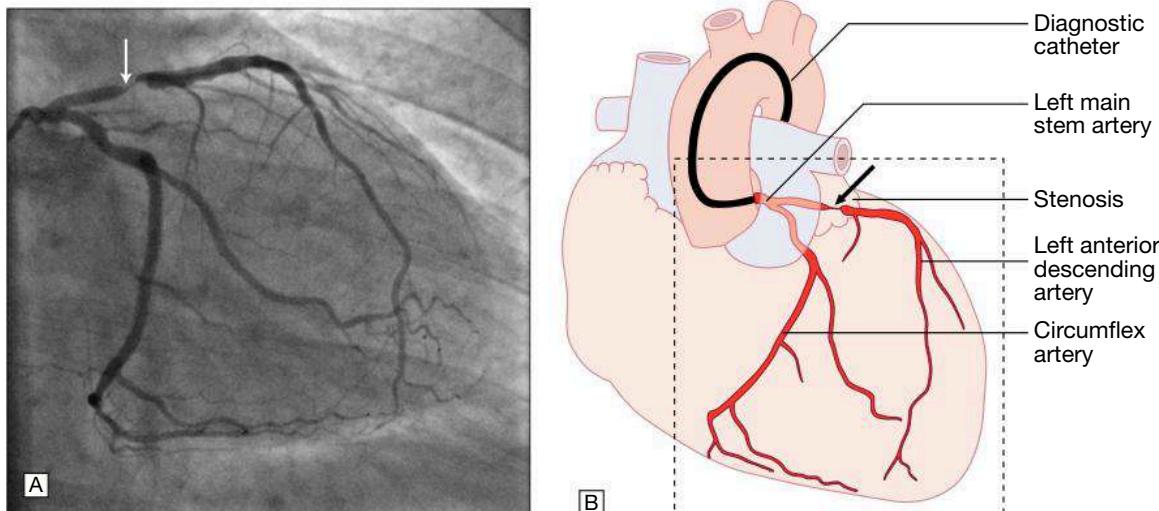


Fig. 16.15 The left anterior descending and circumflex coronary arteries with a stenosis (arrow) in the left anterior descending vessel. **A** Coronary artery angiogram. **B** Schematic of the vessels and branches.

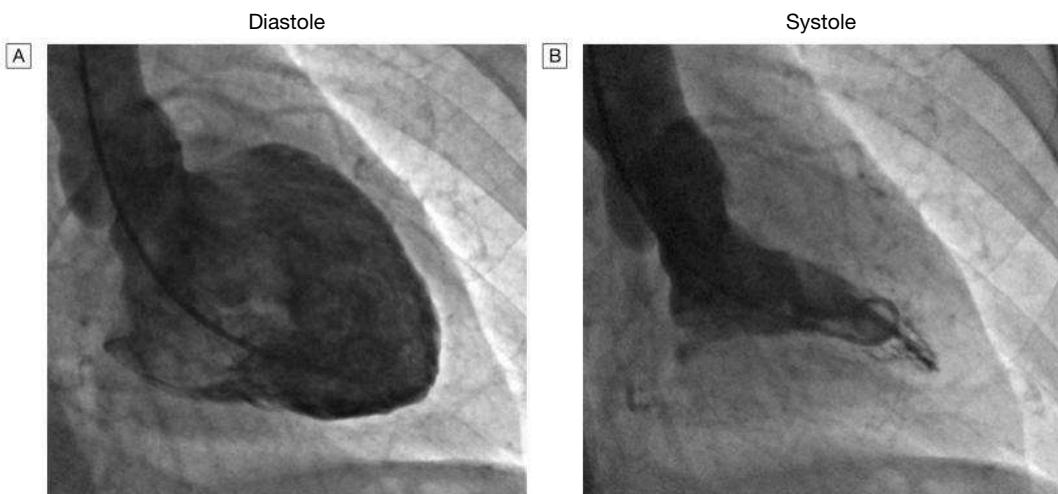


Fig. 16.16 Left ventriculograms in diastole **A** and systole **B** in a patient with normal left ventricular contraction.

Electrophysiology

Patients with known or suspected arrhythmia are investigated by percutaneous placement of electrode catheters into the heart via the femoral and neck veins. An electrophysiology study (EPS) is most commonly performed to evaluate patients for catheter ablation and is normally done at the same time as the ablation procedure. EPS is occasionally used for risk stratification of patients suspected of being at risk of ventricular arrhythmias.

Radionuclide imaging

Radionuclide imaging can be used to evaluate cardiac function but is declining in popularity due to the availability of alternative techniques, such as MRI and CT, that either do not involve exposure to radiation or provide superior quality data to radionuclide imaging.

Blood pool imaging

The patient is given an intravenous injection of radioisotope-labelled blood cells, and after 4–5 minutes, the distribution of isotope in the heart is evaluated by a gamma camera at different phases of the cardiac cycle,

thereby permitting the calculation of ventricular ejection fractions. It can also assess the size and ‘shape’ of the cardiac chambers.

Myocardial perfusion scanning

The patient is given an intravenous injection of a radioactive isotope, such as ^{99m}technetium-tetrofosmin, and scintiscans of the myocardium are subsequently obtained by gamma camera at rest and during stress (see Fig. 16.57). Either exercise stress or pharmacological stress (using the inotrope dobutamine or the vasodilator dipyridamole) can be used. More sophisticated quantitative information can be obtained with positron emission tomography (PET), which can also be used to assess myocardial metabolism, but this is available in only a few centres.

Presenting problems in cardiovascular disease

Cardiovascular disease gives rise to several symptoms, which may overlap those caused by pathologies of other systems. Making the correct diagnosis depends on careful analysis of the factors that provoke symptoms, the subtle differences in how they are described by the

i**16.5 New York Heart Association (NYHA) functional classification****Class I**

- No limitation during ordinary activity

Class II

- Slight limitation during ordinary activity

Class III

- Marked limitation of normal activities without symptoms at rest

Class IV

- Unable to undertake physical activity without symptoms; symptoms may be present at rest

patient, the clinical findings and the results of investigations. A close relationship between symptoms and exertion is usually suggestive of heart disease. The New York Heart Association (NYHA) functional classification is used to grade the degree of disability caused by cardiac symptoms (Box 16.5).

Chest pain on exertion

There are many other non-cardiac causes of chest pain, as discussed in Chapter 9. This section will focus on exertional chest pain (or discomfort), which is a typical presenting symptom of coronary artery disease.

Clinical assessment

Detailed history taking is crucial in determining the likely cause of chest pain. Chest pain on exertion suggests angina pectoris (Fig. 16.17). The reproducibility, predictability and relationship to physical exertion (and occasionally emotion) of the chest pain are the most important features. The duration of symptoms should be noted because patients with recent-onset angina are at greater risk than those with long-standing and unchanged symptoms. Physical examination is often normal but may reveal evidence of risk factors for cardiovascular disease, such as xanthoma or xanthelasma indicating hyperlipidaemia. Signs of anaemia or thyrotoxicosis may be identified, both of which can exacerbate angina. Cardiovascular examination may reveal evidence of left ventricular dysfunction or cardiac murmurs in patients with aortic valve disease and hypertrophic cardiomyopathy. Other manifestations of arterial disease, such as bruits and loss of peripheral pulses, may also be observed.

Investigations

A full blood count, fasting blood glucose, lipids, thyroid function tests and a 12-lead ECG are the most important baseline investigations. Stress testing, including exercise ECG, stress echocardiography and magnetic resonance perfusion imaging, can be helpful in confirming anginal symptoms and identifying high-risk patients who require further investigation and treatment but cannot reliably exclude the presence of coronary artery disease. However, CT coronary angiography is the first-line test of choice to diagnose angina due to coronary artery disease. If a murmur is found, echocardiography should be performed to check for valve disease or hypertrophic cardiomyopathy.

Severe prolonged chest pain

Severe prolonged cardiac chest pain may be due to acute myocardial infarction or to unstable angina – known collectively as acute coronary syndrome.

Clinical assessment

Acute coronary syndrome is suggested by a previous history of stable angina but an episode of acute severe chest pain at rest can also be the

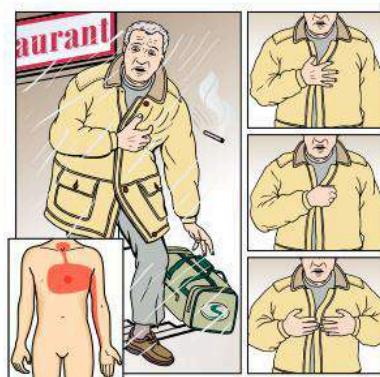


Fig. 16.17 Typical ischaemic cardiac pain. Characteristic hand gestures used to describe cardiac pain. Typical radiation of pain is shown in the schematic.

first presentation of coronary artery disease. Making the correct diagnosis depends on analysing the character of the pain and its associated features. Physical examination may reveal signs of risk factors for coronary artery disease as described for exertional chest pain. There may also be pallor or sweating, which is indicative of autonomic disturbance and typical of acute coronary syndrome. Other features, such as arrhythmia, hypotension and heart failure, may occur. Patients presenting with symptoms consistent with an acute coronary syndrome require hospitalisation and urgent investigation, because there is a high risk of avoidable complications.

Investigations

A 12-lead ECG is mandatory and is the most useful method of initial triage, along with measurement of cardiac troponin I or T. The diagnosis of an acute coronary syndrome is supported by ST segment elevation or depression on ECG and an elevated level of troponin I or T, which demonstrates that there has been myocardial damage.

If the diagnosis remains unclear after initial investigation, repeat ECG recordings should be performed and are particularly useful if they can be obtained during an episode of pain. If the plasma troponin concentrations are normal at baseline, repeat measurements should be made 6–12 hours after the onset of symptoms or admission to hospital. New ECG changes or an elevated plasma troponin concentration usually confirm the diagnosis of an acute coronary syndrome. If the pain settles and does not recur, there are no new ECG changes and troponin concentrations remain normal, the patient can be discharged from hospital but further investigations may be indicated to look for evidence of coronary artery disease, as discussed on page 424.

Management

The differential diagnosis and management of acute coronary syndrome are described in more detail later in this chapter.

Breathlessness

Cardiac causes of breathlessness include cardiac arrhythmias, acute and chronic heart failure, acute coronary syndrome, valvular disease, cardiomyopathy and constrictive pericarditis, all discussed later in this chapter. The differential diagnosis of breathlessness is wide, however, and has many other non-cardiac causes. These are discussed in more detail on pages 181 and 489.

Syncope

The term 'syncope' refers to loss of consciousness due to reduced cerebral perfusion. The differential diagnosis, investigation and management of syncope are discussed on page 184.

Palpitation

Palpitation is a common and sometimes frightening symptom that is usually due to a disorder of cardiac rhythm. Patients use the term to describe many sensations, including an unusually erratic, fast, slow or forceful heart beat, or even chest pain or breathlessness.

Clinical assessment

Initial evaluation should concentrate on determining the likely mechanism of palpitation and whether or not there is significant underlying heart disease. A detailed description of the sensation is essential and patients should be asked to describe their symptoms clearly, or to demonstrate the sensation of rhythm by tapping with their hand. A provisional diagnosis can usually be made on the basis of the history (Box 16.6 and Fig. 16.18). Recurrent but short-lived bouts of an irregular heart rhythm are usually due to atrial or ventricular extrasystoles (ectopic beats). Some patients will describe the experience as a 'flip' or a 'jump' in the chest, while others report dropped or missed beats. Extrasystoles are often more frequent during periods of stress or debility; they can be triggered by alcohol or nicotine.

Episodes of a pounding, forceful and relatively fast (90–120/min) heart beat are a common manifestation of anxiety. These may also reflect a hyperdynamic circulation, such as anaemia, pregnancy and thyrotoxicosis, and can occur in some forms of valve disease such as aortic regurgitation. Discrete bouts of more rapid (over 120/min) heart beats are more likely to be due to a paroxysmal supraventricular or ventricular tachycardia. In contrast, episodes of atrial fibrillation typically present with irregular and usually rapid palpitation.

Investigation

If initial assessment suggests that the palpitation is due to an arrhythmia, the diagnosis should be confirmed by an ECG recording during an episode using an ambulatory ECG monitor. Smartphones and smart watches with additional hardware and apps are extremely helpful in capturing the ECG during episodes. Additional investigations may be required depending on the nature of the arrhythmia, as discussed later in this chapter.

Management

Palpitation is usually benign and even if the patient's symptoms are due to an arrhythmia, the outlook is good if there is no underlying structural heart disease. Most cases are due to an awareness of the normal heart beat, a sinus tachycardia or benign extrasystoles, in which case an explanation and reassurance may be all that is required. Palpitation associated with pre-syncope or syncope (p. 184) may reflect more serious structural or electrical disease and should be investigated without delay. Other arrhythmias may require treatment, such as drugs or ablation, and are discussed in more detail in the section on cardiac arrhythmias.

Cardiac arrest

Cardiac arrest describes the sudden and complete loss of cardiac output due to asystole, ventricular tachycardia or ventricular fibrillation



16.6 How to evaluate palpitation

- Is the palpitation continuous or intermittent?
- Is the heart beat regular or irregular?
- What is the approximate heart rate?
- Do symptoms occur in discrete attacks?
 - Is the onset abrupt? How do attacks terminate?
- Are there any associated symptoms?
Chest pain, lightheadedness, polyuria (a feature of supraventricular tachycardia)
- Are there any precipitating factors, such as exercise or alcohol excess?
- Is there a history of structural heart disease, such as coronary artery disease or valvular heart disease?

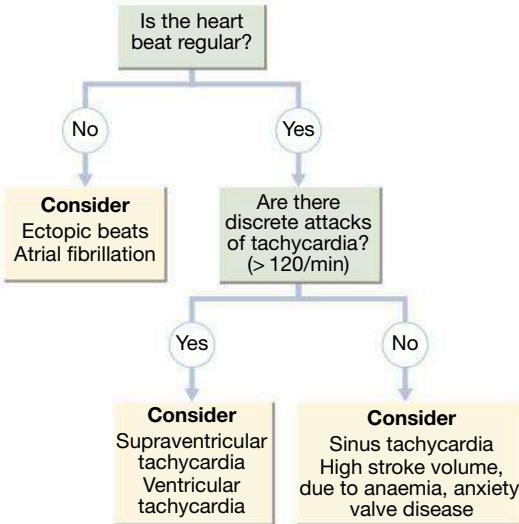
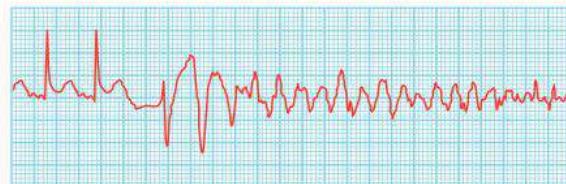


Fig. 16.18 A simple approach to the diagnosis of palpitation.



16

Fig. 16.19 Ventricular fibrillation. A bizarre chaotic rhythm, initiated in this case by two ventricular ectopic beats in rapid succession.

(Fig. 16.19), or loss of mechanical cardiac contraction (pulseless electrical activity). The causes of sudden arrhythmic death are summarised in Box 16.7. The clinical diagnosis is based on the victim being unconscious and pulseless; breathing may take some time to stop completely after cardiac arrest. Death is virtually inevitable, unless effective treatment is given promptly. Sudden cardiac death is usually caused by a catastrophic arrhythmia and accounts for 25%–30% of all deaths from cardiovascular disease, claiming an estimated 70 000 to 90 000 lives each year in the UK. Many of these deaths are potentially preventable. Management of cardiac arrest is further discussed in detail on page 202.



16.7 Causes of sudden arrhythmic death

Coronary artery disease (85%)

- Myocardial ischaemia
- Acute myocardial infarction
- Prior myocardial infarction with myocardial scarring

Structural heart disease (10%)

- Aortic stenosis
- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Arrhythmogenic right ventricular cardiomyopathy
- Congenital heart disease

No structural heart disease (5%)

- Long QT syndrome
- Brugada syndrome
- Wolff–Parkinson–White syndrome
- Adverse drug reactions (torsades de pointes)
- Severe electrolyte abnormalities

Abnormal heart sounds

The first indication of heart disease may be the discovery of an abnormal sound on auscultation (Box 16.8). This may be incidental – for example, during a routine examination – or may be prompted by symptoms of heart disease.

Clinical assessment

The aims of clinical assessment are, first, to determine if the abnormal sound is cardiac; second, to determine if it is pathological; and third, to try to determine its cause.

Is the sound cardiac?

Additional heart sounds and murmurs demonstrate a consistent relationship to the cardiac cycle, whereas extracardiac sounds, such as a pleural rub or venous hum, do not. Pericardial friction produces a characteristic scratching noise termed a pericardial rub, which may have two components corresponding to atrial and ventricular systole, and may vary with posture and respiration.

Is the sound pathological?

Pathological sounds and murmurs are the product of turbulent blood flow or rapid ventricular filling due to abnormal loading conditions. Some added sounds are physiological but may also occur in pathological conditions; for example, a third sound is common in young people and in pregnancy but is also a feature of heart failure (see Box 16.8). Similarly, a systolic murmur due to turbulence across the right ventricular outflow tract may occur in hyperdynamic states such as anaemia or pregnancy, but may also be due to pulmonary stenosis or an intracardiac shunt leading to volume overload of the RV, such as an atrial septal defect. Benign murmurs do not occur in diastole (Box 16.9), and systolic murmurs that radiate or are associated with a thrill are almost always pathological.



16.9 Features of a benign or innocent heart murmur

- Soft
- Mid-systolic
- Heard at left sternal border
- No radiation
- No other cardiac abnormalities

What is the origin of the sound?

Timing, intensity, location, radiation and quality are all useful clues to the origin and nature of an additional sound or murmur (Box 16.10). Radiation of a murmur is determined by the direction of turbulent blood flow and is detectable only when there is a high-velocity jet, such as in mitral regurgitation (radiation from apex to axilla) or aortic stenosis (radiation from base to neck). Similarly, the pitch and quality of the sound can help to distinguish the murmur, such as the ‘blowing’ murmur of mitral regurgitation or the ‘rasping’ murmur of aortic stenosis. The position of a murmur in relation to the cardiac cycle is crucial and should be assessed by timing it with the heart sounds, carotid pulse and apex beat (Figs. 16.20 and 16.21).

Systolic murmurs

Ejection systolic murmurs are associated with ventricular outflow tract obstruction and occur in mid-systole with a crescendo–decrescendo pattern, reflecting the changing velocity of blood flow (Box 16.11). Pansystolic murmurs maintain a constant intensity and extend from the first heart sound throughout systole to the second heart sound, sometimes obscuring it. They occur when blood leaks from a ventricle into a low-pressure chamber at an even or constant velocity. Mitral regurgitation, tricuspid regurgitation and ventricular septal defect are the only causes of a pansystolic murmur. Late systolic murmurs are unusual but may occur in mitral valve prolapse, if the mitral regurgitation is confined to late systole, and hypertrophic obstructive cardiomyopathy, if dynamic obstruction occurs late in systole.



16.8 Normal and abnormal heart sounds

Sound	Timing	Characteristics	Mechanisms	Variable features
First heart sound (S1)	Onset of systole	Usually single or narrowly split	Closure of mitral and tricuspid valves	Loud: hyperdynamic circulation (anaemia, pregnancy, thyrotoxicosis); mitral stenosis Soft: heart failure; mitral regurgitation
Second heart sound (S2)	End of systole	Split on inspiration Single on expiration	Closure of aortic and pulmonary valve A_2 first P_2 second	Fixed wide splitting with atrial septal defect Wide but variable splitting with delayed right heart emptying (right bundle branch block) Reversed splitting due to delayed left heart emptying (left bundle branch block)
Third heart sound (S3)	Early in diastole, just after S2	Low pitch, often heard as ‘gallop’	From ventricular wall due to abrupt cessation of rapid filling	Physiological: young people, pregnancy Pathological: heart failure, mitral regurgitation
Fourth heart sound (S4)	End of diastole, just before S1	Low pitch	Ventricular origin (stiff ventricle and augmented atrial contraction) related to atrial filling	Absent in atrial fibrillation A feature of severe left ventricular hypertrophy
Systolic clicks	Early or mid-systole	Brief, high-intensity sound	Valvular aortic stenosis Valvular pulmonary stenosis Floppy mitral valve Prosthetic heart sounds from opening and closing of normally functioning mechanical valves	Click may be lost when stenotic valve becomes thickened or calcified Prosthetic clicks lost when valve obstructed by thrombus or vegetations
Opening snap (OS)	Early in diastole	High pitch, brief duration	Opening of stenosed leaflets of mitral valve Prosthetic heart sounds	Moves closer to S2 as mitral stenosis becomes more severe. May be absent in calcific mitral stenosis

16.10 How to assess a heart murmur

When does it occur?

- Time the murmur using heart sounds, carotid pulse and the apex beat. Is it systolic or diastolic?
- Does the murmur extend throughout systole or diastole or is it confined to a shorter part of the cardiac cycle?

How loud is it?

- Grade 1: very soft (audible only in ideal conditions)
- Grade 2: soft
- Grade 3: moderate
- Grade 4: loud with associated thrill
- Grade 5: very loud
- Grade 6: heard without stethoscope

Note: Diastolic murmurs are very rarely above grade 4

Where is it heard best?

- Listen over the apex and base of the heart, including the aortic and pulmonary areas

Where does it radiate?

- Listen at the neck, axilla or back

What does it sound like?

- Pitch is determined by flow (high pitch indicates high-velocity flow)
- Is the intensity constant or variable?

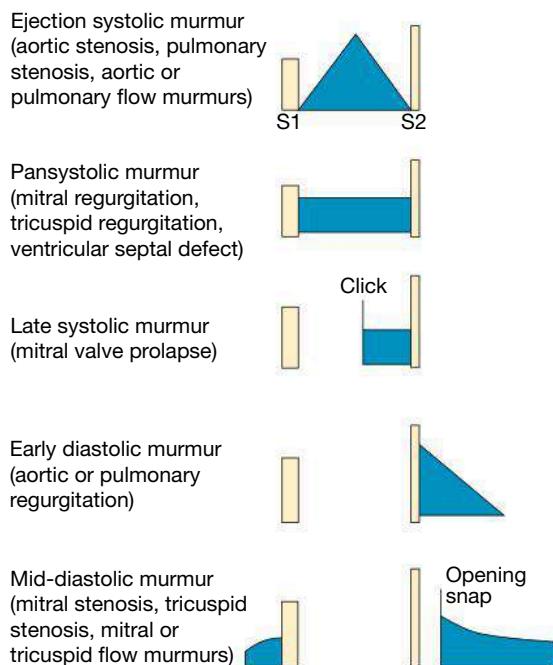


Fig. 16.21 The timing and pattern of cardiac murmurs.

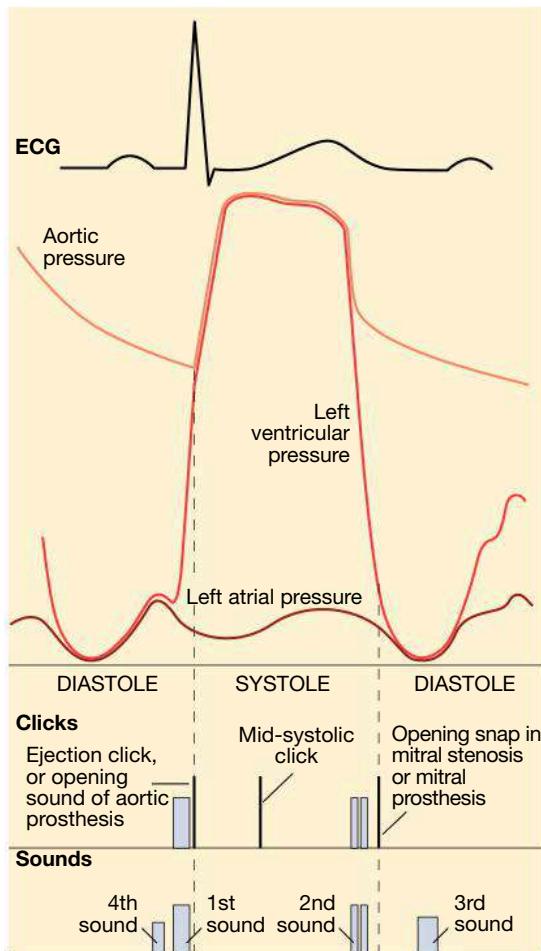


Fig. 16.20 The relationship of the cardiac cycle to the ECG, the left ventricular pressure wave and the position of heart sounds.

Diastolic murmurs

These are due to accelerated or turbulent flow across the mitral or tricuspid valves. They are low-pitched noises that are often difficult to hear and should be evaluated with the bell of the stethoscope. A mid-diastolic murmur may be due to mitral stenosis (located at the apex and axilla), tricuspid stenosis (located at the left sternal border), increased flow across the mitral valve (for example, the to-and-fro murmur of severe mitral regurgitation) or increased flow across the tricuspid valve (for example, a left-to-right shunt through a large atrial septal defect). Early diastolic murmurs have a soft, blowing quality with a decrescendo pattern and should be evaluated with the diaphragm of the stethoscope. They are due to regurgitation across the aortic or pulmonary valves and are best heard at the left sternal border, with the patient sitting forwards in held expiration.

Continuous murmurs

These result from a combination of systolic and diastolic flow, such as occurs with a persistent ductus arteriosus, and must be distinguished from extracardiac noises such as bruits from arterial shunts, venous hums (high rates of venous flow in children) and pericardial friction rubs.

Investigations

If clinical evaluation suggests that the additional sound is cardiac and likely to be pathological, then echocardiography is indicated to determine the underlying cause.

Management

Management of patients with additional heart sounds or murmurs depends on the underlying cause. More details are provided in the sections on specific valve defects and congenital anomalies later in this chapter.

Heart failure

Heart failure describes the clinical syndrome that develops when the heart cannot maintain adequate output, or can do so only at the expense of elevated ventricular filling pressure. In mild to moderate forms of heart failure, symptoms occur only when the metabolic demand increases during exercise or some other form of stress. In severe heart failure, symptoms may be

16.11 Features of some common systolic murmurs				
Condition	Timing and duration	Quality	Location and radiation	Associated features
Aortic stenosis	Mid-systolic	Loud, rasping	Base and left sternal border, radiating to suprasternal notch and carotids	Single second heart sound Ejection click (in young patients) Slow-rising pulse Left ventricular hypertrophy (pressure overload)
Mitral regurgitation	Pansystolic	Blowing	Apex, radiating to axilla	Soft first heart sound Third heart sound Left ventricular hypertrophy (volume overload)
Ventricular septal defect	Pansystolic	Harsh	Lower left sternal border, radiating to whole precordium	Thrill Biventricular hypertrophy
Benign	Mid-systolic	Soft	Left sternal border, no radiation	No other signs of heart disease

present at rest. In clinical practice, heart failure may be diagnosed when a patient with significant heart disease develops the signs or symptoms of a low cardiac output, pulmonary congestion or systemic venous congestion at rest or on exercise. Three types of heart failure are recognised.

Left heart failure

This is characterised by a reduction in left ventricular output and an increase in left atrial and pulmonary venous pressure. If left heart failure occurs suddenly – for example, as the result of an acute MI – the rapid increase in left atrial pressure causes pulmonary oedema. If the rise in atrial pressure is more gradual, as occurs with mitral stenosis, there is reflex pulmonary vasoconstriction, which protects the patient from pulmonary oedema. However, the resulting increase in pulmonary vascular resistance causes pulmonary hypertension, which in turn impairs right ventricular function.

Right heart failure

This is characterised by a reduction in right ventricular output and an increase in right atrial and systemic venous pressure. The most common causes are chronic lung disease, pulmonary embolism and pulmonary valvular stenosis. The term 'cor pulmonale' is used to describe right heart failure that is secondary to chronic lung disease.

Biventricular heart failure

In biventricular failure, both sides of the heart are affected. This may occur because the disease process, such as dilated cardiomyopathy or coronary heart disease, affects both ventricles or because disease of the left heart leads to chronic elevation of the left atrial pressure, pulmonary hypertension and right heart failure.

Epidemiology

Heart failure predominantly affects older people; the prevalence is 1.6% in the UK adult population but affects more than 10% in those aged 80–89 years. In the UK, most patients admitted to hospital with heart failure are more than 70 years old; they typically remain hospitalised for a week or more and may be left with chronic disability. Although the outlook depends, to some extent, on the underlying cause of the problem, untreated heart failure generally carries a poor prognosis; approximately 50% of patients with severe heart failure due to left ventricular dysfunction will die within 2 years because of either pump failure or malignant ventricular arrhythmias. The most common causes are coronary artery disease and myocardial infarction but almost all forms of heart disease can lead to heart failure, as summarised in [Box 16.12](#). An accurate diagnosis is important because treatment of the underlying cause may reverse heart failure or prevent its progression.

Pathogenesis

Heart failure occurs when cardiac output fails to meet the demands of the circulation. Cardiac output is determined by preload (the volume and

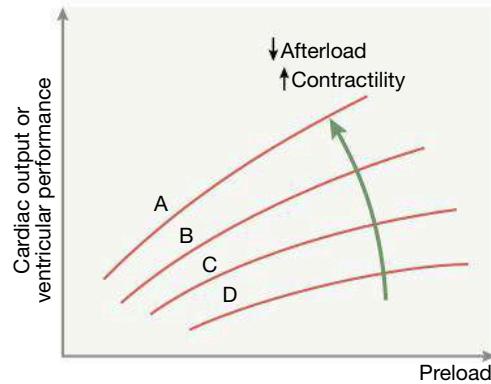


Fig. 16.22 Starling's Law. Normal (A), mild (B), moderate (C) and severe (D) heart failure. Ventricular performance is related to the degree of myocardial stretching. An increase in preload (end-diastolic volume, end-diastolic pressure, filling pressure or atrial pressure) will therefore enhance function; however, overstretching causes marked deterioration. In heart failure, the curve moves to the right and becomes flatter. An increase in myocardial contractility or a reduction in afterload will shift the curve upwards and to the left (green arrow).

pressure of blood in the ventricles at the end of diastole), afterload (the volume and pressure of blood in the ventricles during systole) and myocardial contractility, forming the basis of Starling's Law ([Fig. 16.22](#)). The causes of heart failure are discussed below.

Ventricular dysfunction

Ventricular dysfunction is the most common cause of heart failure. This can occur because of impaired systolic contraction due to myocardial disease, or diastolic dysfunction where there is abnormal ventricular relaxation due to a stiff, non-compliant ventricle. This is most commonly found in patients with left ventricular hypertrophy. Systolic dysfunction and diastolic dysfunction often coexist, particularly in patients with coronary artery disease. Ventricular dysfunction reduces cardiac output, which, in turn, activates the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS). Under normal circumstances, activation of the SNS and RAAS supports cardiac function but, in the setting of impaired ventricular function, the consequences are negative and lead to an increase in both afterload and preload ([Fig. 16.23](#)). A vicious circle may then be established because any additional fall in cardiac output causes further activation of the SNS and RAAS, and an additional increase in peripheral vascular resistance.

Activation of the RAAS causes vasoconstriction and sodium and water retention. This is primarily mediated by angiotensin II, a potent constrictor of arterioles, in both the kidney and the systemic circulation (see [Fig. 16.23](#)). Activation of the SNS also occurs and can initially sustain cardiac output through increased myocardial contractility and heart

16.12 Mechanisms of heart failure

Cause	Examples	Features
Reduced ventricular contractility	Myocardial infarction (segmental dysfunction)	In coronary artery disease, 'akinetic' or 'dyskinetic' segments contract poorly and may impede the function of normal segments by distorting their contraction and relaxation patterns
	Myocarditis/cardiomyopathy (global dysfunction)	Progressive ventricular dilatation
Ventricular outflow obstruction (pressure overload)	Hypertension, aortic stenosis (left heart failure) Pulmonary hypertension, pulmonary valve stenosis (right heart failure)	Initially, concentric ventricular hypertrophy allows the ventricle to maintain a normal output by generating a high systolic pressure. Later, secondary changes in the myocardium and increasing obstruction lead to failure with ventricular dilatation and rapid clinical deterioration
Ventricular inflow obstruction	Mitral stenosis, tricuspid stenosis	Small, vigorous ventricle; dilated, hypertrophied atrium. Atrial fibrillation is common and often causes marked deterioration because ventricular filling depends heavily on atrial contraction
Ventricular volume overload	Left ventricular volume overload (mitral or aortic regurgitation) Ventricular septal defect Right ventricular volume overload (atrial septal defect) Increased metabolic demand (high output)	Dilatation and hypertrophy allow the ventricle to generate a high stroke volume and help to maintain a normal cardiac output. However, secondary changes in the myocardium lead to impaired contractility and worsening heart failure
Arrhythmia	Atrial fibrillation	Tachycardia does not allow for adequate filling of the heart, resulting in reduced cardiac output and back pressure
	Tachycardia	Prolonged tachycardia causes myocardial fatigue
	Complete heart block	Bradycardia limits cardiac output, even if stroke volume is normal
Diastolic dysfunction	Constrictive pericarditis	Marked fluid retention and peripheral oedema, ascites, pleural effusions and elevated jugular veins
	Restrictive cardiomyopathy	Bi-atrial enlargement (restrictive filling pattern and high atrial pressures). Atrial fibrillation may cause deterioration
	Left ventricular hypertrophy and fibrosis	Good systolic function but poor diastolic filling
	Cardiac tamponade	Hypotension, elevated jugular veins, pulsus paradoxus, poor urine output

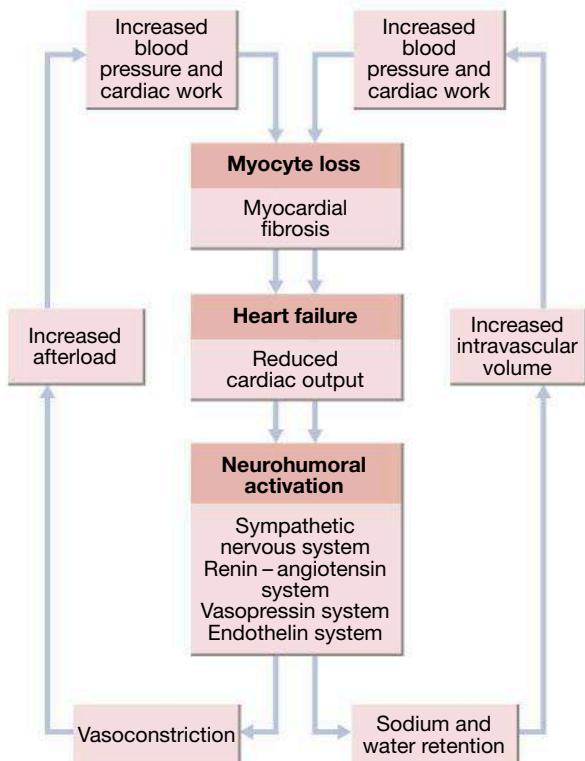


Fig. 16.23 Neurohumoral activation and compensatory mechanisms in heart failure. There is a vicious circle in progressive heart failure.

rate. Prolonged sympathetic stimulation has negative effects, however, causing cardiac myocyte apoptosis, cardiac hypertrophy and focal myocardial necrosis. Sympathetic stimulation also contributes to vasoconstriction and predisposes to arrhythmias. Sodium and water retention is further enhanced by the release of aldosterone, endothelin-1 (a potent vasoconstrictor peptide with marked effects on the renal vasculature) and, in severe heart failure, vasopressin (antidiuretic hormone, ADH). Natriuretic peptides are released from the atria in response to atrial dilatation and compensate to an extent for the sodium-conserving effect of aldosterone, but this mechanism is overwhelmed in heart failure. Pulmonary and peripheral oedema occur because of high left and right atrial pressures, and are compounded by sodium and water retention, caused by impairment of renal perfusion and by secondary hyperaldosteronism. If the underlying cause is a myocardial infarction, cardiac contractility is impaired and SNS and RAAS activation causes hypertrophy of non-infarcted segments, with thinning, dilatation and expansion of the infarcted segment (see Fig. 16.63). This leads to further deterioration in ventricular function and worsening heart failure.

High-output failure

Sometimes cardiac failure can occur in patients without heart disease due to a large arteriovenous shunt, or where there is an excessively high cardiac output due to beri-beri, severe anaemia or thyrotoxicosis.

Valvular disease

Heart failure can also be caused by valvular disease in which there is impaired filling of the ventricles due to mitral or tricuspid stenosis; where there is obstruction to ventricular outflow, as occurs in aortic and pulmonary stenosis and hypertrophic cardiomyopathy; or as the result of ventricular overload secondary to valvular regurgitation.

Clinical assessment

Heart failure may develop suddenly, as in MI, or gradually, as in valvular heart disease. When there is gradual impairment of cardiac function, several compensatory changes take place. The term compensated heart failure is sometimes used to describe the condition of those with impaired cardiac function, in whom adaptive changes have prevented the development of overt heart failure. However, a minor event, such as an intercurrent infection or development of atrial fibrillation, may precipitate acute heart failure in these circumstances (Box 16.13). Similarly, acute heart failure sometimes supervenes as the result of a decompensating episode, on a background of chronic heart failure; this is called acute-on-chronic heart failure.

Acute left heart failure

Acute left heart failure presents with a sudden onset of dyspnoea at rest that rapidly progresses to acute respiratory distress, orthopnoea and ultimately respiratory failure. Often there is a clear precipitating factor, such as an acute MI, which may be apparent from the history. The patient appears agitated, pale and clammy. The peripheries are cool to the touch and the pulse is rapid, but in some cases there may be an inappropriate bradycardia that aggravates the acute episode of heart failure. The BP is usually high because of SNS activation, but may be normal or low if the patient is in cardiogenic shock.

The jugular venous pressure (JVP) is usually elevated, particularly with associated fluid overload or right heart failure. In acute heart failure, there has been no time for ventricular dilatation and the apex is not displaced. A 'gallop' rhythm, with a third heart sound, is heard quite early in the development of acute left-sided heart failure. A new systolic murmur may signify acute mitral regurgitation or ventricular septal rupture. Chest examination may reveal crepitations at the lung bases if there is pulmonary oedema, or



16.13 Factors that may precipitate or aggravate heart failure in pre-existing heart disease

- Myocardial ischaemia or infarction
- Intercurrent illness
- Arrhythmia
- Inappropriate reduction of therapy
- Administration of a drug with negative inotropic (β -blocker) or fluid-retaining properties (non-steroidal anti-inflammatory drugs, glucocorticoids)
- Pulmonary embolism
- Conditions associated with increased metabolic demand (pregnancy, thyrotoxicosis, anaemia)
- Intravenous fluid overload

crepitations throughout the lungs if this is severe. There may be expiratory wheeze. Patients with acute-on-chronic heart failure may have additional features of chronic heart failure (see below). Potential precipitants, such as an upper respiratory tract infection or inappropriate cessation of diuretic medication, may be identified on clinical examination or history-taking.

Chronic heart failure

Patients with chronic heart failure commonly follow a relapsing and remitting course, with periods of stability and episodes of decompensation, leading to worsening symptoms that may necessitate hospitalisation. The clinical picture depends on the nature of the underlying heart disease, the type of heart failure that it has evoked, and the changes in the SNS and RAAS that have developed (see Box 16.12 and Fig. 16.24).

Low cardiac output causes fatigue and poor effort tolerance; the peripheries are cold and the BP is low. To maintain perfusion of vital organs, blood flow is diverted away from skeletal muscle and this may contribute to fatigue and weakness. Poor renal perfusion leads to oliguria and uraemia.

Pulmonary oedema due to left heart failure presents with dyspnoea and inspiratory crepitations over the lung bases. In contrast, right heart

failure produces a high JVP with hepatic congestion and dependent peripheral oedema. In ambulant patients the oedema affects the lower legs, whereas in bed-bound patients it collects around the thighs and sacrum. Ascites or pleural effusion may occur (Fig. 16.24). Heart failure is not the only cause of oedema (see Box 16.14).

Chronic heart failure is sometimes associated with marked weight loss (cardiac cachexia), caused by a combination of anorexia and impaired absorption due to gastrointestinal congestion, poor tissue perfusion due to a low cardiac output, and skeletal muscle atrophy due to immobility.

Complications of heart failure

Several complications may occur in advanced heart failure, as described below.

- *Renal failure* is caused by poor renal perfusion due to low cardiac output and may be exacerbated by diuretic, ACE inhibitor and angiotensin receptor blocker (ARB) therapies.
- *Hypokalaemia* may be caused by potassium-losing diuretics, and also by hyperaldosteronism due to activation of the renin–angiotensin system and impairment of aldosterone metabolism from hepatic congestion. Most of the body's potassium is intracellular and there may be substantial depletion of potassium stores, even when the plasma concentration is in the reference range.
- *Hyperkalaemia* may be due to the effects of drugs that promote renal resorption of potassium, in particular the combination of ACE inhibitors, ARBs and mineralocorticoid receptor antagonists. These effects are amplified if there is renal dysfunction due to low cardiac output or atherosclerotic renal vascular disease.
- *Hyponatraemia* is a feature of severe heart failure and is a poor prognostic sign. It may be caused by diuretic therapy, inappropriate water retention due to high vasopressin secretion, or failure of the cell membrane ion pump due to intracellular energy depletion.

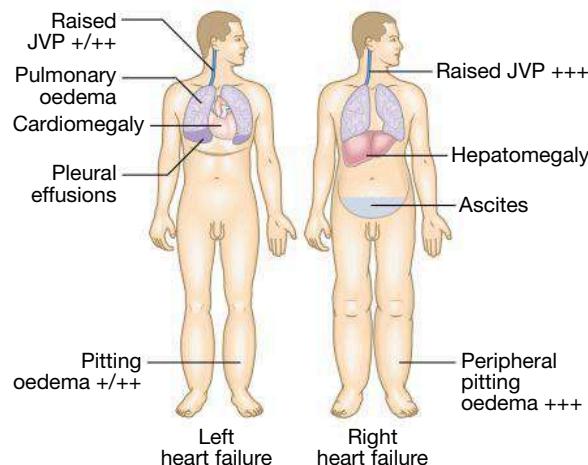


Fig. 16.24 Clinical features of left and right heart failure. (JVP = jugular venous pressure)



16.14 Differential diagnosis of peripheral oedema

- Cardiac failure: right or combined left and right heart failure, pericardial constriction, cardiomyopathy
- Chronic venous insufficiency: varicose veins
- Hypoalbuminaemia: nephrotic syndrome, liver disease, protein-losing enteropathy; often widespread, can affect arms and face
- Drugs:
 - Sodium retention: fludrocortisone, non-steroidal anti-inflammatory drugs
 - Increasing capillary permeability: nifedipine, amlodipine
- Idiopathic: women > men
- Chronic lymphatic obstruction

- *Impaired liver function* is caused by hepatic venous congestion and poor arterial perfusion, which frequently cause mild jaundice and abnormal liver function tests; reduced synthesis of clotting factors can make anticoagulant control difficult.
- *Thromboembolism*. Deep vein thrombosis and pulmonary embolism may occur due to the effects of low cardiac output and enforced immobility. Systemic embolism, including stroke, occurs in patients with atrial fibrillation or flutter, or with intracardiac thrombus complicating mitral stenosis, MI or left ventricular aneurysm.
- *Atrial and ventricular arrhythmias* are very common and may be related to electrolyte changes such as hypokalaemia and hypomagnesaemia, myocardial fibrosis and the pro-arrhythmic effects of sympathetic activation. Atrial fibrillation occurs in approximately 20% of patients with heart failure and causes further impairment of cardiac function. Ventricular ectopic beats and non-sustained ventricular tachycardia are common findings in patients with heart failure and are associated with an adverse prognosis.
- *Sudden death* occurs in up to 50% of patients with heart failure and is most often due to ventricular fibrillation.

Investigations

An erect chest X-ray should be performed in all cases. This may show abnormal distension of the upper lobe pulmonary veins (Fig. 16.25). Vascularity of the lung fields becomes more prominent and the pulmonary arteries dilate. Subsequently, interstitial oedema causes thickened interlobular septa and dilated lymphatics. These are evident as horizontal lines in the costophrenic angles (septal or 'Kerley B' lines). More advanced changes due to alveolar oedema cause a hazy opacification spreading from the hilum, and pleural effusions. Echocardiography should be considered in all patients with heart failure in order to:

- determine the aetiology
- detect valvular heart disease, such as occult mitral or aortic stenosis, and other conditions that may be amenable to treatment
- identify patients who will benefit from long-term drug therapy and cardiac device implantation.

Serum urea, creatinine and electrolytes, haemoglobin and thyroid function may help to establish the nature and severity of the underlying heart disease and detect any complications. BNP is elevated in heart failure and is a prognostic marker, as well as being useful in differentiating heart failure from other causes of breathlessness or peripheral oedema.

Management of acute heart failure

Acute heart failure with pulmonary oedema is a medical emergency that should be treated urgently. The patient should initially be kept rested upright, with continuous monitoring of cardiac rhythm, BP and pulse oximetry. Intravenous opiates can be of value in distressed patients but must be used sparingly, as they may cause respiratory depression and exacerbation of hypoxaemia and hypercapnia. The key elements of management are summarised in Box 16.15.

If these measures prove ineffective, inotropic agents such as dobutamine (2.5–10 µg/kg/min) may be required to augment cardiac output, particularly in hypotensive patients. An intra-aortic balloon pump may be beneficial in patients with acute cardiogenic pulmonary oedema and shock. Following management of the acute episode, additional measures must be used to control heart failure in the longer term, as discussed below.

Management of chronic heart failure

The aims of treatment in chronic heart failure are to improve cardiac function by increasing contractility and coordination of the myocardium, by optimising preload or decreasing afterload, and controlling cardiac rate and rhythm (see Fig. 16.23). This can be achieved by using drug treatments, implantable device therapy, coronary revascularisation, and in resistant cases, mechanical assist devices or cardiac transplantation.

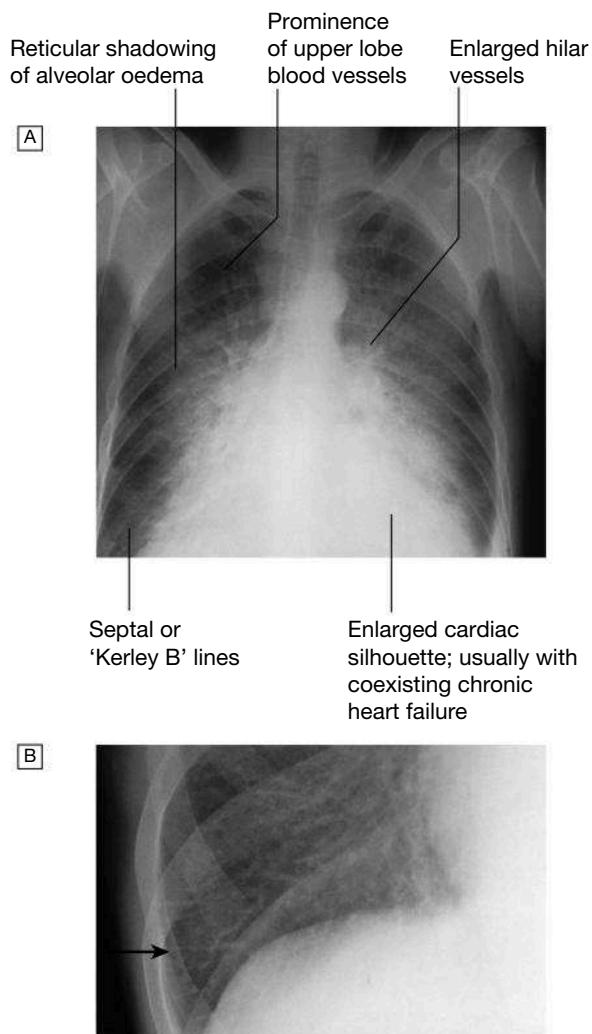


Fig. 16.25 Radiological features of heart failure. **A** Chest X-ray of a patient with pulmonary oedema. **B** Enlargement of lung base showing septal or 'Kerley B' lines (arrow).

16

16.15 Management of acute pulmonary oedema

Action	Effect
Sit the patient up	Reduces preload
Give high-flow oxygen	Corrects hypoxia
Ensure continuous positive airway pressure (CPAP) of 5–10 mmHg by tight-fitting mask	Reduces preload and pulmonary capillary hydraulic gradient
Administer nitrates: IV glyceryl trinitrate (10–200 µg/min) Buccal glyceryl trinitrate 2–5 mg	Reduces preload and afterload
Administer a loop diuretic: Furosemide (50–100 mg IV)	Combats fluid overload

*The dose of nitrate should be titrated upwards every 10 minutes until there is an improvement or systolic blood pressure is <110 mmHg.
(IV = intravenous)

Education

Education of patients and their relatives about the causes and treatment of heart failure can improve adherence to a management plan (Box 16.16). Some patients may need to weigh themselves daily, as a measure of fluid load, and adjust their diuretic therapy accordingly.

i 16.16 General measures for the management of heart failure

Education

- Explanation of nature of disease, treatment and self-help strategies

Diet

- Good general nutrition and weight reduction for the obese
- Avoidance of high-salt foods and added salt, especially for patients with severe congestive heart failure

Alcohol

- Moderation or elimination of alcohol consumption; alcohol-induced cardiomyopathy requires abstinence

Smoking

- Cessation

Exercise

- Regular moderate aerobic exercise within limits of symptoms

Vaccination

- Consideration of influenza and pneumococcal vaccination



16.17 Congestive cardiac failure in old age

- Incidence:** rises with age and affects 5%–10% of those in their eighties.
- Common causes:** coronary artery disease, hypertension and calcific degenerative valvular disease.
- Diastolic dysfunction:** often prominent, particularly in those with a history of hypertension.
- ACE inhibitors and ARBs:** improve symptoms and mortality but are more frequently associated with postural hypotension and renal impairment than in younger patients.
- Loop diuretics:** usually required but may be poorly tolerated in those with urinary incontinence and men with prostate enlargement.

Drug treatment

Many drug treatments are now available for heart failure. Drugs that reduce preload are appropriate in patients with high end-diastolic filling pressures and evidence of pulmonary or systemic venous congestion, whereas those that reduce afterload or increase myocardial contractility are more useful in patients with signs and symptoms of a low cardiac output. Some considerations specific to management of older patients are given in Box 16.17.

Diuretics Diuretics promote urinary sodium and water excretion, leading to a reduction in blood plasma volume, which in turn reduces preload and improves pulmonary and systemic venous congestion. They may also reduce afterload and ventricular volume, leading to a fall in ventricular wall tension and increased cardiac efficiency. Although a fall in preload (ventricular filling pressure) normally reduces cardiac output, patients with heart failure are beyond the apex of the Starling curve, so there may be a substantial and beneficial fall in filling pressure with either no change or an improvement in cardiac output (see Figs. 16.22 and 16.26). Over-diuresis can cause excessive volume depletion, resulting in a fall in cardiac output with hypotension, lethargy and renal failure. This is especially likely in patients with a marked diastolic component to their heart failure.

Oedema may persist, despite oral loop diuretic therapy, in some patients with severe chronic heart failure, particularly if there is renal impairment. Under these circumstances an intravenous infusion of a loop diuretic, such as furosemide (5–10mg/hr), may initiate a diuresis. Combining this with a thiazide diuretic, such as bendroflumethiazide (5mg daily), may augment the diuresis but care must be taken to avoid an excessive fluid loss, hyponatraemia and hypokalaemia.

Cardiac output or ventricular performance

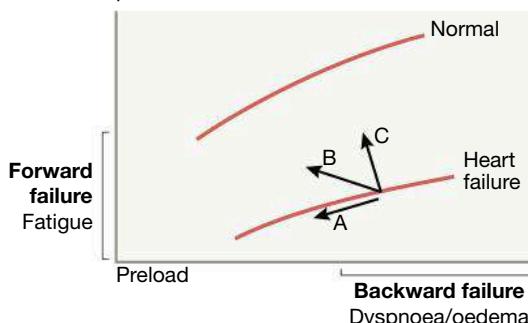


Fig. 16.26 The effect of treatment on ventricular performance curves in heart failure. Diuretics and venodilators (A), angiotensin-converting enzyme (ACE) inhibitors and mixed vasodilators (B), and positive inotropic agents (C).

Mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, are potassium-sparing diuretics that are of particular benefit in patients with heart failure with severe left ventricular systolic dysfunction. They improve long-term clinical outcome in individuals with severe heart failure or heart failure following acute MI but may cause hyperkalaemia, particularly when used with an ACE inhibitor.

Originally developed as a treatment for type 2 diabetes mellitus, sodium-glucose co-transporter 2 (SGLT-2) inhibitors block the resorption of glucose in the nephron of the kidney to cause an osmotic diuresis. Their use is associated with reduced hospitalisations for heart failure and lower mortality in patients with heart failure irrespective of the presence of diabetes. However, they are associated with an increased risk of genitourinary tract infections and diabetic ketoacidosis.

Angiotensin-converting enzyme inhibitors Angiotensin-converting enzyme (ACE) inhibitors play a central role in the management of heart failure since they interrupt the vicious circle of neurohumoral activation that is characteristic of the disease by preventing the conversion of angiotensin I to angiotensin II. This, in turn, reduces peripheral vasoconstriction, activation of the sympathetic nervous system (Fig. 16.27), and salt and water retention due to aldosterone release, as well as preventing the activation of the renin–angiotensin system caused by diuretic therapy.

In moderate and severe heart failure, ACE inhibitors can produce a substantial improvement in effort tolerance and in mortality. They can also improve outcome and prevent the onset of overt heart failure in patients with poor residual left ventricular function following MI.

Adverse effects of ACE inhibitors include hypotension and renal impairment, especially in patients with bilateral renal artery stenosis or those with pre-existing renal disease. An increase in serum potassium concentration may also occur, which can be beneficial in offsetting the hypokalaemia associated with loop diuretic therapy. In stable patients without hypotension (systolic BP over 100mmHg), ACE inhibitors can usually be safely started in the community. In other patients, however, it is usually advisable to withhold diuretics for 24 hours before starting treatment with a small dose of a long-acting agent, preferably given at night (Box 16.18). Renal function and serum potassium must be monitored and should be checked 1–2 weeks after starting therapy.

Angiotensin receptor blockers Angiotensin receptor blockers (ARBs) act by blocking the action of angiotensin II on the heart, peripheral vasculature and kidneys. In heart failure they produce beneficial haemodynamic changes similar to those of ACE inhibitors (see Fig. 16.27) but are generally better tolerated. They have comparable effects on mortality and are a useful alternative for patients who cannot tolerate ACE inhibitors. They should be started at a low dose and titrated upwards, depending on response (see Box 16.18). Unfortunately, they share all the more

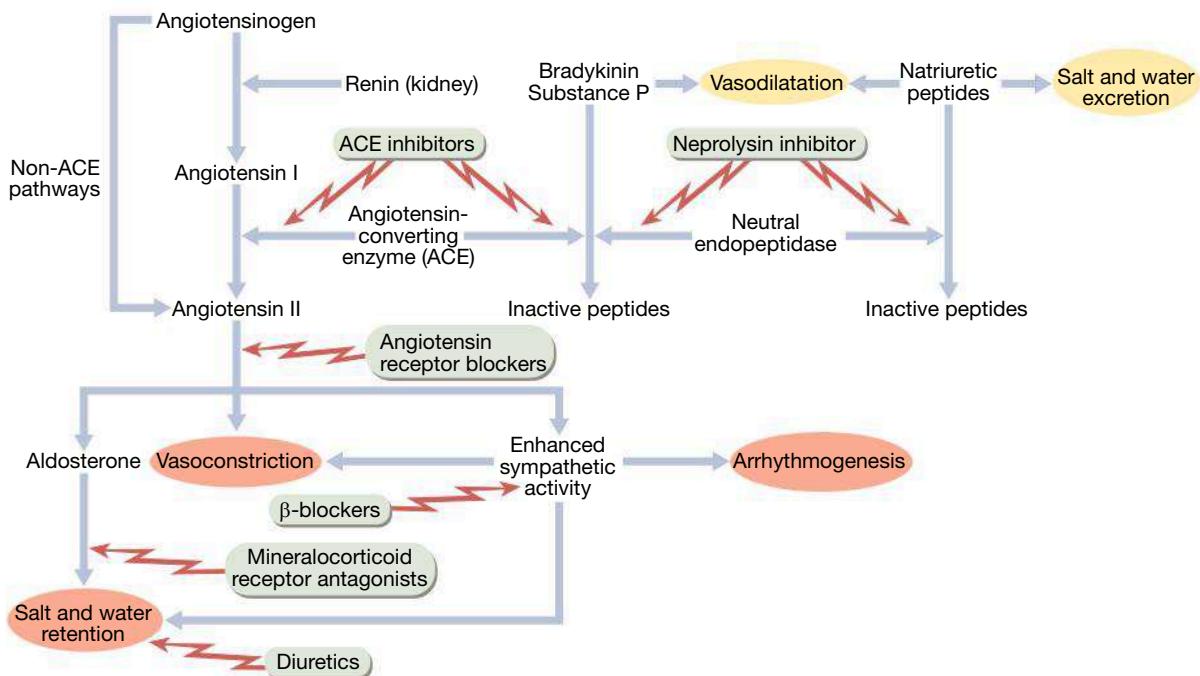


Fig. 16.27 Neurohumoral activation of the renin–angiotensin and sympathetic nervous systems have adverse (red) effects on the cardiovascular system which are counterbalanced by beneficial effects of endogenous natriuretic and vasoactive peptide systems (yellow). Heart failure treatments are targeted at inhibiting the detrimental pathways and enhancing the beneficial compensatory systems.

i**16.18 Dosages of ACE inhibitors, angiotensin receptor blockers, β -blockers and neprilysin inhibitors in heart failure**

	Starting dose	Target dose
ACE inhibitors		
Enalapril	2.5 mg twice daily	10 mg twice daily
Lisinopril	2.5 mg daily	20 mg daily
Ramipril	1.25 mg daily	10 mg daily
Angiotensin receptor blockers		
Losartan	25 mg daily	100 mg daily
Candesartan	4 mg daily	32 mg daily
Valsartan	40 mg daily	160 mg daily
β-blockers		
Bisoprolol	1.25 mg daily	10 mg daily
Metoprolol	25 mg twice daily	100 mg twice daily
Carvedilol	3.125 mg twice daily	25 mg twice daily
Neprilysin inhibitor-ARB		
Sacubitril–valsartan	24/26 mg twice daily	97/103 mg twice daily

serious adverse effects of ACE inhibitors, including renal dysfunction and hyperkalaemia. While ARB are normally used as an alternative to ACE inhibitors, they can be combined in patients with resistant or recurrent heart failure.

Neprilysin inhibitors The only drug currently in this class is sacubitril, a small-molecule inhibitor of neutral endopeptidase, or neprilysin, which is responsible for the breakdown of the endogenous diuretics ANP and BNP as well as vasoactive peptides such as bradykinin and substance P (see Fig. 16.27). If used in combination with the ARB in an initial oral dose of 24 mg sacubitril and 26 mg valsartan daily, it produces additional symptomatic and mortality benefit over ACE inhibition and is increasingly being used in preference to ACE inhibitors in patients with chronic heart failure.

Vasodilators These drugs are valuable in chronic heart failure, when ACE inhibitors or ARBs are contraindicated. Venodilators, such as nitrates, reduce preload. Arterial dilators, such as hydralazine, reduce afterload (see Fig. 16.26). Their use is limited by pharmacological tolerance and hypotension.

Beta-adrenoceptor antagonists (β -blockers) Beta-blockade helps to counteract the deleterious effects of enhanced sympathetic stimulation and reduces the risk of arrhythmias and sudden death. When initiated in standard doses β -blockers may precipitate acute-on-chronic heart failure, but when given in small incremental doses they can increase ejection fraction, improve symptoms, reduce the frequency of hospitalisation and reduce mortality in patients with chronic heart failure. A typical regimen is bisoprolol, starting at 1.25 mg daily and increased gradually over 12 weeks to a target maintenance dose of 10 mg daily. Beta-blockers are more effective at reducing mortality than ACE inhibitors, with a relative risk reduction of 33% versus 20%, respectively.

Ivabradine Ivabradine acts on the I_{f} inward current in the SA node, resulting in reduction of heart rate. Typical dosages are 2.5–5 mg twice daily, increasing to 7.5 mg twice daily if necessary. It reduces hospital admission and mortality rates in patients with heart failure due to moderate or severe left ventricular systolic impairment. In trials, its effects were most marked in patients with a relatively high heart rate (over 77/min), so ivabradine is best suited to patients who cannot take β -blockers or whose heart rate remains high despite β -blockade. It is ineffective in patients with atrial fibrillation.

Digoxin Digoxin in maintenance doses of 0.0625–0.25 mg daily can be used to provide rate control in patients with heart failure and atrial fibrillation. In patients with severe heart failure (NYHA class III–IV, see Box 16.5), digoxin reduces the likelihood of hospitalisation for heart failure, although it has no effect on long-term survival.

Amiodarone This is a potent anti-arrhythmic drug that has little negative inotropic effect and may be valuable in patients with poor left ventricular function. It is effective only in the treatment of symptomatic

arrhythmias and should not be used as a preventative agent in asymptomatic patients. Amiodarone is used for prevention of symptomatic atrial arrhythmias and of ventricular arrhythmias when other pharmacological options have been exhausted.

Non-pharmacological treatments

Implantable cardiac defibrillators These devices are indicated in patients with heart failure who have had, or who are at high risk of, life-threatening ventricular arrhythmias, since they reduce the risk of sudden death.

Cardiac resynchronisation therapy devices In patients with marked conduction system disease, especially left bundle branch block, there is uncoordinated left ventricular contraction which exacerbates heart failure. Cardiac resynchronisation therapy (CRT) uses pacemaker technology to overcome dyssynchronous contraction by pacing the LV and RV simultaneously (Fig. 16.28). This improves cardiac output and is associated with improved symptoms and reduced mortality.

Coronary revascularisation Coronary artery bypass surgery or percutaneous coronary intervention may improve function in areas of the myocardium that are 'hibernating' because of inadequate blood supply, and can be used to treat carefully selected patients with heart failure and coronary artery disease. If necessary, 'hibernating' myocardium can be identified by stress echocardiography and specialised nuclear or magnetic resonance imaging.

Cardiac transplantation Cardiac transplantation is an established and successful treatment for patients with intractable heart failure. Coronary artery disease and dilated cardiomyopathy are the most common indications. The use of transplantation is limited by the efficacy of modern drug and device therapies, as well as the availability of donor hearts, so it is generally reserved for young patients with severe symptoms despite optimal therapy.

Conventional heart transplantation is contraindicated in patients with pulmonary vascular disease due to long-standing left heart failure, complex congenital heart disease such as Eisenmenger syndrome, or primary pulmonary hypertension because the RV of the donor heart may fail in the face of high pulmonary vascular resistance. However, heart-lung transplantation can be successful in patients with Eisenmenger syndrome, and lung transplantation has been used for primary pulmonary hypertension.

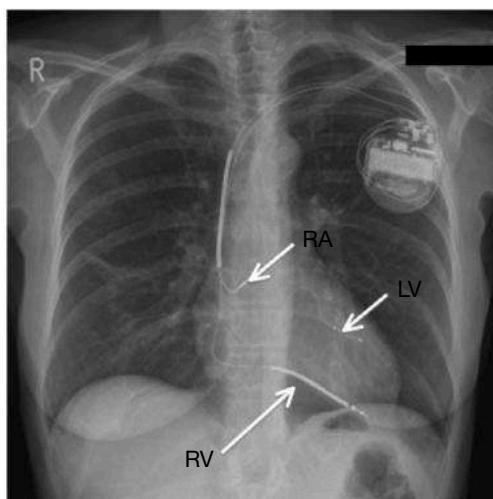


Fig. 16.28 Chest X-ray of a biventricular pacemaker and defibrillator (cardiac resynchronisation therapy). The right ventricular lead (RV) is in position in the ventricular apex and is used for both pacing and defibrillation. The left ventricular lead (LV) is placed via the coronary sinus, and the right atrial lead (RA) is placed in the right atrial appendage; both are used for pacing only.

Although cardiac transplantation usually produces a dramatic improvement in the recipient's quality of life, serious complications may occur:

- **Rejection.** In spite of routine therapy with ciclosporin A, azathioprine and corticosteroids, episodes of rejection are common and may present with heart failure, arrhythmias or subtle ECG changes. Cardiac biopsy is often used to confirm the diagnosis before starting treatment with high-dose corticosteroids.
- **Accelerated atherosclerosis.** Recurrent heart failure is often due to progressive atherosclerosis in the coronary arteries of the donor heart. This is not confined to patients who underwent transplantation for coronary artery disease and is probably a manifestation of chronic rejection. Angina is rare because the heart has been denervated.
- **Infection.** Opportunistic infection with organisms such as cytomegalovirus or *Aspergillus* remains a major cause of death in transplant recipients.

Ventricular assist devices Because of the limited supply of donor organs, ventricular assist devices (VAD) may be employed as a bridge to cardiac transplantation and as short-term restoration therapy following a potentially reversible insult such as viral myocarditis. In some patients, VADs may be used as a long-term therapy if no other options exist.

These devices assist cardiac output by using a roller, centrifugal or pulsatile pump that, in some cases, is implantable and portable. They withdraw blood through cannulae inserted in the atria or ventricular apex and pump it into the pulmonary artery or aorta. They are designed not only to unload the ventricles but also to provide support to the pulmonary and systemic circulations. Their more widespread application is limited by high complication rates (haemorrhage, systemic embolism, infection, neurological and renal sequelae), although some improvements in survival and quality of life have been demonstrated in patients with severe heart failure.

Cardiac arrhythmias

A cardiac arrhythmia is defined as a disturbance of the electrical rhythm of the heart. Arrhythmias are often a manifestation of structural heart disease but may also occur because of abnormal conduction or depolarisation in an otherwise healthy heart. There are many types of cardiac arrhythmia, as discussed later in this section. By convention, however, a heart rate of more than 100/min is a tachycardia, and a heart rate of less than 60/min is a bradycardia.

Pathogenesis

Arrhythmias usually occur as the result of pathology affecting the conduction system of the heart. The cardiac cycle is normally initiated by spontaneous depolarisation in the SA node. The atria and ventricles then activate sequentially as the depolarisation wave passes through specialised conducting tissues (see Fig. 16.4). The SA node acts as a pacemaker and its intrinsic rate is regulated by the autonomic nervous system; parasympathetic (vagal) activity decreases the heart rate and sympathetic activity increases it via cardiac sympathetic nerves and circulating catecholamines.

There are three main mechanisms of tachycardia:

- **Increased automaticity.** The tachycardia is produced by spontaneous depolarisation of an ectopic focus in the atria, atrioventricular junction or ventricles, often in response to catecholamines. Single depolarisations lead to atrial, junctional or ventricular premature (ectopic) beats. Repeated depolarisation leads to atrial, junctional or ventricular tachycardia.
- **Re-entry.** The tachycardia is initiated by an ectopic beat and sustained by a re-entry circuit (Fig. 16.29). Most tachyarrhythmias are caused by re-entry.
- **Triggered activity.** This can cause ventricular arrhythmias in patients with coronary artery disease. It is a form of secondary depolarisation

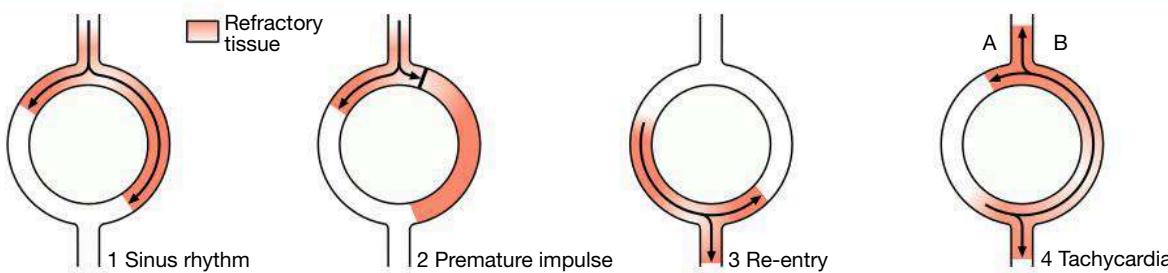


Fig. 16.29 The mechanism of re-entry. Re-entry can occur when there are two alternative pathways with different conducting properties, such as the atrioventricular node and an accessory pathway, or an area of normal and an area of ischaemic tissue. Here, pathway A conducts slowly and recovers quickly, while pathway B conducts rapidly and recovers slowly. (1) In sinus rhythm, each impulse passes down both pathways before entering a common distal pathway. (2) As the pathways recover at different rates, a premature impulse may find pathway A open and B closed. (3) Pathway B may recover while the premature impulse is travelling selectively down pathway A. The impulse can then travel retrogradely up pathway B, setting up a closed loop or re-entry circuit. (4) This may initiate a tachycardia that continues until the circuit is interrupted by a change in conduction rates or electrical depolarisation.

arising from an incompletely repolarised cell membrane. Arrhythmias may be supraventricular (sinus, atrial or junctional) or ventricular in origin.

Supraventricular rhythms usually produce narrow QRS complexes because the ventricles are depolarised in their normal sequence via the AV node, the bundle of His, bundle branches and Purkinje fibres. In contrast, ventricular arrhythmias often produce broad, bizarre QRS complexes because the ventricles are activated in sequence rather than in parallel, and activation occurs via myocardial cells rather than the rapidly conducting Purkinje fibres. Occasionally, supraventricular tachycardia can mimic ventricular tachycardia and present as a broad-complex tachycardia due to coexisting bundle branch block or the presence of an additional atrioventricular connection (accessory pathway, see below).

Bradycardia is caused by either reduced automaticity of the SA node or impaired conduction through the AV node or His-Purkinje system. If the sinus rate becomes unduly slow, another, more distal part of the conducting system may assume the role of pacemaker. This is known as an escape rhythm and may arise in the AV node or His bundle (junctional rhythm) or in the ventricles (idioventricular rhythm).

Clinical features

Many arrhythmias are asymptomatic but sustained tachycardias typically present with rapid palpitation. Dizziness, chest discomfort or breathlessness may also occur. Extreme tachycardias can also cause syncope because the heart is unable to fill properly at extreme rates. Bradycardias tend to cause symptoms of low cardiac output, including fatigue, light-headedness and syncope. Extreme bradycardias or tachycardias can precipitate sudden death or cardiac arrest.

Investigations

The first-line investigation is a 12-lead ECG, which can be diagnostic in many cases. If arrhythmias are intermittent and the resting ECG is normal, an attempt should be made to capture the abnormal rhythm using an ambulatory ECG or a patient-activated ECG.

Management

Features of individual arrhythmias are discussed below. Management depends on the nature of the arrhythmia and the general principles of medical management are discussed later in this chapter.

Sinus arrhythmia

This is defined as a cyclical alteration of the heart rate during respiration, with an increase during inspiration and a decrease during expiration. Sinus arrhythmia is a normal phenomenon and can be quite pronounced in children. Absence of heart rate variation with breathing or with changes in

posture may be a feature of diabetic neuropathy autonomic neuropathy or increased sympathetic drive. Sinus arrhythmia does not require treatment.

Sinus bradycardia

This may occur in healthy people at rest and is a common finding in athletes. Some pathological causes are listed in Box 16.19. If sinus bradycardia is asymptomatic, then no treatment is required. Symptomatic sinus bradycardia may occur acutely during an MI and can be treated with intravenous atropine (0.6–1.2 mg). Patients with recurrent or persistent symptomatic sinus bradycardia should be considered for permanent pacemaker implantation.

Sinus tachycardia

Sinus tachycardia is usually due to an increase in sympathetic activity associated with exercise or emotion. Healthy young adults can produce a rapid sinus rate, up to 200/min, during intense exercise. Sinus tachycardia usually does not require treatment but sometimes may reflect an underlying disease, as summarised in Box 16.19.

Sinoatrial disease

Sinoatrial disease or 'sick sinus syndrome' can occur at any age but is most common in older people. It is caused by degenerative changes in the SA node and is characterised by a variety of arrhythmias (Box 16.20). The typical presentation is with palpitation, dizzy spells or syncope, due to intermittent tachycardia, bradycardia, or pauses in sinus rhythm with no atrial or ventricular activity (Fig. 16.30).

In sinoatrial disease, a permanent pacemaker improves symptoms but not prognosis so is not indicated in asymptomatic patients. It is used in

i 16.19 Some pathological causes of sinus bradycardia and tachycardia

Sinus bradycardia

- Myocardial infarction
- Sinus node disease (sick sinus syndrome)
- Hypothermia
- Hypothyroidism
- Cholestatic jaundice
- Raised intracranial pressure
- Drugs (β -blockers, digoxin, verapamil)

Sinus tachycardia

- Anxiety
- Fever
- Anaemia
- Heart failure
- Thyrotoxicosis
- Phaeochromocytoma
- Drugs (β -agonists)

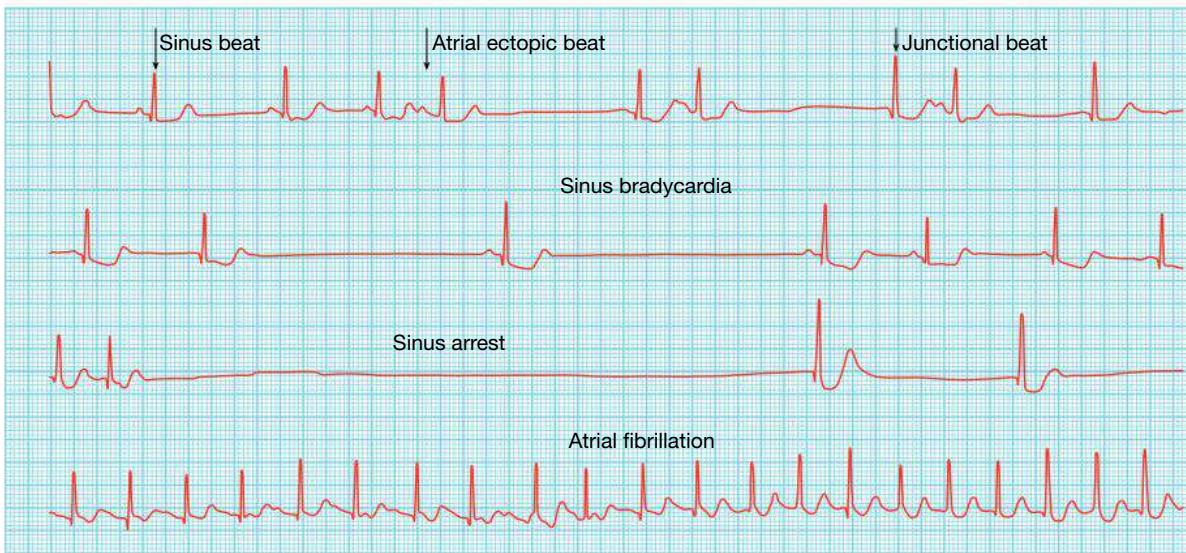


Fig. 16.30 Sinoatrial disease (sick sinus syndrome). A continuous rhythm strip from a 24-hour ECG tape recording illustrating periods of sinus rhythm, atrial ectopics, junctional beats, sinus bradycardia, sinus arrest and paroxysmal atrial fibrillation.

i

16.20 Common features of sinoatrial disease

- Sinus bradycardia
- Sinoatrial block (sinus arrest)
- Paroxysmal atrial fibrillation
- Paroxysmal atrial tachycardia
- Atrioventricular block



Fig. 16.31 First-degree atrioventricular block. The PR interval is prolonged and measures 0.32 sec.

patients with symptomatic bradycardia, including bradycardia induced by drugs required to prevent tachyarrhythmias. A dual-chamber pacemaker is normally used (see p. 422). The right atrial lead is used to assist the SA node, and the right ventricular lead is a backup in case AV nodal block occurs later on.

Atrioventricular block

This usually occurs as the result of disease affecting the AV node. AV block can be intermittent, however, and may become evident only when the conducting tissue is stressed by a rapid atrial rate. Reflecting this fact, atrial tachyarrhythmias are often associated with AV block (see Fig. 16.36). Episodes of ventricular asystole may also complicate complete heart block or Mobitz type II second-degree AV block. Several types of AV block are recognised.

First-degree atrioventricular block

In this condition, AV conduction is delayed and so the PR interval is prolonged (> 0.20 sec; Fig. 16.31). It rarely causes symptoms and does not usually require treatment.

Second-degree atrioventricular block

Here dropped beats occur because some impulses from the atria fail to conduct to the ventricles. Two subtypes are recognised. In Mobitz type I second-degree AV block (Fig. 16.32), there is progressive lengthening of successive PR intervals, culminating in a dropped beat. The cycle then repeats itself. This is known as the Wenckebach phenomenon and is usually due to impaired conduction in the AV node itself. The phenomenon may be physiological and is sometimes observed at rest or during sleep in athletic young adults with high vagal tone.

In Mobitz type II second-degree AV block (Fig. 16.33), the PR interval of the conducted impulses remains constant but some P waves are not conducted. This is usually caused by disease of the His–Purkinje system and carries a risk of asystole.

In 2:1 AV block (Fig. 16.34), alternate P waves are not conducted, so it is impossible to distinguish between Mobitz type I and type II block.

Third-degree atrioventricular block

In third-degree AV block, conduction fails completely and the atria and ventricles beat independently. This is known as AV dissociation, as shown in Fig. 16.35. Ventricular activity is maintained by an escape rhythm arising in the AV node or bundle of His (narrow QRS complexes) or the distal Purkinje tissues (broad QRS complexes). Distal escape rhythms tend to be slower and less reliable. Complete AV block (Box 16.21) produces a slow (25–50/min), regular pulse that does not vary with exercise, except in the case of congenital complete AV block. There is usually a compensatory increase in stroke volume, producing a large-volume pulse. Cannon waves may be visible in the neck and the intensity of the first heart sound varies due to the loss of AV synchrony.

Clinical features

The typical presentation is with recurrent syncope or ‘Stokes–Adams’ attacks. These episodes are characterised by sudden loss of consciousness that occurs without warning and results in collapse. A brief anoxic seizure (due to cerebral ischaemia) may occur if there is prolonged asystole. There is pallor and a death-like appearance during the attack, but when the heart starts beating again there is a characteristic flush. In distinction to epilepsy, recovery is rapid. Sinoatrial disease and neurocardiogenic syncope (p. 184) may cause similar symptoms.

Management

This depends on the clinical circumstances. Inferior ST elevation MI is sometimes complicated by transient AV block because the right coronary artery (RCA) supplies the AV node. There is usually a reliable



Fig. 16.32 Second-degree atrioventricular block (Mobitz type I – the Wenckebach phenomenon). The PR interval progressively increases until a P wave is not conducted. The cycle then repeats itself. In this example, conduction is at a ratio of 4:3, leading to groupings of three ventricular complexes in a row.



Fig. 16.33 Second-degree atrioventricular block (Mobitz type II). The PR interval of conducted beats is normal but some P waves are not conducted. The constant PR interval distinguishes this from the Wenckebach phenomenon.



Fig. 16.34 Second-degree atrioventricular block with fixed 2:1 block. Alternate P waves are not conducted. This may be due to Mobitz type I or II block.

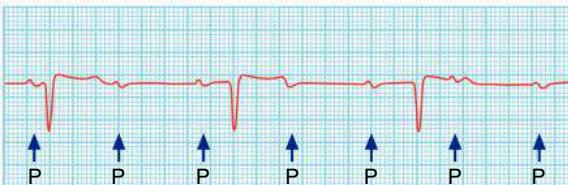


Fig. 16.35 Complete (third-degree) atrioventricular block. There is complete dissociation of atrial and ventricular complexes. The atrial rate is 80/min and the ventricular rate is 38/min.



16.21 Causes of complete atrioventricular block

Congenital

Acquired

- Idiopathic fibrosis
- Myocardial infarction/ischaemia
- Inflammation:
 - Infective endocarditis
 - Sarcoidosis
 - Chagas' disease
- Trauma
- Drugs:
 - Digoxin
 - β -blockers
 - Calcium antagonists

Second- or third-degree AV heart block complicating acute anterior MI indicates extensive ventricular damage involving both bundle branches and carries a poor prognosis. Asystole may ensue and a temporary pacemaker should be inserted promptly. If the patient presents with asystole, intravenous atropine (3mg) or intravenous isoprenaline (2mg in 500mL 5% dextrose, infused at 10–60mL/hr) may help to maintain the circulation until a temporary pacing electrode can be inserted. Temporary pacing can provide effective rhythm support in the short term.

Patients with symptomatic bradyarrhythmias associated with AV block should be treated with a permanent pacemaker. Asymptomatic first-degree or Mobitz type I second-degree AV block (Wenckebach phenomenon) does not require treatment but may be an indication of underlying heart disease. A permanent pacemaker is usually indicated in patients with asymptomatic Mobitz type II second-degree AV block or third-degree AV heart block because of the risk of asystole and sudden death. Pacing improves prognosis.

Bundle branch block

Damage to the right or left bundle branch of the conducting system can occur as a result of many pathologies, including ischaemic heart disease, hypertensive heart disease and cardiomyopathy. However, right bundle branch block (RBBB) can occur as a normal variant in healthy individuals (Box 16.22). In left bundle branch block (LBBB) and RBBB, depolarisation proceeds through a slow myocardial route in the affected ventricle rather than through the rapidly conducting Purkinje tissues that constitute the bundle branches. This causes delayed conduction into the LV or RV, broadens the QRS complex (≥ 0.12 sec) and produces characteristic alterations in QRS morphology (Figs. 16.36 and 16.37). Damage to the left bundle can also occur after it divides into anterior and posterior fascicles, when it is called hemiblock. In this case, the QRS complex is not broad but the direction of ventricular depolarisation is changed, causing left axis deviation in left anterior hemiblock and right axis deviation in left posterior hemiblock (see Fig. 16.7). The combination of RBBB and left anterior or posterior hemiblock is known as bifascicular block. LBBB usually signifies important underlying heart disease and also causes ventricular incoordination, which may aggravate symptoms in patients with heart failure. This can be treated in selected patients by cardiac resynchronisation therapy.

Atrial ectopic beats

Atrial ectopic beats usually cause no symptoms but can give the sensation of a missed beat or an abnormally strong beat. The ECG (Fig. 16.39)

escape rhythm and, if the patient remains well, no treatment is required. Symptomatic second- or third-degree AV block may respond to atropine (0.6mg IV, repeated as necessary) or, if this fails, a temporary pacemaker. In most cases, the AV block will resolve within 7–10 days.

i	16.22 Common causes of bundle branch block
Right bundle branch block	<ul style="list-style-type: none"> Normal variant Right ventricular hypertrophy or strain, e.g. pulmonary embolism Congenital heart disease, e.g. atrial septal defect Coronary artery disease
Left bundle branch block	<ul style="list-style-type: none"> Coronary artery disease Hypertension Aortic valve disease Cardiomyopathy

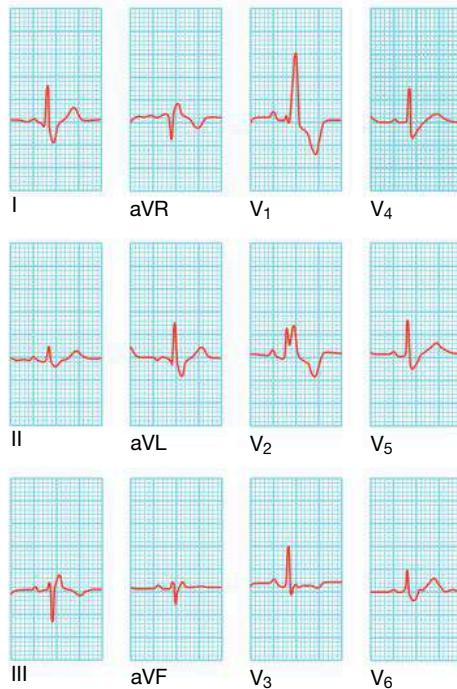


Fig. 16.36 Right bundle branch block. Note the wide QRS complexes with 'M'-shaped configuration in leads V_1 and V_2 and a wide S wave in lead I.

shows a premature but otherwise normal QRS complex; if visible, the preceding P wave has a different morphology because the atria activate from an abnormal site. In most cases these are of no consequence, although very frequent atrial ectopic beats may herald the onset of atrial fibrillation. Treatment is rarely necessary but β -blockers can be used if symptoms are intrusive.

Atrial tachycardia

Atrial tachycardia may be a manifestation of increased atrial automaticity, sinoatrial disease or digoxin toxicity. It produces a narrow-complex tachycardia with abnormal P-wave morphology, sometimes associated with AV block if the atrial rate is rapid. It may respond to β -blockers, which reduce automaticity, or class I or III anti-arrhythmic drugs (see Box 16.30). The ventricular response in rapid atrial tachycardias may be controlled by AV node-blocking drugs. Catheter ablation (p. 423) can be used to target the ectopic site and should be offered as an alternative to anti-arrhythmic drugs in patients with recurrent atrial tachycardia.

Atrial flutter

Atrial flutter is characterised by a large (macro) re-entry circuit, usually within the right atrium encircling the tricuspid annulus. The atrial rate is approximately 300/min, and is usually associated with 2:1, 3:1 or 4:1 AV

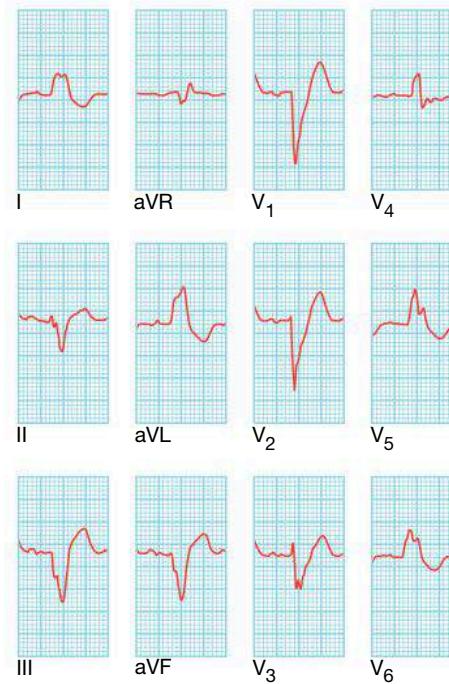


Fig. 16.37 Left bundle branch block. Note the wide QRS complexes with loss of the Q wave or septal vector in lead I and 'M'-shaped QRS complexes in V_5 and V_6 .



Fig. 16.38 Atrial ectopic beats. The first, second and fifth complexes are normal sinus beats. The third, fourth and sixth complexes are atrial ectopic beats with identical QRS complexes and abnormal (sometimes barely visible) P waves.

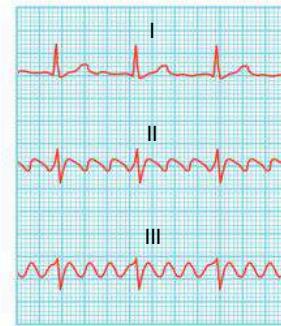


Fig. 16.39 Atrial flutter. Simultaneous recording showing atrial flutter with 4:1 atrioventricular block. Flutter waves are visible only in leads II and III.

block (with corresponding heart rates of 150, 100 or 75/min). Rarely, in young patients, every flutter wave is conducted, producing a rate of 300/min and, potentially, haemodynamic compromise. The ECG shows saw-tooth flutter waves (Fig. 16.39). When there is regular 2:1 AV block, it may be difficult to identify flutter waves that are buried in QRS complexes and T waves. Atrial flutter should be suspected when there is a narrow-complex tachycardia of 150/min. Carotid sinus pressure or intravenous adenosine may help to establish the diagnosis by temporarily increasing the degree of AV block and revealing flutter waves (Fig. 16.40).

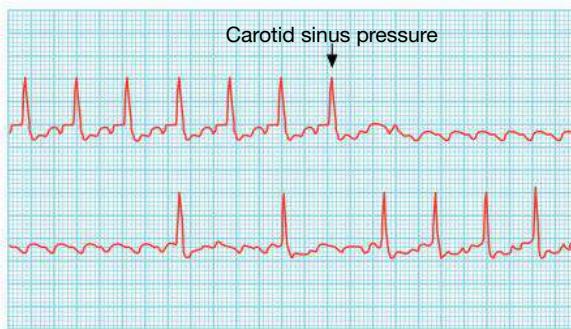


Fig. 16.40 Carotid sinus pressure in atrial flutter: continuous trace. The diagnosis of atrial flutter with 2:1 block was established when carotid sinus pressure produced temporary atrioventricular block, revealing the flutter waves.

Management

Atrial flutter can be managed by either 'rate control' or 'rhythm control'. Rate control uses AV node-blocking drugs, such as β -blockers, verapamil or digoxin at the dosages shown in [Box 16.30](#), to control the ventricular rate. In most cases rhythm control is preferable. This can be achieved by either direct current (DC) cardioversion, or catheter ablation. DC cardioversion is associated with a high recurrence rate even when drugs, such as β -blockers or amiodarone, are used afterwards. Class Ic anti-arrhythmic drugs, such as flecainide, are contraindicated because they can produce a paradoxical extreme tachycardia and haemodynamic compromise. Catheter ablation offers a greater than 90% chance of permanent cure and is the treatment of choice for patients with persistent symptoms. Anticoagulant management in patients with atrial flutter, including management around cardioversion, is identical to that of patients with atrial fibrillation.

Atrial fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with an overall prevalence of 0.5% in the adult population of the UK. The prevalence rises with age, affecting 1% of those aged 60–64 years, increasing to 9% of those aged over 80 years. It is associated with significant morbidity and a twofold increase in mortality. This is mainly because of its association with underlying heart disease but also because of its association with systemic embolism and stroke.

Pathogenesis

AF is a complex arrhythmia characterised by both abnormal automatic firing and the presence of multiple interacting re-entry circuits within the atria. Episodes of AF are initiated by rapid bursts of ectopic beats arising from conducting tissue in the pulmonary veins or from diseased atrial tissue. It becomes sustained because of re-entrant conduction within the atria or sometimes because of continuous ectopic firing ([Fig. 16.41](#)). Re-entry is more likely to occur in atria that are enlarged or in which conduction is slow, as is the case in many forms of heart disease. During episodes of AF, the atria beat rapidly but in an uncoordinated and ineffective manner. The ventricles are activated irregularly at a rate determined by conduction through the AV node. This produces the characteristic 'irregularly irregular' pulse. The ECG ([Fig. 16.42](#)) shows normal but irregular QRS complexes; there are no P waves but the baseline may show irregular fibrillation waves. Commonly, AF is classified as paroxysmal (intermittent episodes that self-terminate within 7 days), persistent (prolonged episodes that can be terminated by electrical or pharmacological cardioversion) or permanent. It can be difficult to identify what type of AF patients have at first presentation but this usually becomes clearer as time progresses. Unfortunately for many patients, paroxysmal AF becomes permanent as the underlying disease process progresses. This is partly because of electrophysiological changes that occur in the atria within a few hours of the onset of AF and which tend to maintain fibrillation: a

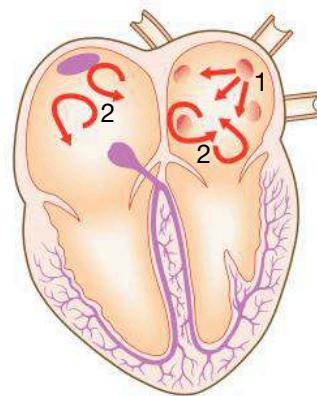


Fig. 16.41 Mechanisms initiating atrial fibrillation. (1) Ectopic beats, often arising from the pulmonary veins, trigger atrial fibrillation. (2) Re-entry within the atria maintains atrial fibrillation, with multiple interacting re-entry circuits operating simultaneously.



Fig. 16.42 Two examples of atrial fibrillation. The QRS complexes are irregular and there are no P waves. **A** There is usually a fast ventricular rate, between 120 and 160/min, at the onset of atrial fibrillation. **B** In chronic atrial fibrillation, the ventricular rate may be much slower, due to the effects of medication and AV nodal fatigue.

process called electrical remodelling. When AF persists for a period of months, structural remodelling also occurs, leading to atrial fibrosis and dilatation that predispose to chronicity of the AF. Early treatment of AF can sometimes prevent the arrhythmia from becoming persistent.

Many forms of heart disease can present with AF ([Box 16.23](#)), particularly those that are associated with enlargement or dilatation of the atria. Alcohol excess, hyperthyroidism and chronic lung disease are also common causes of AF, although multiple predisposing factors may coexist, such as the combination of alcohol, hypertension and coronary artery disease. About 50% of all patients with paroxysmal AF and 20% of patients with persistent or permanent AF have structurally normal hearts; this is known as 'lone atrial fibrillation'. Aspects of atrial fibrillation that pertain particularly to old age are listed in [Box 16.24](#).

Clinical features

The typical presentation is with palpitation, breathlessness and fatigue. In patients with poor ventricular function or valve disease, AF may precipitate or aggravate cardiac failure because of loss of atrial function and heart rate control. A fall in BP may cause lightheadedness, and chest pain may occur with underlying coronary artery disease, sometimes accompanied by ST segment and T-wave abnormalities on the ECG, and troponin elevation. In older patients, AF may not be associated with a rapid ventricular rate and may be asymptomatic, only to be discovered as a result of a routine examination or an ECG. Asymptomatic AF may also present with systemic embolism and is a major cause of stroke in older people.

Investigations

Assessment of patients with newly diagnosed AF should include a full history, physical examination, a 12-lead ECG, echocardiogram and thyroid function tests to exclude thyrotoxicosis. The echocardiogram is used to identify any structural heart disease, particularly mitral valve disease.



16.23 Common causes of atrial fibrillation

- Coronary artery disease (including acute MI)
- Valvular heart disease, especially rheumatic mitral valve disease
- Hypertension
- Sinoatrial disease
- Hyperthyroidism
- Alcohol
- Cardiomyopathy
- Congenital heart disease
- Chest infection
- Pulmonary embolism
- Pericardial disease
- Idiopathic (lone atrial fibrillation)



16.24 Atrial fibrillation in old age

- **Prevalence:** rises with age, reaching 9% in those over 80 years.
- **Symptoms:** sometimes asymptomatic but often accompanied by diastolic heart failure.
- **Hyperthyroidism:** atrial fibrillation may emerge as the dominant feature of otherwise silent or occult hyperthyroidism.
- **Cardioversion:** followed by high rates (~70% at 1 year) of recurrent atrial fibrillation.
- **Stroke:** atrial fibrillation is an important cause of cerebral embolism, found in 15% of all stroke patients and 2%–8% of those with transient ischaemic attacks (TIAs).
- **Anticoagulation:** although the risk of thromboembolism rises, the hazards of anticoagulation also become greater with age because of increased comorbidity, particularly cognitive impairment and falls.
- **Direct oral anticoagulants:** alternatives to warfarin. No blood monitoring is required, there are fewer drug interactions, and fixed dosing may aid adherence. Renal impairment affects dosing, for example apixaban dose is reduced from 5 mg twice daily to 2.5 mg twice daily if two or more of the following apply: serum creatinine more than 132 µmol/L, age 80 years or greater, weight 60 kg or less.
- **Warfarin:** in those over 75 years, care should be taken to maintain an INR (International Normalised Ratio) below 3.0 because of the increased risk of intracranial haemorrhage.

Management

Management depends on whether the AF is transient or persistent and whether there is a clear precipitating factor. When AF complicates an acute illness such as a chest infection or pulmonary embolism, treatment of the underlying disorder will often restore sinus rhythm. Where AF does not resolve, the choice lies between rate control or rhythm control. Stroke risk stratification and prevention are the most important issues in managing atrial fibrillation. Management of paroxysmal and persistent AF is discussed below.

Paroxysmal atrial fibrillation

Occasional attacks of AF that are well tolerated do not require treatment. Beta-blockers are normally used as first-line therapy if symptoms are troublesome, since they reduce the ectopic firing that normally initiates the arrhythmia. They are particularly useful for treating patients with AF associated with coronary artery disease, hypertension and cardiac failure. Class Ic drugs (see Box 16.30), such as propafenone or flecainide, are also effective at preventing episodes but should not be given to patients with coronary artery disease or left ventricular dysfunction. Flecainide is seldom used alone, since it can precipitate atrial flutter, and is usually prescribed with a rate-limiting β-blocker. Class III drugs can also be used; amiodarone is the most effective agent for preventing AF but side-effects restrict its use to when other measures fail. Dronedarone is an effective alternative but is contraindicated in patients with heart failure or significant left ventricular impairment. Calcium channel blockers, such as diltiazem (200–400 mg daily), are sometimes used to prevent atrial fibrillation but they are not as effective.

Catheter ablation can be considered as an alternative to anti-arrhythmic drug therapy. Ablation targets the left atrial to pulmonary venous connections, preventing ectopic triggering of AF. In addition, lines of conduction block can be created within the atria to prevent re-entry. Ablation

prevents AF in approximately 75% of patients, although a repeat procedure is sometimes required before this is achieved. There is emerging evidence that ablation may improve prognosis in some patients with AF and heart failure. Ablation for AF is an attractive treatment but is not risk-free, and may be complicated by cardiac tamponade, stroke, phrenic nerve injury and, rarely, pulmonary vein stenosis.

Persistent atrial fibrillation

There are two options for treating persistent AF – rate control or rhythm control. With both options prophylaxis against thromboembolism is required on either a short-term or long-term basis.

Rhythm control Restoration of sinus rhythm is appropriate if the arrhythmia causes troublesome symptoms and if there is a treatable underlying cause. Electrical DC cardioversion or pharmacological cardioversion may be used. Cardioversion is initially successful in most patients but relapse is frequent (25%–50% at 1 month and 70%–90% at 1 year). Attempts to restore and maintain sinus rhythm are most successful if AF has been present for less than 3 months, the patient is young and there is no important structural heart disease.

Immediate cardioversion is appropriate if AF has been present for less than 48 hours. In stable patients with no history of structural heart disease, intravenous flecainide (2 mg/kg over 30 mins, maximum dose 150 mg) can be used and will restore sinus rhythm in 75% of patients within 8 hours. In patients with structural or ischaemic heart disease, intravenous amiodarone can be given through a central venous catheter. DC cardioversion may also be used but requires deep sedation or general anaesthesia. If AF has been present for 48 hours or longer, or if there is doubt about its duration, DC cardioversion should be deferred until the patient has been established on effective oral anticoagulation for a minimum of 4 weeks and any underlying problems, such as hypertension or alcohol excess, have been corrected. Prophylactic treatment with amiodarone can reduce the risk of recurrence. Catheter ablation is sometimes used to restore and to maintain sinus rhythm in persistent AF but is a less effective treatment than for paroxysmal AF.

Rate control If sinus rhythm cannot be restored, treatment should be directed at controlling the heart rate. Beta-blockers, rate-limiting calcium antagonists, such as verapamil or diltiazem (see Box 16.29 and Fig. 16.49), and digoxin all reduce the ventricular rate by slowing AV conduction. This alone may produce a striking improvement in cardiac function, particularly in patients with mitral stenosis. Beta-blockers and rate-limiting calcium antagonists are more effective than digoxin at controlling the heart rate during exercise and have additional benefits in patients with hypertension or structural heart disease. Combination therapy with digoxin and a β-blocker can help with rate control but calcium channel antagonists should not be used with β-blockers because of the risk of bradycardia.

In exceptional cases, poorly controlled and symptomatic AF can be treated by implanting a permanent pacemaker and then deliberately inducing complete AV nodal block with catheter ablation. This is known as the ‘pace and ablate’ strategy.

Prevention of thromboembolism and stroke Loss of atrial contraction and left atrial dilatation cause stasis of blood in the LA and may lead to thrombus formation in the left atrial appendage. This predisposes patients to stroke and systemic embolism. Patients undergoing cardioversion for AF of greater than 48 hours' duration require temporary anticoagulation to reduce these risks. Direct oral anticoagulants or warfarin may be used. Anticoagulation should be started for at least 4 weeks before cardioversion and should be maintained for at least 3 months following successful cardioversion.

In patients with AF, the annual risk of stroke is influenced by many factors and a decision has to be made in which the risk of stroke is balanced against the risk of bleeding with anticoagulation. Patients with AF secondary to mitral valve disease should always be anticoagulated

because the risk is so high. In other patients, clinical scoring systems can be used to assess the risk of stroke and bleeding. The risk of stroke is usually assessed by the CHA₂DS₂-VASc score (Box 16.25), and the HAS-BLED score can be used to estimate the bleeding risk (Box 16.26). Patients with a HAS-BLED score of 3 or more points may require more careful monitoring if anticoagulated.

In patients with paroxysmal AF, stroke risk is similar to that in patients with persistent AF when adjusted for CHA₂DS₂-VASc score. The risk of embolism is only weakly related to the frequency and duration of AF episodes, so stroke prevention guidelines do not distinguish between those with paroxysmal, persistent and permanent AF.

Several agents can be used to reduce stroke risk in AF. The factor Xa inhibitors rivaroxaban, apixaban and edoxaban, and the direct thrombin inhibitor dabigatran (collectively referred to as direct-acting oral anticoagulants, or DOACs) have largely replaced warfarin for stroke prevention in AF. These drugs are described in more detail in Chapter 25. They are at least as effective at preventing thrombotic stroke and are generally associated with a lower risk of intracranial haemorrhage. Other advantages include the lack of requirement for monitoring and the fact that they have fewer drug and food interactions. They should be considered in patients with AF and CHA₂DS₂-VASc score of 1 or more (male), or 2 or more (female). Stroke risk is reduced by around two-thirds, with an annual major bleeding risk of around 1%. Risk factors for bleeding include active peptic ulcer disease, uncontrolled hypertension, alcohol misuse and frequent falls. Agents that reverse the effects of DOACs have been developed. These include idarucizumab, which binds to dabigatran, and andexanet alfa, which binds to apixaban and rivaroxaban.

Warfarin can be used, adjusted to a target INR (International Normalised Ratio) of 2.0–3.0. If bleeding does occur in warfarin-treated patients, anticoagulation can be reversed by administering vitamin K or clotting factors.

Aspirin should not be used since it has little or no effect on embolic stroke and is associated with significant bleeding risk.

Supraventricular tachycardia

The term supraventricular tachycardia (SVT) describes a group of regular tachycardias that have a similar appearance on ECG. These are usually narrow-complex tachycardias and are characterised by a re-entry circuit or automatic focus involving the atria. The three principal types are atrioventricular nodal re-entrant tachycardia (AVNRT), atrioventricular re-entrant tachycardia (AVRT) and atrial tachycardia. The term SVT is not strictly accurate as, in many cases, the ventricles also form part of the re-entry circuit.

Atrioventricular nodal re-entrant tachycardia

Atrioventricular nodal re-entrant tachycardia (AVNRT) is a type of SVT caused by re-entry in a circuit involving the AV node and its two right atrial input pathways: a superior ‘fast’ pathway and an inferior ‘slow’ pathway (see Fig. 16.44A). This produces a regular tachycardia with a rate of 120–240/min. It tends to occur in the absence of structural heart disease and episodes may last from a few seconds to many hours. The patient is usually aware of a rapid, very forceful, regular heart beat and may experience chest discomfort, lightheadedness or breathlessness. Polyuria, mainly due to the release of ANP, is sometimes a feature. The ECG (Fig. 16.43) usually shows a tachycardia with normal QRS complexes but occasionally there may be rate-dependent bundle branch block.

Management

Treatment is not always necessary. However, an acute episode may be terminated by carotid sinus pressure or by the Valsalva manoeuvre. Adenosine (3–12mg rapidly IV in incremental doses until tachycardia stops) or verapamil (5mg IV over 1 min) will restore sinus rhythm in most cases. Intravenous β-blocker or flecainide can also be used. In rare

16.25 CHA₂DS₂-VASc stroke risk scoring system for non-valvular atrial fibrillation

Parameter	Score
C	Congestive heart failure 1 point
H	Hypertension history 1 point
A₂	Age ≥ 75 years 2 points
D	Diabetes mellitus 1 point
S₂	Previous stroke or transient ischaemic attack (TIA) 2 points
V	Vascular disease 1 point
A	Age 65–74 years 1 point
Sc	Sex category female 1 point
	Maximum total score 9 points
Annual stroke risk	
0 points = 0% (no prophylaxis required)	
1 point = 1.3% (oral anticoagulant recommended in males only)	
2+ points = > 2.2% (oral anticoagulant recommended)	

From European Society of Cardiology clinical practice guidelines: atrial fibrillation (management of) 2010 and focused update (2012). Eur Heart J 2012; 33:2719–2747.

16.26 HAS-BLED bleeding risk scoring system for patients receiving oral anticoagulation

Parameter	Score
H	Hypertension; current systolic blood pressure > 160mmHg 1 point
A	Abnormal liver function (cirrhosis OR bilirubin > twice upper limit of reference range or transaminases > three times upper limit of reference range) 1 point Abnormal renal function (creatinine > 200 µmol/L (2.26mg/dL)) 1 point
S	Stroke history 1 point
B	Bleeding: prior major event 1 point
L	Labile INR on warfarin 1 point
E	Elderly: age ≥ 65 years 1 point
D	Drugs: Use of antiplatelet drug High alcohol consumption Maximum total score 1 point 1 point 9 points

HAS-BLED score of ≥3 points requires close patient monitoring

cases, when there is severe haemodynamic compromise, the tachycardia should be terminated by DC cardioversion.

In patients with recurrent SVT, catheter ablation is the most effective therapy and will permanently prevent SVT in more than 90% of cases. Alternatively, prophylaxis with oral β-blocker, verapamil or flecainide may be used but commits predominantly young patients to long-term drug therapy and can create difficulty in female patients, as these drugs should be avoided during pregnancy where possible.

Atrioventricular re-entrant tachycardia

In this condition there is an abnormal band of conducting tissue that connects the atria and ventricles. This so-called accessory pathway comprises rapidly conducting fibres that resemble Purkinje tissue,

in that they conduct very rapidly and are rich in sodium channels. In about 50% of cases, this pathway conducts only in the retrograde direction (from ventricles to atria) and thus does not alter the appearance of the ECG in sinus rhythm. This is known as a concealed accessory pathway. In the rest, the pathway also conducts in an antegrade direction (from atria to ventricles), so AV conduction in sinus rhythm is mediated via both the AV node and the accessory pathway, distorting the QRS complex. Premature ventricular activation via the pathway shortens the PR interval and produces a 'slurred' initial deflection of the QRS complex, called a delta wave (Fig. 16.44B). This is known as a manifest accessory pathway. As the AV node and accessory pathway have different conduction speeds and refractory periods, a re-entry circuit can develop, causing tachycardia (Fig. 16.44C); when associated with symptoms, the condition is known as Wolff–Parkinson–White (WPW) syndrome. The ECG during this tachycardia is almost indistinguishable from that of AVNRT (Fig. 16.44A).

Management

Carotid sinus pressure or intravenous adenosine can terminate the tachycardia. If AF occurs, it may produce a dangerously rapid ventricular rate because the accessory pathway lacks the rate-limiting properties of



Fig. 16.43 Supraventricular tachycardia. The rate is 180/min and the QRS complexes are normal.

the AV node (Fig. 16.44D). This is known as pre-excited atrial fibrillation and may cause collapse, syncope and even death. It should be treated as an emergency, usually with DC cardioversion.

Catheter ablation is first-line treatment in symptomatic patients and is nearly always curative. Alternatively, prophylactic anti-arrhythmic drugs, such as flecainide or propafenone (see Box 16.30) can be used to slow conduction in, and prolong the refractory period of, the accessory pathway. Long-term drug therapy is not the preferred treatment for most patients and amiodarone should not be used, as its side-effect profile cannot be justified and ablation is safer and more effective. Digoxin and verapamil shorten the refractory period of the accessory pathway and should not be used.

Ventricular premature beats

Ventricular premature beats (VPBs) are frequently found in healthy people and their prevalence increases with age. Ectopic beats in patients with otherwise normal hearts are more prominent at rest and disappear with exercise. Sometimes VPBs are a manifestation of subclinical coronary artery disease or cardiomyopathy but also may occur in patients with established heart disease following an MI. Most patients with VPBs are asymptomatic but some present with an irregular heart beat, missed beats or abnormally strong beats, due to increased cardiac output of the post-ectopic sinus beat. On examination the pulse is irregular, with weak or missed beats as a result of the fact that the stroke volume is low because left ventricular contraction occurs before filling is complete (Fig. 16.45). The ECG shows broad and bizarre complexes because the ventricles are activated sequentially rather than simultaneously. The complexes may be unifocal (identical beats arising from a single ectopic focus) or multifocal (varying morphology with multiple foci, see Fig. 16.46). 'Couplet' and 'triplet' are the terms used to describe two or three successive ectopic beats. A run of alternating

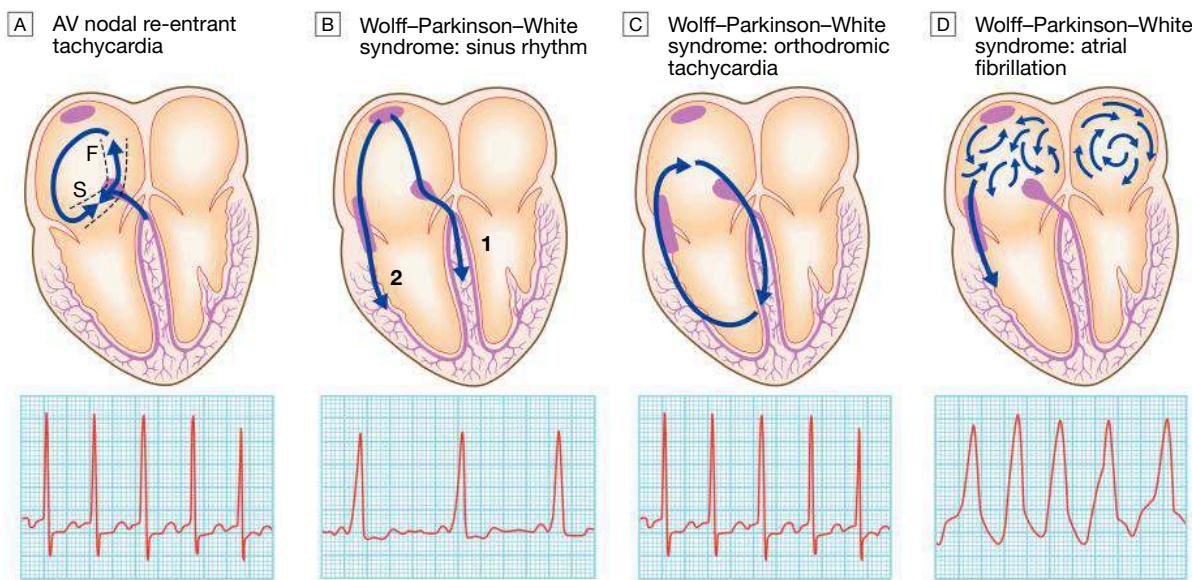


Fig. 16.44 Atrioventricular nodal re-entrant tachycardia (AVNRT) and Wolff–Parkinson–White (WPW) syndrome. **[A]** Atrioventricular (AV) nodal re-entrant tachycardia. The mechanism of AVNRT occurs via two right atrial AV nodal input pathways: the slow (S) and fast (F) pathways. Antegrade conduction occurs via the slow pathway; the wavefront enters the AV node and passes into the ventricles, at the same time re-entering the atria via the fast pathway. In WPW syndrome, there is a strip of accessory conducting tissue that allows electricity to bypass the AV node and spread from the atria to the ventricles rapidly and without delay. When the ventricles are depolarised through the AV node the ECG is normal, but when the ventricles are depolarised through the accessory conducting tissue the ECG shows a very short PR interval and a broad QRS complex. **[B]** Sinus rhythm. In sinus rhythm, the ventricles are depolarised through (1) the AV node and (2) the accessory pathway, producing an ECG with a short PR interval and broadened QRS complexes; the characteristic slurring of the upstroke of the QRS complex is known as a delta wave. The degree of pre-excitation (the proportion of activation passing down the accessory pathway) and therefore the ECG appearances may vary a lot, and at times the ECG can look normal. **[C]** Orthodromic tachycardia. This is the most common form of tachycardia in WPW. The re-entry circuit passes antegradely through the AV node and retrogradely through the accessory pathway. The ventricles are therefore depolarised in the normal way, producing a narrow-complex tachycardia that is indistinguishable from other forms of supraventricular tachycardia. **[D]** Atrial fibrillation. In this rhythm, the ventricles are largely depolarised through the accessory pathway, producing an irregular broad-complex tachycardia that is often more rapid than the example shown.

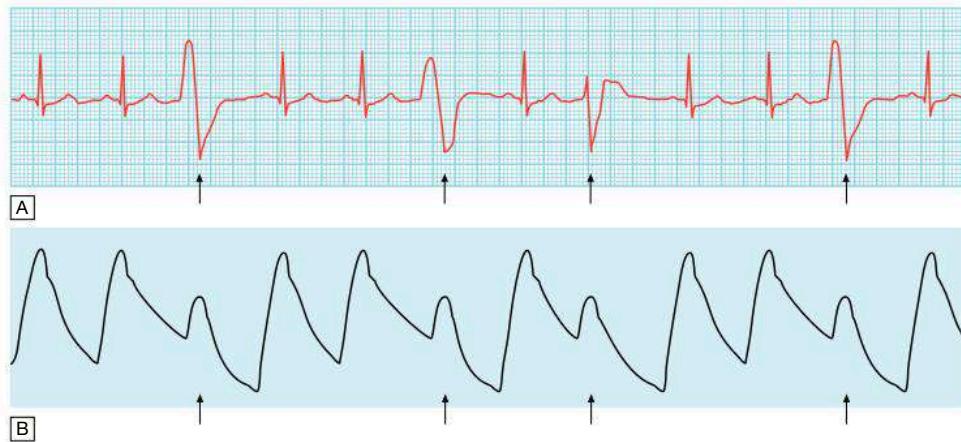


Fig. 16.45 Ventricular ectopic beats. **A** There are broad, bizarre QRS complexes (arrows) with no preceding P wave in between normal sinus beats. Their configuration varies, so these are multifocal ectopics. **B** A simultaneous arterial pressure trace is shown. The ectopic beats result in a weaker pulse (arrows), which may be perceived as a 'dropped beat'.

sinus and ventricular ectopic beats is known as ventricular 'bigeminy'. The significance depends on the presence or absence of underlying heart disease.

Management

Treatment may not be necessary, unless the patient is highly symptomatic, in which case β -blockers or, in some situations, catheter ablation can be used. There is no evidence that anti-arrhythmic therapy improves prognosis but the discovery of very frequent VPBs in a patient not known to have heart disease should prompt further investigations with echocardiography and an exercise ECG to screen for structural heart disease and ischaemic heart disease. It is common for VPBs to occur during the course of an acute MI. Persistent, frequent VPBs (over 10/hr) in patients who have survived the acute phase of MI indicate a poorer long-term outcome. In this situation, anti-arrhythmic drugs do not improve and may even worsen prognosis. The exception is β -blockers, which should be prescribed for other reasons following MI. Similarly, heart failure of any cause is associated with VPBs. While they indicate an adverse prognosis, this is not improved by anti-arrhythmic drugs. Effective treatment of the heart failure may suppress the ectopic beats.

Ventricular tachycardia

Ventricular tachycardia (VT) occurs most commonly in the settings of acute MI, chronic coronary artery disease and cardiomyopathy. It is associated with extensive ventricular disease, impaired left ventricular function and ventricular aneurysm. In these settings, VT may cause haemodynamic compromise or degenerate into ventricular fibrillation (see Fig. 16.19). VT is most often caused by re-entry within scarred ventricular tissue, and less often by abnormal automaticity or triggered activity in ischaemic tissue. Patients may experience palpitation, dyspnoea, lightheadedness and syncope. The ECG shows tachycardia and broad, abnormal QRS complexes with a rate of more than 120/min (Fig. 16.46). It may be difficult to distinguish VT from SVT with bundle branch block or pre-excitation (WPW syndrome) on ECG but features in favour of VT are listed in Box 16.27. A 12-lead ECG (Fig. 16.47) or electrophysiology study may help establish the diagnosis. When there is doubt, it is safer to manage the problem as VT.

Patients recovering from MI sometimes have periods of idioventricular rhythm ('slow' VT) at a rate only slightly above the preceding sinus rate and below 120/min. These episodes often reflect reperfusion of the infarct territory and may be a good sign. They are usually self-limiting and asymptomatic, and do not require treatment. Other forms of sustained VT require treatment, often as an emergency.

Occasionally, VT occurs in patients with otherwise healthy hearts ('normal heart VT'), usually because of abnormal automaticity in the right ventricular outflow tract or one of the fascicles of the left bundle branch.

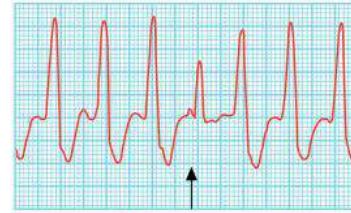


Fig. 16.46 Ventricular tachycardia: fusion beat. In ventricular tachycardia, there is independent atrial and ventricular activity. Occasionally, a P wave is conducted to the ventricles through the AV node, producing a normal sinus beat in the middle of the tachycardia (a capture beat); more commonly, however, the conducted impulse fuses with an impulse from the tachycardia (a fusion beat, arrow). This can occur only when there is atrioventricular dissociation and is therefore diagnostic of ventricular tachycardia.



16.27 Features more in keeping with ventricular tachycardia

- History of myocardial infarction
- Atrioventricular dissociation (pathognomonic)
- Capture/fusion beats (pathognomonic; see Fig. 16.40)
- Extreme left axis deviation
- Very broad QRS complexes (> 140 msec)
- No response to carotid sinus massage or intravenous adenosine

Management

Prompt action to restore sinus rhythm is required and should usually be followed by prophylactic therapy. Synchronised DC cardioversion is the treatment of choice if systolic BP is less than 90 mmHg. If the arrhythmia is well tolerated, intravenous amiodarone may be given as a bolus, followed by a continuous infusion (see Box 16.30). Intravenous lidocaine can also be used but may depress left ventricular function, causing hypotension or acute heart failure. Hypokalaemia, hypomagnesaemia, acidosis and hypoxia should be corrected if present.

Beta-blockers are effective at preventing VT by reducing ventricular automaticity. Amiodarone can be added if additional control is needed. Class Ic anti-arrhythmic drugs should not be used for prevention of VT in patients with coronary artery disease or heart failure because they depress myocardial function and can increase the likelihood of a dangerous arrhythmia. In patients with poor left ventricular function or where VT is associated with haemodynamic compromise, the use of an implantable cardiac defibrillator is recommended. In resistant cases of focal or infarct scar-mediated VT, catheter ablation can be used to interrupt the

arrhythmia focus or circuit. The treatment of choice for VT occurring in a normal heart is catheter ablation, which often can be curative.

Torsades de pointes

This form of polymorphic VT is a complication of prolonged ventricular repolarisation (prolonged QT interval). The ECG shows rapid irregular complexes that seem to twist around the baseline as the mean QRS axis changes (Fig. 16.48). The arrhythmia is usually non-sustained and repetitive, but may degenerate into ventricular fibrillation. During periods of sinus rhythm, the ECG will usually show a prolonged QT interval (>0.44 sec in men, >0.46 sec in women when corrected to a heart rate of 60/min).

Some of the common causes are listed in Box 16.28. The arrhythmia is more common in women and is often triggered by a combination of factors, such as administration of QT-prolonging medications and hypokalaemia. The congenital long QT syndromes are a family of genetic

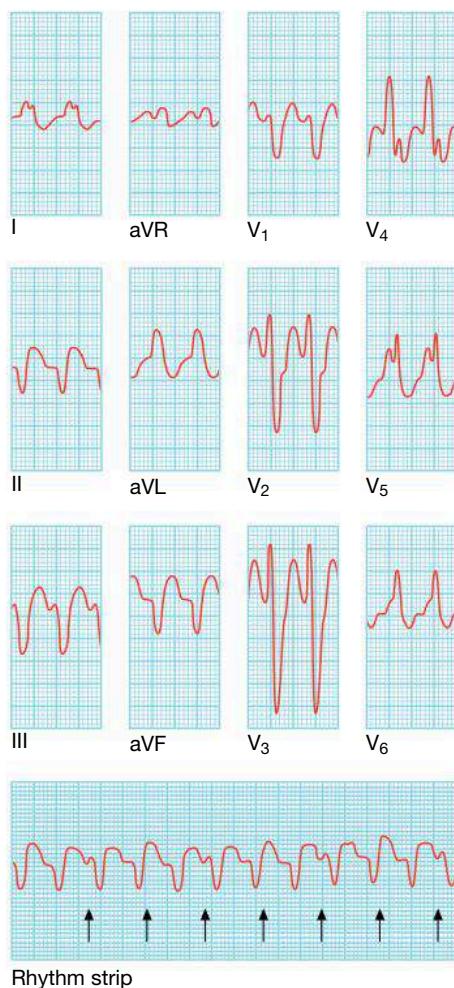


Fig. 16.47 Ventricular tachycardia: 12-lead ECG. There are typically very broad QRS complexes and marked left axis deviation. There is also atrioventricular dissociation; some P waves are visible and others are buried in the QRS complexes (arrows).

disorders that are characterised by mutations in genes that code for cardiac potassium or sodium channels. Long QT syndrome subtypes have different triggers, which are important when counselling patients. Adrenergic stimulation through vigorous exercise is a common trigger in long QT type 1, and a sudden noise may trigger arrhythmias in long QT type 2. Arrhythmias are more common during sleep in type 3.

Management

Intravenous magnesium (8 mmol over 15 mins, then 72 mmol over 24 hrs) should be given in all cases. If this is ineffective, atrial pacing should be tried, since it can suppress the arrhythmia through rate-dependent shortening of the QT interval. Intravenous isoprenaline is a reasonable alternative to pacing but should be avoided in patients with the congenital long QT syndromes. Once initial control has been achieved, efforts should be made to identify and treat the underlying cause or stop medications that predispose to the arrhythmia. If the underlying cause cannot be corrected or the arrhythmia is the result of an inherited syndrome, then long-term pharmacological therapy may be necessary. Beta-blockers are effective at preventing syncope in patients with congenital long QT syndrome. Some patients, particularly those with extreme QT interval prolongation (>500 msec) or certain high-risk genotypes, should be considered for an implantable defibrillator. Left stellate ganglion block may be of value in patients with resistant arrhythmias.

Brugada syndrome is a related genetic disorder that may present with polymorphic VT or sudden death. It is most commonly caused by mutations in the SCN5A gene which encodes a sodium channel expressed in cardiac myocytes. It is characterised by an abnormal ECG (right bundle branch block and ST elevation in V_1 and V_2 but not usually prolongation of the QT interval). The only known effective treatment is an implantable defibrillator.

16.28 Causes of long QT interval and torsades de pointes

Bradycardia

- Bradycardia potentiates other factors that cause torsades de pointes

Electrolyte disturbance

- Hypokalaemia
- Hypomagnesaemia
- Hypocalcaemia

Drugs*

- Disopyramide, flecainide and other class Ia, Ic anti-arrhythmic drugs (Box 16.29 and Fig. 16.49)
- Sotalol, amiodarone and other class III anti-arrhythmic drugs
- Amitriptyline and other tricyclic antidepressants
- Chlorpromazine and other phenothiazines
- Erythromycin and other macrolides
- Hydroxychloroquine and chloroquine

Congenital syndromes

- Long QT1: gene affected KCNQ1: K⁺ channel, 30%–35%
- Long QT2: gene affected HERG: K⁺ channel, 25%–30%
- Long QT3: gene affected SCN5A: Na⁺ channel, 5%–10%
- Long QT4–12: rare; various genes implicated

*Many other drugs that are not shown can be associated with prolongation of the QT interval. See www.crediblemeds.org for a complete list.



Fig. 16.48 Torsades de pointes. A bradycardia with a long QT interval is followed by polymorphic ventricular tachycardia that is triggered by an R on T ectopic.

Principles of management of cardiac arrhythmias

Cardiac arrhythmias can be managed with anti-arrhythmic drug therapy, cardiac implantable electronic devices (CIEDs), or catheter ablation.

Anti-arrhythmic drugs

Traditionally, the Vaughan Williams system has been used to categorise anti-arrhythmic drugs based on their effects on the action potential. Increased understanding of the mechanisms of action has allowed further subclassification, based on the cardiac ion channels and receptors on which they act see (Box 16.29 and Fig. 16.49). The individual agents, dosages and most common side-effects are summarised in Box 16.30 and the general principles of use are summarised in Box 16.31.

Class I drugs

Class I drugs act principally by suppressing excitability and slowing conduction in atrial or ventricular muscle. They block sodium channels, of which there are several types in cardiac tissue. These drugs should generally be avoided in patients with heart failure because they depress myocardial function, and class Ia and Ic drugs are often pro-arrhythmic.

Class Ia drugs

These prolong cardiac action potential duration and increase the tissue refractory period. They are used to prevent both atrial and ventricular arrhythmias.

Disopyramide

This is an effective drug but causes anticholinergic side-effects, such as urinary retention, and can precipitate glaucoma. It can depress myocardial function and should be avoided in cardiac failure.

Quinidine

This drug is effective at preventing AF and is occasionally used in Brugada syndrome. It is strongly pro-arrhythmic and can cause gastrointestinal upset.

i 16.29 Classification of anti-arrhythmic drugs by effect on the intracellular action potential*

Class I: membrane-stabilising agents (sodium channel blockers)

- (a) Block Na^+ channel and prolong action potential
 - Quinidine, disopyramide
- (b) Block Na^+ channel and shorten action potential
 - Lidocaine, mexiletine
- (c) Block Na^+ channel with no effect on action potential
 - Flecainide, propafenone

Class II: β -adrenoceptor antagonists (β -blockers)

- Atenolol, bisoprolol, metoprolol

Class III: drugs whose main effect is to prolong the action potential

- Amiodarone, dronedarone, sotalol

Class IV: slow calcium channel blockers

- Verapamil, diltiazem

*Some drugs such as digoxin, ivabradine and adenosine have no place in this classification, while others such as amiodarone have properties in more than one class.

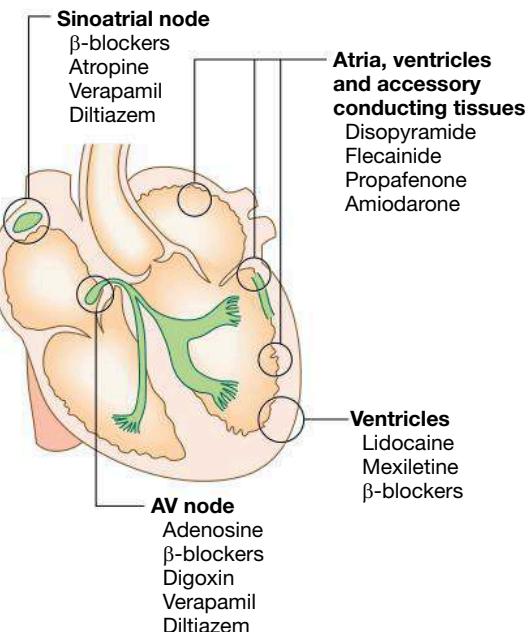


Fig. 16.49 Classification of anti-arrhythmic drugs by site of action.
(AV = atrioventricular)

16

Class Ib drugs

These shorten the action potential and tissue refractory period. They act on channels found predominantly in ventricular myocardium and so are used to treat or prevent VT and VF.

Lidocaine

This must be given intravenously and has a very short plasma half-life.

Mexiletine

This can be given intravenously or orally but has many side-effects.

Class Ic drugs

These affect the slope of the action potential without altering its duration or refractory period. They are used mainly for prophylaxis of AF but are effective in prophylaxis and treatment of supraventricular or ventricular arrhythmias. They are useful for WPW syndrome because they block conduction in accessory pathways. They should not be used in patients with previous MI because they increase the risk of arrhythmia in this setting.

Flecainide

This is effective for prevention of AF, and an intravenous infusion may be used for pharmacological cardioversion of AF of less than 24 hours' duration. Since flecainide can cause slow atrial flutter with a paradoxically rapid ventricular rate, it should be prescribed along with an AV node-blocking drug such as a β -blocker to control the ventricular rate.

Propafenone

This also has some β -blocker (class II) properties. Important interactions with digoxin, warfarin and cimetidine have been described.

Class II drugs

This group comprises the β -adrenoceptor antagonists (β -blockers). These agents reduce the rate of SA node depolarisation and cause relative block in the AV node, making them useful for rate control in atrial flutter and AF. They can be used to prevent VT and SVT. They reduce myocardial excitability and the risk of arrhythmic death in patients with coronary artery disease and heart failure.

16.30 Uses, dosage and side-effects of anti-arrhythmic drugs					
Drug	Main uses	Route	Dosage (adult)	Important side-effects	
Class I					
Disopyramide	Prevention and treatment of atrial and ventricular tachyarrhythmias	IV	2 mg/kg at 30 mg/min, then 0.4 mg/kg/hr (max 800 mg/day)	Myocardial depression, hypotension, dry mouth, urinary retention	
Lidocaine	Treatment and short-term prevention of VT and VF	Oral IV	300–800 mg daily in divided dosage Bolus 50–100 mg, 4 mg/min for 30 mins, then 2 mg/min for 2 hrs, then 1 mg/min for 24 hrs	Myocardial depression, delirium, convulsions	
Mexiletine	Prevention and treatment of ventricular tachyarrhythmias	IV	Loading dose: 100–250 mg at 25 mg/min, then 250 mg in 1 hr, then 250 mg in 2 hrs Maintenance therapy: 0.5 mg/min	Myocardial depression, gastrointestinal irritation, delirium, dizziness, tremor, nystagmus, ataxia	
Flecainide	Prevention and treatment of atrial and ventricular tachyarrhythmias	Oral IV	167–500 mg daily 2 mg/kg over 10 mins, then if required 1.5 mg/kg/hr for 1 hr, then 0.1 mg/kg/hr	Myocardial depression, dizziness	
Propafenone	Prevention and treatment of atrial and ventricular tachyarrhythmias	Oral	50–150 mg twice daily	Myocardial depression, dizziness	
		Oral	150 mg 3 times daily for 1 week, then 300 mg twice daily		
Class II					
Atenolol	Treatment and prevention of SVT and AF, prevention of VEs and exercise-induced VF	IV Oral	2.5 mg at 1 mg/min, repeated at 5-min intervals (max 10 mg) 25–100 mg daily	Myocardial depression, bradycardia, bronchospasm, fatigue, depression, nightmares, cold peripheries	
Bisoprolol		Oral	2.5–10 mg daily		
Metoprolol		IV	5 mg over 2 mins to a maximum of 15 mg		
Class III					
Amiodarone	Serious or resistant atrial and ventricular tachyarrhythmias	IV Oral	5 mg/kg over 20–120 mins, then up to 15 mg/kg/24 hrs Initially 600–1200 mg/day, then 100–400 mg daily	Photosensitivity skin discolouration, corneal deposits, thyroid dysfunction, alveolitis, nausea and vomiting, hepatotoxicity, peripheral neuropathy, torsades de pointes; potentiates digoxin and warfarin	
Dronedarone	Paroxysmal atrial fibrillation	Oral	400 mg twice daily	Renal and hepatic dysfunction requiring regular blood monitoring	
Sotalol*	AF, rarely ventricular tachyarrhythmias	IV Oral	10–20 mg slowly 40–160 mg twice daily	Can cause torsade de pointes	
Class IV					
Verapamil	Treatment of SVT, control of AF	IV Oral	5–10 mg over 30 secs 40–120 mg 3 times daily or 240 mg SR daily	Myocardial depression, hypotension, bradycardia, constipation	
Other					
Atropine	Treatment of bradycardia and/or hypotension due to vagal over-activity (see Box 16.32)	IV	0.6–3 mg	Dry mouth, thirst, blurred vision, atrial and ventricular extrasystoles	
Adenosine	Treatment of SVT, aid to diagnosis in unidentified tachycardia	IV	3 mg over 2 secs, followed if necessary by 6 mg, then 12 mg at intervals of 1–2 mins	Flushing, dyspnoea, chest pain Avoid in asthma	
Digoxin	Rate control of AF	IV Oral	Loading dose: 0.5–1 mg (total), 0.5 mg over 30 mins, then 0.25–0.5 mg after 4–6 hrs 0.5 mg repeated after 6 hrs, then 0.0625–0.25 mg daily	Gastrointestinal disturbance, xanthopsia, arrhythmias	

*Sotalol also has class II activity as a β -blocker.

(AF = atrial fibrillation; IV = intravenous; SR = sustained-release formulation; SVT = supraventricular tachycardia; VE = ventricular ectopic; VF = ventricular fibrillation; VT = ventricular tachycardia)

Non-selective β -blockers

These act on both β_1 and β_2 receptors. Beta₂-blockade causes side-effects, such as bronchospasm and peripheral vasoconstriction. Propranolol is non-selective and is subject to extensive first-pass metabolism in the liver. The effective oral dose is therefore unpredictable and must be titrated after treatment is started with a small dose. Other non-selective drugs include nadolol and carvedilol.

Cardioselective β -blockers

These act mainly on myocardial β_1 receptors and are relatively well tolerated. Bisoprolol and metoprolol are examples of cardioselective β -blockers.

Sotalol

This is a racemic mixture of two isomers with non-selective β -blocker (mainly L-sotalol) and class III (mainly D-sotalol) activity. It may cause torsades de pointes.



16.31 Anti-arrhythmic drugs: principles of use

Anti-arrhythmic drugs are potentially toxic and should be used carefully according to the following principles:

- Many arrhythmias are benign and do not require specific treatment
- Precipitating or causal factors should be corrected if possible:
 - Alcohol excess
 - Myocardial ischaemia
 - Hyperthyroidism
 - Acidosis
 - Hypokalaemia
 - Hypomagnesaemia
- If drug therapy is required, it is best to use as few drugs as possible
- In difficult cases, programmed electrical stimulation (electrophysiological study) may help to identify the optimum therapy
- When managing life-threatening arrhythmias, it is essential to ensure that prophylactic treatment is effective. Ambulatory monitoring and exercise testing may be of value
- Patients on long-term anti-arrhythmic drugs should be reviewed regularly and attempts made to withdraw therapy if the factors that precipitated the arrhythmias are no longer operative
- For patients with recurrent supraventricular tachycardia or atrial flutter, radiofrequency ablation is the treatment of choice

Class III drugs

Class III drugs act by prolonging the plateau phase of the action potential, thus lengthening the refractory period. These drugs are very effective at preventing atrial and ventricular tachyarrhythmias. They cause QT interval prolongation and can predispose to torsades de pointes and VT, especially in patients with other predisposing risk factors (see Box 16.28). Disopyramide and sotalol have some class III activity but the main drug in this class is amiodarone, as discussed below.

Amiodarone

While amiodarone is primarily considered a class III drug, it also has class I, II and IV activity. It is probably the most effective drug currently available for controlling paroxysmal AF. It is also used to prevent episodes of recurrent VT, particularly in patients with poor left ventricular function or those with implantable defibrillators (to prevent unnecessary DC shocks). Amiodarone has a very long tissue half-life (25–110 days). An intravenous or oral loading regime is often used to achieve therapeutic tissue concentrations. The drug's effects may last for weeks or months after treatment has been stopped. Side-effects are common (up to one-third of patients), numerous and potentially serious. Drug interactions are also common (see Box 16.30).

Dronedarone

Dronedarone is related to amiodarone but has a short tissue half-life and fewer side-effects. It has recently been shown to be effective at preventing episodes of atrial flutter and AF. It is contraindicated in patients with permanent AF, or if there is heart failure or left ventricular impairment, because it increases mortality. Regular liver and renal function test monitoring is required.

Class IV drugs

These block the 'slow calcium channel', which is important for impulse generation and conduction in atrial and nodal tissue, although it is also present in ventricular muscle. Their main indications are prevention of SVT (by blocking the AV node) and rate control in patients with AF.

Verapamil

This is the most widely used drug in this class. Intravenous verapamil may cause profound bradycardia or hypotension, and should not be used in conjunction with β -blockers.



16.32 Response to intravenous adenosine

Arrhythmia	Response
Supraventricular tachycardia	Termination
Atrial fibrillation, atrial flutter, atrial tachycardia	Transient atrioventricular block
Ventricular tachycardia	No effect

Diltiazem

This has similar properties to verapamil.

Other anti-arrhythmic drugs

Atropine sulphate

Atropine is a muscarinic receptor antagonist that increases the sinus rate and SA and AV conduction. It is the treatment of choice for severe bradycardia or hypotension due to vagal over-activity. It is used for initial management of symptomatic bradyarrhythmias complicating inferior MI, and in cardiac arrest due to asystole. The usual dose is 0.6mg IV, repeated if necessary to a maximum of 3mg. Repeat dosing may be necessary because the drug disappears rapidly from the circulation after parenteral administration. Side-effects are listed in Box 16.30.

Adenosine

This works by binding to A1 receptors in conducting tissue, producing a transient AV block lasting a few seconds. It is used to terminate SVTs when the AV node is part of the re-entry circuit, or to help establish the diagnosis in difficult arrhythmias, such as atrial flutter with 2:1 AV block (see Fig. 16.40) or broad-complex tachycardia (see Boxes 16.30 and 16.32). Adenosine is given as an intravenous bolus, initially 3mg over 2 seconds (see Box 16.30). If there is no response after 1–2 minutes, 6mg should be given; if necessary, after another 1–2 minutes the maximum dose of 12mg may be given. Patients should be warned to expect short-lived and sometimes distressing flushing, breathlessness and chest pain. Adenosine can cause bronchospasm and should be avoided in patients with asthma; its effects are greatly potentiated by dipyridamole and inhibited by theophylline and other xanthines.

Digoxin

Digoxin is a glycoside purified from the European foxglove, *Digitalis lanata*, which slows conduction and prolongs the refractory period in the AV node. This effect helps to control the ventricular rate in AF. Digoxin also shortens refractory periods and enhances excitability and conduction in other parts of the heart, including accessory pathways. It may therefore increase atrial and ventricular ectopic activity and can lead to more complex atrial and ventricular tachyarrhythmias. Digoxin is largely excreted by the kidneys, and the maintenance dose (see Box 16.30) should be reduced in children, older people and those with renal impairment. It is widely distributed and has a long tissue half-life (36 hours), so that effects may persist for several days. Measurement of plasma digoxin concentration helps identify digoxin toxicity or under-treatment (Box 16.33).

Non-pharmacological treatments

Electrical cardioversion

Electrical cardioversion, also known as direct current (DC) cardioversion, is useful for terminating an organised rhythm, such as AF or VT. The shock depolarises the myocardium, interrupts the arrhythmia and produces a brief period of asystole, followed by the resumption of sinus rhythm. Cardioversion is usually carried out as an elective procedure under general anaesthesia. The shock is delivered immediately after the R wave because, if it is applied during ventricular repolarisation (on the T wave), it may provoke VF. A 100–150 Joule shock is normally used.

i	16.33 Digoxin toxicity
Extracardiac manifestations	
• Anorexia, nausea, vomiting	• Altered colour vision (xanthopsia)
Cardiac manifestations	
• Bradycardia	• Atrial tachycardia (with variable block)
• Multiple ventricular ectopics	• Ventricular tachycardia
• Ventricular bigeminy (alternate ventricular ectopics)	• Ventricular fibrillation

Defibrillation

Defibrillators deliver a DC, high-energy, short-duration shock via two large electrodes or paddles coated with conducting jelly or a gel pad, positioned over the upper right sternal border and the apex. Defibrillators are primarily used in the management of cardiac arrest due to VF and deliver an unsynchronised shock, since the precise timing of the discharge is not important in this situation. A biphasic shock is used during which the shock polarity is reversed mid-shock. This reduces the total shock energy required to depolarise the heart. In VF and other emergencies, the energy of the first and second shocks should be 150 Joules and thereafter up to 200 Joules; there is no need for an anaesthetic, as the patient is unconscious.

Temporary pacemakers

Temporary pacing involves delivery of an electrical impulse into the heart to initiate tissue depolarisation and to trigger cardiac contraction. This is achieved by inserting a bipolar pacing electrode through the internal jugular, subclavian or femoral vein and positioning it at the apex of the RV, using fluoroscopic imaging. The electrode is connected to an external pacemaker with an adjustable energy output and pacing rate. The ECG of right ventricular pacing is characterised by regular broad QRS complexes with a left bundle branch block pattern. Each complex is immediately preceded by a 'pacing spike' (Fig. 16.50). The pacemaker will operate only if the heart rate falls below a preset level. Occasionally, temporary atrial or dual-chamber pacing (see below) is used.

Temporary pacing is indicated for transient AV block and other arrhythmias complicating acute MI or cardiac surgery, to maintain the rhythm in other situations of reversible bradycardia (such as metabolic disturbance or drug overdose), or as a bridge to permanent pacing. Complications include pneumothorax, brachial plexus or subclavian artery injury, local infection or sepsis (usually with *Staphylococcus aureus*), and pericarditis. Failure of the system may be due to lead displacement or a progressive increase in the threshold (exit block) caused by tissue oedema. Complication rates increase with time and so a temporary pacing system should ideally not be used for more than 7 days.

Transcutaneous pacing is administered by delivering an electrical stimulus through two large adhesive gel pad electrodes placed over the apex and upper right sternal border, or over the anterior and posterior chest. It is easy and quick to set up, but causes discomfort because it induces forceful pectoral and intercostal muscle contraction. Modern external defibrillators often incorporate a transcutaneous pacing system that can be used until transvenous pacing is established.

Permanent pacemakers

Permanent pacemakers are small, flat, metal devices that are implanted under the skin, usually in the pectoral area (Fig. 16.51). They contain a battery, a pulse generator, and programmable electronics that allow adjustment of pacing and memory functions. Pacing electrodes (leads) can be placed via the subclavian or cephalic veins into the RV (usually at the apex), the right atrial appendage or, to maintain AV synchrony, both.



Fig. 16.50 Dual-chamber pacing. The first three beats show atrial and ventricular pacing with narrow spikes in front of each P wave and QRS complex. The last four beats show spontaneous P waves with a different morphology and no pacing spike; the pacemaker senses or tracks these P waves and maintains atrioventricular synchrony by pacing the ventricle after an appropriate interval.



Fig. 16.51 Cardiac implantable electronic devices. **A** Single-chamber pacemaker. **B** Dual-chamber pacemaker. **C** Cardiac resynchronisation therapy pacemaker (CRT-P). **D** Cardiac resynchronisation therapy defibrillator (CRT-D).

Permanent pacemakers are controlled using an external programmer through a wireless telemetry system, allowing rate, output, timing and other parameters to be adjusted. This allows the device settings to be tailored to the patient's needs. Aside from their therapeutic role, pacemakers store useful diagnostic data about the patient's heart rate trends and the occurrence of tachyarrhythmias, such as VT.

Single-chamber atrial pacing is indicated in patients with SA disease without AV block and ventricular pacing in patients with continuous AF and bradycardia. Here the pacemaker acts as an external sinus node. Dual-chamber pacing is most often used in patients with second- or third-degree AV block. Here, the atrial electrode is used to detect spontaneous atrial activity and trigger ventricular pacing (see Fig. 16.50), thereby preserving AV synchrony and allowing the ventricular rate to increase, together with the sinus node rate, during exercise and other forms of stress. Dual-chamber pacing has many advantages over single-chamber ventricular pacing, including superior haemodynamics and better effort tolerance; a lower prevalence of atrial arrhythmias in patients with SA disease; and avoidance of 'pacemaker syndrome', in which a fall in BP and dizziness occur due to loss of AV synchrony.

A code is used to signify the pacing mode (Box 16.34). For example, a system that paces the atrium, senses the atrium and is inhibited if it senses spontaneous activity is designated AAI. Most dual-chamber pacemakers are programmed to a mode termed DDD; in this case, ventricular pacing is triggered by a sensed sinus P wave and inhibited by a sensed spontaneous QRS complex. A fourth letter, 'R', is added if the pacemaker has a rate response function. For example, the letters



16.34 International generic pacemaker code

Chamber paced	Chamber sensed	Response to sensing
O = none	O = none	O = none
A = atrium	A = atrium	T = triggered
V = ventricle	V = ventricle	I = inhibited
D = both	D = both	D = both



16.35 Key indications for implantable cardiac defibrillator therapy

Primary prevention

- After myocardial infarction, if the left ventricular ejection fraction is < 30%
- Mild to moderate symptomatic heart failure on optimal drug therapy, with left ventricular ejection fraction < 35%
- Some patients with inherited cardiac conditions (long QT syndrome, cardiomyopathy)

Secondary prevention

- Survivors of ventricular fibrillation or ventricular tachycardia cardiac arrest not having a transient or reversible cause
- Ventricular tachycardia with haemodynamic compromise or significant left ventricular impairment (left ventricular ejection fraction < 35%)

cardioversion or defibrillation. ICD leads are similar to pacing leads but have one or two shock coils along the length of the lead, used for delivering defibrillation. ICDs treat ventricular tachyarrhythmias using overdrive pacing, cardioversion or defibrillation. They are implanted in a similar manner to pacemakers and carry a similar risk of complications. In addition, patients can be prone to psychological problems and anxiety, particularly if they have experienced repeated shocks from their device.

The evidence-based indications for ICD implantation are shown in Box 16.35. These can be divided into secondary prevention indications, when patients have already had a potentially life-threatening ventricular arrhythmia, and primary prevention indications, when patients are considered to be at significant future risk of arrhythmic death. A common primary prevention indication is in patients with inherited conditions associated with a high risk of sudden cardiac death, such as long QT syndrome, hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy. Treatment with ICDs is expensive and so the indications for which the devices are routinely implanted depend on the health-care resources available.

Cardiac resynchronisation therapy

Cardiac resynchronisation therapy (CRT) is a useful treatment for selected patients with heart failure, in whom cardiac function is impaired by the presence of left bundle branch block. This conduction defect is associated with poorly coordinated left ventricular contraction that can aggravate heart failure in susceptible patients. The systems used to deliver CRT comprise a right atrial lead, a right ventricular lead and a third lead that is placed via the coronary sinus into one of the veins on the epicardial surface of the LV (see Fig. 16.28). Simultaneous septal and left ventricular epicardial pacing resynchronises left ventricular contraction.

CRT improves symptoms and quality of life, and reduces mortality in patients with moderate to severe (NYHA class III–IV) heart failure who are in sinus rhythm, with left bundle branch block and left ventricular ejection fraction of 35% or less. CRT also prevents heart failure progression in similar patients with mild (NYHA class I–II) heart failure symptoms. These devices are more effective in patients in sinus rhythm than in those with AF. Most devices are also defibrillators (CRT-D) because many patients with heart failure are predisposed to ventricular arrhythmias. CRT pacemakers (CRT-P) are used when the focus is palliation of symptoms rather than prolonging life.

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AAIR indicate an atrial demand pacemaker with a rate response function. Rate-responsive pacemakers are used in patients with chronotropic incompetence, who are unable to increase their heart rate during exercise. These devices have a sensor that triggers an increase in heart rate in response to movement or increased respiratory rate. The sensitivity of the sensor is programmable, as is the maximum paced heart rate.

Early complications of permanent pacing include pneumothorax, cardiac tamponade, infection and lead displacement. Late complications include infection (which usually necessitates removing the pacing system), erosion of the generator or lead, chronic pain related to the implant site, and lead fracture due to mechanical fatigue.

Implantable cardiac defibrillators

In addition to the functions of a permanent pacemaker, implantable cardiac defibrillators (ICDs) can also detect and terminate life-threatening ventricular tachyarrhythmias. ICDs are larger than pacemakers mainly because of the need for a large battery and capacitor to enable

Catheter ablation therapy

Catheter ablation therapy is the treatment of choice for patients with SVT or atrial flutter, and is a useful treatment for some patients with AF or ventricular arrhythmias (Fig. 16.52). It involves inserting a series of catheter

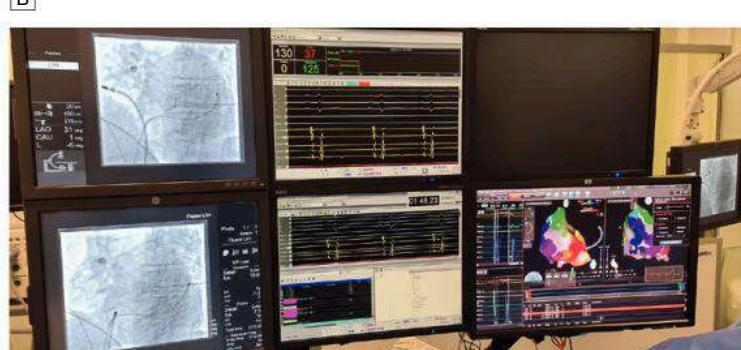
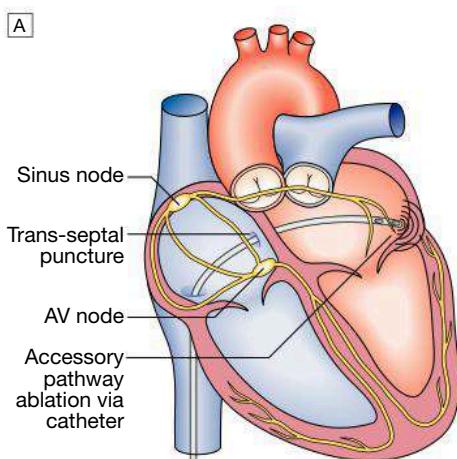


Fig. 16.52 Radiofrequency ablation. **A** Schematic of an ablation of the accessory conducting pathway in Wolff–Parkinson–White syndrome (see text for details). **B** Fluoroscopy and mapping for an ablation procedure. (AV = atrioventricular)

electrodes into the heart through the venous system. These are used to record the activation sequence of the heart in sinus rhythm, during tachycardia and after pacing manoeuvres. Once the arrhythmia focus or circuit, such as an accessory pathway in WPW syndrome, has been identified, a catheter is used to ablate the culprit tissue. This can be done either by using heat, which is termed radiofrequency ablation, or by freezing, which is termed cryoablation. The procedure takes approximately 1–4 hours and does not require a general anaesthetic, although the patient may experience some discomfort during the ablation procedure. Serious complications are rare (<1%) but include complete heart block requiring pacemaker implantation, and cardiac tamponade. For many arrhythmias, radiofrequency ablation is very attractive because it offers the prospect of a lifetime cure, thereby eliminating the need for long-term drug therapy.

The technique has revolutionised the management of many arrhythmias and is now the treatment of choice for AVNRT and AV re-entrant (accessory pathway) tachycardias, when it is curative in over 90% of cases. Focal atrial tachycardias and atrial flutter can also be treated by radiofrequency ablation, although some patients subsequently experience episodes of AF. Ablation is highly effective in patients with VT occurring in a structurally normal heart, and can be life-saving in patients with refractory VT due to ventricular scar or structural disease. Catheter ablation techniques are also employed to prevent AF. This involves ablation at two sites: the ostia of the pulmonary veins, from which ectopic beats may trigger paroxysms of arrhythmia, and in the LA itself, where re-entry circuits maintain AF, once established. This is effective at reducing episodes of AF in around 70–80% of younger patients with structurally normal hearts.

In patients with permanent AF and poor rate control, in whom drugs are ineffective or are not tolerated, rate control can be achieved by implantation of a permanent pacemaker, followed by ablation of the AV node to induce complete AV block and bradycardia, thus allowing the pacemaker to assume control of the heart rate.

Coronary artery disease

Coronary artery disease (CAD) is the commonest cause of angina and acute coronary syndrome and the leading cause of death worldwide. It also has a devastating effect on quality of life. Disability-adjusted life years, a measure of healthy years of life lost, can be used to indicate the burden of disease rather than the resulting deaths. It has been estimated that CAD is responsible for 10% of disability-adjusted life years in low-income countries and 18% in high-income ones. In the UK, 1 in 3 men and 1 in 4 women die from CAD, an estimated 188 000 people have a myocardial infarct each year, and approximately 2.3 million people are living with CAD. The death rates from CAD in the UK are among the highest in Western Europe (more than 70 000 people) but are falling, particularly in younger age groups; over the last 50 years, CAD mortality has more than halved. In Eastern Europe and much of Asia, the rates of CAD are rapidly rising. Occult CAD is common in those who present with other forms of atherosclerotic vascular disease, such as intermittent claudication or stroke, and is an important cause of morbidity and mortality in these patients.

Pathogenesis

In the vast majority of patients, CAD is caused by atherosclerosis (Box 16.36) but rarely it can occur as the result of aortitis, vasculitis and autoimmune connective tissue diseases. Atherosclerosis is a progressive inflammatory disorder of the arterial wall that is characterised by focal lipid-rich deposits of atheroma that remain clinically silent until they become large enough to impair tissue perfusion, or until ulceration and disruption of the lesion occurs resulting in thrombotic occlusion or distal embolisation of the vessel. Atherosclerosis begins early in life with deposits of lipids in the vessel wall, which tend to occur at sites of altered arterial shear stress, such as bifurcations, and are associated with abnormalities of endothelial function at that site. Abnormalities of arterial function have been detected among high-risk children and adolescents, such as cigarette smokers and those with familial hyperlipidaemia or

16.36 Coronary artery disease: clinical manifestations and pathology

Clinical problem	Pathology
Stable angina	Ischaemia due to fixed atheromatous stenosis of one or more coronary arteries
Unstable angina	Ischaemia caused by dynamic complete or partial obstruction of a coronary artery due to plaque rupture or erosion with superimposed thrombosis
Myocardial infarction (type 1)	Myocardial necrosis caused by acute occlusion of a coronary artery due to plaque rupture or erosion with superimposed thrombosis
Myocardial infarction (type 2)	Supply demand imbalance where blood flow cannot meet the needs of the myocardium. This may be caused by fixed atheromatous obstruction with high myocardial demand for blood
Heart failure	Myocardial dysfunction due to infarction or ischaemia
Arrhythmia	Altered conduction due to ischaemia or infarction
Sudden death	Ventricular arrhythmia, asystole or massive myocardial infarction

hypertension. Early lesions have been found in the arteries of victims of accidental death in the second and third decades of life but clinical manifestations often do not appear until the sixth, seventh or eighth decade. During evolution of an atherosclerotic plaque, monocytes and other inflammatory cells bind to receptors expressed by endothelial cells. Subsequently, they migrate into the intima, and take up oxidised low-density lipoprotein (LDL) particles by phagocytosis to become lipid-laden macrophages or foam cells. Extracellular lipid pools appear in the intimal space when foam cells die and release their contents (Fig. 16.53). In response to cytokines and growth factors produced by activated macrophages, smooth muscle cells migrate from the media of the arterial wall into the intima, and change from a contractile to a fibroblastic phenotype, which can stabilise the atherosclerotic lesion. If this is successful, the lipid core will be covered by smooth muscle cells and matrix, producing a stable atherosclerotic plaque that will remain asymptomatic until it becomes large enough to obstruct arterial flow.

In an established atherosclerotic plaque, macrophages mediate inflammation and smooth muscle cells promote repair. If inflammation predominates, the plaque becomes active or unstable and may be complicated by ulceration and thrombosis. Cytokines, such as interleukin-1, tumour necrosis factor-alpha, interferon-gamma, platelet-derived growth factors and matrix metalloproteinases, are released by activated macrophages. They cause the intimal smooth muscle cells overlying the plaque to become senescent and the collagen cross-links within the plaque to degrade. This results in thinning of the protective fibrous cap, making the lesion vulnerable to mechanical stress that ultimately causes erosion, fissuring or rupture of the plaque surface (see Fig. 16.53). Any breach in the integrity of the plaque will expose its contents to blood and will trigger platelet aggregation and thrombosis that extend into the atheromatous plaque and the arterial lumen. This may cause partial or complete obstruction at the site of the lesion or distal embolisation, resulting in infarction or ischaemia of the affected organ. This common mechanism underlies acute coronary syndromes, as well as other manifestations of atherosclerotic disease such as lower limb ischaemia and stroke (Ch. 29).

The number and complexity of arterial plaques increase with age and risk factors (see below) but the rate of progression of individual plaques is variable. There is a complex and dynamic interaction between mechanical wall stress and atherosclerotic lesions. Vulnerable plaques are characterised by a lipid-rich core, a thin fibrocellular cap, speckled calcification and an increase in inflammatory cells that release specific enzymes to degrade matrix proteins. In contrast, stable plaques are typified by a small lipid pool, a thick fibrous cap, heavy calcification and

Nomenclature and main histology	Sequences in progression	Main growth mechanism	Earliest onset	Clinical correlation
Type I (initial) lesion Isolated macrophage foam cells	I		From first decade	
Type II (fatty streak) lesion Mainly intracellular lipid accumulation	II	Growth mainly by lipid accumulation		Clinically silent
Type III (intermediate) lesion Type II changes and small extracellular lipid pools	III		From third decade	
Type IV (atheroma) lesion Type II changes and core of extracellular lipid	IV			
Type V (fibroatheroma) lesion Lipid core and fibrotic layer, or multiple lipid cores and fibrotic layers, or mainly calcific, or mainly fibrotic	V	Accelerated smooth muscle and collagen increase	From fourth decade	Clinically silent or overt
Type VI (complicated) lesion Surface defect, haematoma-haemorrhage, thrombus	VI	Thrombosis, haematoma		

Fig. 16.53 The six stages of atherosclerosis: American Heart Association classification. From Stary HC, Chandler B, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. Circulation 1995; 92:1355–1374. © 1995 American Heart Association.

plentiful collagenous cross-links. Fissuring or rupture tends to occur at sites of maximal mechanical stress, particularly the margins of an eccentric plaque, and may be triggered by a surge in BP, such as during exercise or emotional stress. Surprisingly, most plaque events are subclinical and heal spontaneously, although this may allow thrombus to be incorporated into the lesion, producing plaque growth and further obstruction to flow.

Atherosclerosis may induce complex changes in the media that lead to arterial remodelling. Some arterial segments may slowly constrict (negative remodelling), while others may gradually enlarge (positive remodelling). These changes are important because they may amplify or minimise the degree to which atheroma encroaches into the arterial lumen.

Many risk factors have been identified for atherosclerosis but the causes are incompletely understood, since unknown factors account for up to 40% of the variation in risk from one person to the next.

Age and sex

Age is the most powerful independent risk factor for atherosclerosis and sex also plays a role. Pre-menopausal women have lower rates of disease than men, although the sex difference disappears after the menopause. Hormone replacement therapy (HRT) is not effective in the prevention of CAD, and HRT in post-menopausal women is associated with an increased risk of cardiovascular events.

Genetics

Atherosclerotic CAD often runs in families and a positive family history is common in patients with early-onset disease (age < 50 in men and < 55 in women). Twin studies have shown that a monozygotic twin of an affected individual has an eightfold increased risk and a dizygotic twin a fourfold increased risk of dying from CAD, compared to the general population due to a combination of shared genetic, environmental and lifestyle factors. The most common risk factors, such as hypertension, hyperlipidaemia and diabetes mellitus, are inherited in a polygenic manner.

Smoking

There is a strong relationship between cigarette smoking and CAD, especially in younger (< 70 years) individuals, and this is the most important modifiable risk factor.

Hypertension

The incidence of atherosclerosis increases as BP rises, and this is related to systolic and diastolic BP, as well as pulse pressure. Antihypertensive therapy reduces cardiovascular mortality, stroke and heart failure.

Hypercholesterolaemia

The risk of atherosclerosis rises with serum cholesterol concentrations and lowering serum total and LDL cholesterol concentrations reduces the risk of cardiovascular events.

Diabetes mellitus

This is a potent risk factor for all forms of atherosclerosis, especially type 2 diabetes mellitus. It is often associated with diffuse disease that is difficult to treat. Insulin resistance (normal glucose homeostasis with high levels of insulin) is associated with obesity and physical inactivity, and is also a risk factor for CAD. Glucose intolerance makes a major contribution to the high incidence of CAD in people from South Asia and some other ethnic groups.

Haemostatic factors

Platelet activation and high plasma fibrinogen concentrations are associated with an increased risk of coronary thrombosis, whereas antiphospholipid antibodies are associated with recurrent arterial thromboses.

Physical activity

Regular exercise (brisk walking, cycling or swimming for 20 minutes two or three times a week) has a protective effect, whereas inactivity roughly doubles the risk of CAD and is a major risk factor for stroke.

Obesity

Obesity, particularly if central or truncal, is an independent risk factor, although it is often associated with other adverse factors such as hypertension, diabetes mellitus and physical inactivity.

Alcohol

Excess alcohol consumption is associated with hypertension and cerebrovascular disease.

Diet

Diets deficient in fresh fruit, vegetables and polyunsaturated fatty acids are associated with an increased risk of cardiovascular disease. The introduction of a Mediterranean-style diet reduces cardiovascular events. However, dietary supplements, such as vitamins C and E, beta-carotene, folate and fish oils, do not reduce cardiovascular events and, in some cases, have been associated with harm.

Personality

While certain personality traits are associated with an increased risk, there is no evidence to support the popular belief that stress is a major cause of CAD.

Social deprivation

Social deprivation is strongly associated with cardiovascular disease. This may be partly due to associations with lifestyle risk factors, such as smoking and alcohol excess, which are more common in socially deprived individuals. Current guidelines recommend that treatment thresholds should be lowered for patients from socially deprived areas.

The effect of risk factors can be multiplicative rather than additive. People with a combination of risk factors are at greatest risk and so assessment should take account of all identifiable risk factors. It is important to distinguish between relative risk (the proportional increase in risk) and absolute risk (the actual chance of an event). For example, a man of 35 years with a plasma cholesterol of 7 mmol/L (approximately 170 mg/dL), who smokes 40 cigarettes a day, is much more likely to die from CAD within the next decade than a non-smoking man of the same age with a normal cholesterol, but the absolute likelihood of his dying during this time is small (high relative risk, low absolute risk).

Management

Two approaches can be employed. Primary prevention aims to introduce lifestyle changes or therapeutic interventions to prevent CAD and other forms of atherosclerosis in the whole population or in healthy individuals with an elevated risk of disease. Secondary prevention involves initiating treatment in patients who already have had an event, with the aim of reducing the risk of subsequent events. The distinction between primary and secondary prevention is increasingly seen as arbitrary since many people will have CAD despite having no symptoms or experienced any clinical events.

Primary prevention

The population-based strategy aims to modify the risk factors of the whole population through diet and lifestyle advice, on the basis that even a small reduction in smoking or average cholesterol, or modification of exercise and diet, will produce worthwhile benefits (Box 16.37). Some risk factors, such as obesity and smoking, are also associated with a higher risk of other diseases and should be actively discouraged through public health measures. The effectiveness of this approach has been demonstrated by introduction of legislation to restrict smoking in public places, which has been associated with reductions in rates of MI.

The targeted strategy aims to identify and to treat high-risk individuals who have a combination of risk factors that can be quantified by composite scoring systems. It is important to consider the absolute risk of atheromatous cardiovascular disease that an individual is facing before initiating treatment since this will help to determine whether the potential benefits of intervention are likely to outweigh the expense, inconvenience and possible side-effects of treatment. For example, a 65-year-old man



16.37 Population-based strategies to prevent coronary disease

- Do not smoke
- Take regular exercise (minimum of 20 mins, three times per week)
- Maintain an 'ideal' body weight
- Eat a mixed diet rich in fresh fruit and vegetables
- Aim to get no more than 10% of energy intake from saturated fat



16.38 Factors influencing myocardial oxygen supply and demand

Oxygen demand: cardiac work

- Heart rate
- Blood pressure
- Myocardial contractility
- Left ventricular hypertrophy
- Valve disease

Oxygen supply: coronary blood flow*

- Duration of diastole
- Coronary perfusion pressure (aortic diastolic minus coronary sinus or right atrial diastolic pressure)
- Coronary vasomotor tone
- Oxygenation:
Haemoglobin
Oxygen saturation

*Coronary blood flow occurs mainly in diastole.

with an average BP of 150/90 mmHg, who smokes and has diabetes mellitus with a total:high-density lipoprotein (HDL) cholesterol ratio of 8, has a 10-year risk of MI or stroke of 56%. Conversely, a 55-year-old woman who has an identical BP, is a non-smoker, does not have diabetes mellitus, and has a total:HDL cholesterol ratio of 6 has a much better outlook, with a 10-year coronary MI or stroke risk of 5.7%. Lowering cholesterol will reduce the risk in both of these individuals by 30% and lowering BP will produce a further 20% reduction. In combination, both strategies would reduce the risk of an event from 56% to 25% in the male patient (treat 4 patients to prevent one event) and from 5.7% to 2.5% in the female patient (treat 40 patients to prevent one event). Thresholds for treatment vary in different countries. In the UK and North America, current guidelines recommend initiation of cholesterol and BP-lowering therapies in individuals with a 10-year cardiovascular risk of 7.5%–10%.

Secondary prevention

This involves targeting interventions at individuals who have had cardiovascular disease. Patients who recover from a clinical event such as an MI are usually keen to help themselves and are particularly receptive to lifestyle advice, such as dietary modification and smoking cessation. Additional interventions that should be introduced in patients with angina pectoris or an acute coronary syndrome are discussed in more detail below.

Angina pectoris

Angina pectoris is a symptom complex caused by transient myocardial ischaemia, which occurs whenever there is an imbalance between myocardial oxygen supply and demand (Box 16.38).

Pathogenesis

Coronary atherosclerosis is by far the most common cause of angina pectoris. Angina may also occur in aortic valve disease and hypertrophic cardiomyopathy, and when the coronary arteries are involved with vasculitis or aortitis. The underlying mechanisms and risk factors for atherosclerosis have already been discussed. Approximately 10% of patients who report stable angina on effort have normal coronary arteries on angiography. The main causes are discussed in more detail below.

Coronary artery spasm

Angina may result from vasospasm of the coronary arteries. This may coexist with atherosclerosis, especially in unstable angina (see below),



16.39 Classification of angina pectoris and chest pain

Three characteristic features of angina

1. Constricting discomfort in the centre of the chest, or in the neck, shoulders, jaw or arms
2. Precipitated by physical exertion
3. Relieved by rest (or GTN) within 5 minutes

Classification

- **Typical angina:** All three features
- **Atypical angina:** Two features
- **Non-anginal chest pain:** One or no features

NICE classification

- **Possible angina:** Typical angina, atypical angina or non-anginal chest pain with an abnormal resting 12-lead ECG
- **Non-anginal chest pain:** Non-anginal chest pain with a normal resting 12-lead ECG

(ECG = electrocardiogram; GTN = glyceryl trinitrate; NICE = National Institute for Health and Care Excellence)

Physical examination is frequently unremarkable but should include a careful search for an ejection systolic murmur (particularly aortic stenosis and hypertrophic obstructive cardiomyopathy), important risk factors (hypertension, diabetes mellitus), left ventricular dysfunction (cardiomegaly, gallop rhythm), other manifestations of arterial disease (carotid bruits, peripheral arterial disease), and unrelated conditions that may exacerbate angina (anaemia, thyrotoxicosis).

Investigations

Stress testing and non-invasive imaging are advisable to confirm the diagnosis and to risk stratify patients with possible angina (see Box 16.39). An algorithm for the investigation and treatment of patients with stable angina is shown in Fig. 16.54. An exercise ECG is commonly performed using a standard treadmill or bicycle ergometer protocol, while monitoring the patient's pulse, BP and general condition. Planar or down-sloping ST segment depression of 1 mm or more is indicative of ischaemia (Fig. 16.55). Up-sloping ST depression is less specific; it often occurs in normal individuals and false-positive results can occur with digoxin therapy, left ventricular hypertrophy, bundle branch block and WPW syndrome. Overall, the exercise ECG confirms the history of exertional angina, provides an objective measure of the patient's exercise tolerance and is indicative of the underlying disease severity (Fig. 16.56) that can identify high-risk individuals with severe coronary disease in combination with other clinical features (Box 16.41). However, exercise testing may be normal in a substantial proportion of patients with CAD or may be inconclusive because of inadequate exercise tolerance due to reduced mobility or other non-cardiac problems.

If the diagnosis is unclear following the investigations listed above, CT coronary angiography is the imaging investigation of first choice. It clarifies the diagnosis and guides the use of preventative and anti-anginal therapies. It also serves as an excellent guide to the appropriate use of invasive cardiac catheterisation, reducing its use in those with normal coronary arteries (see Fig. 16.13) and targeting it to those with significant disease (see Fig. 16.54). Its use is also associated with a marked reduction in the future risk of MI, likely due to better targeted preventative interventions in those with previously unrecognised CAD.

In patients with known CAD, further imaging with myocardial perfusion scanning or stress echocardiography is indicated. A perfusion defect present during stress but not at rest provides evidence of reversible myocardial ischaemia (Fig. 16.57), whereas a persistent perfusion defect seen during both phases of the study is usually indicative of previous MI.

Coronary angiography provides detailed anatomical information about the extent and nature of CAD (see Fig. 16.15). It is usually performed when coronary artery bypass graft surgery or percutaneous coronary intervention is being considered.

Management

This should begin with a careful explanation of the problem and a discussion of the lifestyle and medical interventions that can be deployed to relieve symptoms and improve prognosis (Box 16.42). Anxiety and misconceptions often contribute to disability. For example, some patients avoid all forms of exertion because they believe that each attack of angina is a 'mini-heart attack' that results in permanent damage. Education and reassurance can dispel these misconceptions and make a huge difference to the patient's quality of life.

The principles of management involve:

- identification and treatment of risk factors
- advice on smoking cessation
- introduction of drug treatment for symptom control
- a careful assessment of the extent and severity of CAD
- identification of high-risk patients for treatment to improve life expectancy.

All patients with angina secondary to CAD should receive antiplatelet therapy. Low-dose (75 mg) aspirin should be prescribed and continued



16.40 Canadian Cardiovascular Society (CCS) angina score

Class I

- Angina only during strenuous or prolonged physical activity

Class II

- Slight limitation, with angina only during vigorous physical activity

Class III

- Moderate limitation where symptoms occur with everyday activities

Class IV

- Inability to perform any activity without angina or angina at rest, i.e. severe limitation

but may rarely occur as an isolated phenomenon in patients with normal coronary arteries on angiography. This is sometimes known as variant angina; when it is accompanied by transient ST elevation on the ECG, it is termed Prinzmetal's angina.

Syndrome X and microvascular angina

The constellation of typical angina on effort and normal coronary arteries on angiography with objective evidence of myocardial ischaemia on stress testing is sometimes known as Syndrome X. Many of these patients are women and the mechanisms of their symptoms are unclear. In a subset of patients, there is evidence of impaired myocardial vasodilatory reserve giving rise to the term microvascular angina. These disorders are poorly understood but carry a good prognosis and respond variably to anti-anginal therapy.

Other causes

Angina can occur in association with aortic stenosis, hypertrophic obstructive cardiomyopathy and aortitis, all of which are discussed in more detail later in this chapter. It may also rarely be found in association with some types of systemic vasculitis (Ch. 26).

Clinical features

The history is the most important factor in making the diagnosis. Stable angina is categorised as typical angina, atypical angina or non-anginal chest pain (Box 16.39; see also Fig. 9.1). Some patients find the discomfort comes when they start walking and that later it does not return despite greater effort ('warm-up angina'). The Canadian Cardiovascular Society (CCS) scoring system is commonly used to grade the severity of angina (Box 16.40). This is of clinical value, not only in documenting the severity of angina but also in assessing prognosis.

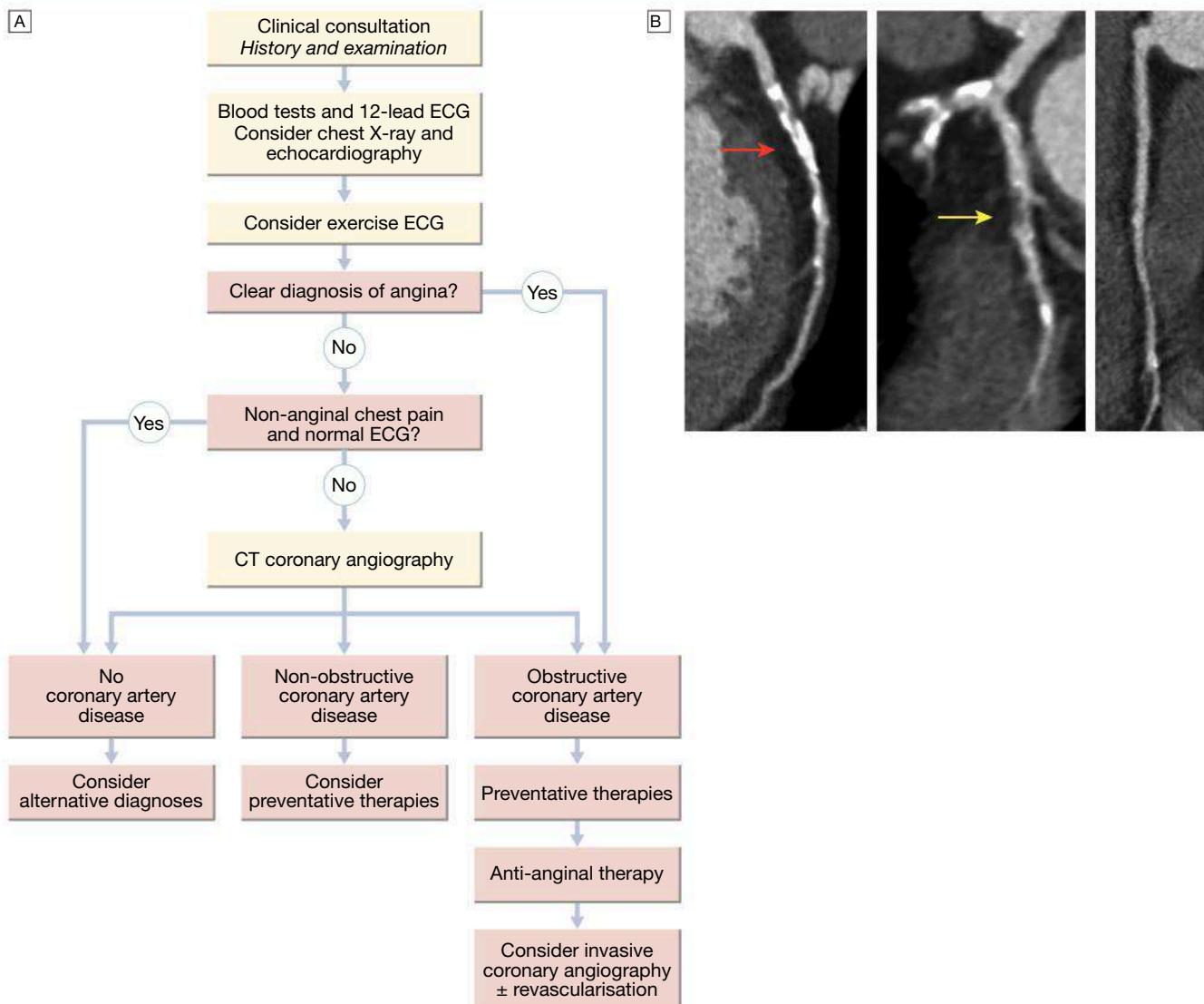


Fig. 16.54 **A** A scheme for the investigation and treatment of stable angina on effort. This scheme is best adopted for patients without prior known coronary artery disease and possible angina. For patients with known coronary artery disease, further stress imaging (echocardiography, radionuclide perfusion or magnetic resonance perfusion) rather than computed tomography coronary angiography is recommended. **B** An example CT coronary angiogram showing coronary artery disease in all three vessels with evidence of 'soft' lipid-rich plaque (yellow arrow) and extensive calcified coronary atheroma (red arrow).



Fig. 16.55 Forms of exercise-induced ST depression. **A** Planar ST depression is usually indicative of myocardial ischaemia. **B** Down-sloping depression also usually indicates myocardial ischaemia. **C** Up-sloping depression may be a normal finding.

indefinitely since it reduces the risk of MI. Clopidogrel (75 mg daily) is an equally effective alternative if aspirin causes dyspepsia or other side-effects. Similarly, all patients should be prescribed a statin, even if the serum cholesterol concentration is normal.

Anti-anginal drug therapy

The goal of anti-anginal therapy is to control symptoms using a regimen that is as simple as possible and does not cause side-effects. Five main groups of drug are used in the treatment of angina but there is

little evidence that one group is more effective than another. It is conventional to start therapy with sublingual glyceryl trinitrate (GTN) and a β -blocker, and then add a calcium channel antagonist or a long-acting nitrate if needed. If the combination of two drugs fails to achieve an acceptable symptomatic response, the addition of further classes of drug has modest additional benefits and coronary revascularisation should be considered.

Nitrates

Nitrates act directly on vascular smooth muscle to produce venous and arteriolar dilatation. Several preparations are available, as shown in Box 16.43. They help angina by lowering preload and afterload, which reduces myocardial oxygen demand, and by increasing myocardial oxygen supply through coronary vasodilatation. Sublingual GTN, administered from a metered-dose aerosol (400 μ g per spray) or as a tablet (300 or 500 μ g), is indicated for acute attacks and relieves symptoms in 2–3 minutes. It can also be used before taking exercise to avoid provoking symptoms. Sublingual GTN has a short duration of action and side-effects include headache, symptomatic hypotension and, rarely, syncope. A more prolonged therapeutic effect can be achieved by giving GTN transcutaneously as a patch (5–10 mg daily) or as a slow-release

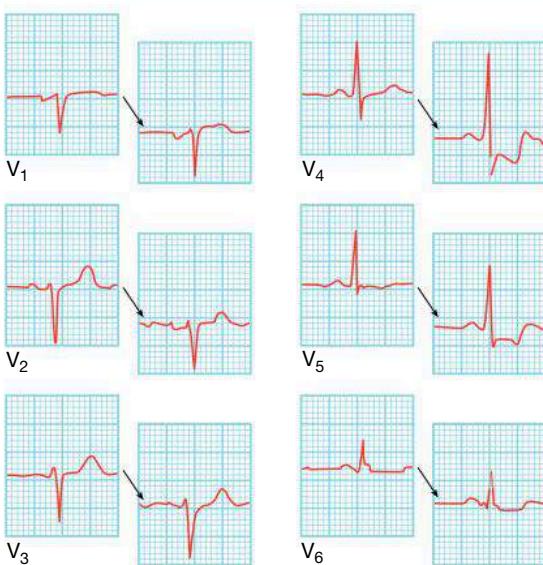


Fig. 16.56 A positive exercise test (chest leads only). The resting 12-lead ECG shows some minor T-wave changes in the inferolateral leads but is otherwise normal. After 3 minutes' exercise on a treadmill, there is marked planar ST depression in leads V_4 and V_5 (right-hand offset). Subsequent coronary angiography revealed critical three-vessel coronary artery disease.

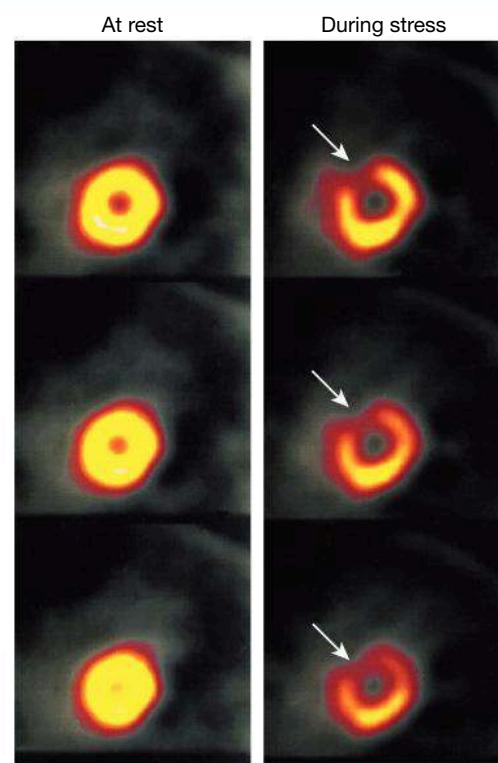


Fig. 16.57 A myocardial perfusion scan showing reversible anterior myocardial ischaemia. The images are cross-sectional tomograms of the left ventricle. The resting scans (left) show even uptake of the ^{99}Tc -labelled tetrofosmin and look like doughnuts. During stress there is reduced uptake of technetium, particularly along the anterior wall (arrows), and the scans look like crescents (right).

16



16.41 Risk stratification in patients with stable angina¹

High risk	Low risk
Recent-onset symptoms (< 6 months)	Long-standing symptoms
Class II to IV symptoms [†]	Class I symptoms [‡]
Diabetes mellitus	
Comorbidity	
Post-infarct angina	Predictable exertional angina
Ischaemia at low workload	Ischaemia only at high workload
Left main or three-vessel disease	Single-vessel or two-vessel disease
Poor left ventricular function	Good left ventricular function

¹Patients may fall between these two categories. ²Canadian Cardiovascular Society Classification.

buccal tablet (1–5 mg 4 times daily). Isosorbide dinitrate (10–20 mg 3 times daily) and isosorbide mononitrate (20–60 mg once or twice daily) can be given by mouth, unlike GTN, which undergoes extensive metabolism in the liver. Headache is common with oral nitrates but tends to diminish if the patient perseveres with the treatment. Continuous nitrate therapy can cause pharmacological tolerance but this can be avoided by a 6–8-hour nitrate-free period, best achieved at night when the patient is inactive. If nocturnal angina is a predominant symptom, long-acting nitrates can be taken at the end of the day.

Beta-blockers

These lower myocardial oxygen demand by reducing heart rate, BP and myocardial contractility, but they may provoke bronchospasm in patients with asthma. Dosages of commonly used beta-blockers are shown in Box 16.18. In theory, non-selective β -blockers may aggravate coronary vasospasm by blocking coronary artery β_2 -adrenoceptors, and so a once-daily cardioselective preparation such as slow-release metoprolol (50–200 mg daily) or bisoprolol (5–15 mg daily) is preferable. Beta-blockers should not be withdrawn abruptly, as rebound effects may precipitate dangerous arrhythmias, worsening angina or precipitate MI: the β -blocker withdrawal syndrome.



16.42 Advice to patients with stable angina

- Do not smoke
- Aim for an ideal body weight
- Take regular exercise (exercise up to, but not beyond, the point of chest discomfort is beneficial and may promote collateral vessels)
- Avoid severe unaccustomed exertion, and vigorous exercise after a heavy meal or in very cold weather
- Take sublingual nitrate before undertaking exertion that may induce angina



16.43 Duration of action of some nitrate preparations

Preparation	Peak action	Duration of action
Sublingual GTN	4–8 mins	10–30 mins
Buccal GTN	4–10 mins	30–300 mins
Transdermal GTN	1–3 hrs	Up to 24 hrs
Oral isosorbide dinitrate	45–120 mins	2–6 hrs
Oral isosorbide mononitrate	45–120 mins	6–10 hrs

(GTN = glyceryl trinitrate)

Calcium channel antagonists

These drugs lower myocardial oxygen demand by reducing BP and myocardial contractility. Since dihydropyridine calcium antagonists, such as nifedipine and amlodipine, may cause a reflex tachycardia, it is best to use them in combination with a β -blocker. In contrast, verapamil and diltiazem can be used as monotherapy because they slow SA node

i	16.44 Calcium channel antagonists used for the treatment of angina		
Drug	Dose	Feature	
Nifedipine	5–20 mg 3 times daily*	May cause marked tachycardia	
Nicardipine	20–40 mg 3 times daily	May cause less myocardial depression than the other calcium antagonists	
Amlodipine	2.5–10 mg daily	Long-acting	
Verapamil	40–80 mg 3 times daily*	Commonly causes constipation; useful anti-arrhythmic properties	
Diltiazem	60–120 mg 3 times daily*	Similar anti-arrhythmic properties to verapamil	

*Once- or twice-daily sustained-release preparations are available.

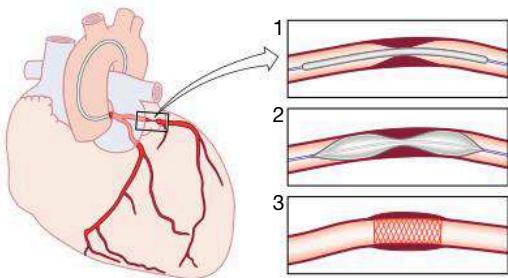


Fig. 16.58 Percutaneous coronary intervention. A guidewire is advanced from the radial (or femoral) artery to the coronary artery under radiographic control (1). A fine balloon catheter is then advanced over the guidewire to the stenotic coronary artery and the balloon is inflated to dilate the stenosis (2). When this has been achieved, a stent is usually placed at the site of the stenosis to maintain patency of the artery (3) (see text for more details).

firing, inhibit conduction through the AV node and tend to cause bradycardia. They are particularly useful when β -blockers are contraindicated. Calcium channel antagonists reduce myocardial contractility and must be used with care in patients with poor LV function, since they can aggravate or precipitate heart failure. Other unwanted effects include peripheral oedema, flushing, headache and dizziness (Box 16.44).

Potassium channel activators

Nicorandil (10–30 mg twice daily orally) is the only drug in this class that is currently available for clinical use. It acts as a vasodilator with effects on the arterial and venous systems, and has the advantage that it does not exhibit the tolerance seen with nitrates.

I₁ channel antagonist

Ivabradine (initial dose 2.5–5 mg twice daily orally) is the first in this class of drug. It induces bradycardia by modulating ion channels in the sinus node. It does not inhibit myocardial contractility and appears to be safe in patients with heart failure.

Ranolazine

Ranolazine (initial dose 375 mg twice daily) inhibits the late inward sodium current in coronary artery smooth muscle cells, with a secondary effect on calcium flux and vascular tone, reducing angina symptoms.

Non-pharmacological treatments

Percutaneous coronary intervention

Percutaneous coronary intervention (PCI) involves passing a fine guide-wire across a coronary stenosis under radiographic control and using

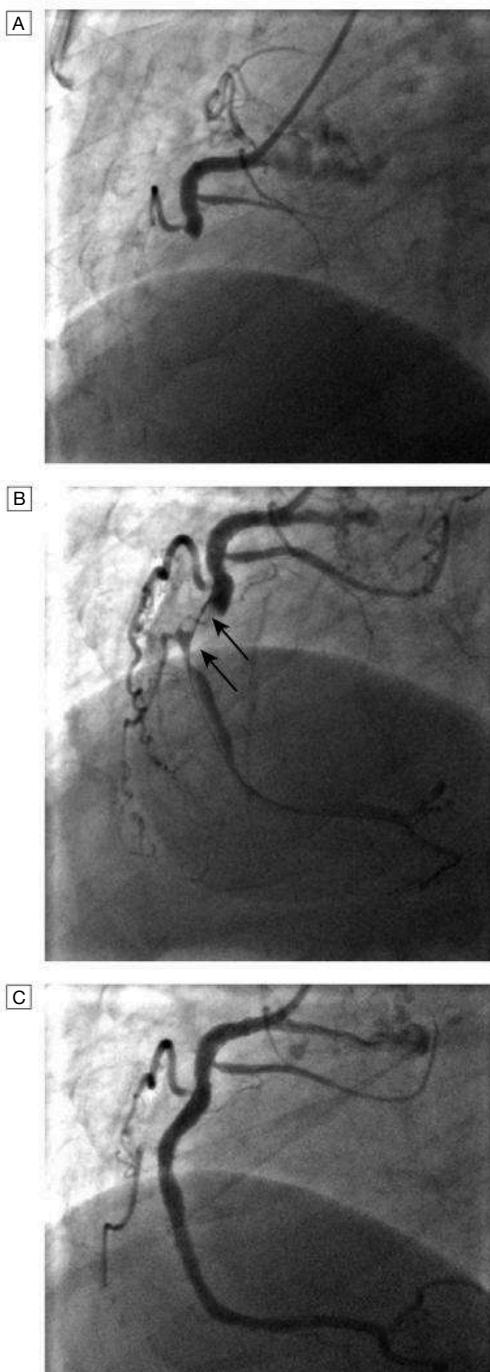


Fig. 16.59 Primary percutaneous coronary intervention. **A** Acute right coronary artery occlusion. **B** Initial angioplasty demonstrates a large thrombus filling defect (arrows). **C** Complete restoration of normal flow following intracoronary stenting.

it to position a balloon, which is then inflated to dilate the stenosis (Fig. 16.58). This can be combined with deployment of a coronary stent, which is a piece of metallic ‘scaffolding’ that can be impregnated with drugs with antiproliferative properties and that helps to maximise and maintain dilatation of a stenosed vessel. The routine use of stents in appropriate vessels reduces both acute complications and the incidence of clinically important restenosis (Fig. 16.59).

Treatment with PCI often provides excellent symptom control but it does not reduce MI or improve survival in patients with chronic stable angina. It is mainly used in single- or two-vessel disease. Stenoses in bypass grafts can be dilated, as well as those in the native coronary arteries. The technique is often used to provide

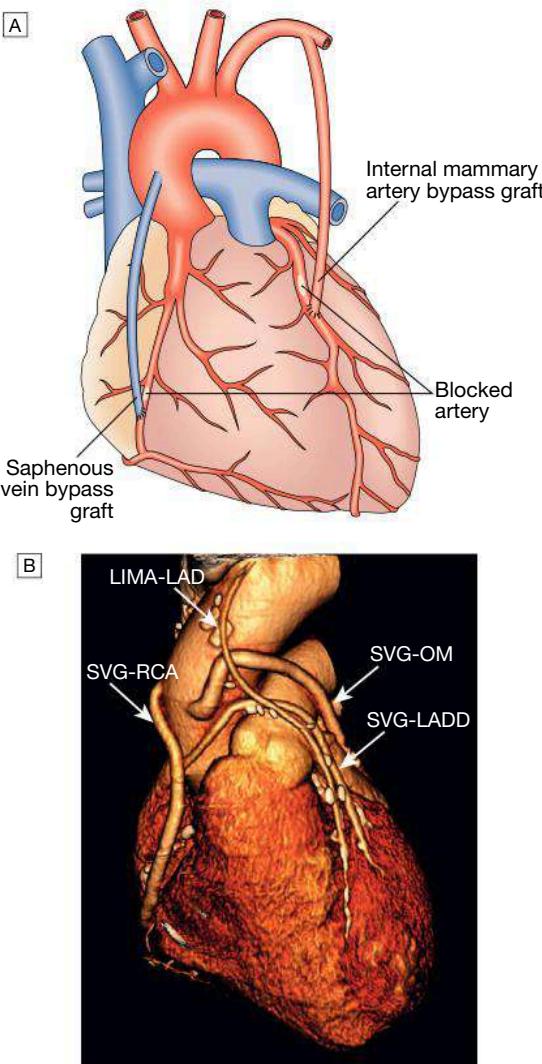


Fig. 16.60 Coronary artery bypass graft surgery. **A** Narrowed or stenosed arteries are bypassed using saphenous vein grafts connected to the aorta or by utilising the internal mammary artery. **B** Three-dimensional reconstruction of multidetector CT of the heart. The image shows the patent saphenous vein grafts (SVG) to the right coronary artery (RCA), obtuse marginal branch (OM) and diagonal branch (LADD), and left internal mammary artery graft (LIMA) to the left anterior descending (LAD) coronary artery.

palliative therapy for patients with recurrent angina after coronary artery bypass grafting.

The main acute complications of PCI are occlusion of the coronary artery by thrombus or a loose flap of intima (coronary artery dissection), and consequent MI. This occurs in about 2%–5% of procedures and can often be corrected by further intervention, although emergency coronary artery bypass grafting may occasionally be required. Mild myocardial damage, as indicated by elevation of cardiac troponin, occurs in up to 25%–30% of cases. The main long-term complication of PCI is restenosis, in up to one-third of cases. This is due to a combination of elastic recoil and smooth muscle proliferation and tends to occur within 3 months. Stenting substantially reduces the risk of restenosis, probably because it allows the operator to achieve more complete dilatation. Drug-eluting stents reduce this risk further by allowing an antiproliferative drug, such as sirolimus or paclitaxel, to elute slowly from the coating and prevent neo-intimal hyperplasia and in-stent restenosis. These are especially indicated in patients with diabetes, or in arteries with long calcific lesions or small diameters. Recurrent angina (affecting up to 5%–10% of patients at 6 months) may require further PCI or bypass grafting.

The risk of complications and the likely success of the procedure are closely related to the complexity of the disease, the experience of the operator and the presence of important comorbidity, such as diabetes and peripheral arterial disease. A good outcome is less likely if the target lesion is complex, long, eccentric or calcified, lies on a bend or within a tortuous vessel, involves a branch or contains thrombus.

Adjunctive therapy with a potent platelet inhibitor such as the P2Y12 receptor antagonists (clopidogrel, prasugrel or ticagrelor) in combination with aspirin and heparin improves the outcome following PCI.

Coronary artery bypass grafting

The internal mammary arteries, radial arteries or reversed segments of the patient's own saphenous vein can be used to bypass coronary artery stenoses (Fig. 16.60). This usually involves major surgery under cardio-pulmonary bypass but, in some cases, grafts can be applied to the beating heart: 'off-pump' surgery. The operative mortality is approximately 1.5% but risks are higher in older patients, those with poor left ventricular function and those with significant comorbidity, such as renal failure.

Approximately 90% of patients are free of angina 1 year after coronary artery bypass grafting (CABG), but fewer than 60% of patients are asymptomatic after 5 or more years. Early post-operative angina is usually due to graft failure arising from technical problems during the operation, or poor 'run-off' due to disease in the distal native coronary vessels. Late recurrence of angina may be caused by progressive disease in the native coronary arteries or graft degeneration. Fewer than 50% of vein grafts are patent 10 years after surgery. Arterial grafts have a much better long-term patency rate with more than 80% of internal mammary artery grafts patent at 10 years. This has led many surgeons to consider total arterial revascularisation during CABG surgery. Aspirin (75–150mg daily) and clopidogrel (75mg daily) both improve graft patency, and one or the other should be prescribed indefinitely. Intensive lipid-lowering therapy slows the progression of disease in the native coronary arteries and bypass grafts and reduces clinical cardiovascular events. There is substantial excess cardiovascular morbidity and mortality in patients who continue to smoke after bypass grafting. Persistent smokers are twice as likely to die in the 10 years following surgery than those who give up at surgery.

Survival is improved by CABG in symptomatic patients with left main stem stenosis or three-vessel coronary disease when the LAD, CX and right coronary arteries are involved, or two-vessel disease involving the proximal LAD coronary artery. Improvement in survival is most marked in those with impaired left ventricular function or positive stress testing prior to surgery and in those who have undergone left internal mammary artery grafting.

Neurological complications are common, with a 1%–5% risk of perioperative stroke. Between 30% and 80% of patients develop short-term cognitive impairment that typically resolves within 6 months. There are also reports of long-term cognitive decline that may be evident in more than 30% of patients at 5 years. PCI and CABG are compared in Box 16.45.

Prognosis

The prognosis of CAD is related to the burden of CAD and the degree of left ventricular dysfunction. A patient with single-vessel disease and good left ventricular function has a 5-year survival of more than 90%. In contrast, a patient with severe left ventricular dysfunction and extensive three-vessel disease has a 5-year survival of less than 30% unless revascularisation is performed. Although symptoms are a poor guide to prognosis, the 5-year mortality of patients with severe angina (CCS angina scale III or IV, see Box 16.40) is nearly double that of patients with mild symptoms.

Some considerations specific to angina in old age are listed in Box 16.46.

Acute coronary syndrome

Acute coronary syndrome is a term that encompasses both unstable angina and myocardial infarction. Unstable angina is characterised by

i	16.45 Comparison of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG)	
	PCI	CABG
Death	<0.5%	< 1.5%
Myocardial infarction*	2%	10%
Hospital stay	6–18 hrs	5–8 days
Return to work	2–5 days	6–12 weeks
Recurrent angina	15%–20% at 6 months	10% at 1 year
Repeat revascularisation	10%–20% at 2 years	2% at 2 years
Neurological complications	Rare	Common (see text)
Other complications	Emergency CABG Vascular damage related to access site	Diffuse myocardial damage Infection (chest, wound) Wound pain

*Defined as CK-MB > 2× normal



16.46 Angina in old age

- Incidence:** coronary artery disease increases in old age and affects women almost as often as men.
- Comorbid conditions:** anaemia and thyroid disease are common and may worsen angina.
- Calcific aortic stenosis:** common and should be sought in all older people with angina.
- Atypical presentations:** when myocardial ischaemia occurs, age-related changes in myocardial compliance and diastolic relaxation can cause the presentation to be with symptoms of heart failure, such as breathlessness, rather than with chest discomfort.
- Angioplasty and coronary artery bypass surgery:** provide symptomatic relief, although with increased procedure-related morbidity and mortality. Outcome is determined by the number of diseased vessels, severity of cardiac dysfunction and the number of concomitant diseases, as much as by age itself.

new-onset or rapidly worsening angina (crescendo angina), angina on minimal exertion or angina at rest in the absence of myocardial injury. Myocardial infarction (MI) is distinguished from unstable angina by the occurrence of myocardial necrosis and is diagnosed when myocardial injury occurs in the presence of clinical evidence of acute myocardial ischaemia (Box 16.47). The diagnosis of a prior MI can be made when any one of the features shown in Box 16.48 is present.

Acute coronary syndrome may present as a new phenomenon in patients with no previous history of heart disease or against a background of chronic stable angina. Approximately 12% of patients with acute coronary syndrome die within 1 month and 20% within 6 months of the index event. The risk markers that are indicative of an adverse prognosis include recurrent ischaemia, extensive ECG changes at rest or during pain, raised plasma troponin I or T concentrations, arrhythmias and haemodynamic complications (hypotension, mitral regurgitation) during episodes of ischaemia. Careful assessment and risk stratification are important because these guide the use of more complex pharmacological and interventional treatments (Fig. 16.61 and see Fig. 16.69), which can improve outcome.

Pathogenesis

Acute coronary syndrome almost always occurs in patients who have coronary atherosclerosis. The culprit lesion that precipitates the acute event is usually a complex ulcerated or fissured atheromatous plaque with adherent platelet-rich thrombus and local coronary artery spasm

i	16.47 Classification and criteria for diagnosis of acute myocardial infarction
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Criteria for acute myocardial infarction

The term acute myocardial infarction (MI) should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th centile upper reference limit and at least one of the following:

- Symptoms of myocardial ischaemia
- New ischaemic ECG changes
- Development of pathological Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology
- Identification of a coronary thrombus by angiography or autopsy

Classification of acute myocardial infarction

- **Type 1 MI:** Acute atherothrombosis in the artery supplying the infarcted myocardium
- **Type 2 MI:** An imbalance between myocardial oxygen supply and demand unrelated to acute atherothrombosis
- **Type 3 MI:** Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cardiac troponin values become available or abnormal
- **Type 4 MI:** MI caused during percutaneous coronary intervention (PCI; type 4a). Other types include stent thrombosis (type 4b) and restenosis (type 4c) and consistent with type 1 MI
- **Type 5 MI:** MI caused during coronary artery bypass grafting

Coronary procedure-related MI ≤ 48 hours after the index procedure is arbitrarily defined by an elevation of cardiac troponin values > 5× for type 4a MI and > 10× for type 5 MI of the 99th centile upper reference limit in patients with normal baseline values together with at least one of the following:

- New ischaemic ECG changes (this criterion is related to type 4a MI only)
- Development of new pathological Q waves
- Imaging evidence of loss of viable myocardium that is presumed to be new and consistent with an ischaemic aetiology
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolisation

Adapted from Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. Eur Heart J 2019; 40: 237–269.

i	16.48 Criteria for diagnosis of a previously unrecognised myocardial infarction
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- Abnormal Q waves with or without symptoms in the absence of non-ischaemic causes
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology
- Patho-anatomical findings of a prior MI

Adapted from Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. Eur Heart J 2019; 40: 237–269.

(see Fig. 16.53). These vascular changes during an acute coronary syndrome are dynamic, such that the degree of obstruction may either increase, leading to complete vessel occlusion, or regress due to the effects of platelet disaggregation and endogenous fibrinolysis.

Myocardial infarction

The criteria for diagnosis classification of acute MI and classification of subtypes of MI are shown in Box 16.47. In acute type 1 MI, occlusive thrombus is present at the site of rupture or erosion of an atherosomatous plaque; so-called atherothrombosis. The thrombus may undergo spontaneous lysis over the course of the next few days, although irreversible myocardial damage will have occurred. Without treatment, the artery responsible for the type 1 MI remains permanently occluded in 20%–30% of patients. Since the process of infarction progresses over several hours (Fig. 16.62), most patients present when it is still possible to salvage myocardium and improve outcome.

1. Find points for each predictive factor

Killip class	Points	SBP (mmHg)	Points	Heart rate Points (beats/min)	Age (years)	Points	Serum creatinine Points level ($\mu\text{mol/L}$)	Other risk factors	Points
I	0	≤ 80	58	≤ 50	0	≤ 30	0	0–34	1
II	20	80–99	53	50–69	3	30–39	8	35–70	4
III	39	100–119	43	70–89	9	40–49	25	71–105	7
IV	59	120–139	34	90–109	15	50–59	41	106–140	10
		140–159	24	110–149	24	60–69	58	141–176	21
		160–199	10	150–199	38	70–79	75	177–353	14
		≥ 200	0	≥ 200	46	80–89	≥ 95	28	
					≥ 90	100			

2. Sum points for all predictive factors

Killip class	+	SBP	+	Heart rate	+	Age	+	Creatinine level	+	Cardiac arrest at admission	+	ST-segment deviation	+	Elevated cardiac biomarker concentrations	=	Total points
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3. Look up risk corresponding to total points

Total points	≤ 60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	≥ 250
Probability of in-hospital death (%)	≤ 0.2	0.3	0.4	0.6	0.8	1.1	1.6	2.1	2.9	3.9	5.4	7.3	9.8	13	18	23	29	36	44	≥ 52

Examples

A patient has Killip class II, SBP of 99 mmHg, heart rate of 100 beats/min, is 65 years of age, has a serum creatinine level of 76 $\mu\text{mol/L}$, did not have a cardiac arrest at admission but did have ST-segment deviation and elevated cardiac troponin. His score would be: $20 + 53 + 15 + 58 + 7 + 0 + 28 + 14 = 195$. This gives about a 16% risk of having an in-hospital death.

Similarly, a patient with Killip class I, SBP of 80 mmHg, heart rate of 60 beats/min, who is 55 years of age, has a serum creatinine level of 30 $\mu\text{mol/L}$, and no risk factors would have the following score: $0 + 58 + 3 + 41 + 1 = 103$. This gives about a 0.9% risk of having an in-hospital death.

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Fig. 16.61 Risk stratification in the acute coronary syndrome: the GRACE score. Killip class refers to a categorisation of the severity of heart failure based on easily obtained clinical signs. The main clinical features are as follows: class I = no heart failure; class II = crackles audible halfway up the chest; class III = crackles heard in all the lung fields; class IV = cardiogenic shock. To convert creatinine in $\mu\text{mol/L}$ to mg/dL, divide by 88.4. (SBP = systolic blood pressure) From Scottish Intercollegiate Guidelines Network (SIGN) Guideline no. 93 – Acute coronary syndromes; updated February 2013.

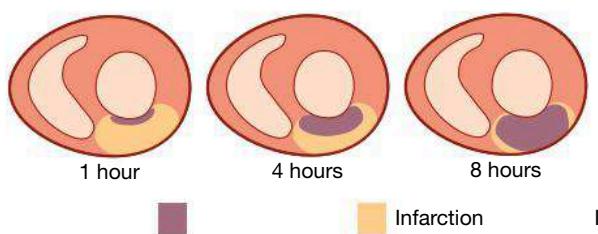


Fig. 16.62 The time course of myocardial infarction. The relative proportion of ischaemic, infarcting and infarcted tissue slowly changes over a period of 12 hours. In the early stages of myocardial infarction, a significant proportion of the myocardium in jeopardy is potentially salvageable.

Myocardial infarction may also occur as the result of an imbalance between the blood supply and metabolic demands of the heart (type 2 MI). This may occur because of the presence of CAD and major non-cardiac stress, such as sepsis in a patient with three-vessel CAD, or because there is overwhelming demand in the presence of unobstructed coronary arteries, such as an excessively fast heart rate from a primary arrhythmia. For the diagnosis of type 2 MI, there needs to be clinical evidence of ischaemia, such as ECG changes or symptoms of chest pain. This should be distinguished from myocardial injury where there is evidence of elevated cardiac troponin concentration

(myocardial necrosis) without evidence of myocardial ischaemia, such as occurs in myocarditis. Myocardial injury can be acute or chronic depending upon its underlying cause.

The term type 3 MI is used to describe the situation where there is sudden death presumed to be due to MI. The terms type 4 and type 5 MI are used to describe the situations where MI occurs during or following the conduct of the coronary revascularisation procedures PCI and CABG, respectively. In these situations, clinical evidence of ischaemia is required to distinguish MI from procedure-related myocardial injury.

Clinical features

The differential diagnosis of acute coronary syndrome is wide and includes most causes of central chest pain or collapse. Chest pain at rest is the cardinal symptom but breathlessness, vomiting and collapse are also common features (Box 16.49). The pain occurs in the same sites as angina but is usually more severe and lasts longer; it is often described as a tightness, heaviness or constriction in the chest. In acute MI, the pain can be excruciating, and the patient's expression and pallor may vividly convey the seriousness of the situation. Most patients are breathless and, in some, this is the only symptom. Painless or 'silent' MI may also occur and is particularly common in older patients or those with diabetes mellitus. If syncope occurs, it is usually caused by an arrhythmia or profound hypotension. Vomiting and sinus bradycardia are often due to vagal stimulation and are particularly common in patients with inferior MI. Nausea and vomiting may also be caused or aggravated by opiates given for pain relief. Sometimes



16.49 Clinical features of acute coronary syndromes

Symptoms

- Prolonged cardiac pain: chest, throat, arms, epigastrum or back
- Anxiety and fear of impending death
- Nausea and vomiting
- Breathlessness
- Collapse/syncope

Physical signs

Signs of sympathetic activation

- Pallor
- Sweating
- Tachycardia

Signs of vagal activation

- Vomiting
- Bradycardia

Signs of impaired myocardial function

- Hypotension, oliguria, cold peripheries
- Narrow pulse pressure
- Raised jugular venous pressure
- Third heart sound
- Quiet first heart sound
- Diffuse apical impulse
- Lung crepitations

Low-grade fever

temporary and often resolves following reperfusion therapy. If there is clinical deterioration due to second-degree or complete AV block, a temporary pacemaker should be considered. AV block complicating anterior infarction is more serious because asystole may suddenly supervene. A prophylactic temporary pacemaker should be inserted in these patients.

Recurrent angina

Patients who develop recurrent angina at rest or on minimal exertion following an acute coronary syndrome are at high risk and should be considered for prompt coronary angiography with a view to revascularisation. Patients with dynamic ECG changes and ongoing pain should be treated with intravenous glycoprotein IIb/IIIa receptor antagonists (tirofiban 400 ng/kg/min for 30 min, then 100 ng/kg/min for 48 hrs, or abciximab, initially 180 µg/kg, then 2 µg/kg/min for up to 72 hrs). Patients with resistant pain or marked haemodynamic changes should be considered for intra-aortic balloon counterpulsation and emergency coronary revascularisation. Post-infarct angina occurs in up to 50% of patients treated with thrombolysis. Most patients have a residual stenosis in the infarct-related vessel, despite successful thrombolysis, and this may cause angina if there is still viable myocardium downstream. For this reason, all patients who have received successful thrombolysis should be considered for early (within the first 24 hours) coronary angiography with a view to coronary revascularisation.



16.50 Common arrhythmias in acute coronary syndrome

- Ventricular fibrillation
- Ventricular tachycardia
- Accelerated idioventricular rhythm
- Ventricular ectopics
- Atrial fibrillation
- Sinus bradycardia (particularly after inferior myocardial infarction)
- Atrioventricular block

infarction occurs in the absence of physical signs. Sudden death, from ventricular fibrillation or asystole, may occur immediately and often within the first hour. If the patient survives this most critical stage, the liability to dangerous arrhythmias remains, but diminishes as each hour goes by. It is vital that patients know not to delay calling for help if symptoms occur. Complications may occur in all forms of acute coronary syndrome but have become less frequent in the modern era of immediate or early coronary revascularisation. Specific complications of acute coronary syndromes and their management are discussed below.

Arrhythmias

Arrhythmias are common in patients with acute coronary syndrome (Box 16.50) but are often transient and of no haemodynamic or prognostic importance. The risk of arrhythmia can be minimised by adequate pain relief, rest and the correction of hypokalaemia. VF occurs in 5%–10% of patients who reach hospital and is thought to be the major cause of death in those who die before receiving medical attention. Prompt defibrillation restores sinus rhythm and is life-saving. The prognosis of patients with early VF (within the first 48 hours) who are successfully and promptly resuscitated is identical to that of patients who do not suffer VF. The presence of ventricular arrhythmias during the convalescent phase of acute coronary syndrome may be a marker of poor ventricular function and may herald sudden death. Selected patients may benefit from electrophysiological testing and specific anti-arrhythmic therapy, including ICDs, as discussed in the previous section on cardiac arrhythmias. AF is a common but frequently transient arrhythmia, and usually does not require emergency treatment. However, if it causes a rapid ventricular rate with hypotension or circulatory collapse, prompt cardioversion is essential. In other situations, digoxin or a β-blocker is usually the treatment of choice. AF may be a feature of impending or overt left ventricular failure, and therapy may be ineffective if heart failure is not recognised and treated appropriately. Anticoagulation is required if AF persists. Bradycardia may occur but does not require treatment unless there is hypotension or haemodynamic deterioration, in which case atropine (0.6–1.2 mg IV) may be given. Inferior MI may be complicated by AV block, which is usually

Acute heart failure

Acute heart failure usually reflects extensive myocardial damage and is associated with a poor prognosis. All the other complications of MI are more likely to occur when acute heart failure is present. The assessment and management of heart failure is discussed in more detail earlier in this chapter.

Pericarditis

This only occurs following infarction and is particularly common on the second and third days. The patient may recognise that a different pain has developed, even though it is at the same site, and that it is positional and tends to be worse or sometimes present only on inspiration. A pericardial rub may be audible. Opiate-based analgesia should be used. Non-steroidal (NSAIDs) and steroidal anti-inflammatory drugs may increase the risk of aneurysm formation and myocardial rupture in the early recovery period, and should be avoided.

Dressler syndrome

This syndrome is characterised by persistent fever, pericarditis and pleurisy, and is probably due to autoimmunity. The symptoms tend to occur a few weeks or even months after MI and often subside after a few days. If the symptoms are prolonged or severe, treatment with high-dose aspirin, NSAIDs or even glucocorticoid steroids may be required.

Papillary muscle rupture

This typically presents with acute pulmonary oedema and shock due to the sudden onset of severe mitral regurgitation. Examination usually reveals a pansystolic murmur and third heart sound but the murmur may be quiet or absent in patients with severe regurgitation. The diagnosis is confirmed by echocardiography, and emergency valve replacement may be necessary. Lesser degrees of mitral regurgitation due to papillary muscle dysfunction are common and may be transient.

Ventricular septal rupture

This usually presents with sudden haemodynamic deterioration accompanied by a new loud pansystolic murmur radiating to the right sternal border, which may be difficult to distinguish from acute mitral regurgitation. Rupture of the intraventricular septum causes left-to-right shunting through a ventricular septal defect, which tends to cause acute right heart failure rather than pulmonary oedema. Doppler echocardiography and right heart catheterisation will confirm the diagnosis. Treatment is by emergency surgical repair; without this, the condition is usually fatal.

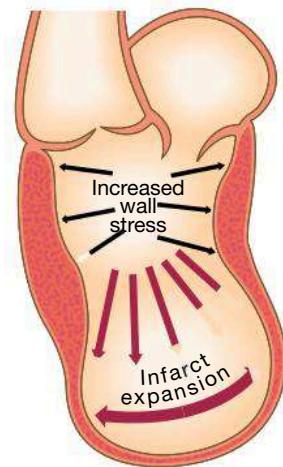


Fig. 16.63 Infarct expansion and ventricular remodelling. Full-thickness myocardial infarction causes thinning and stretching of the infarcted segment (infarct expansion), which leads to increased wall stress with progressive dilatation and hypertrophy of the remaining ventricle (ventricular remodelling).

Ventricular rupture

Rupture of the ventricle may lead to cardiac tamponade and is usually fatal, although it is occasionally possible to support a patient with an incomplete rupture until emergency surgery can be performed.

Embolism

Thrombus often forms on the endocardial surface of freshly infarcted myocardium. This can lead to systemic embolism and occasionally causes a stroke or ischaemic limb. Venous thrombosis and pulmonary embolism may occur but have become less common with the use of prophylactic anticoagulants and early mobilisation.

Ventricular remodelling

This is a potential complication of an acute transmural MI due to thinning and stretching of the infarcted segment. This leads to an increase in wall stress with progressive dilatation and hypertrophy of the remaining ventricle (ventricular remodelling, Fig. 16.63). As the ventricle dilates, it becomes less efficient and heart failure may supervene. Infarct expansion occurs over a few days and weeks but ventricular remodelling can take years. Beta-blocker, ACE inhibitor and mineralocorticoid receptor antagonist therapies can reduce late ventricular remodelling and prevent the onset of heart failure.

Ventricular aneurysm

Ventricular aneurysm develops in approximately 10% of patients with MI and is particularly common when there is persistent occlusion of the infarct-related vessel. Heart failure, ventricular arrhythmias, mural thrombus and systemic embolism are all recognised complications of aneurysm formation. Other features include a paradoxical impulse on the chest wall, persistent ST elevation on the ECG, and sometimes an unusual bulge from the cardiac silhouette on the chest X-ray. Echocardiography is diagnostic. Surgical removal of a left ventricular aneurysm carries a high morbidity and mortality but is sometimes necessary.

Investigations

Electrocardiogram

The standard 12-lead ECG is central to confirming the diagnosis and deciding immediate management but may be difficult to interpret if there is bundle branch block or previous MI. The initial ECG may be normal or non-diagnostic in one-third of cases. Repeated ECGs are important, especially where the diagnosis is uncertain or the patient has recurrent or persistent symptoms. The earliest ECG change is usually ST-segment deviation. With proximal occlusion of a major coronary artery, ST-segment elevation

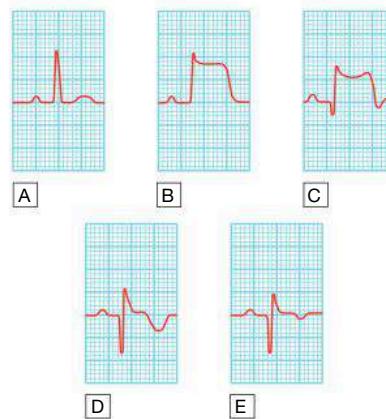


Fig. 16.64 The serial evolution of ECG changes in transmural myocardial infarction. **A** Normal ECG complex. **B** Acute ST elevation ('the current of injury'). **C** Progressive loss of the R wave, developing Q wave, resolution of the ST elevation and terminal T-wave inversion. **D** Deep Q wave and T-wave inversion. **E** Old or established infarct pattern; the Q wave tends to persist but the T-wave changes become less marked. The rate of evolution is very variable but, in general, stage B appears within minutes, stage C within hours, stage D within days and stage E after several weeks or months. This should be compared with the 12-lead ECGs in Figs. 16.65–16.67.

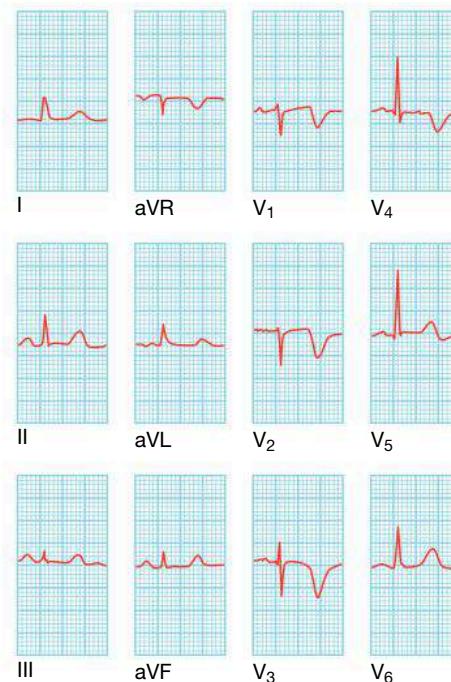


Fig. 16.65 Recent anterior non-ST elevation (subendocardial) myocardial infarction. This ECG demonstrates deep symmetrical T-wave inversion, together with a reduction in the height of the R wave in leads V₁, V₂, V₃ and V₄.

(or new bundle branch block) is seen initially, with later diminution in the size of the R wave and, in transmural (full-thickness) infarction, development of a Q wave. Subsequently, the T wave becomes inverted because of a change in ventricular repolarisation; this change persists after the ST segment has returned to normal. These sequential features (Fig. 16.64) are sufficiently reliable for the approximate age of the infarct to be deduced.

In non-ST segment elevation acute coronary syndrome, there is partial occlusion of a major vessel or complete occlusion of a minor vessel, causing unstable angina or partial-thickness (subendocardial) MI. This is usually associated with ST-segment depression and T-wave changes. In the presence of infarction, this may be accompanied by some loss of R waves in the absence of Q waves (Fig. 16.65).

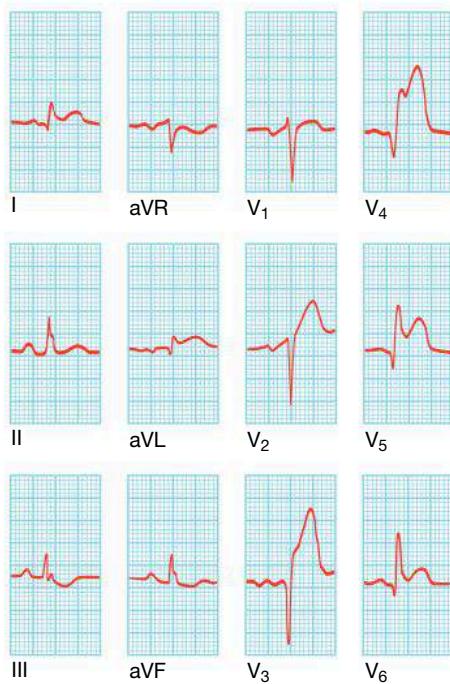


Fig. 16.66 Acute transmural anterior myocardial infarction. This ECG was recorded from a patient who had developed severe chest pain 6 hours earlier. There is ST elevation in leads I, aVR, V_1 , V_3 , V_4 , V_5 and V_6 , and there are Q waves in leads V_3 , V_4 and V_5 . Anterior infarcts with prominent changes in leads V_2 , V_3 and V_4 are sometimes called ‘anteroseptal’ infarcts, as opposed to ‘anterolateral’ infarcts, in which the ECG changes are predominantly found in V_4 , V_5 and V_6 .

The ECG changes are best seen in the leads that ‘face’ the ischaemic or infarcted area. When there has been anteroseptal infarction, abnormalities are found in one or more leads from V_1 to V_4 , while anterolateral infarction produces changes from V_4 to V_6 , in aVL and in lead I. Inferior infarction is best shown in leads II, III and aVF, while, at the same time, leads I, aVL and the anterior chest leads may show ‘reciprocal’ changes of ST depression (Figs. 16.66 and 16.67). Infarction of the posterior wall of the LV does not cause ST elevation or Q waves in the standard leads, but can be diagnosed by the presence of reciprocal changes (ST depression and a tall R wave in leads V_1 – V_4). Some infarctions (especially inferior) also involve the RV. This may be identified by recording from additional leads placed over the right precordium.

Cardiac biomarkers

Serial measurements of cardiac troponin concentration should be taken. In unstable angina, there is no detectable rise in troponin and the diagnosis is made on the basis of the clinical features and investigations such as ECG or coronary angiography. In contrast, MI causes a rise in plasma concentrations of troponin T and I and other cardiac muscle enzymes (Fig. 16.68 and see Box 16.47). Levels of troponins T and I increase within 3–6 hours, peak at about 36 hours and remain elevated for up to 2 weeks. A full blood count may reveal the presence of a leucocytosis, which reaches a peak on the first day. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are also elevated. Lipids should be measured within 24 hours of presentation because there is often a transient fall in cholesterol in the 3 months following infarction.

Radiography

A chest X-ray should be performed since this may demonstrate pulmonary oedema that is not evident on clinical examination (see Fig. 16.25). The heart size is often normal but there may be cardiomegaly due to pre-existing myocardial damage.

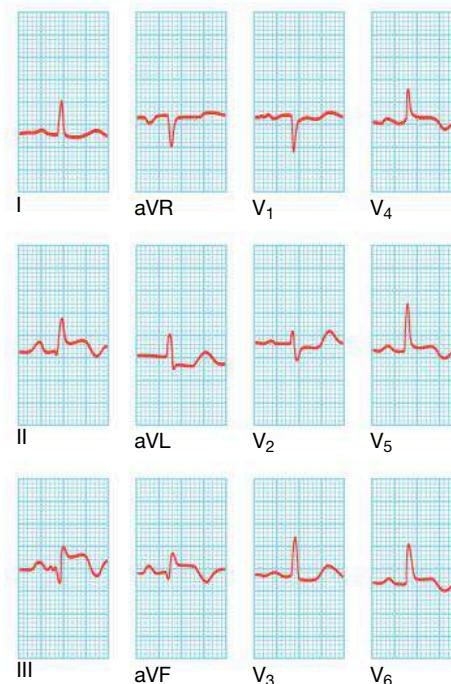


Fig. 16.67 Acute transmural inferolateral myocardial infarction. This ECG was recorded from a patient who had developed severe chest pain 4 hours earlier. There is ST elevation in inferior leads II, III and aVF and lateral leads V_4 , V_5 and V_6 . There is also ‘reciprocal’ ST depression in leads aVL and V_2 .

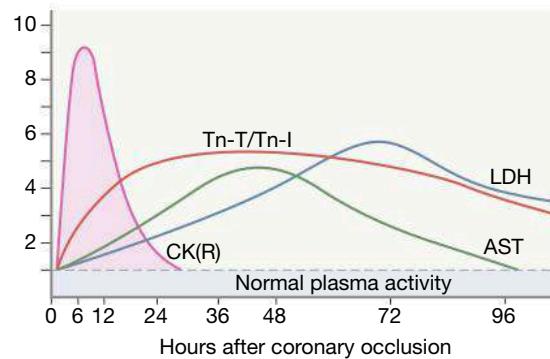


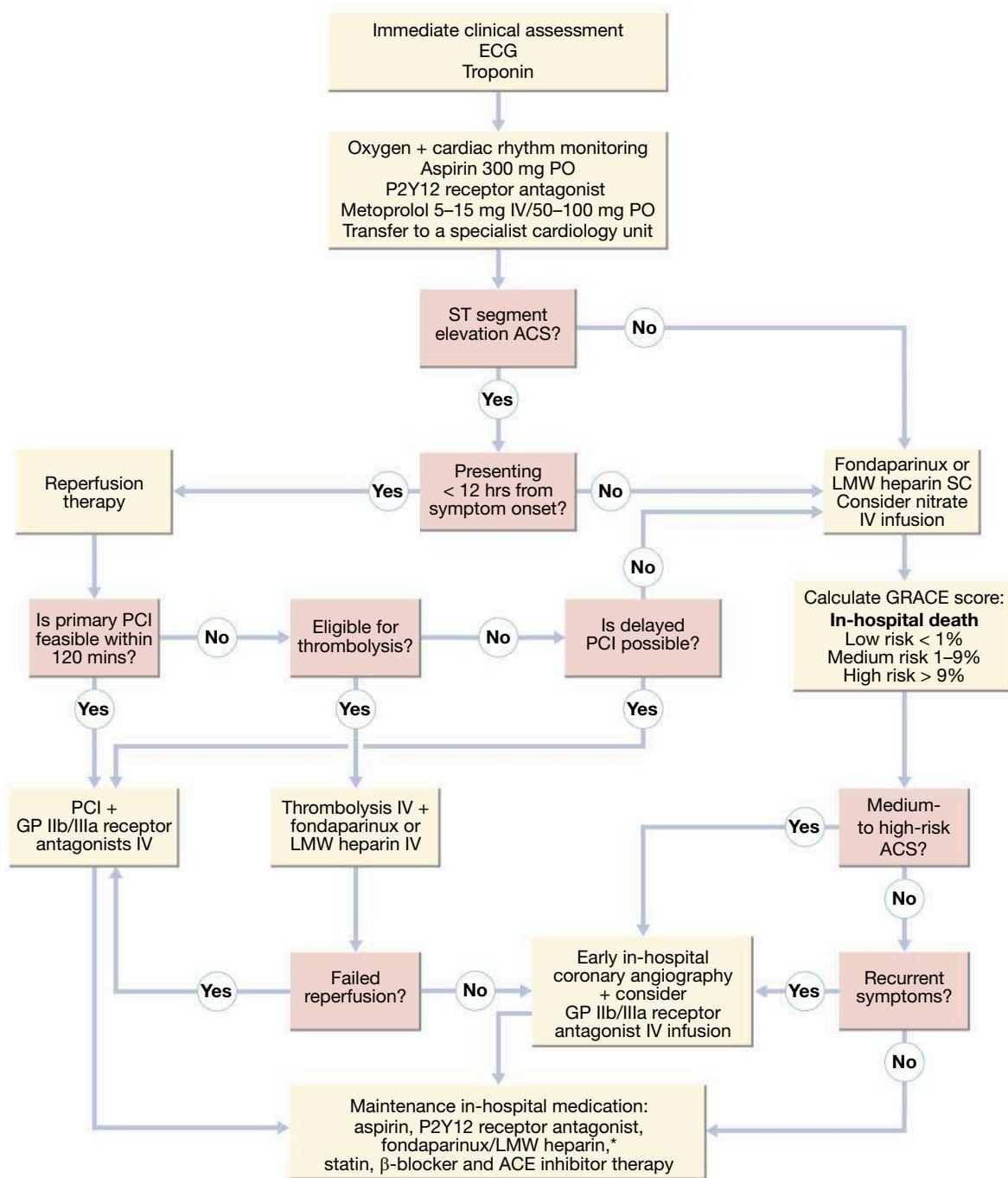
Fig. 16.68 Changes in plasma cardiac biomarker concentrations after myocardial infarction. Creatine kinase (CK) and troponins T (Tn-T) and I (Tn-I) are the first to rise, followed by aspartate aminotransferase (AST) and then lactate (hydroxybutyrate) dehydrogenase (LDH). In patients treated with reperfusion therapy, a rapid rise in plasma creatine kinase (curve CK(R)) occurs, due to a washout effect.

Echocardiography

Echocardiography is normally performed before discharge from hospital and is useful for assessing ventricular function and for detecting important complications, such as mural thrombus, cardiac rupture, ventricular septal defect, mitral regurgitation and pericardial effusion.

Coronary angiography

Coronary arteriography should be considered with a view to revascularisation in all patients at moderate or high risk of a further event, including those who fail to settle on medical therapy, those with extensive ECG changes, those with an elevated cardiac troponin and those with severe pre-existing stable angina (see Fig. 16.69). This often reveals disease that is amenable to PCI or urgent CABG (see below).



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Fig. 16.69 Summary of treatment for acute coronary syndrome (ACS). *Not required following PCI. For details of the GRACE score, see Fig. 16.61. (ACE = angiotensin-converting enzyme; ECG = electrocardiogram; GP = glycoprotein; IV = intravenous; LMW = low-molecular-weight; PCI = percutaneous coronary intervention; PO = by mouth; SC = subcutaneous) Adapted from Scottish Intercollegiate Guidelines Network (SIGN) Guideline no. 93 – Acute coronary syndromes, February 2007 and updated in SIGN 148, April 2016.

Management

All patients with suspected acute coronary syndrome should be admitted urgently to hospital because there is a risk of death or recurrent myocardial ischaemia during the early unstable phase. Appropriate medical therapy can reduce the incidence of these complications by at least 60%. The key elements of immediate in-hospital management are shown in Fig. 16.69. Patients should ideally be managed in a dedicated cardiac unit, where the necessary expertise, monitoring and resuscitation facilities are available. Clinical risk factor analysis using tools such as the GRACE score (see Fig. 16.61) should be performed to identify patients that should be selected for intensive therapy, and

specifically early inpatient coronary angiography (thresholds vary, but a score of 140 points or more supports early intervention). If there are no complications and risk factor analysis shows that angiography is not required, the patient can be mobilised from the second day and discharged after 2–3 days. Low-risk patients without spontaneous angina may be considered for an exercise tolerance test 4–6 weeks after the acute coronary syndrome. This will help to identify those individuals who may require further investigation, and may help to boost the confidence of the remainder. Management of the acute event is discussed below and the principles of long-term management are summarised in Box 16.51.

i	16.51 Late management of myocardial infarction
	Risk stratification and further investigation See text for details
	Lifestyle modification
	<ul style="list-style-type: none"> • Diet (weight control, lipid-lowering, 'Mediterranean diet') • Cessation of smoking • Regular exercise
	Secondary prevention drug therapy
	<ul style="list-style-type: none"> • Antiplatelet therapy (aspirin and/or clopidogrel) • β-blocker • ACE inhibitor/ARB • Statin • Additional therapy for control of diabetes and hypertension • Mineralocorticoid receptor antagonist
	Rehabilitation
	Devices
	<ul style="list-style-type: none"> • Implantable cardiac defibrillator (high-risk patients)
	(ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker)

Analgesia

Adequate analgesia is essential, not only to relieve distress but also to lower adrenergic drive and thereby reduce vascular resistance, BP, infarct size and susceptibility to ventricular arrhythmias. Intravenous opiates (initially, morphine sulphate 5–10 mg or diamorphine 2.5–5 mg) and antiemetics (initially, metoclopramide 10 mg) should be administered, and titrated until the patient is comfortable. Intramuscular injections should be avoided because the clinical effect may be delayed by poor skeletal muscle perfusion, and a painful haematoma may form following thrombolytic or antithrombotic therapy.

Reperfusion therapy

Immediate reperfusion therapy with PCI (see Fig. 16.59) is indicated when the ECG shows new bundle branch block or characteristic ST-segment elevation in two contiguous leads of 1 mm or more in the limb leads or 2 mm or more in the chest leads. This is the treatment of choice for those presenting within 12 hours of symptom onset (see Fig. 16.69). If PCI cannot be performed within 120 minutes for any reason, and thrombolysis is contraindicated, the procedure should be performed as soon as practically possible. Patients should be considered for PCI within the first 24 hours, even if they have reperfused spontaneously or with thrombolytic therapy. Coronary artery patency is restored in over 95% of patients undergoing PCI. The procedure preserves left ventricular function with a marked reduction in the progression to heart failure, more than halves rates of recurrent MI and dramatically improves mortality with more than 95% 1-year survival rates in clinical trials. Successful therapy is also associated with rapid pain relief, resolution of acute ST elevation and occasional transient arrhythmias.

Reperfusion therapy with PCI confers no immediate mortality benefit in patients with non-ST segment elevation acute coronary syndrome. Selected medium- to high-risk patients do benefit from in-hospital coronary angiography and coronary revascularisation but this does not need to take place in the first 12 hours unless there are high-risk features, such as ongoing chest pain or ECG changes.

Thrombolytic therapy

If primary PCI cannot be achieved in a timely manner in patients with ST-segment elevation MI (see Fig. 16.69), thrombolytic therapy should be administered. Although the survival advantage is not as good as primary PCI, mortality is reduced and this is maintained for at least 10 years. The benefit of thrombolytic therapy is greatest in those patients who receive treatment within the first 12 hours and especially the first 2 hours. Modern thrombolytic agents, such as tenecteplase (TNK) and reteplase (rPA), are analogues of human tissue plasminogen activator and can be given as an intravenous bolus, allowing prompt treatment to be given in

i	16.52 Relative contraindications to thrombolytic therapy
	<ul style="list-style-type: none"> • Active internal bleeding • Previous subarachnoid or intracerebral haemorrhage • Uncontrolled hypertension • Recent surgery (within 1 month) • Recent trauma (including traumatic resuscitation) • High probability of active peptic ulcer • Pregnancy

the emergency department or in the pre-hospital setting. The major hazard of thrombolytic therapy is bleeding. Cerebral haemorrhage causes 4 extra strokes per 1000 patients treated, and the incidence of other major bleeds is between 0.5% and 1%. Accordingly, the treatment should be withheld if there is a significant risk of serious bleeding (Box 16.52). For some patients, thrombolytic therapy is contraindicated or fails to achieve coronary arterial reperfusion (see Fig. 16.69). Emergency PCI may then be considered, particularly where there is evidence of cardiogenic shock. Even where thrombolysis successfully achieves reperfusion, PCI should be considered within 24 hours to prevent recurrent infarction and improve outcome.

Antithrombotic therapy

Oral administration of 75–325 mg aspirin daily improves survival, with a 25% relative risk reduction in mortality. The first tablet (300 mg) should be given orally within the first 12 hours and therapy should be continued indefinitely if there are no side-effects. A P2Y12 receptor antagonist (ticagrelor 180 mg, followed by 90 mg twice daily), prasugrel (60 mg, followed by 10 mg daily) or clopidogrel (300 mg, followed by 75 mg daily) should be given in combination with aspirin for up to 12 months. Glycoprotein IIb/IIIa receptor antagonists, such as tirofiban and abciximab, block the final common pathway of platelet aggregation and are potent inhibitors of platelet-rich thrombus formation. They are of particular benefit in high-risk patients with acute coronary syndromes who undergo PCI, especially those with a high thrombus burden at angiography or who have received inadequate prior antiplatelet therapy. These intravenous agents should be administered in addition to oral aspirin and a P2Y12 receptor antagonist. Anticoagulation further reduces the risk of thromboembolic complications, and prevents re-infarction in the absence of reperfusion therapy or after successful thrombolysis. Anticoagulation can be achieved using unfractionated heparin, fractionated (low-molecular-weight) heparin or a pentasaccharide, such as subcutaneous fondaparinux (2.5 mg daily). Comparative clinical trials show that the pentasaccharides have the best safety and efficacy profile but low-molecular-weight heparin, such as subcutaneous enoxaparin (1 mg/kg twice daily), is a reasonable alternative. Anticoagulation should be continued for 8 days or until discharge from hospital or coronary revascularisation has been completed. A period of treatment with an oral anticoagulant should be considered if there is persistent AF or evidence of extensive anterior infarction with mural thrombus because these patients are at increased risk of systemic thromboembolism.

Anti-anginal therapy

Sublingual glyceryl trinitrate (300–500 μ g) is a valuable first-aid measure in unstable angina or threatened infarction, and intravenous nitrates (glyceryl trinitrate 0.6–1.2 mg/hr or isosorbide dinitrate 1–2 mg/hr) are useful for the treatment of left ventricular failure and the relief of recurrent or persistent ischaemic pain. Intravenous β -blockade (atenolol 5–10 mg or metoprolol 5–15 mg given over 5 min) relieves pain, reduces arrhythmias and improves short-term mortality in patients who present within 12 hours of symptom onset (see Fig. 16.69). However, they should be avoided if there is heart failure (pulmonary oedema), hypotension (systolic BP < 105 mmHg) or bradycardia (heart rate < 65/min). Nifedipine or amlodipine can be added if there is persistent chest discomfort but these drugs may cause tachycardia if used alone. Verapamil and diltiazem should be used if β -blockade

is contraindicated. In the longer term, treatment with an oral β -blocker reduces long-term mortality by approximately 25% among the survivors of an acute MI, especially those with left ventricular systolic dysfunction. Patients with heart failure, COPD or peripheral arterial disease appear to derive similar secondary preventative benefits from β -blocker therapy and should receive maintenance therapy unless poorly tolerated. Unfortunately, a minority of patients do not tolerate β -blockade because of bradycardia, AV block, hypotension or asthma.

Renin–angiotensin blockade

Long-term treatment with ACE inhibitors such as enalapril (10 mg twice daily) or ramipril (2.5–5 mg twice daily) can counteract ventricular remodelling, prevent the onset of heart failure, improve survival, reduce recurrent MI and avoid rehospitalisation. The benefits are greatest in those with overt heart failure (clinical or radiological) but extend to patients with asymptomatic left ventricular systolic dysfunction and those with preserved left ventricular function. They should be considered in all patients with acute coronary syndrome. Caution must be exercised in hypovolaemic or hypotensive patients because ACE inhibition may exacerbate hypotension and impair coronary perfusion. In patients intolerant of ACE inhibitors, ARBs such as valsartan (40–160 mg twice daily) or candesartan (4–16 mg daily) are alternatives that are better tolerated.

Mineralocorticoid receptor antagonists

Patients with acute MI and left ventricular dysfunction (ejection fraction <35%) and either pulmonary oedema or diabetes mellitus further benefit from additional mineralocorticoid receptor antagonists (eplerenone 25–50 mg daily, or spironolactone 25–50 mg daily).

Lipid-lowering therapy

The benefits of lowering serum cholesterol following acute coronary syndrome have been demonstrated in several large-scale randomised trials. All patients should receive therapy with HMG CoA reductase enzyme inhibitors (statins) after acute coronary syndrome, irrespective of serum cholesterol concentrations. Patients with serum LDL cholesterol concentrations above 3.2 mmol/L (approximately 120 mg/dL) benefit from more intensive therapy, such as atorvastatin (80 mg daily). Other agents, such as ezetimibe, fibrates, anion exchange resins and injectable PCSK9 inhibitors, may be used in cases where total cholesterol or LDL cholesterol cannot be lowered adequately using statins alone.

Smoking cessation

The 5-year mortality of patients who continue to smoke cigarettes is double that of those who quit smoking at the time of their acute coronary syndrome. Giving up smoking is the single most effective contribution a patient can make to their future. The success of smoking cessation can be increased by supportive advice and pharmacological therapy.

Diet and exercise

Maintaining an ideal body weight, eating a Mediterranean-style diet, taking regular exercise, and achieving good control of hypertension and diabetes mellitus may all improve the long-term outlook.

Rehabilitation

When there are no complications, the patient can mobilise on the second day, return home in 2–3 days and gradually increase activity, with the aim of returning to work in 4 weeks. The majority of patients may resume driving after 1–4 weeks, although, in most countries, drivers of heavy goods and public service vehicles require special assessment before returning to work. Emotional problems, such as denial, anxiety and depression, are common and must be addressed. Some patients are severely and even permanently incapacitated as a result of the psychological effects of acute coronary syndrome rather than the physical ones, and all benefit from thoughtful explanation, counselling and reassurance. Many patients



16.53 Myocardial infarction in old age

- **Atypical presentation:** often with anorexia, fatigue, weakness, delirium or falls rather than chest pain.
- **Case fatality:** rises steeply. Hospital mortality exceeds 25% in those over 75 years old, which is five times greater than that seen in those aged less than 55 years.
- **Survival benefit of treatments:** not influenced by age. The absolute benefit of evidence-based treatments may therefore be greatest in older people.
- **Hazards of treatments:** rise with age (for example, increased risk of intracerebral bleeding after thrombolysis) and are due partly to increased comorbidity.
- **Quality of evidence:** older patients, particularly those with significant comorbidity, were under-represented in many of the randomised controlled clinical trials that helped to establish the treatment of myocardial infarction. The balance of risk and benefit for many treatments, such as thrombolysis and primary percutaneous transluminal coronary angiography, in frail older people is uncertain.

mistakenly believe that stress was the cause of their heart attack and may restrict their activity inappropriately. The patient's spouse or partner will also require emotional support, information and counselling. Formal rehabilitation programmes, based on graded exercise protocols with individual and group counselling, are often very successful and, in some cases, have been shown to improve quality of life and long-term outcome.

Implantable defibrillators

These devices are of benefit in preventing sudden cardiac death in patients who have severe left ventricular impairment (ejection fraction $\leq 30\%$) after MI. More details are provided in the section on treatment of cardiac arrhythmias.

Type 2 myocardial infarction

The optimal management and treatment of patients with type 2 MI has yet to be established. There is currently no evidence that treatments for type 1 MI are effective in the setting of type 2 MI. The focus for patients with type 2 MI should be on treating the underlying cause of their presentation and, where applicable, their previously undiagnosed concomitant CAD.

Prognosis

The prognosis of patients who have survived an acute coronary syndrome is related to the extent of residual myocardial ischaemia, the degree of myocardial damage and the presence of ventricular arrhythmias. In almost one-quarter of all cases of MI, death occurs within a few minutes without medical care. Half the deaths occur within 24 hours of the onset of symptoms and about 40% of all affected patients die within the first month. The prognosis of those who survive to reach hospital is much better, with a 28-day survival of more than 85%. Patients with unstable angina have a mortality of approximately half that of patients with MI. Early death is usually due to an arrhythmia and is independent of the extent of MI. However, late outcomes are determined by the extent of myocardial damage, and unfavourable features include poor left ventricular function, AV block and persistent ventricular arrhythmias. The prognosis is worse for anterior than for inferior infarcts. Bundle branch block and high cardiac marker concentrations both indicate extensive myocardial damage. Old age, depression and social isolation are also associated with a higher mortality. Of those who survive an acute attack, more than 80% live for a further year, about 75% for 5 years, 50% for 10 years and 25% for 20 years.

Some considerations specific to myocardial infarction in old age are listed in Box 16.53.

Non-cardiac surgery in patients with heart disease

Non-cardiac surgery, particularly major vascular, abdominal or thoracic surgery, can precipitate serious perioperative cardiac complications,

i 16.54 Major risk factors for cardiac complications of non-cardiac surgery

- Recent (< 6 months) myocardial infarction or unstable angina
- Severe coronary artery disease: left main stem or three-vessel disease
- Severe stable angina on effort
- Severe left ventricular dysfunction
- Severe valvular heart disease (especially aortic stenosis)

such as MI and death, in patients with CAD and other forms of heart disease. Careful pre-operative cardiac assessment may help to determine the balance of benefit versus risk on an individual basis, and identify measures that minimise the operative risk (Box 16.54).

A hypercoagulable state is part of the normal physiological response to surgery, and may promote coronary thrombosis leading to an acute coronary syndrome in the early post-operative period. Patients with a history of recent PCI or acute coronary syndrome are at greatest risk and, whenever possible, elective non-cardiac surgery should be avoided for 3 months after such an event. Where possible, antiplatelet, statin and β-blocker therapies should be continued throughout the perioperative period.

Careful attention to fluid balance during and after surgery is particularly important in patients with impaired left ventricular function and valvular heart disease because vasopressin is released as part of the normal physiological response to surgery and, in these circumstances, the over-zealous administration of intravenous fluids can easily precipitate heart failure. Patients with severe valvular heart disease, particularly aortic stenosis and mitral stenosis, are also at increased risk because they may not be able to increase their cardiac output in response to the stress of surgery.

Atrial fibrillation is a common post-operative complication in patients with pre-existing heart disease which may be triggered by hypoxia, myocardial ischaemia or heart failure. It usually terminates spontaneously when the precipitating factors have been eliminated, but digoxin or β-blockers can be prescribed to control the heart rate if necessary.

Peripheral arterial disease

Peripheral arterial disease (PAD) has been estimated to affect about 20% of individuals aged 55–75 years in the UK. Only 25% of patients present with symptoms, the commonest of which is intermittent claudication (IC). About 1%–2% of patients with IC per year progress to a point where amputation or revascularisation is required. However, the annual mortality rate of people with IC is about 5%, which is 2–3 times higher than the general population of the same age and sex. The cause of death is typically an MI or stroke, reflecting the fact that IC nearly always occurs in association with widespread atherosclerosis.

Pathogenesis

In developed countries, almost all PAD is due to atherosclerosis and the risk factors are the same as described in patients with CAD. As with CAD, plaque rupture is responsible for the most serious manifestations of PAD, and not infrequently occurs in a plaque that hitherto has been asymptomatic. The clinical manifestations depend on the anatomical site, the presence or absence of a collateral supply, the speed of onset and the mechanism of injury (Box 16.55). Approximately 5%–10% of patients with PAD have diabetes but this proportion increases to 30%–40% in those with severe limb ischaemia. The mechanism of PAD in diabetes is atheroma affecting the medium to large-sized arteries rather than obstructive microangiopathy and so diabetes is not a contraindication to lower limb revascularisation. Nevertheless, patients with diabetes and PAD pose a number of particular problems (Box 16.56).

i 16.55 Factors influencing the clinical manifestations of peripheral arterial disease (PAD)

Anatomical site

Cerebral circulation

- TIA, amaurosis fugax, vertebrobasilar insufficiency

Renal arteries

- Hypertension and renal failure

Mesenteric arteries

- Mesenteric angina, acute intestinal ischaemia

Limbs (legs >> arms)

- Intermittent claudication, critical limb ischaemia, acute limb ischaemia

Collateral supply

- In a patient with a complete circle of Willis, occlusion of one carotid artery may be asymptomatic
- In a patient without cross-circulation, stroke is likely

Speed of onset

- Where PAD develops slowly, a collateral supply will develop
- Sudden occlusion of a previously normal artery is likely to cause severe distal ischaemia

Mechanism of injury

Haemodynamic

- Plaque must reduce arterial diameter by 70% ('critical stenosis') to reduce flow and pressure at rest. On exertion a moderate stenosis may become 'critical'. This mechanism tends to have a relatively benign course due to collateralisation

Thrombotic

- Occlusion of a long-standing critical stenosis may be asymptomatic due to collateralisation. However, acute rupture and thrombosis of a non-haemodynamically significant plaque usually has severe consequences

Atheroembolic

- Symptoms depend on embolic load and size
- Carotid (TIA, amaurosis fugax or stroke) and peripheral arterial (blue toe/finger syndrome) plaque are common examples

Thromboembolic

- Usually secondary to atrial fibrillation
- The consequences are usually dramatic, as the thrombus load is often large and occludes a major, previously healthy, non-collateralised artery suddenly and completely

(TIA = transient ischaemic attack)

Clinical features

Symptomatic PAD affects the legs about eight times more commonly than the arms. Several locations may be affected, including the aortoiliac vessels, the femoropopliteal vessels and the infrapopliteal vessels. One or more of these segments may be affected in a variable and asymmetric manner. In the arm, the subclavian artery is the most common site of disease. Peripheral artery disease can present clinically in a variety of ways, as detailed below.

Intermittent claudication

This is the most common presentation of PAD affecting the lower limbs. It is characterised by ischaemic pain affecting the muscles of the leg. The pain is usually felt in the calf because the disease most commonly affects the superficial femoral artery, but it may be felt in the thigh or buttock if the iliac arteries are involved. Typically, the pain comes on after walking, often once a specific distance has been covered, and rapidly subsides on resting. Resumption of walking leads to a return of the pain. Most patients describe a cyclical pattern of exacerbation and resolution due to the progression of disease and the subsequent development of collaterals. When PAD affects the upper limbs, arm claudication may occur, although this is uncommon.

Critical limb ischaemia

Critical limb ischaemia (CLI) is defined as rest pain requiring opiate analgesia, or ulceration or gangrene that has been present for more than

16.56 Peripheral vascular disease in diabetes	
Feature	Difficulty
Arterial calcification	Spuriously high ABPI due to incompressible ankle vessels. Inability to clamp arteries for the purposes of bypass surgery. Resistant to angioplasty
Immunocompromise	Prone to rapidly spreading cellulitis, gangrene and osteomyelitis
Multisystem arterial disease	Coronary and cerebral arterial disease increase the risks of intervention
Distal disease	Diabetic vascular disease has a predilection for the calf vessels. Although vessels in the foot are often spared, performing a satisfactory bypass or angioplasty to these small vessels is a technical challenge
Sensory neuropathy	Even severe ischaemia and/or tissue loss may be completely painless. Diabetic patients often present late with extensive destruction of the foot. Loss of proprioception leads to abnormal pressure loads and worsens joint destruction (Charcot joints)
Motor neuropathy	Weakness of the long and short flexors and extensors leads to abnormal foot architecture, abnormal pressure loads, callus formation and ulceration
Autonomic neuropathy	Leads to a dry foot deficient in sweat that normally lubricates the skin and is antibacterial. Scaling and fissuring create a portal of entry for bacteria. Abnormal blood flow in the bones of the ankle and foot may also contribute to osteopenia and bony collapse

(ABPI = ankle–brachial pressure index)

2 weeks, in the presence of an ankle BP of less than 50 mmHg. The typical progression of symptoms in CLI is summarised in Fig. 16.70. Rest pain only, with ankle pressures above 50 mmHg, is known as subcritical limb ischaemia (SCLI). The term severe limb ischaemia (SLI) is used to describe the situation where either CLI and SCLI occurs. Whereas IC is usually due to single-segment plaque, SLI is always due to multilevel disease. Many patients with SLI have not previously sought medical advice, principally because they have other comorbidity that prevents them from walking to a point where IC develops. Patients with SLI are at high risk of losing their limb, and sometimes their life, in a matter of weeks or months without surgical bypass or endovascular revascularisation by angioplasty or stenting. Treatment of these patients is difficult because most are older adults with extensive and severe disease and major multisystem comorbidities.

Acute limb ischaemia

This is most frequently caused by acute thrombotic occlusion of a pre-existing stenotic arterial segment, thromboembolism and trauma that may be iatrogenic. The typical presentation is with paralysis (inability to wiggle toes or fingers) and paraesthesia (loss of light touch over the dorsum of the foot or hand); the so-called 'Ps of acute ischaemia' (Box 16.57). These features are non-specific and inconsistently related to its severity. Pain on squeezing the calf indicates muscle infarction and impending irreversible ischaemia. All patients with suspected acutely ischaemic limbs must be discussed immediately with a vascular surgeon; a few hours can make the difference between death/amputation and complete recovery of limb function. If there are no contraindications (acute aortic dissection or trauma, particularly head injury), an intravenous bolus of heparin (3000–5000 U) should be administered to limit propagation of thrombus and protect the collateral circulation. Distinguishing thrombosis from embolism is frequently difficult but is important because

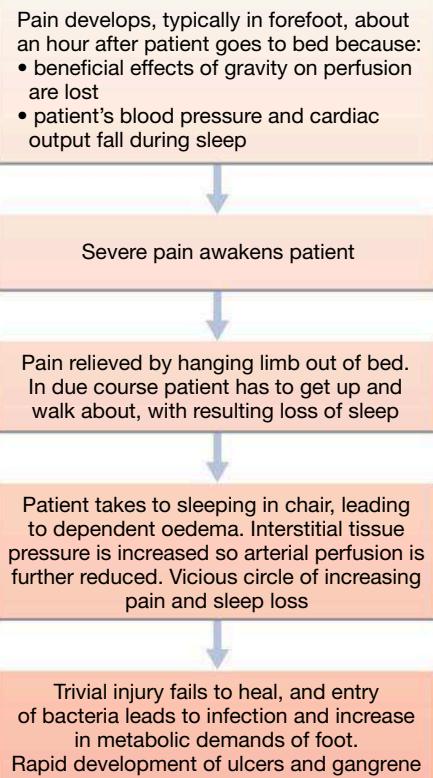


Fig. 16.70 Progressive night pain and the development of tissue loss.

16.57 Symptoms and signs of acute limb ischaemia	
Symptoms/signs	Comment
Pain	May be absent in complete acute ischaemia, and can be present in chronic ischaemia
Pallor	
Pulselessness	
Perishing cold	Unreliable, as the ischaemic limb takes on the ambient temperature
Paraesthesia	Important features of impending irreversible ischaemia
Paralysis	

treatment and prognosis are different (Box 16.58). Acute limb ischaemia due to thrombosis in situ can usually be treated medically in the first instance with intravenous heparin (target activated partial thromboplastin time (APTT) 2.0–3.0), antiplatelet agents, high-dose statins, intravenous fluids to avoid dehydration, correction of anaemia, oxygen and sometimes prostaglandins, such as iloprost. Embolism will normally result in extensive tissue necrosis within 6 hours unless the limb is revascularised. The indications for thrombolysis, if any, remain controversial. Irreversible ischaemia mandates early amputation or palliative care.

Atheroembolism

This may be a presenting feature of PAD affecting the subclavian arteries. The presentation is with blue fingers, which are due to small emboli lodging in digital arteries. This may be confused with Raynaud's phenomenon but the symptoms of atheroembolism are typically unilateral rather than bilateral as in Raynaud's.

Subclavian steal

This can be a feature of PAD affecting the upper limbs. The presentation is with dizziness, cortical blindness and/or collapse, which occurs when the arm is used and is thought to be caused by diversion (or steal) of blood from the brain to the limbs via the vertebral artery.

i 16.58 Distinguishing features of embolism and thrombosis in peripheral arteries		
Clinical features	Embolism	Thrombosis
Severity	Complete (no collaterals)	Incomplete (collaterals)
Onset	Seconds or minutes	Hours or days
Limb	Leg 3:1 arm	Leg 10:1 arm
Multiple sites	Up to 15%	Rare
Embolic source	Present (usually atrial fibrillation)	Absent
Previous claudication	Absent	Present
Palpation of artery	Soft, tender	Hard, calcified
Bruits	Absent	Present
Contralateral leg pulses	Present	Absent
Diagnosis	Clinical	Angiography
Treatment	Embolectomy, warfarin	Medical, bypass, thrombolysis
Prognosis	Loss of life > loss of limb	Loss of limb > loss of life

Investigations

The presence and severity of ischaemia can usually be determined by clinical examination (Box 16.59) and measurement of the ankle–brachial pressure index (ABPI), which is the ratio between the highest systolic ankle and brachial blood pressures. In health, the ABPI is over 1.0, in IC typically 0.5–0.9 and in CLI usually less than 0.5. Further investigation with duplex ultrasonography, MRI or CT with intravenous injection of contrast agents may be used to characterise the sites of involvement further. Intra-arterial digital subtraction angiography (IA-DSA) is used for those undergoing endovascular revascularisation. Other investigations should look for evidence of treatable secondary causes including a full blood count (for thrombocythaemia), lipids (for hyperlipidaemia) and blood glucose (for diabetes mellitus).

Management

Key elements of medical management are summarised in Box 16.60. This consists of smoking cessation (if applicable), taking regular exercise, antiplatelet therapy with low-dose aspirin or clopidogrel, therapy with a statin, and treatment of coexisting disease such as diabetes, hypertension or polycythaemia. Recent evidence suggests that low-dose factor Xa inhibition (rivaroxaban 2.5 mg twice daily) when used in combination with aspirin can further reduce cardiovascular events, ischaemic limb events and mortality in patients with PAD although there is a modest increase in bleeding risk. The peripheral vasodilator cilostazol has been shown to improve walking distance and should be considered in patients who do not respond adequately to best medical therapy. Intervention with angioplasty, stenting, endarterectomy or bypass is usually considered only after medical therapy has been given for at least 6 months to effect symptomatic improvement, and then just in patients who are severely disabled or whose livelihood is threatened by their disability. Subclavian artery disease is usually treated by means of angioplasty and stenting, as carotid–subclavian bypass surgery can be technically difficult.

Some considerations specific to atherosclerotic vascular disease in old age are listed in Box 16.61.

Buerger's disease

Buerger's disease or thromboangiitis obliterans is an inflammatory disease of the arteries that is distinct from atherosclerosis and usually presents in young (20–30 years) male smokers. It is most common in those from the Mediterranean and North Africa. It characteristically affects distal

i 16.59 Clinical features of chronic lower limb ischaemia		
<ul style="list-style-type: none"> Pulses: diminished or absent Bruits: denote turbulent flow but bear no relationship to the severity of the underlying disease Reduced skin temperature Pallor on elevation and rubor on dependency (Buerger's sign) Superficial veins that fill sluggishly and empty ('gutter') on minimal elevation Muscle-wasting Skin and nails: dry, thin and brittle Loss of hair 		

i Box 16.60 Medical therapy for peripheral arterial disease		
<ul style="list-style-type: none"> Smoking cessation Regular exercise (30 mins of walking, three times per week) Antiplatelet agent (aspirin 75 mg or clopidogrel 75 mg daily) Consider low-dose factor Xa inhibitor (rivaroxaban 2.5 mg twice daily) Reduction of cholesterol: statins Diet and weight loss Diagnosis and treatment of diabetes mellitus Diagnosis and treatment of associated conditions: <ul style="list-style-type: none"> Hypertension Anaemia Heart failure 		

i 16.61 Atherosclerotic vascular disease in old age		
<ul style="list-style-type: none"> Prevalence: related almost exponentially to age in developed countries, although atherosclerosis is not considered part of the normal ageing process. Statin therapy: no role in the primary prevention of atherosclerotic disease in those over 75 years but reduces cardiovascular events in those with established vascular disease, albeit with no reduction in overall mortality. Presentation in the frail: frequently with advanced multisystem arterial disease, along with a host of other comorbidities. Intervention in the frail: in those with extensive disease and limited life expectancy, the risks of surgery may outweigh the benefits, and symptomatic care is all that should be offered. 		

arteries, giving rise to claudication in the feet or rest pain in the fingers or toes. Wrist and ankle pulses are absent but brachial and popliteal pulses are present. It may also affect the veins, giving rise to superficial thrombophlebitis. It often remits if the patient stops smoking. Symptomatic therapy with vasodilators such as prostacyclin and calcium antagonists or sympathectomy may also be helpful. Major limb amputation is the most frequent outcome if patients continue to smoke.

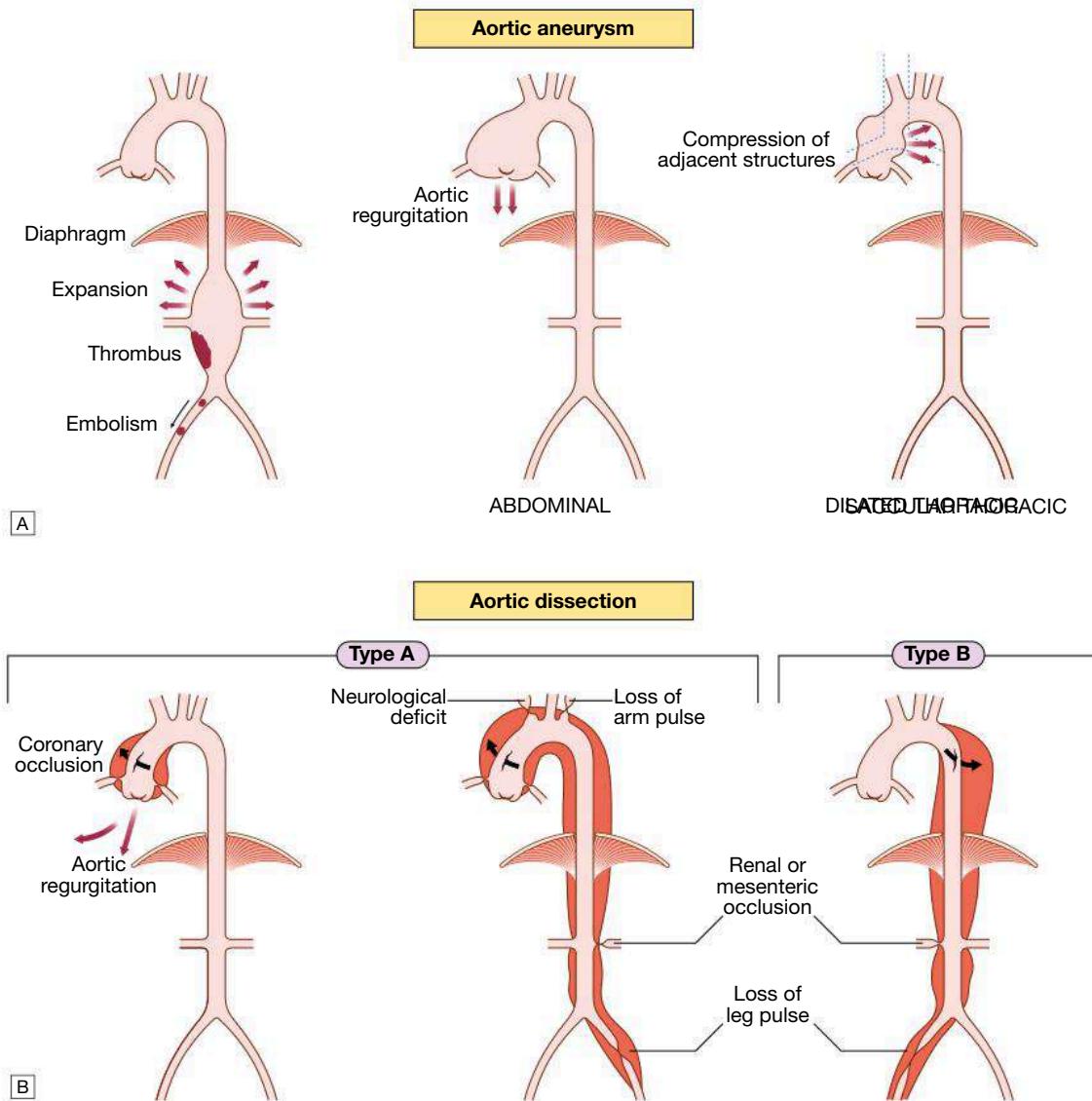
Raynaud's syndrome

This common disorder affects 5%–10% of young women aged 15–30 years in temperate climates. It does not progress to ulceration or infarction, and significant pain is unusual. The underlying cause is unclear and no investigation is necessary. The patient should be reassured and advised to avoid exposure to cold. Usually, no other treatment is required, although vasodilators such as nifedipine can be helpful if symptoms are troublesome. More severe Raynaud's syndrome can also occur in association with digital ulceration in patients with connective tissue disease.

Diseases of the aorta

Aortic aneurysm

Aortic aneurysm is defined as an abnormal dilatation of the aortic lumen. The most common site is the infrarenal abdominal aorta. The suprarenal abdominal aorta and a variable length of the descending thoracic aorta



16

Fig. 16.71 Types of aortic disease and their complications. **A** Types of aortic aneurysm. **B** Types of aortic dissection.

may be affected in 10%–20% of patients but the ascending aorta is usually spared. Abdominal aortic aneurysms (AAAs) affect men three times more commonly than women and are estimated to occur in about 5% of men over the age of 60 years.

Pathogenesis

The most common cause of aortic aneurysm is atherosclerosis, the risk factors for which have previously been described. However, smoking and hypertension predominate with 90%–95% of patients having one or both of these risk factors. There also appears to be an additional and specific genetic component since aortic aneurysm tends to run in families. This may explain in part why only some patients with risk factors for atheroma develop aneurysmal disease. Marfan syndrome is an inherited disorder of connective tissue that is associated with aortic aneurysm and aortic dissection.

Clinical features

The clinical presentation is dependent on the site of the aneurysm. Thoracic aneurysms may typically present with acute severe chest pain but other features, including aortic regurgitation, compressive symptoms such as stridor (trachea, bronchus), hoarseness (recurrent laryngeal nerve) and superior vena cava syndrome, may occur (Fig. 16.71A). If the aneurysm erodes into an adjacent structure, such as the oesophagus or

bronchus, the presentation may be with massive bleeding. AAAs affect the infrarenal segment of the aorta. They can present in a number of ways, as summarised in Box 16.62. The usual age at presentation is 65–75 years for elective presentations and 75–85 years for emergency presentations.

Investigations

Ultrasound is the best way of establishing the diagnosis of an abdominal aneurysm and of following up patients with asymptomatic aneurysms that are not yet large enough to warrant surgical repair. In the UK, a national screening programme for men over 65 years of age has been introduced using ultrasound scanning. For every 10 000 men scanned, 65 ruptures are prevented and 52 lives saved. CT provides more accurate information about the size and extent of the aneurysm, the surrounding structures and the presence of any other intra-abdominal pathology. It is the standard pre-operative investigation but is not suitable for surveillance because of the high cost and radiation dose.

Management

The risks of surgery generally outweigh the risks of rupture until an asymptomatic AAA has reached a maximum of 5.5 cm in diameter. All symptomatic AAAs should be considered for repair, not only to rid the patient of symptoms but also because pain often predates rupture. Distal

i 16.62 Abdominal aortic aneurysm (AAA): common presentations

Incidental

- On physical examination, plain X-ray or, most commonly, abdominal ultrasound
- Even large AAAs can be difficult to feel, so many remain undetected until they rupture
- Studies are currently under way to determine whether screening will reduce the number of deaths from rupture

Pain

- In the central abdomen, back, loin, iliac fossa or groin

Thromboembolic complications

- Thrombus within the aneurysm sac may be a source of emboli to the lower limbs
- Less commonly, the aorta may undergo thrombotic occlusion

Compression

- Surrounding structures such as the duodenum (obstruction and vomiting) and the inferior vena cava (oedema and deep vein thrombosis)

Rupture

- Into the retroperitoneum, the peritoneal cavity or surrounding structures (most commonly the inferior vena cava, leading to an aortocaval fistula)

embolisation is a strong indication for repair, regardless of size, because otherwise limb loss is common. Most patients with a ruptured AAA do not survive to reach hospital, but if they do and surgery is thought to be appropriate, there must be no delay in getting them to the operating theatre to clamp the aorta.

Open AAA repair has been the treatment of choice in both the elective and the emergency settings, and entails replacing the aneurysmal segment with a prosthetic (usually Dacron) graft. The 30-day mortality for this procedure is approximately 5%–8% for elective asymptomatic AAA, 10%–20% for emergency symptomatic AAA and 50% for ruptured AAA. However, patients who survive the operation to leave hospital have a long-term survival approaching that of the normal population. Increasingly, endovascular aneurysm repair (EVAR), using a stent graft introduced via the femoral arteries in the groin, is replacing open surgery. It is cost-effective and likely to become the treatment of choice for infrarenal AAA. It is possible to treat many suprarenal and thoraco-abdominal aneurysms by EVAR too. If the aneurysm is secondary to Marfan syndrome, treatment with β -blockers reduces the rate of aortic dilatation and the risk of rupture. Elective replacement of the ascending aorta may also be considered in patients with evidence of progressive aortic dilatation but carries a mortality of 5%–10%.

Aortic dissection

Aortic dissection occurs when a breach in the integrity of the aortic wall allows arterial blood to enter the media, which is then split into two layers, creating a false lumen alongside the existing or true lumen (Fig. 16.71B). The aortic valve may be damaged and the branches of the aorta may be compromised. Typically, the false lumen eventually re-enters the true lumen, creating a double-barrelled aorta, but it may also rupture into the left pleural space or pericardium with fatal consequences. The peak incidence is in the sixth and seventh decades but dissection can occur in younger patients, usually in association with Marfan syndrome, pregnancy or trauma; men are affected twice as frequently as women.

Pathogenesis

The primary event is often a spontaneous or iatrogenic tear in the intima of the aorta; multiple tears or entry points are common. Other dissections are triggered by primary haemorrhage in the media of the aorta, which then ruptures through the intima into the true lumen. This form of spontaneous bleeding from the vasa vasorum is sometimes confined to the aortic wall, when it may present as a painful intramural haematoma.

i 16.63 Risk factors for aortic dissection

- Hypertension (in 80%)
- Atherosclerosis
- Coarctation
- Genetic:
 - Marfan syndrome
 - Ehlers–Danlos syndrome
- Fibromuscular dysplasia
- Previous cardiac surgery:
 - CABG
 - Aortic valve replacement
- Pregnancy (usually third trimester)
- Trauma
- Iatrogenic:
 - Cardiac catheterisation
 - Intra-aortic balloon pumping

(CABG = coronary artery bypass grafting)

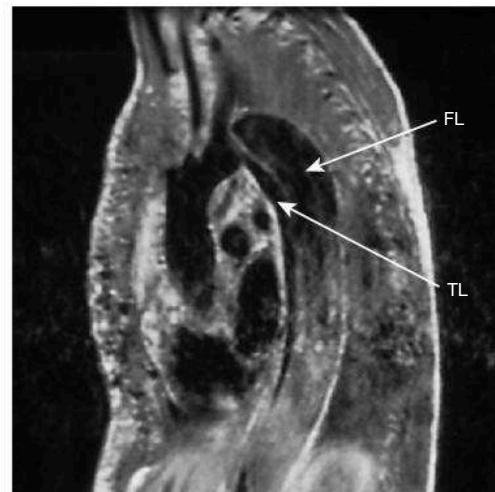


Fig. 16.72 Sagittal view of an MRI scan from a patient with long-standing aortic dissection, illustrating a biluminal aorta. There is sluggish flow in the false lumen (FL), accounting for its grey appearance. (TL = true lumen)

Aortic disease and hypertension are the most important aetiological factors but other conditions may also be implicated (Box 16.63). Chronic dissections may lead to aneurysmal dilatation of the aorta, and thoracic aneurysms may be complicated by dissection. It can therefore be difficult to identify the primary pathology.

Aortic dissection is classified anatomically and for management purposes into type A and type B (see Fig. 16.71B), involving or sparing the ascending aorta, respectively. Type A dissections account for two-thirds of cases and frequently also extend into the descending aorta.

Clinical features

Involvement of the ascending aorta typically gives rise to anterior chest pain, and involvement of the descending aorta to intrascapular back pain. The pain is typically described as ‘tearing’ and very abrupt in onset; collapse is common. Unless there is major haemorrhage, the patient is invariably hypertensive. There may be asymmetry of the brachial, carotid or femoral pulses and signs of aortic regurgitation. Occlusion of aortic branches may cause MI (coronary), stroke (carotid), paraplegia (spinal), mesenteric infarction with an acute abdomen (coeliac and superior mesenteric), renal failure (renal) and acute limb (usually leg) ischaemia.

Investigations

The investigations of choice are CT or MR angiography (Figs. 16.72 and 16.73), both of which are highly specific and sensitive. A chest X-ray should be performed. It characteristically shows broadening of the upper mediastinum and distortion of the aortic ‘knuckle’ but these findings are absent in 10% of cases. A left-sided pleural effusion is common. The

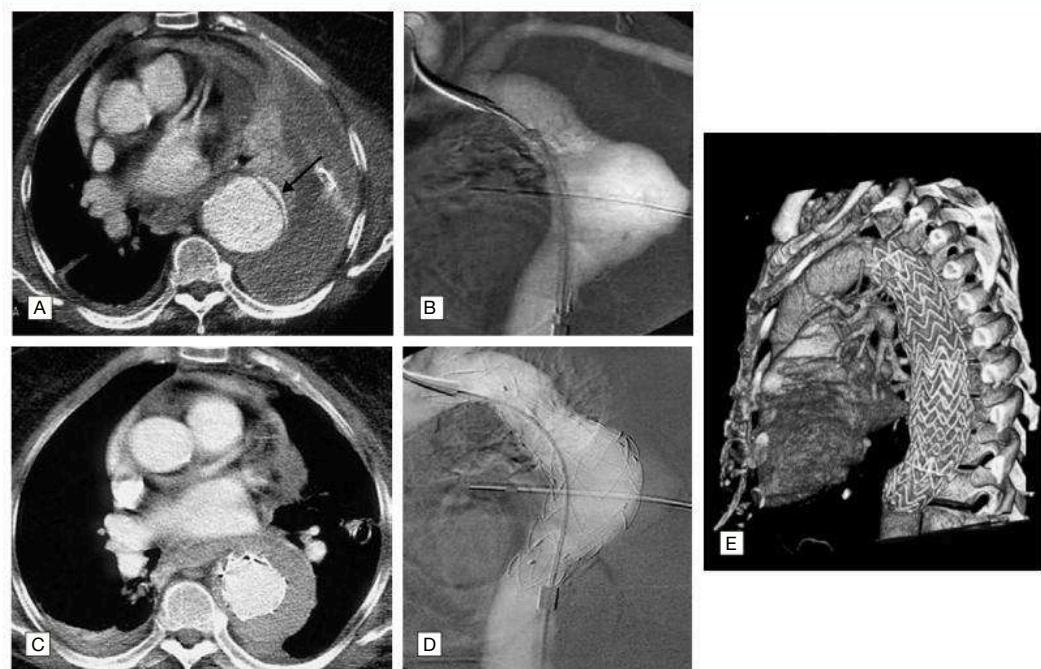


Fig. 16.73 Images from a patient with an acute type B aortic dissection that had ruptured into the left pleural space and was repaired by deploying an endoluminal stent graft. **A** CT scan illustrating an intimal flap (arrow) in the descending aorta and a large pleural effusion. **B** Aortogram illustrating aneurysmal dilatation; a stent graft has been introduced from the right femoral artery and is about to be deployed. **C** CT scan after endoluminal repair. The pleural effusion has been drained but there is a haematoma around the descending aorta. **D** Aortogram illustrating the stent graft. **E** Three-dimensional reconstruction of an aortic stent graft. (**E**) Courtesy of Dr T. Lawton.

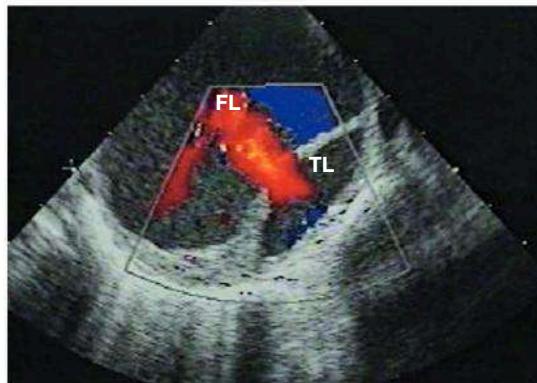


Fig. 16.74 Echocardiograms from a patient with a chronic aortic dissection. Colour-flow Doppler shows flow from the larger false lumen (FL) into the true lumen (TL), characteristic of chronic disease.

ECG may show left ventricular hypertrophy in patients with hypertension or, rarely, changes of acute MI (usually inferior). Doppler echocardiography may show aortic regurgitation, a dilated aortic root and, occasionally, the flap of the dissection. TOE is particularly helpful because transthoracic echocardiography can provide images of the first 3–4 cm of the ascending aorta only (Fig. 16.74).

Management

The early mortality of acute dissection is approximately 1%–5% per hour and so treatment is urgently required. Initial management comprises pain control and antihypertensive treatment. Type A dissections require emergency surgery to replace the ascending aorta. Type B dissections are treated medically unless there is actual or impending external rupture, or vital organ (gut, kidneys) or limb ischaemia, as the morbidity and mortality associated with surgery are very high. The aim of medical management is to maintain a mean arterial pressure (MAP) of 60–75 mmHg to reduce the force of the ejection of blood from the

LV. First-line therapy is with β -blockers; the additional α -blocking properties of labetalol make it especially useful. Rate-limiting calcium channel blockers, such as verapamil or diltiazem, are used if β -blockers are contraindicated. Sodium nitroprusside may be considered if these fail to control BP adequately.

Percutaneous or minimal access endoluminal repair is sometimes possible and involves either ‘fenestrating’ (perforating) the intimal flap so that blood can return from the false to the true lumen (so decompressing the former), or implanting a stent graft placed from the femoral artery (see Fig. 16.73).

Aortitis

Syphilis is a rare cause of aortitis that characteristically produces saccular aneurysms of the ascending aorta containing calcification. Other conditions that may be associated with aortitis include Takayasu’s disease, giant cell arteritis and axial spondyloarthritis, all of which are discussed in more detail in Chapter 26.

Marfan syndrome

Marfan syndrome is a rare (0.02% of the population) inherited autosomal dominant disorder of connective tissue with a high risk of aortic aneurysm and dissection. It is caused by mutations of the *FBN1* gene which leads to deficiency of fibrillin-1 leading to reduced microfibril formation. This disrupts the mechanical integrity of connective tissue, giving rise to a wide range of clinical features.

Clinical features

Aortic dissection and aneurysm are the most serious complications of Marfan syndrome but many other clinical manifestations may be observed. These include aortic and mitral valve regurgitation; skin laxity and joint hypermobility; abnormalities of body habitus, including long arms, legs and fingers (arachnodactyly), scoliosis, pectus excavatum and a high-arched palate; ocular abnormalities, such as lens dislocation and retinal detachment; and an increased risk of pneumothorax.

Investigations

The diagnosis is usually suspected on the basis of the characteristic clinical features and can be confirmed by genetic testing. Imaging by chest X-ray may reveal evidence of aortic dilatation but echocardiography is more sensitive and can also demonstrate valvular disease, if present. Patients with Marfan syndrome should undergo serial monitoring of the aortic root by echocardiography; if evidence of dilatation is observed, then elective surgery should be considered.

Management

Treatment with β -blockers or angiotensin receptor blockers may reduce the risk of aortic dilatation and should be given in all patients with Marfan syndrome. Activities that are associated with increases in cardiac output are best avoided. Surgery to replace the aortic root can be performed in patients with progressive aortic dilatation.

Coarctation of the aorta

Coarctation of the aorta is the term used to describe a narrowing distal to the origin of the left subclavian artery. It is most commonly due to congenital heart disease, but narrowing of the aorta leading to similar symptoms can occur in other conditions such as Takayasu's arteritis and trauma. Diagnosis and management of coarctation are discussed later in this chapter in the section on congenital heart disease.

Hypertension

The risk of cardiovascular diseases such as stroke and CAD is closely related to levels of BP, which follows a normal distribution in the general population. Although there is no specific cut-off above which the risk of cardiovascular risk suddenly increases, the diagnosis of hypertension is made when systolic and diastolic values rise above a specific threshold that corresponds to the level of BP at which the risk of cardiovascular complications and benefits of treatment outweigh the treatment costs and potential side-effects of therapy. The British Hypertension Society classification, provided in Box 16.64, defines mild hypertension as existing when the BP is above 140/90 mmHg. Similar thresholds have been published by the European Society of Hypertension and the WHO–International Society of Hypertension. The cardiovascular risks associated with high BP depend on the combination of risk factors in an individual, such as age, sex, weight, physical activity, smoking, family history, serum cholesterol, diabetes mellitus and pre-existing vascular disease.



16.64 Definition of hypertension

Category	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Blood pressure		
Optimal	<120	<80
Normal	<130	85
High normal	130–139	85–89
Hypertension		
Grade 1 (mild)	140–159	90–99
Grade 2 (moderate)	160–179	100–109
Grade 3 (severe)	≥ 180	>110
Isolated systolic hypertension		
Grade 1	140–159	<90
Grade 2	≥ 160	<90

Pathogenesis

Many factors may contribute to the regulation of BP and the development of hypertension, including renal dysfunction, peripheral resistance, vessel tone, endothelial dysfunction, autonomic tone, insulin resistance and neurohumoral factors. In more than 95% of cases, no specific underlying cause of hypertension can be found. Such patients are said to have essential hypertension. Hypertension is more common in some ethnic groups, particularly African Americans and Japanese, and approximately 40%–60% is explained by genetic factors. Age is a strong risk factor in all ethnic groups. Important environmental factors include a high salt intake, heavy consumption of alcohol, obesity and lack of exercise. Impaired intrauterine growth and low birth weight are associated with an increased risk of hypertension later in life. In about 5% of cases, hypertension is secondary to a specific disease, as summarised in Box 16.65.

Hypertension has a number of adverse effects on the cardiovascular system. In larger arteries (>1 mm in diameter), the internal elastic lamina is thickened, smooth muscle is hypertrophied and fibrous tissue is deposited. The vessels dilate and become tortuous, and their walls become less compliant. In smaller arteries (<1 mm), hyaline arteriosclerosis occurs in the wall, the lumen narrows and aneurysms may develop. Widespread atheroma develops and may lead to coronary and cerebrovascular disease, particularly if other risk factors are present. These structural changes in the vasculature often perpetuate and aggravate hypertension by increasing peripheral vascular resistance and reducing renal blood flow, thereby activating the renin–angiotensin–aldosterone axis.

Clinical features

Hypertension is usually asymptomatic until the diagnosis is made at a routine physical examination or when a complication arises. Reflecting this fact, a BP check is advisable every 5 years in adults over 40 years of age to pick up occult hypertension. Sometimes clinical features may be observed that can give a clue to the underlying cause of hypertension. These include radio-femoral delay in patients with coarctation of the aorta (see Fig. 16.93), enlarged kidneys in patients with polycystic kidney disease, abdominal bruits that may suggest renal artery stenosis and the characteristic facies and habitus of Cushing's syndrome (see Box 16.65). Examination may also reveal evidence of risk factors for hypertension, such as central obesity and hyperlipidaemia. Other signs may be observed that are due to the complications of hypertension. These include signs of left ventricular hypertrophy, accentuation of the aortic component of the second heart sound, and a fourth heart sound.



16.65 Causes of secondary hypertension

Alcohol

Obesity

Pregnancy

Renal disease

- Parenchymal renal disease, particularly glomerulonephritis
- Renal vascular disease
- Polycystic kidney disease

Endocrine disease

- Phaeochromocytoma
- Cushing's syndrome
- Primary hyperaldosteronism (Conn syndrome)
- Glucocorticoid-suppressible hyperaldosteronism
- Hyperparathyroidism
- Acromegaly
- Primary hypothyroidism
- Thyrotoxicosis
- Congenital adrenal hyperplasia due to 11 β -hydroxylase or 17 α -hydroxylase deficiency
- Liddle syndrome
- 11 β -hydroxysteroid dehydrogenase deficiency

Drugs

Coarctation of the aorta

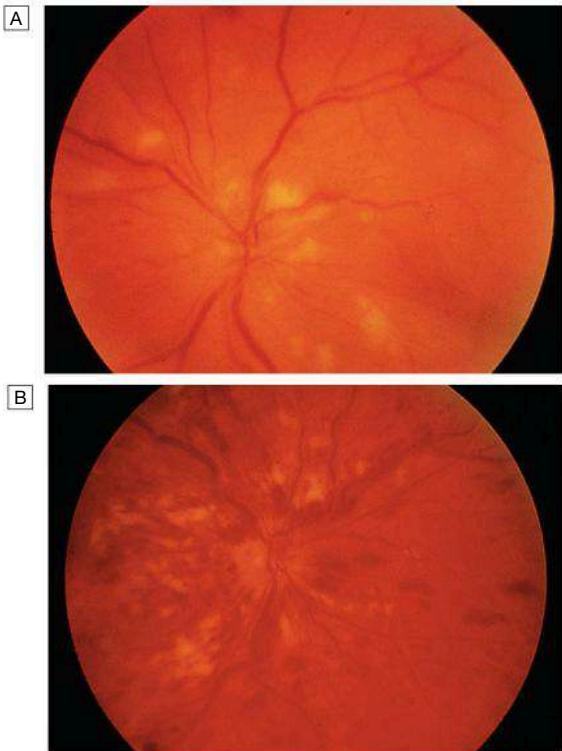


Fig. 16.75 Retinal changes in hypertension. **A** Grade 4 hypertensive retinopathy showing swollen optic disc, retinal haemorrhages and multiple cotton wool spots (infarcts). **B** Central retinal vein thrombosis showing swollen optic disc and widespread fundal haemorrhage, commonly associated with systemic hypertension. (A and B) Courtesy of Dr B. Cullen.

AF is common and may be due to diastolic dysfunction caused by left ventricular hypertrophy or the effects of CAD.

Severe hypertension can cause left ventricular failure in the absence of CAD, particularly when there is an impairment of renal function. The optic fundi are often abnormal (see Fig. 16.75 below) and there may be evidence of generalised atheroma or specific complications, such as aortic aneurysm, PAD or stroke. Examination of the optic fundi reveals a gradation of changes linked to the severity of hypertension; fundoscopy can provide an indication of the arteriolar damage occurring elsewhere (Box 16.66). ‘Cotton wool’ exudates are associated with retinal ischaemia or infarction, and fade in a few weeks (Fig. 16.75A). ‘Hard’ exudates (small, white, dense deposits of lipid) and microaneurysms ('dot' haemorrhages) are more characteristic of diabetic retinopathy (see Fig. 30.12A). Hypertension is also associated with central retinal vein thrombosis (Fig. 16.75B).

Investigations

A decision to embark on antihypertensive therapy effectively commits the patient to life-long treatment, so readings must be as accurate as possible. The objectives are to:

- confirm the diagnosis by obtaining accurate, representative BP measurements
- identify contributory factors and any underlying causes
- assess other risk factors and quantify cardiovascular risk
- detect any complications that are already present
- identify comorbidity that may influence the choice of antihypertensive therapy.

Blood pressure measurements

Measurements should be made to the nearest 2 mmHg, in the sitting position with the arm supported, and repeated after 5 minutes' rest if

i	16.66 Hypertensive retinopathy
	Grade 1
	• Arteriolar thickening, tortuosity and increased reflectiveness ('silver wiring')
	Grade 2
	• Grade 1 plus constriction of veins at arterial crossings ('arteriovenous nipping')
	Grade 3
	• Grade 2 plus evidence of retinal ischaemia (flame-shaped or blot haemorrhages and 'cotton wool' exudates)
	Grade 4
	• Grade 3 plus papilloedema

Y	16.67 How to measure blood pressure
	<ul style="list-style-type: none"> • Use a machine that has been validated, well maintained and properly calibrated • Measure sitting BP routinely, with additional standing BP in older and diabetic patients and those with possible postural hypotension; rest the patient for 2 minutes • Remove tight clothing from the arm • Support the arm at the level of the heart • Use a cuff of appropriate size (the bladder must encompass more than two-thirds of the arm) • Lower the pressure slowly (2 mmHg per second) • Read the BP to the nearest 2 mmHg • Use phase V (disappearance of sounds) to measure diastolic BP • Take two measurements at each visit

the first recording is high (Box 16.67). To avoid spuriously high readings in obese subjects, the cuff should contain a bladder that encompasses at least two-thirds of the arm circumference. Exercise, anxiety, discomfort and unfamiliar surroundings can all lead to a transient rise in BP. Sphygmomanometry, particularly when performed by a doctor, can cause a transient elevation in BP, which has been termed ‘white coat’ hypertension. It has been estimated that up to 20% of patients with a raised BP at outpatient clinics have a normal BP when it is recorded by automated devices used at home. The risk of cardiovascular disease in these patients is less than that in patients with sustained hypertension but greater than that in normotensive subjects. If clinic BP measurements show borderline levels or if white coat hypertension is suspected, then ambulatory measurement or home-based measurements are of value in confirming the diagnosis.

Ambulatory blood pressure measurements

A series of automated ambulatory BP measurements obtained over 24 hours or longer provide a better profile than a limited number of clinic readings and correlate more closely with evidence of target organ damage than casual BP measurements. Treatment thresholds and targets (see Box 16.71) must be adjusted downwards, because ambulatory BP readings are systematically lower (approximately 12/7 mmHg) than clinic measurements. The average ambulatory daytime (not 24-hour or night-time) BP should be used to guide management decisions.

Home blood pressure measurements

Patients can measure their own BP at home using a range of commercially available semi-automatic devices. The value of such measurements is dependent on the environment and timing of the readings measured. Home or ambulatory BP measurements are particularly helpful in patients with unusually labile BP, those with refractory hypertension, those who may have symptomatic hypotension, and those in whom white coat hypertension is suspected.



16.68 Investigation of hypertension

- Urinalysis for blood, protein and glucose
- Blood urea, electrolytes and creatinine
Hypokalaemic alkalosis may indicate primary hyperaldosteronism but is usually due to diuretic therapy
- Blood glucose
- Serum total and HDL cholesterol
- Thyroid function tests
- 12-lead ECG (left ventricular hypertrophy, coronary artery disease)

(HDL = high-density lipoprotein)



16.69 Specialised investigation of hypertension

- Chest X-ray: to detect cardiomegaly, heart failure, coarctation of the aorta
- Ambulatory BP recording: to assess borderline or 'white coat' hypertension
- Echocardiogram: to detect or quantify left ventricular hypertrophy
- Renal ultrasound: to detect possible renal disease
- Renal angiography: to detect or confirm the presence of renal artery stenosis
- Urinary catecholamines: to detect possible phaeochromocytoma
- Urinary cortisol and dexamethasone suppression test: to detect possible Cushing's syndrome
- Plasma renin activity and aldosterone: to detect possible primary aldosteronism

Other investigations

All hypertensive patients should undergo a limited number of investigations (Box 16.68) but additional investigations are appropriate in patients younger than 40 years of age or those with resistant hypertension (Box 16.69). Family history, lifestyle (exercise, salt intake, smoking habit) and other risk factors should also be recorded. A careful history will identify those patients with drug- or alcohol-induced hypertension and may elicit the symptoms of other causes of secondary hypertension, such as phaeochromocytoma (paroxysmal headache, palpitation and sweating) or complications such as CAD.

Management

The objective of antihypertensive therapy is to reduce the incidence of adverse cardiovascular events, particularly CAD, stroke and heart failure. Randomised controlled trials have demonstrated that antihypertensive therapy can reduce the incidence of stroke and, to a lesser extent, CAD. The relative benefits (approximately 30% reduction in risk of stroke and 20% reduction in risk of CAD) are similar in all patient groups, so the absolute benefit of treatment (total number of events prevented) is greatest in those at highest risk. For example, to extrapolate from the Medical Research Council (MRC) Mild Hypertension Trial (1985), 566 young patients would have to be treated with bendroflumethiazide for 1 year to prevent 1 stroke, while in the MRC trial of antihypertensive treatment in older adults (1992), 1 stroke was prevented for every 286 patients treated for 1 year.

A formal estimate of absolute cardiovascular risk, which takes account of all the relevant risk factors, may help to determine whether the likely benefits of therapy will outweigh its costs and hazards. Several online risk calculators are available for this purpose, such as the Joint British Societies risk calculator (<http://www.jbs3risk.com> and see 'Further information'). Most of the excess morbidity and mortality associated with hypertension are attributable to CAD and many treatment guidelines are therefore based on estimates of the 10-year CAD risk. Total cardiovascular risk can be estimated by multiplying CAD risk by 4/3 (i.e. if CAD risk is 30%, cardiovascular risk is 40%). The value of this approach can be illustrated by comparing the two hypothetical cases on page 426.

Intervention thresholds

Systolic BP and diastolic BP are both powerful predictors of cardiovascular risk. The British Hypertension Society management guidelines use

both readings, and treatment should be initiated if they exceed the given threshold (Fig. 16.76).

Patients with diabetes or cardiovascular disease are at particularly high risk and the threshold for initiating antihypertensive therapy is therefore lower ($\leq 130/80$) in these patient groups. The thresholds for treatment in older adults are the same as for younger patients (Box 16.70).

Treatment targets

The optimum BP for reduction of major cardiovascular events has been found to be 139/83 mmHg, and even lower in patients with diabetes mellitus. The targets suggested by the British Hypertension Society (Box 16.71) are ambitious. Primary care strategies have been devised to improve screening and detection of hypertension that, in the past, remained undetected in up to half of affected individuals. Application of new guidelines should help establish patients on appropriate treatment, and allow step-up if lifestyle modification and first-line drug therapy fail to control hypertension.

Patients taking antihypertensive therapy require follow-up at regular intervals to monitor BP, minimise side-effects and reinforce lifestyle advice.

Non-drug therapy

Appropriate lifestyle measures may obviate the need for drug therapy in patients with borderline hypertension, reduce the dose or the number of drugs required in patients with established hypertension, and directly reduce cardiovascular risk.

Correcting obesity, reducing alcohol intake, restricting salt intake, taking regular physical exercise and increasing consumption of fruit and vegetables can all lower BP. Moreover, stopping smoking, eating oily fish and adopting a diet that is low in saturated fat may produce further reductions in cardiovascular risk that are independent of changes in BP.

Drug therapy

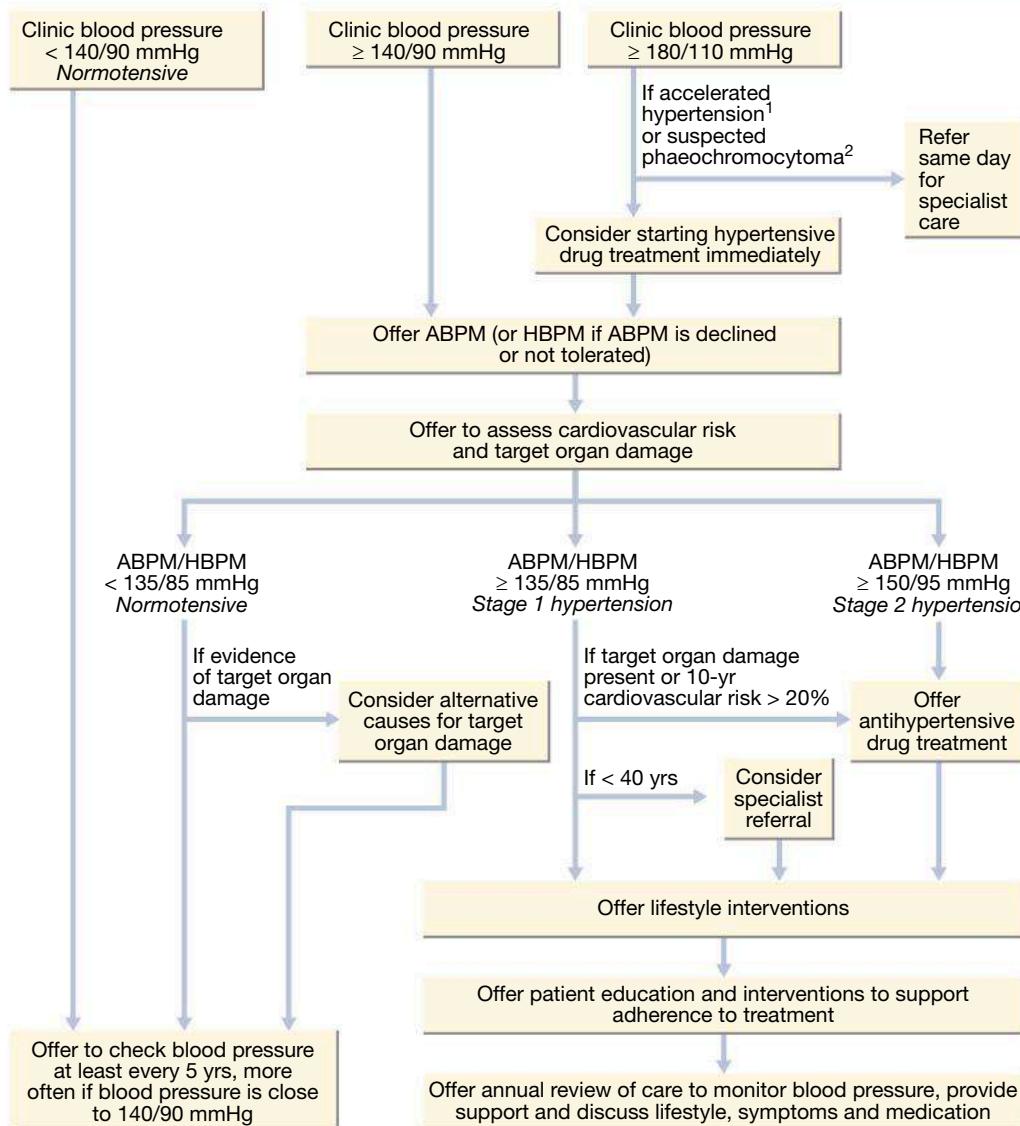
Thiazides The mechanism of action of these drugs is incompletely understood and it may take up to a month for the maximum effect to be observed. An appropriate daily dose is 2.5 mg bendroflumethiazide or 0.5 mg cyclopentthiazide. More potent loop diuretics, such as furosemide (40 mg daily) or bumetanide (1 mg daily), have few advantages over thiazides in the treatment of hypertension, unless there is substantial renal impairment or they are used in conjunction with an ACE inhibitor.

ACE inhibitors ACE inhibitors (enalapril 5–40 mg daily, ramipril 5–10 mg daily or lisinopril 10–40 mg daily) are effective and usually well tolerated. They should be used with care in patients with impaired renal function or renal artery stenosis because they can reduce glomerular filtration rate and precipitate renal failure. Electrolytes and creatinine should be checked before and 1–2 weeks after commencing therapy. Side-effects include first-dose hypotension, cough, rash, hyperkalaemia and renal dysfunction.

Angiotensin receptor blockers ARBs (irbesartan 75–300 mg daily, valsartan 40–160 mg daily) have similar efficacy to ACE inhibitors but they do not cause cough and are better tolerated.

Calcium channel antagonists Amlodipine (5–10 mg daily) and nifedipine (30–90 mg daily) are effective and usually well tolerated antihypertensive drugs that are particularly useful in older people. Side-effects include flushing, palpitations and fluid retention. The rate-limiting calcium channel antagonists (diltiazem 200–500 mg daily, verapamil 240–480 mg daily in divided doses) can be useful when hypertension coexists with angina but may cause bradycardia. The main side-effect of verapamil is constipation.

Beta-blockers These are no longer used as first-line antihypertensive therapy, except in patients with another indication for the drug such as angina. Metoprolol (100–200 mg daily), atenolol (50–100 mg daily) and bisoprolol (5–10 mg daily), which preferentially block cardiac



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Fig. 16.76 Management of hypertension. ¹Signs of papilloedema or retinal haemorrhage. ²Labile or postural hypotension, headache, palpitations, pallor and diaphoresis. (ABPM = ambulatory blood pressure monitoring; HBPM = home blood pressure monitoring). Adapted from 2020 International Society of Hypertension Global Hypertension Practice Guidelines.

	16.70 Hypertension in old age
<ul style="list-style-type: none"> Prevalence: hypertension affects more than half of all people over the age of 60 years (including isolated systolic hypertension). Risks: hypertension is the most important risk factor for myocardial infarction, heart failure and stroke in older people. Benefit of treatment: absolute benefit from therapy is greatest in older people (at least up to age 80 years). Target blood pressure: targets may be relaxed in older people to 150/90 mmHg. Tolerance of treatment: antihypertensives are tolerated as well as in younger patients. Drug of choice: low-dose thiazides but, in the presence of coexistent disease such as gout or diabetes, other agents may be more appropriate. 	

β_1 -adrenoceptors, should be used rather than non-selective agents that also block β_2 -adrenoceptors, which mediate vasodilatation and bronchodilatation.

Combined β - and α -blockers Labetalol (200 mg–2.4 g daily in divided doses) and carvedilol (6.25–25 mg twice daily) are combined β - and

16.71 Optimal target blood pressures ¹		
Age	Clinic BP (mmHg)	Ambulatory or home BP (mmHg) ²
< 80 years	< 140/90	< 135/85
≥ 80 years	< 150/90	< 140/85

¹Both systolic and diastolic values should be attained. ²Average BP during waking hours.

α -adrenoceptor antagonists that are sometimes more effective than pure β -blockers. Labetalol can be used as an infusion in malignant phase hypertension (see below).

Other vasodilators A variety of other vasodilators may be used. These include the α_1 -adrenoceptor antagonists prazosin (0.5–20 mg daily in divided doses), indoramin (25–100 mg twice daily) and doxazosin (1–16 mg daily), and drugs that act directly on vascular smooth muscle, such as hydralazine (25–100 mg twice daily) and minoxidil (10–50 mg daily). Side-effects include first-dose and postural hypotension,

16.72 The influence of comorbidity on choice of antihypertensive drug therapy				
Class of drug	Compelling indications	Possible indications	Caution	Compelling contraindications
α -blockers	Benign prostatic hypertrophy	–	Postural hypotension, heart failure ¹	Urinary incontinence
ACE inhibitors	Heart failure	Chronic renal disease ²	Renal impairment ²	Pregnancy
	Left ventricular dysfunction, post-MI or established CAD	Type 2 diabetic nephropathy	PAD ³	Renovascular disease ²
	Type 1 diabetic nephropathy			
	Secondary stroke prevention ⁴			
Angiotensin II receptor blockers	ACE inhibitor intolerance	Left ventricular dysfunction after MI	Renal impairment ²	Pregnancy
	Type 2 diabetic nephropathy	Intolerance of other antihypertensive drugs	PAD ³	
	Hypertension with left ventricular hypertrophy	Proteinuric or chronic renal disease ²		
	Heart failure in ACE-intolerant patients, after MI	Heart failure		
β -blockers	MI, angina	–	Heart failure ⁵	Asthma or chronic obstructive pulmonary disease
	Heart failure ⁵		PAD	Heart block
				Diabetes (except with CAD)
Calcium channel blockers (dihydropyridine)	Older patients, isolated systolic hypertension	Angina	–	–
Calcium channel blockers (rate-limiting)	Angina	Older patients	Combination with β -blockade	Atrioventricular block, heart failure
Thiazides or thiazide-like diuretics	Older patients, isolated systolic hypertension, heart failure, secondary stroke prevention	–	–	Gout ⁶

¹In heart failure when used as monotherapy. ²ACE inhibitors or ARBs may be beneficial in chronic renal failure and renovascular disease but should be used with caution, close supervision and specialist advice when there is established and significant renal impairment. ³Caution with ACE inhibitors and ARBs in PAD because of association with renovascular disease.

⁴In combination with a thiazide or thiazide-like diuretic. ⁵ β -blockers are used increasingly to treat stable heart failure but may worsen acute heart failure. ⁶Thiazides or thiazide-like diuretics may sometimes be necessary to control BP in people with a history of gout, ideally used in combination with allopurinol.

(ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; CAD = coronary artery disease; MI = myocardial infarction; PAD = peripheral arterial disease)

headache, tachycardia and fluid retention. Minoxidil also causes increased facial hair and is therefore unsuitable for female patients.

Aspirin Antiplatelet therapy is a powerful means of reducing cardiovascular risk but may cause bleeding, particularly intracerebral haemorrhage, in a small number of patients. The benefits are thought to outweigh the risks in hypertensive patients aged 50 years or over who have well-controlled BP and either target organ damage or diabetes or a 10-year CAD risk of at least 15% (or 10-year cardiovascular disease risk of at least 20%).

Statins Treating hyperlipidaemia can produce a substantial reduction in cardiovascular risk. These drugs are strongly indicated in patients who have established vascular disease, or hypertension with a high (at least 10% in 10 years) risk of developing cardiovascular disease.

Choice of antihypertensive drug

Trials that have compared thiazides, calcium antagonists, ACE inhibitors and ARBs have not shown consistent differences in outcome, efficacy, side-effects or quality of life. Beta-blockers, which previously featured as first-line therapy in guidelines, have a weaker evidence base. The choice of antihypertensive therapy is initially dictated by the patient's age and ethnic background, although cost and convenience will influence the exact drug and preparation used. Response to initial therapy

and side-effects guide subsequent treatment. Comorbid conditions also have an influence on initial drug selection (Box 16.72); for example, a β -blocker might be the most appropriate treatment for a patient with angina. Thiazide diuretics and dihydropyridine calcium channel antagonists are the most suitable drugs for treatment in older people.

Combination therapy

Although some patients can be treated with a single antihypertensive drug, a combination of drugs is often required to achieve optimal control (Fig. 16.77). Combination therapy may be desirable for other reasons; for example, low-dose therapy with two drugs may produce fewer unwanted effects than treatment with the maximum dose of a single drug. Some drug combinations have complementary or synergistic actions; for example, thiazides increase activity of the renin–angiotensin system, while ACE inhibitors block it.

Refractory hypertension

Refractory hypertension refers to the situation where multiple drug treatments do not give adequate control of BP. Although this may be due to genuine resistance to therapy in some cases, a more common cause of treatment failure is non-adherence to drug therapy. Resistant hypertension can also be caused by failure to recognise an underlying cause, such as renal artery stenosis or phaeochromocytoma. There is no easy solution to problems with adherence, but simple treatment regimens,

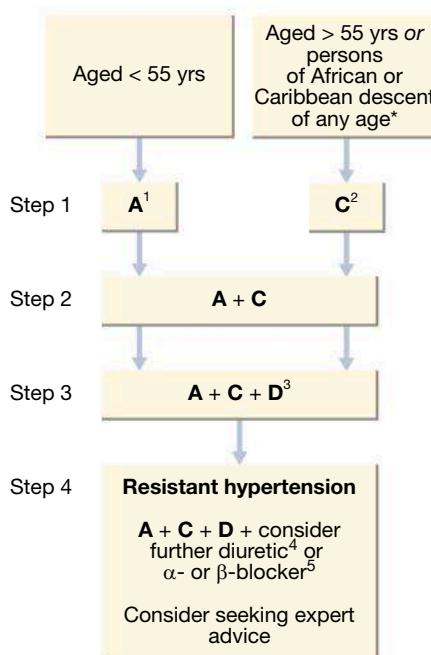


Fig. 16.77 Antihypertensive drug combinations. *Does not apply to those who are of mixed race. ¹A = Angiotensin-converting enzyme (ACE) inhibitor or consider angiotensin II receptor blocker (ARB); choose a low-cost ARB. ²C = calcium channel blocker (CCB); a CCB is preferred but consider a thiazide-like diuretic if a CCB is not tolerated or the person has oedema, evidence of heart failure or a high risk of heart failure. ³D = thiazide-type diuretic. ⁴Consider a low dose of spironolactone or higher doses of a thiazide-like diuretic. ⁵Consider an α- or β-blocker if further diuretic therapy is not tolerated, or is contraindicated or ineffective. Adapted from 2020 International Society of Hypertension Global Hypertension Practice Guidelines.

attempts to improve rapport with the patient and careful supervision can all help. Spironolactone is a particularly useful addition in patients with treatment-resistant hypertension.

Accelerated hypertension

Accelerated or malignant hypertension is a rare condition that can complicate hypertension of any aetiology. It is characterised by accelerated microvascular damage with necrosis in the walls of small arteries and arterioles (fibrinoid necrosis) and by intravascular thrombosis. The diagnosis is based on evidence of high BP and rapidly progressive end-organ damage, such as retinopathy (grade 3 or 4), renal dysfunction (especially proteinuria) and hypertensive encephalopathy (see above). Left ventricular failure may occur and death occurs within months if untreated.

Management

In accelerated phase hypertension, lowering BP too quickly may compromise tissue perfusion due to altered autoregulation and can cause cerebral damage, including occipital blindness, and precipitate coronary or renal insufficiency. Even in the presence of cardiac failure or hypertensive encephalopathy, a controlled reduction to a level of about 150/90 mmHg over a period of 24–48 hours is ideal.

In most patients, it is possible to avoid parenteral therapy and bring BP under control with bed rest and oral drug therapy. Intravenous or intramuscular labetalol (2 mg/min to a maximum of 200 mg), intravenous GTN (0.6–1.2 mg/hr), intramuscular hydralazine (5 or 10 mg aliquots repeated at half-hourly intervals) and intravenous sodium nitroprusside (0.3–1.0 µg/kg body weight/min) are all effective but require careful supervision, preferably in a high-dependency unit.

Diseases of the heart valves

The heart valves allow forward movement of blood through the cardiac chambers when they are open and prevent backward flow when they are closed. A diseased valve may become narrowed, obstructing forward flow, or become leaky, causing backward flow or regurgitation. Breathlessness is a common symptom of valve disease, and acute severe breathlessness may be a presenting symptom of valve failure. The causes of this are shown in Box 16.73. Predisposition to valvular disease may be genetically determined, can arise as the result of rheumatic fever or infections, or can occur in association with dilatation of the cardiac chambers in heart failure. The principal causes of valvular disease are summarised in Box 16.74.

Rheumatic heart disease

Acute rheumatic fever

Acute rheumatic fever usually affects children and young adults between the ages of 5 and 15 years. It is now rare in high-income countries in Western Europe and North America, where the incidence is about 0.5 cases per 100 000, but remains endemic in South Asia, Africa and South America. Recent studies indicate that the current incidence of rheumatic heart disease in India ranges between 13 and 150 cases per 100 000 population per year, where it is the commonest cause of acquired heart disease in childhood and adolescence.

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Pathogenesis

The condition is triggered by an immune-mediated delayed response to infection with specific strains of group A streptococci, which have antigens that cross-react with cardiac myosin and sarcolemmal membrane proteins. Antibodies produced against the streptococcal antigens cause inflammation in the endocardium, myocardium and pericardium, as well as the joints and skin. Histologically, fibrinoid degeneration is seen in the collagen of connective tissues. Aschoff nodules are pathognomonic and



16.73 Causes of acute valve failure

Aortic regurgitation

- Aortic dissection
- Infective endocarditis

Mitral regurgitation

- Papillary muscle rupture due to acute myocardial infarction
- Infective endocarditis
- Rupture of chordae due to myxomatous degeneration

Prosthetic valve failure

- Mechanical valves: fracture, jamming, thrombosis, dehiscence
- Biological valves: degeneration with cusp tear



16.74 Principal causes of valve disease

Valve regurgitation

- Congenital
- Acute rheumatic carditis
- Chronic rheumatic carditis
- Infective endocarditis
- Cardiac failure*
- Syphilitic aortitis
- Traumatic valve rupture
- Senile degeneration
- Damage to chordae and papillary muscles

Valve stenosis

- Congenital
- Rheumatic carditis
- Senile degeneration

*Causes dilatation of the valve ring.

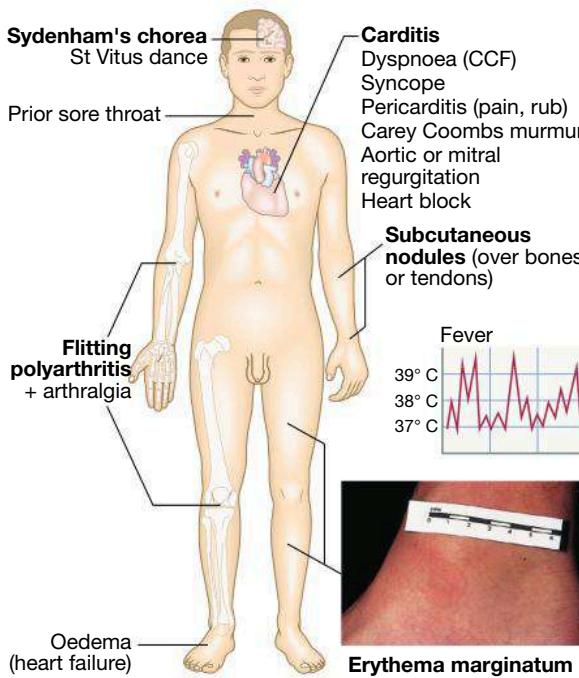


Fig. 16.78 Clinical features of rheumatic fever. Bold labels indicate Jones major criteria. (CCF = congestive cardiac failure) Inset (Erythema marginatum) From Savin JA, Hunter JAA, Hepburn NC. *Skin signs in clinical medicine*. London: Mosby-Wolfe; Elsevier; 1997.

occur only in the heart. They are composed of multinucleated giant cells surrounded by macrophages and T lymphocytes, and are not seen until the subacute or chronic phases of rheumatic carditis.

Clinical features

Acute rheumatic fever is a multisystem disorder that usually presents with fever, anorexia, lethargy and joint pain, 2–3 weeks after an episode of streptococcal pharyngitis although there may be no history of sore throat. Arthritis occurs in approximately 75% of patients. Other features include rashes, subcutaneous nodules, carditis and neurological changes (Fig. 16.78). Using the revised Jones criteria (Box 16.75), the diagnosis is based on two or more major manifestations, or one major and two or more minor manifestations, along with evidence of preceding streptococcal infection. A presumptive diagnosis of acute rheumatic fever can be made without evidence of preceding streptococcal infection in cases of isolated chorea or pancarditis, if other causes have been excluded. In cases of established rheumatic heart disease or prior rheumatic fever, acute rheumatic fever can be diagnosed based only on the presence of multiple minor criteria and evidence of preceding group A streptococcal pharyngitis.

Carditis

Rheumatic fever causes a pancarditis involving the endocardium, myocardium and pericardium to varying degrees. Its incidence declines with increasing age, ranging from 90% at 3 years to around 30% in adolescence. It may manifest as breathlessness (due to heart failure or pericardial effusion), palpitations or chest pain (usually due to pericarditis or pancarditis). Other features include tachycardia, cardiac enlargement and new or changed murmurs. A soft systolic murmur due to mitral regurgitation is very common. A soft mid-diastolic murmur (the Carey Coombs murmur) is typically due to valvulitis, with nodules forming on the mitral valve leaflets. Aortic regurgitation occurs in 50% of cases but the tricuspid and pulmonary valves are rarely involved. Pericarditis may cause chest pain, a pericardial friction rub and precordial tenderness. Cardiac failure may be due to myocardial dysfunction or valvular regurgitation. ECG evidence commonly includes ST and T wave changes. Conduction defects, including AV block, sometimes occur and may cause syncope.

16.75 Jones criteria for the diagnosis of rheumatic fever

Major manifestations

- Carditis
- Polyarthritis
- Chorea
- Erythema marginatum
- Subcutaneous nodules

Minor manifestations

- Fever
- Arthralgia
- Raised erythrocyte sedimentation rate or C-reactive protein
- Previous rheumatic fever
- Leucocytosis
- First-degree atrioventricular block

Plus

- Supporting evidence of preceding streptococcal infection: recent scarlet fever, raised antistreptolysin O or other streptococcal antibody titre, positive throat culture*

*Evidence of recent streptococcal infection is particularly important if there is only one major manifestation.

Arthritis

This is the commonest major manifestation and occurs early when streptococcal antibody titres are high. An acute painful, asymmetric and migratory inflammation of the large joints typically affects the knees, ankles, elbows and wrists. The joints are involved in quick succession and are usually red, swollen and tender for between a day and 4 weeks.

Skin lesions

Erythema marginatum occurs in less than 5% of patients. The lesions start as red macules that fade in the centre but remain red at the edges, and occur mainly on the trunk and proximal extremities but not the face. The resulting red rings or 'margins' may coalesce or overlap (see Fig. 16.78). Subcutaneous nodules occur in 5%–7% of patients. They are small (0.5–2.0 cm), firm and painless, and are best felt over extensor surfaces of bone or tendons. They typically appear more than 3 weeks after the onset of other manifestations and therefore help to confirm rather than make the diagnosis.

Sydenham's chorea

Sydenham's chorea, also known as St Vitus dance, is a late neurological manifestation that appears at least 3 months after the episode of acute rheumatic fever, when all the other signs may have disappeared. It occurs in up to one-third of cases and is more common in females. Emotional lability may be the first feature and is typically followed by purposeless, involuntary, choreiform movements of the hands, feet or face. Speech may be explosive and halting. Spontaneous recovery usually occurs within a few months. Approximately one-quarter of affected patients will go on to develop chronic rheumatic valve disease.

Other features

Other systemic manifestations, such as pleurisy, pleural effusion and pneumonia, may occur but are rare.

Investigations

Blood should be taken for measurement of ESR and CRP since these are useful for monitoring progress of the disease (Box 16.76). Throat cultures should be taken but positive results are obtained in only 10%–25% of cases since the infection has often resolved by the time of presentation. Serology for antistreptolysin O antibodies (ASO) should be performed and provide supportive evidence for the diagnosis but are normal in one-fifth of adult cases of rheumatic fever and most cases of chorea. Echocardiography should be carried out and typically shows mitral regurgitation with dilatation of the mitral annulus and prolapse of the anterior mitral leaflet; it may also demonstrate aortic regurgitation and pericardial effusion.



16.76 Investigations in acute rheumatic fever

Evidence of a systemic illness

- Leucocytosis, raised erythrocyte sedimentation rate and C-reactive protein

Evidence of preceding streptococcal infection

- Throat swab culture: group A β-haemolytic streptococci (also from family members and contacts)
- Antistreptolysin O antibodies (ASO titres): rising titres, or levels of > 200 U (adults) or > 300 U (children)

Evidence of carditis

- Chest X-ray: cardiomegaly; pulmonary congestion
- ECG: first- and, rarely, second-degree atrioventricular block; features of pericarditis; T-wave inversion; reduction in QRS voltages
- Echocardiography: cardiac dilatation and valve abnormalities

Management

The aims of management are to limit cardiac damage and relieve symptoms.

Bed rest

Bed rest is important, as it lessens joint pain and reduces cardiac workload. The duration should be guided by symptoms, along with temperature, leucocyte count and ESR, and should be continued until these have settled. Patients can then return to normal physical activity but strenuous exercise should be avoided in those who have had carditis.

Treatment of cardiac failure

Some patients, particularly those in early adolescence, can develop a fulminant form of the disease with severe mitral regurgitation and, sometimes, concomitant aortic regurgitation. If heart failure does not respond to medical treatment, valve replacement may be necessary and is often associated with a dramatic decline in rheumatic activity. Occasionally, AV block may occur but is seldom progressive and usually resolves spontaneously. Rarely, pacemaker insertion may be required.

Antibiotic therapy

A single dose of benzathine benzylpenicillin (1.2 million U IM) or oral phenoxymethylpenicillin (250 mg 4 times daily for 10 days) should be given on diagnosis to eliminate any residual streptococcal infection. If the patient is penicillin-allergic, erythromycin or a cephalosporin can be used. Patients are susceptible to further attacks of rheumatic fever if another streptococcal infection occurs, and long-term prophylaxis with penicillin should be given with oral phenoxymethylpenicillin (250 mg twice daily) or as benzathine benzylpenicillin (1.2 million U IM monthly), if adherence is in doubt. Sulfadiazine or erythromycin may be used if the patient is allergic to penicillin; sulphonamides prevent infection but are not effective in the eradication of group A streptococci. Further attacks of rheumatic fever are unusual after the age of 21, when antibiotic treatment can usually be stopped. The duration of prophylaxis should be extended if an attack has occurred in the last 5 years, or if the patient lives in an area of high prevalence and has an occupation (such as teaching) with a high risk of exposure to streptococcal infection. In those with residual heart disease, prophylaxis should continue until 10 years after the last episode or 40 years of age, whichever is later. While long-term antibiotic prophylaxis prevents further attacks of acute rheumatic fever, it does not protect against infective endocarditis.

Aspirin

This usually relieves the symptoms of arthritis rapidly and a response within 24 hours helps confirm the diagnosis. A reasonable starting dose is 60 mg/kg body weight/day, divided into six doses. In adults, 100 mg/kg per day may be needed up to the limits of tolerance or a maximum of 8 g per day. Mild toxicity includes nausea, tinnitus and deafness; vomiting, tachypnoea and acidosis are more serious. Aspirin should be continued until the ESR has fallen and then gradually tailed off.

Glucocorticoid steroids

These produce more rapid symptomatic relief than aspirin and are indicated in cases with carditis or severe arthritis. There is no evidence that long-term steroids are beneficial. Prednisolone (1.0–2.0 mg/kg per day in divided doses) should be continued until the ESR is normal and then gradually reduced.

Chronic rheumatic heart disease

Chronic valvular heart disease develops in at least half of those affected by rheumatic fever with carditis. Two-thirds of cases occur in women. Some episodes of rheumatic fever pass unrecognised and it is possible to elicit a history of rheumatic fever or chorea in only about half of all patients with chronic rheumatic heart disease.

The mitral valve is affected in more than 90% of cases; the aortic valve is the next most frequently involved, followed by the tricuspid and then the pulmonary valve. Isolated mitral stenosis accounts for about 25% of all cases, and an additional 40% have mixed mitral stenosis and regurgitation.

Pathogenesis

The main pathological process in chronic rheumatic heart disease is progressive fibrosis. The heart valves are predominantly affected but involvement of the pericardium and myocardium also occurs and may contribute to heart failure and conduction disorders. Fusion of the mitral valve commissures and shortening of the chordae tendineae may lead to mitral stenosis with or without regurgitation. Similar changes in the aortic and tricuspid valves produce distortion and rigidity of the cusps, leading to stenosis and regurgitation. Once a valve has been damaged, the altered haemodynamic stresses perpetuate and extend the damage, even in the absence of a continuing rheumatic process.

Mitral valve disease

Mitral stenosis

Mitral stenosis is almost always rheumatic in origin, although in older people it can be caused by heavy calcification of the mitral valve. There is also a rare form of congenital mitral stenosis.

Pathogenesis

In rheumatic mitral stenosis, the mitral valve orifice is slowly diminished by progressive fibrosis, calcification of the valve leaflets, and fusion of the cusps and subvalvular apparatus. The mitral valve orifice is normally about 5 cm² in diastole but can be reduced to < 1 cm² in severe mitral stenosis. The patient is usually asymptomatic until the orifice is < 2 cm². As stenosis progresses, left ventricular filling becomes more dependent on left atrial contraction. There is dilatation and hypertrophy of the LA and left atrial pressure rises, leading to pulmonary venous congestion and breathlessness. Any increase in heart rate shortens diastole when the mitral valve is open and produces a further rise in left atrial pressure. Situations that demand an increase in cardiac output, such as pregnancy and exercise, also increase left atrial pressure and are poorly tolerated.

Atrial fibrillation is very common due to progressive dilatation of the LA. Its onset often precipitates pulmonary oedema because the accompanying tachycardia and loss of atrial contraction lead to haemodynamic deterioration and a rapid rise in left atrial pressure. In the absence of AF, a more gradual rise in left atrial pressure may occur. Irrespective of AF, pulmonary hypertension may occur, which can protect the patient from pulmonary oedema. Pulmonary hypertension leads to right ventricular hypertrophy and dilatation, tricuspid regurgitation and right heart failure. Fewer than 20% of patients remain in sinus rhythm but many of these have a small fibrotic LA and severe pulmonary hypertension.

16.77 Clinical features of mitral stenosis	
Clinical feature	Cause
Symptoms	
Breathlessness	Pulmonary congestion, low cardiac output
Fatigue	Low cardiac output
Oedema, ascites	Right heart failure
Palpitation	Atrial fibrillation
Haemoptysis	Pulmonary congestion
Cough	Pulmonary congestion
Chest pain	Pulmonary hypertension
Thromboembolism	Atrial stasis and atrial fibrillation
Signs	
Atrial fibrillation	Atrial dilatation
Mitral facies	Low cardiac output
Auscultation:	
Loud first heart sound, opening snap	Non-compliant, stenotic valve
Mid-diastolic murmur	
Crepitations	Left heart failure
Pulmonary oedema	
Pleural effusions	
Right ventricular heave, loud P ₂	Pulmonary hypertension

Clinical features

Effort-related dyspnoea is usually the dominant symptom (Box 16.77). Typically, exercise tolerance diminishes very slowly over many years until symptoms eventually occur at rest. Patients frequently do not appreciate the extent of their disability until the diagnosis is made and their valve disease is treated. Acute pulmonary oedema or pulmonary hypertension can lead to haemoptysis. Fatigue is a common symptom due to a low cardiac output. Thromboembolism is a common complication, especially in patients with AF. Prior to the advent of anticoagulant therapy, emboli caused one-quarter of all deaths.

The physical signs of mitral stenosis are often found before symptoms develop and their recognition is of particular importance in pregnancy. The forces that open and close the mitral valve increase as left atrial pressure rises. The first heart sound (S1) is therefore loud and can be palpable (tapping apex beat). An opening snap may be audible and moves closer to the second sound (S2) as the stenosis becomes more severe and left atrial pressure rises. However, the first heart sound and opening snap may be inaudible if the valve is heavily calcified.

Turbulent flow produces the characteristic low-pitched mid-diastolic murmur and sometimes a thrill (Fig. 16.79). The murmur is accentuated by exercise and during atrial systole (pre-systolic accentuation). Early in the disease a pre-systolic murmur may be the only auscultatory abnormality, but in patients with symptoms, the murmur extends from the opening snap to the first heart sound. Coexisting mitral regurgitation causes a pansystolic murmur that radiates towards the axilla.

Pulmonary hypertension may ultimately lead to right ventricular hypertrophy and dilatation with secondary tricuspid regurgitation, which causes a parasternal lift, and a systolic murmur and giant 'v waves' in the venous pulse.

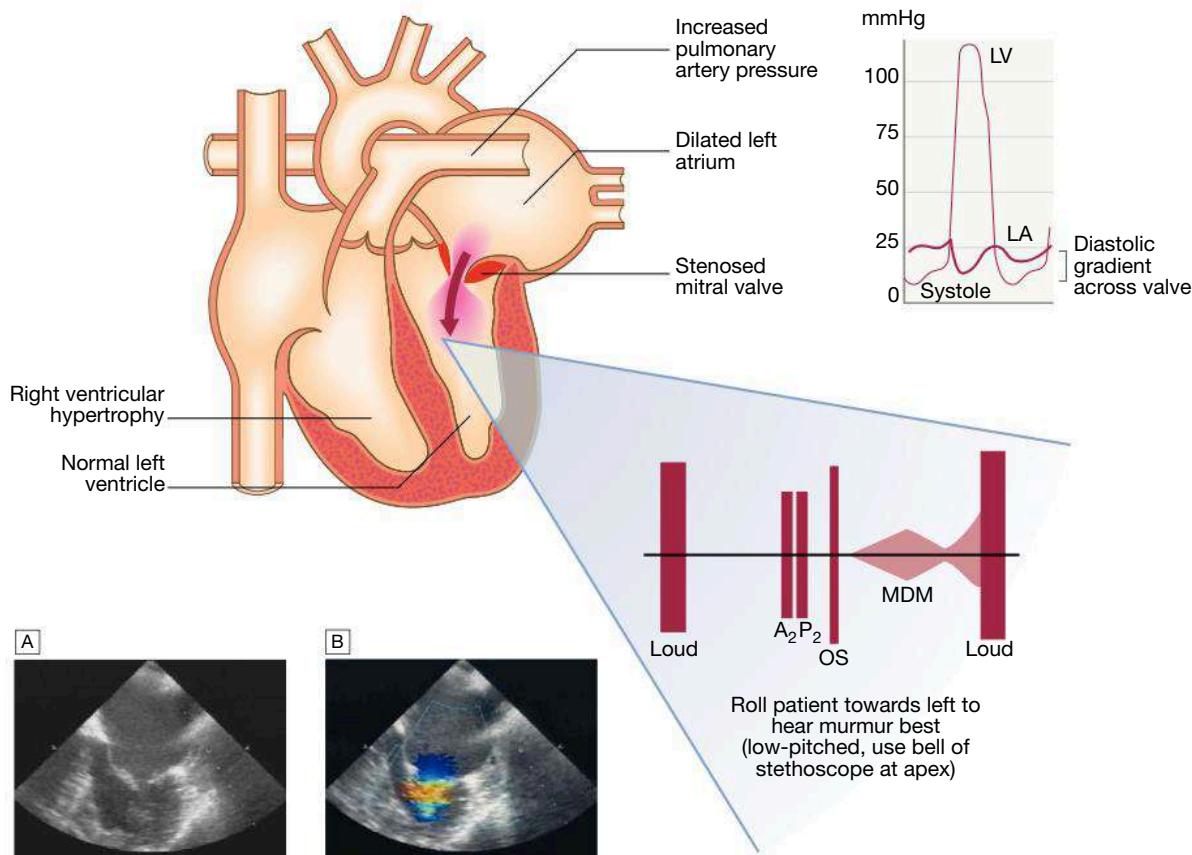


Fig. 16.79 Mitral stenosis: murmur and the diastolic pressure gradient between left atrium (LA) and left ventricle (LV). (Mean gradient is reflected by the area between LA and LV in diastole.) The first heart sound is loud, and there is an opening snap (OS) and mid-diastolic murmur (MDM) with pre-systolic accentuation. **A** Echocardiogram showing reduced opening of the mitral valve in diastole. **B** Colour Doppler showing turbulent flow.

Investigations

Doppler echocardiography is the investigation of choice for evaluation of suspected mitral stenosis (see Fig. 16.79). Cardiac catheterisation may also be required if surgery or valvuloplasty is being considered, to screen for coexisting conditions such as CAD. The ECG may show either AF or bifid P waves (*P mitrale*) associated with left atrial hypertrophy (Box 16.78). A typical chest X-ray is shown in Fig. 16.9.

Management

Patients with mild symptoms can be treated medically but intervention by balloon valvuloplasty, mitral valvotomy or mitral valve replacement should be considered if the patient remains symptomatic despite medical treatment or if pulmonary hypertension develops.

Medical management

This consists of anticoagulation to reduce the risk of systemic embolism, ventricular rate control with digoxin, β -blockers or rate-limiting calcium antagonists for AF, and diuretic to control pulmonary congestion. Antibiotic prophylaxis against infective endocarditis is no longer routinely recommended.

Mitral balloon valvuloplasty and valve replacement

Valvuloplasty is the treatment of choice if specific criteria are fulfilled (Box 16.79 and Fig. 16.80), although surgical closed or open mitral valvotomy is an acceptable alternative. Patients who have undergone mitral valvuloplasty or valvotomy should be followed up at 1–2-yearly intervals because restenosis may occur. Clinical symptoms and signs are a guide to the severity of mitral restenosis but Doppler echocardiography provides a more accurate assessment.

Valve replacement is indicated if there is substantial mitral reflux or if the valve is rigid and calcified.

16.78 Investigations in mitral stenosis

ECG

- Right ventricular hypertrophy: tall R waves in V_1-V_3
- *P mitrale* or atrial fibrillation

Chest X-ray

- | | |
|------------------------------------|--------------------------------------|
| Enlarged left atrium and appendage | Signs of pulmonary venous congestion |
|------------------------------------|--------------------------------------|

Echo

- | | |
|----------------------------|---|
| • Thickened immobile cusps | • Reduced rate of diastolic filling of left ventricle |
| • Reduced valve area | |
| • Enlarged left atrium | |

Doppler

- | | |
|---|-----------------------------|
| • Pressure gradient across mitral valve | • Left ventricular function |
| • Pulmonary artery pressure | |

Cardiac catheterisation

- | | |
|-----------------------------|-------------------------------------|
| • Coronary artery disease | • Mitral stenosis and regurgitation |
| • Pulmonary artery pressure | |



16.79 Criteria for mitral valvuloplasty*

- Significant symptoms
- Isolated mitral stenosis
- No (or trivial) mitral regurgitation
- Mobile, non-calcified valve/subvalve apparatus on echo
- Left atrium free of thrombus

*For comprehensive guidelines on valvular heart disease, see www.acc.org.

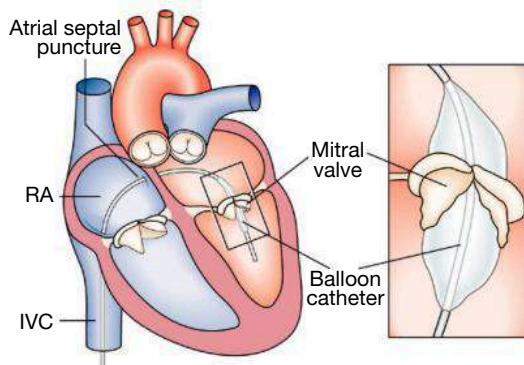


Fig. 16.80 Mitral valvuloplasty. A guidewire is introduced into the right atrium (RA) from the femoral vein and the inferior vena cava (IVC). The interatrial septum is punctured, providing access to the left atrium and mitral valve. A balloon catheter is then advanced over the guidewire across the mitral valve and the balloon dilated to stretch the valve and reduce the degree of stenosis.



16.80 Causes of mitral regurgitation

- Mitral valve prolapse
- Dilatation of the left ventricle and mitral valve ring (coronary artery disease, cardiomyopathy)
- Damage to valve cusps and chordae (rheumatic heart disease, endocarditis)
- Ischaemia or infarction of the papillary muscle
- Myocardial infarction

Mitral regurgitation

Rheumatic disease is the principal cause in countries where rheumatic fever is common but elsewhere, including in the UK, other causes are more important (Box 16.80). Mitral regurgitation may also follow mitral valvotomy or valvuloplasty.

Pathogenesis

Chronic mitral regurgitation causes gradual dilatation of the LA with little increase in pressure and relatively few symptoms. Nevertheless, the LV dilates slowly and the left ventricular diastolic and left atrial pressures gradually increase as a result of chronic volume overload of the LV. In contrast, acute mitral regurgitation causes a rapid rise in left atrial pressure (because left atrial compliance is normal) and marked symptomatic deterioration.

Mitral valve prolapse

This is also known as 'floppy' mitral valve and is a common cause of mild mitral regurgitation (Fig. 16.81). Some cases are thought to be due to a developmental abnormality of the mitral valve and others due to degenerative myxomatous change in a normal mitral valve. Rarely, mitral valve prolapse may occur in association with Marfan syndrome.

In its mildest forms, the valve remains competent but bulges back into the atrium during systole, causing a mid-systolic click but no murmur. In the presence of a regurgitant valve, the click is followed by a late systolic murmur, which lengthens as the regurgitation becomes more severe. A click is not always audible and the physical signs may vary with both posture and respiration. Progressive elongation of the chordae tendineae leads to increasing mitral regurgitation, and if chordal rupture occurs, regurgitation suddenly becomes severe. This is rare before the fifth or sixth decade of life.

Mitral valve prolapse is associated with a variety of typically benign arrhythmias, atypical chest pain and a very small risk of embolic stroke or transient ischaemic attack (TIA). Nevertheless, the overall long-term prognosis is good.

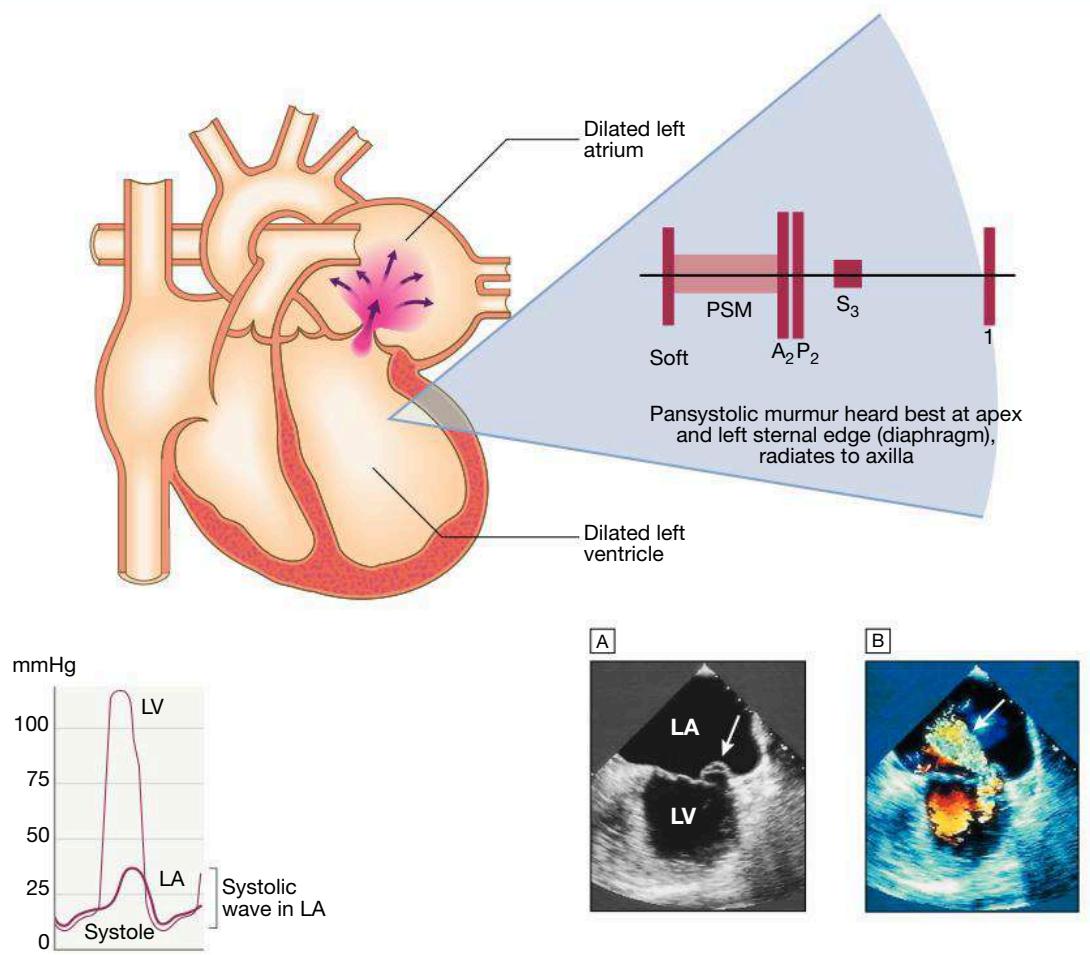


Fig. 16.81 Mitral regurgitation: murmur and systolic wave in left atrial pressure. The first sound is normal or soft and merges with a pansystolic murmur (PSM) extending to the second heart sound. A third heart sound occurs with severe regurgitation. [A] A transoesophageal echocardiogram shows mitral valve prolapse, with one leaflet bulging towards the left atrium (LA, arrow). [B] This results in a jet of mitral regurgitation on colour Doppler (arrow). (LV = left ventricle)

Other causes of mitral regurgitation

Mitral valve function depends on the chordae tendineae and their papillary muscles; dilatation of the LV distorts the geometry of these and may cause mitral regurgitation (see Box 16.80). Dilated cardiomyopathy and heart failure from CAD are common causes of so-called 'functional' mitral regurgitation. Endocarditis is an important cause of acute mitral regurgitation.

Clinical features

Symptoms and signs depend on the underlying cause and how suddenly the regurgitation develops (Box 16.81). Chronic mitral regurgitation produces a symptom complex that is similar to that of mitral stenosis but sudden-onset mitral regurgitation usually presents with acute pulmonary oedema.

The regurgitant jet causes an apical systolic murmur (Fig. 16.82), which radiates into the axilla and may be accompanied by a thrill. Increased forward flow through the mitral valve causes a loud third heart sound and even a short mid-diastolic murmur. The apex beat feels active and rocking due to left ventricular volume overload and is usually displaced to the left as a result of left ventricular dilatation.

Investigations

Echocardiography is a pivotal investigation. The severity of regurgitation can be assessed by Doppler and information may also be gained on papillary muscle function and valve prolapse. An ECG should be performed and commonly shows AF, as a consequence of atrial dilatation.

i 16.81 Clinical features of mitral regurgitation	
Clinical feature	Cause
Symptoms	
Breathlessness	Pulmonary congestion
Fatigue	Low cardiac output
Oedema, ascites	Right heart failure
Palpitation	Atrial fibrillation
Signs	
Atrial fibrillation	Atrial dilatation
Displaced apex beat	Cardiomegaly
Auscultation:	
Apical pansystolic murmur	Regurgitation of blood from left ventricle to left atrium
Soft S ₁	Valve does not close properly
Apical S ₃	Rapid flow of blood into left ventricle
Crepitations	
Pulmonary oedema	
Pleural effusions	
Right ventricular heave	
Raised jugular venous pressure	
Oedema	
	{ Left heart failure
	Pulmonary hypertension
	Right heart failure
	Right heart failure

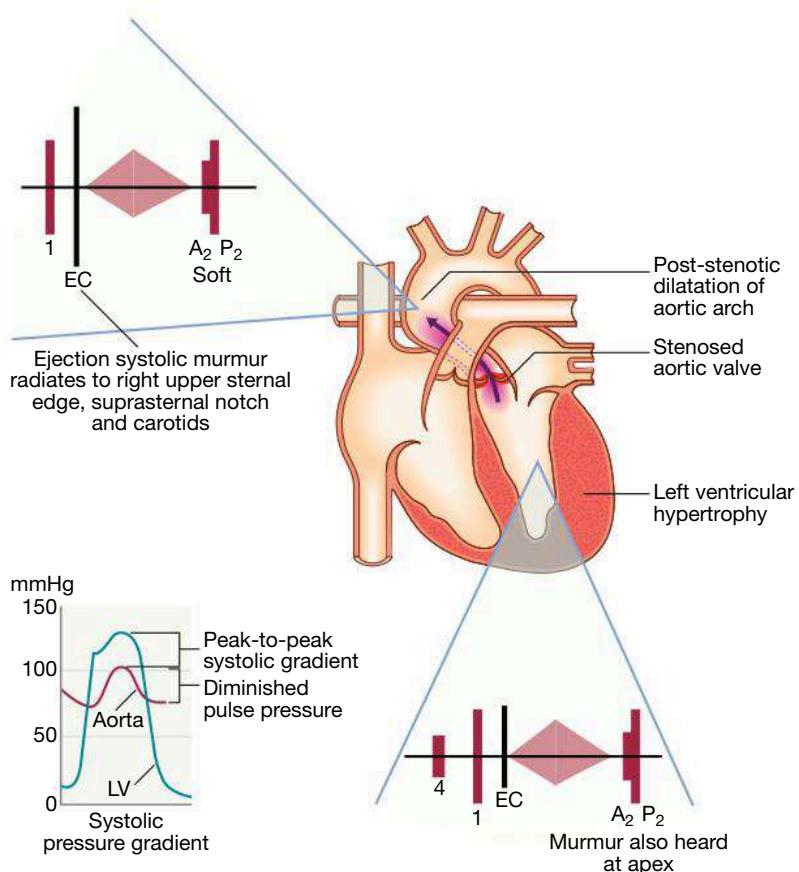


Fig. 16.82 Aortic stenosis. Pressure traces show the systolic gradient between left ventricle (LV) and aorta. The 'diamond-shaped' murmur is heard best with the diaphragm in the aortic outflow and also at the apex. An ejection click (EC) may be present in young patients with a bicuspid aortic valve but not in older patients with calcified valves. Aortic stenosis may lead to left ventricular hypertrophy with a fourth sound at the apex and post-stenotic dilatation of the aortic arch. Fig. 16.11 shows the typical Doppler signal with aortic stenosis.

Cardiac catheterisation is indicated when surgery is being considered (Box 16.82). During catheterisation, the severity of mitral regurgitation can be assessed by left ventriculography and by the size of the *v* (systolic) waves in the left atrial or pulmonary artery wedge pressure trace.

Management

Mitral regurgitation of moderate severity can be treated medically with diuretics and vasodilators. Digoxin and anticoagulants should be given if AF is present (Box 16.83). If systemic hypertension is present, it should be treated with vasodilators such as ACE inhibitors or ARBs, since high



16.83 Medical management of mitral regurgitation

- Diuretics
- Vasodilators if hypertension is present
- Digoxin if atrial fibrillation is present
- Anticoagulants if atrial fibrillation is present

afterload may worsen the degree of regurgitation. All patients should be reviewed at regular intervals, both clinically and by echocardiography. Worsening symptoms, progressive cardiomegaly or echocardiographic evidence of deteriorating left ventricular function are indications for mitral valve replacement or repair. Mitral valve repair is now the treatment of choice for severe mitral regurgitation, because early repair appears to prevent irreversible left ventricular damage. Mitral regurgitation often accompanies left ventricular failure associated with CAD. If such patients are to undergo CABG surgery, it is common practice to repair the valve and restore mitral valve function by inserting an annuloplasty ring to overcome annular dilatation and to bring the valve leaflets closer together. Unfortunately, it can be difficult to determine whether it is the ventricular dilatation or the mitral regurgitation that is the predominant problem. If ventricular dilatation is the underlying cause of mitral regurgitation, then mitral valve repair or replacement may actually worsen ventricular function, as the ventricle can no longer empty into the low-pressure LA.



16.82 Investigations in mitral regurgitation

ECG

- P-mitrale
- Atrial fibrillation

Chest X-ray

- Enlarged left atrium
- Enlarged left ventricle
- Pulmonary venous congestion
- Pulmonary oedema (if acute)

Echo

- Dilated left atrium, left ventricle
- Dynamic left ventricle (unless myocardial dysfunction predominates)
- Structural abnormalities of mitral valve

Doppler

- Detects and quantifies regurgitation

Cardiac catheterisation

- Dilated left atrium, dilated left ventricle, mitral regurgitation
- Pulmonary hypertension
- Coexisting coronary artery disease

Aortic valve disease

Aortic stenosis

There are several causes of aortic stenosis but the age at which patients present can give a clue to the most likely diagnosis (Box 16.84).

16.84 Causes of aortic stenosis

Infants, children, adolescents

- Congenital aortic stenosis
- Congenital subvalvular aortic stenosis
- Congenital supravalvular aortic stenosis

Young to middle-aged adults

- Calcification and fibrosis of congenitally bicuspid aortic valve
- Rheumatic aortic stenosis

Middle-aged to older adults

- Senile degenerative aortic stenosis
- Calcification of bicuspid valve
- Rheumatic aortic stenosis

In congenital aortic stenosis, obstruction is present from birth or becomes apparent during infancy. With bicuspid aortic valves, obstruction may take years to develop as the valve becomes fibrotic and calcified, and these patients present as young to middle-aged adults. Rheumatic disease of the aortic valve presents at a similar age but is usually accompanied by mitral valve disease. In older people, tricuspid aortic valves may become stenotic as the result of fibrosis and calcification. Stenosis develops slowly, typically occurring at 30–60 years in those with rheumatic disease, 50–60 years in those with bicuspid aortic valves and 70–90 years in those with calcific aortic disease.

Pathogenesis

Cardiac output is initially maintained in patients with aortic stenosis at the cost of a steadily increasing pressure gradient across the aortic valve. With progression of the stenosis, the LV becomes increasingly hypertrophied and coronary blood flow may be inadequate to supply the myocardium, such that angina can develop even in the absence of coexisting CAD. The fixed outflow obstruction limits the increase in cardiac output required on exercise. Eventually, the LV can no longer overcome the outflow tract obstruction and LV failure results, leading to pulmonary oedema.

Clinical features

Aortic stenosis is commonly picked up in asymptomatic patients at routine clinical examination but the three cardinal symptoms are angina, breathlessness and syncope (Box 16.85). Angina arises either because of the increased demands of the hypertrophied LV working against the high-pressure outflow tract obstruction, or the presence of coexisting CAD, which affects over 50% of patients. Exertional breathlessness suggests cardiac decompensation as a consequence of the excessive pressure overload placed on the LV. Syncope usually occurs on exertion when cardiac output fails to rise to meet demand, leading to a fall in BP. Sometimes patients with severe aortic stenosis do not complain of symptoms. If, on clinical evaluation, this appears to be due to a sedentary lifestyle, a careful exercise test may reveal symptoms on modest exertion.

The characteristic clinical signs of severe aortic stenosis are shown in Box 16.85. A harsh ejection systolic murmur radiates to the neck, with a soft second heart sound, particularly in those with calcific valves. The murmur is often likened to a saw cutting wood and may (especially in older patients) have a musical quality like the ‘mew’ of a seagull (see Fig. 16.82). The severity of aortic stenosis may be difficult to gauge clinically, as older patients with a non-compliant ‘stiff’ arterial system may have an apparently normal carotid upstroke in the presence of severe aortic stenosis. Milder degrees of stenosis may be difficult to distinguish from aortic sclerosis, in which the valve is thickened or calcified but not obstructed. A careful examination should be made for other valve lesions, particularly in rheumatic heart disease, when there is frequently concomitant mitral valve disease. In contrast to patients with mitral stenosis, which tends to progress very slowly, patients with aortic stenosis

16.85 Clinical features of aortic stenosis

Symptoms

- | | |
|--|--|
| <ul style="list-style-type: none"> • Mild or moderate stenosis: usually asymptomatic • Exertional dyspnoea • Angina | <ul style="list-style-type: none"> • Exertional syncope • Sudden death • Episodes of acute pulmonary oedema |
|--|--|

Signs

- | | |
|---|---|
| <ul style="list-style-type: none"> • Ejection systolic murmur • Slow-rising carotid pulse • Heaving apex beat (left ventricular pressure overload) | <ul style="list-style-type: none"> • Narrow pulse pressure • Signs of pulmonary venous congestion |
|---|---|

typically remain asymptomatic for many years but deteriorate rapidly when symptoms develop; if otherwise untreated, they usually die within 3–5 years of presentation.

Investigations

Echocardiography is a pivotal investigation in patients suspected of having aortic stenosis. It can demonstrate restricted valve opening (Fig. 16.83) and Doppler assessment permits calculation of the systolic gradient across the aortic valve, from which the severity of stenosis can be assessed (see Fig. 16.11). In patients with impaired left ventricular function, velocities across the aortic valve may be diminished because of a reduced stroke volume; this is called low-flow aortic stenosis. When marked aortic regurgitation or elevated cardiac output is present, velocities are increased because of an increased stroke volume and this may overestimate stenosis severity on Doppler echocardiography. In advanced cases, ECG features of LV hypertrophy (Box 16.86) are often pronounced (Fig. 16.84), and down-sloping ST segments and T inversion ('strain pattern') are seen in the lateral leads, reflecting left ventricular fibrosis. Nevertheless, the ECG can be normal, despite severe stenosis. Occasionally, there is evidence of AV block due to the encroachment of the fibrocalcific process on the adjacent AV node and His-Purkinje system; an occasional cause of syncope in these patients. Imaging with CT may be useful in assessing the degree of valve calcification where there is uncertainty of disease severity.

Management

Irrespective of the severity of valve stenosis, patients with asymptomatic aortic stenosis have a good immediate prognosis and conservative management is appropriate. Such patients should be kept under review, as the development of angina, syncope, symptoms of low cardiac output or heart failure has a poor prognosis and is an indication for prompt surgery. In practice, patients with moderate or severe stenosis should be evaluated every 1–2 years with Doppler echocardiography to detect evidence of progression in severity. The intervals between reviews should be more frequent (typically 3–6-monthly) in older patients with heavily calcified valves.

Patients with symptomatic severe aortic stenosis should have prompt aortic valve replacement. Delay exposes the patient to the risk of sudden death or irreversible deterioration in ventricular function. Old age is not a contraindication to valve replacement and results are very good in experienced centres, even for those in their eighties (Box 16.87). This is especially the case with transcatheter aortic valve implantation (TAVI, see Fig. 16.86). Aortic balloon valvuloplasty is useful in congenital aortic stenosis but has limited value in older patients with calcific aortic stenosis.

Anticoagulants are required only in patients who have AF or those who have had a valve replacement with a mechanical prosthesis.

Aortic regurgitation

This condition can result from either disease of the aortic valve cusps, infection, trauma or dilatation of the aortic root. The causes are summarised in Box 16.88.

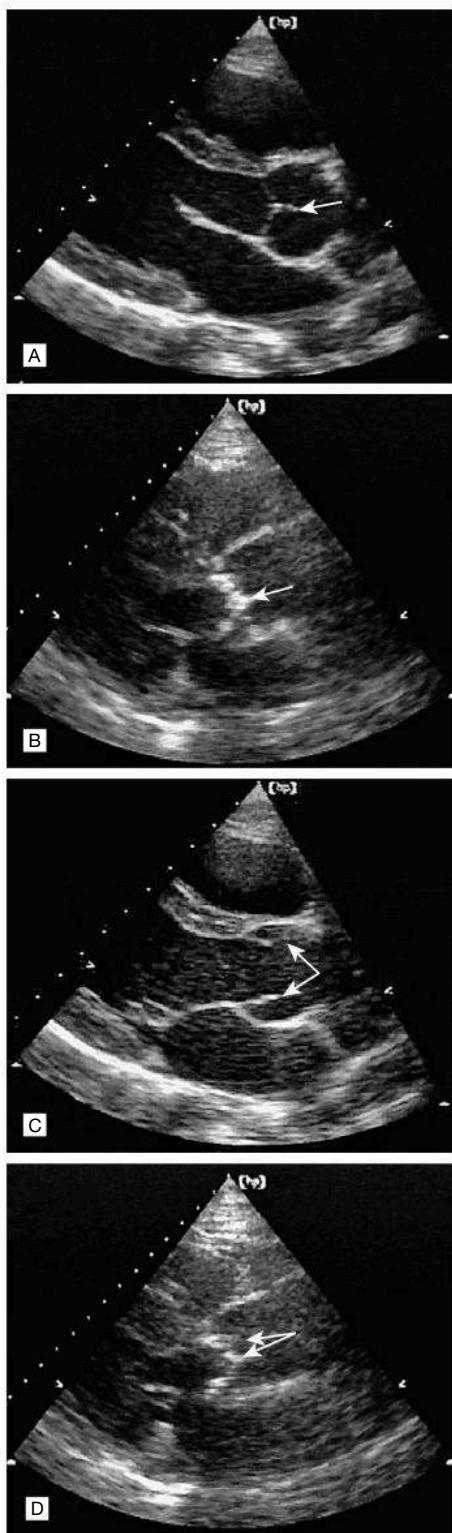


Fig. 16.83 Two-dimensional echocardiogram comparing a normal individual and a patient with calcific aortic stenosis. **A** Normal individual in diastole; the aortic leaflets are closed and thin, and a point of coaptation is seen (arrow). **B** Calcific aortic stenosis in diastole; the aortic leaflets are thick and calcified (arrow). **C** Normal in systole; the aortic leaflets are open (arrows). **D** Calcific aortic stenosis in systole; the thickened leaflets have barely moved (arrows). From Newby D, Grubb N. *Cardiology: an illustrated colour text*. Edinburgh: Churchill Livingstone, Elsevier Ltd; 2005.

Pathogenesis

Regurgitation of blood through the aortic valve causes the LV to dilate as cardiac output increases to maintain the demands of the circulation.

16.86 Investigations in aortic stenosis

ECG

- Left ventricular hypertrophy
- Left bundle branch block

Chest X-ray

- May be normal; sometimes enlarged left ventricle and dilated ascending aorta on postero-anterior view, calcified valve on lateral view

Echo

- Calcified valve with restricted opening, hypertrophied left ventricle

Doppler

- Measurement of severity of stenosis
- Detection of associated aortic regurgitation

Cardiac catheterisation

- Mainly to identify associated coronary artery disease
- May be used to measure gradient between left ventricle and aorta



16

Fig. 16.84 Left ventricular hypertrophy. QRS complexes in limb leads have increased amplitude with very large R waves in V_4 and V_5 and a deep S wave in V_3 . There is ST depression and T-wave inversion in leads II, III, aVF, V_5 and V_6 ; a 'left ventricular strain' pattern.

The stroke volume of the LV may eventually be doubled and the major arteries are then conspicuously pulsatile. As the disease progresses, left ventricular failure develops, leading to a rise in left ventricular end-diastolic pressure and pulmonary oedema.

Clinical features

Until the onset of breathlessness, the only symptom may be an awareness of the heart beat (Box 16.89), particularly when lying on the left side, which results from the increased stroke volume. Paroxysmal nocturnal



16.87 Aortic stenosis in old age

- Incidence:** the most common form of valve disease affecting the very old.
- Symptoms:** a common cause of syncope, angina and heart failure in the very old.
- Signs:** because of increasing stiffening in the central arteries, low pulse pressure and a slow-rising pulse may not be present.
- Transcatheter aortic valve implantation (TAVI):** a good option in older individuals because less invasive than surgery.
- Surgery:** can be successful in those aged 80 years or more in the absence of comorbidity, but with a higher operative mortality. The prognosis without surgery is poor once symptoms have developed.
- Valve replacement type:** a biological valve is often preferable to a mechanical one because this obviates the need for anticoagulation, and the durability of biological valves usually exceeds the patient's anticipated life expectancy.



16.88 Causes of aortic regurgitation

Congenital

- Bicuspid valve or disproportionate cusps

Acquired

- Rheumatic disease
- Infective endocarditis
- Trauma
- Causes of aortic dilatation:
 - Marfan syndrome
 - Aneurysm
 - Aortic dissection
 - Syphilis
 - Ankylosing spondylitis

dyspnoea is sometimes the first symptom, and peripheral oedema or angina may occur. The characteristic murmur is best heard to the left of the sternum during held expiration (Fig. 16.85); a thrill is rare. A systolic murmur due to the increased stroke volume is common and does not necessarily indicate stenosis. The regurgitant jet causes fluttering of the mitral valve and, if severe, causes partial closure of the anterior mitral leaflet, leading to functional mitral stenosis and a soft mid-diastolic (Austin Flint) murmur.

Acute severe regurgitation may occur as the result of perforation or tear of an aortic cusp in endocarditis. In this circumstance there may be no time for compensatory left ventricular hypertrophy and dilatation to develop and the features of heart failure may predominate. The classical signs of aortic regurgitation in such patients may be masked by tachycardia and an abrupt rise in left ventricular end-diastolic pressure. The pulse pressure may also be normal or near-normal and the diastolic murmur may be short or even absent.

Investigations

Doppler echocardiography is the investigation of first choice for detecting regurgitation (Box 16.90). In severe acute aortic regurgitation the rapid rise in left ventricular diastolic pressure may cause premature mitral valve closure. Cardiac catheterisation and aortography are usually performed to assess the severity of regurgitation, to determine if there is dilatation of the aorta and to screen for the presence of coexisting CAD. MRI can also be useful in assessing the degree and extent of aortic dilatation if this is suspected on chest X-ray or echocardiography.

Management

Treatment may be required for underlying conditions, such as endocarditis or syphilis. Aortic valve replacement is indicated if aortic regurgitation causes symptoms, and this may need to be combined with aortic root replacement and coronary bypass surgery. Those with chronic aortic regurgitation can remain asymptomatic for many years because compensatory ventricular dilatation and hypertrophy occur, but should be advised to report the development of any symptoms of breathlessness



16.89 Clinical features of aortic regurgitation

Symptoms

Mild to moderate aortic regurgitation

- Often asymptomatic
- Palpitations

Severe aortic regurgitation

- Breathlessness
- Angina

Signs

Pulses

- Large-volume or 'collapsing' pulse
- Low diastolic and increased pulse pressure
- Bounding peripheral pulses
- Capillary pulsation in nail beds: Quincke's sign
- Femoral bruit ('pistol shot'): Duroziez's sign
- Head nodding with pulse: de Musset's sign

Murmurs

- Early diastolic murmur
- Systolic murmur (increased stroke volume)
- Austin Flint murmur (soft mid-diastolic)

Other signs

- Displaced, thrusting apex beat (volume overload)
- Pre-systolic impulse
- Third heart sound
- Fourth heart sound
- Crepitations (pulmonary venous congestion)

or angina. Asymptomatic patients should also be followed up annually with echocardiography for evidence of increasing ventricular size. If this occurs or if the end-systolic dimension increases to 55 mm or more, then aortic valve replacement should be undertaken. If systemic hypertension is present, non-rate-limiting vasodilators, such as nifedipine, should be used to control systolic BP. There is conflicting evidence regarding the need for aortic valve replacement in asymptomatic patients with severe aortic regurgitation. When aortic root dilatation is the cause of aortic regurgitation, as can occur in Marfan syndrome, aortic root replacement is usually necessary.

Tricuspid valve disease

Tricuspid stenosis

Tricuspid stenosis is usually rheumatic in origin and is rare in higher-income countries. Tricuspid disease occurs in fewer than 5% of patients with rheumatic heart disease and then nearly always occurs in association with mitral and aortic valve disease. Tricuspid stenosis and regurgitation may also occur in the carcinoid syndrome.

Clinical features and investigations

Although the symptoms of mitral and aortic valve disease predominate, tricuspid stenosis may cause symptoms of right heart failure, including hepatic discomfort and peripheral oedema.

The main clinical feature is a raised JVP with a prominent a wave, and a slow y descent due to the loss of normal rapid right ventricular filling. There is also a mid-diastolic murmur, best heard at the lower left or right sternal border. This is generally higher-pitched than the murmur of mitral stenosis and is increased by inspiration. Right heart failure causes hepatomegaly with pre-systolic pulsation (large a wave), ascites and peripheral oedema. The diagnosis can be confirmed by Doppler echocardiography, which shows similar appearances to those of rheumatic mitral stenosis.

Management

In patients who require surgery to other valves, the tricuspid valve can either be replaced or treated with valvotomy. Balloon valvuloplasty can be used to treat rare cases of isolated tricuspid stenosis.

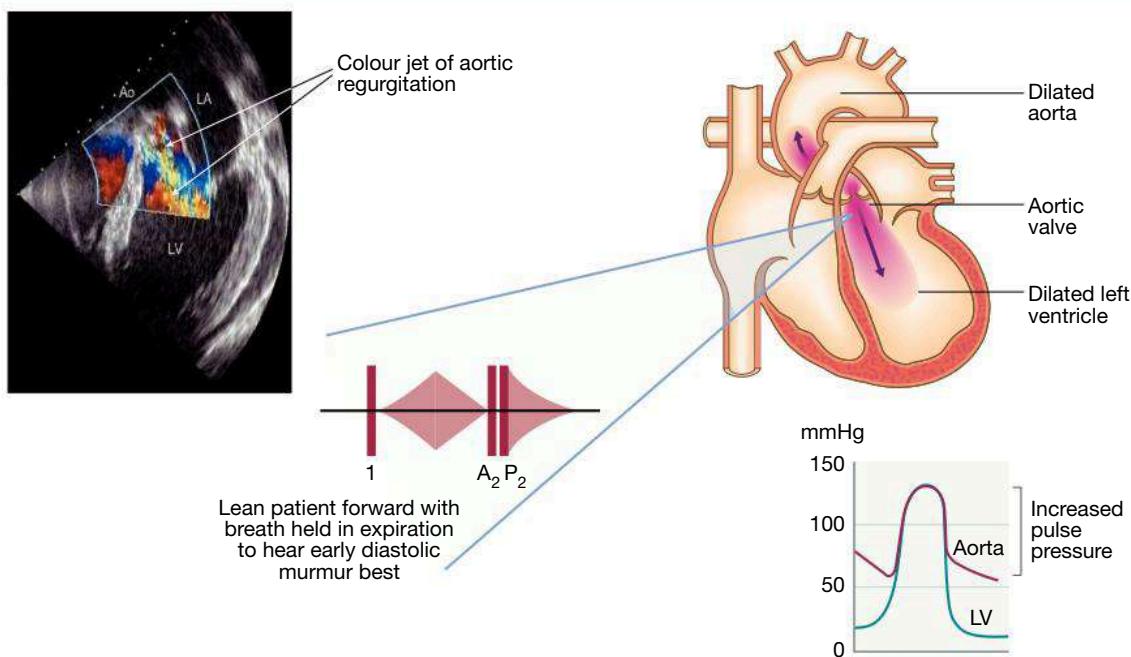


Fig. 16.85 Aortic regurgitation. The early diastolic murmur is best heard at the left sternal border and may be accompanied by an ejection systolic ('to-and-fro') murmur. The aortic arch and left ventricle (LV) may become dilated. The inset shows a Doppler echocardiogram with the regurgitant jet (arrows). Inset (Colour Doppler echo) From Newby D, Grubb N. *Cardiology: an illustrated colour text*. Edinburgh: Churchill Livingstone, Elsevier Ltd; 2005.

i	16.90 Investigations in aortic regurgitation	i	16.91 Causes of tricuspid regurgitation
ECG	<ul style="list-style-type: none"> Initially normal, later left ventricular hypertrophy and T-wave inversion 	Primary	<ul style="list-style-type: none"> Rheumatic heart disease Endocarditis, particularly in intravenous drug users Ebstein's congenital anomaly (see Box 16.102)
Chest X-ray	<ul style="list-style-type: none"> Cardiac dilatation, maybe aortic dilatation Features of left heart failure 	Secondary	<ul style="list-style-type: none"> Right ventricular failure Right ventricular infarction Pulmonary hypertension, secondary to chronic pulmonary disease
Echo	<ul style="list-style-type: none"> Dilated left ventricle Hyperdynamic left ventricle Doppler detects reflux Fluttering anterior mitral leaflet 		
Cardiac catheterisation*	<ul style="list-style-type: none"> Dilated left ventricle Aortic regurgitation Dilated aortic root 		
*Not always required.			

Tricuspid regurgitation

Tricuspid regurgitation is common, and is most frequently functional, occurring as a result of right ventricular dilatation due to right heart failure or biventricular failure. It may also be the result of other conditions, as summarised in Box 16.91.

Clinical features

Symptoms are usually non-specific, with tiredness related to reduced cardiac output, and oedema and hepatic enlargement due to venous congestion. The most prominent sign is a 'giant' v wave in the jugular venous pulse (a cv wave replaces the normal x descent). Other features include a pansystolic murmur at the left sternal border and a pulsatile liver. Echocardiography may reveal dilatation of the RV. If the valve has been affected by rheumatic disease, the leaflets will appear thickened and, in endocarditis, vegetations may be seen.

Management

Tricuspid regurgitation due to right ventricular dilatation often improves when the cardiac failure is treated. Patients with a normal pulmonary

artery pressure tolerate isolated tricuspid reflux well, and valves damaged by endocarditis do not usually need to be replaced. Patients undergoing mitral valve replacement, who have tricuspid regurgitation due to marked dilatation of the tricuspid annulus, benefit from valve repair with an annuloplasty ring to bring the leaflets closer together. Those with rheumatic damage may require tricuspid valve replacement.

Pulmonary valve disease

Pulmonary stenosis

This can occur in the carcinoid syndrome but is usually congenital, in which case it may be isolated or associated with other abnormalities, such as Fallot's tetralogy.

Clinical features

The principal finding on examination is an ejection systolic murmur, loudest at the left upper sternum and radiating towards the left shoulder. There may be a thrill, best felt when the patient leans forwards and breathes out. The murmur is often preceded by an ejection sound (click). Delay in right ventricular ejection may cause wide splitting of the second heart sound. Severe pulmonary stenosis is characterised by a loud, harsh murmur, an inaudible pulmonary closure sound (P_2), an increased right ventricular heave, and prominent a waves in the jugular pulse.

Investigations

Doppler echocardiography is the definitive investigation. ECG may show evidence of right ventricular hypertrophy, and post-stenotic dilatation in the pulmonary artery may be observed on the chest X-ray.

Management

Mild to moderate isolated pulmonary stenosis is relatively common and does not usually progress or require treatment. Severe pulmonary stenosis (resting gradient >50 mmHg with a normal cardiac output) can be treated by percutaneous pulmonary balloon valvuloplasty or, if this is not available, by surgical valvotomy. Long-term results are very good. Post-operative pulmonary regurgitation is common but benign.

Pulmonary regurgitation

This is rare in isolation and is usually associated with pulmonary artery dilatation due to pulmonary hypertension. It may complicate mitral stenosis, producing an early diastolic decrescendo murmur at the left sternal border that is difficult to distinguish from aortic regurgitation (Graham Steell murmur). The pulmonary hypertension may be secondary to other disease of the left side of the heart, primary pulmonary vascular disease or Eisenmenger syndrome. Trivial pulmonary regurgitation is a frequent finding in normal individuals and has no clinical significance.

Prosthetic valves

Diseased heart valves can be replaced with mechanical or biological prostheses. The three main types of mechanical prosthesis are the ball and cage, tilting single disc and tilting bi-leaflet valves. All generate prosthetic sounds or clicks on auscultation. Pig or allograft valves mounted on a supporting stent are the most commonly used biological valves. They generate normal heart sounds. All prosthetic valves used in the aortic position produce a systolic flow murmur.

All mechanical valves require long-term anticoagulation because they can cause systemic thromboembolism or may develop valve thrombosis or obstruction (Box 16.92); the prosthetic clicks may become inaudible if the valve malfunctions. Biological valves have the advantage of not requiring anticoagulants to maintain proper function although many patients undergoing valve replacement surgery, especially mitral valve replacement, will have AF that requires anticoagulation anyway. Biological valves are less durable than mechanical valves and may degenerate 7 or more years after implantation, particularly when used in the mitral position. They are more durable in the aortic position and in older patients, so are particularly appropriate for patients over 65 undergoing aortic valve replacement.

Transcatheter aortic valve implantation

For patients being considered for aortic valve surgery, especially due to aortic stenosis, transcatheter aortic valve implantation (TAVI) is an alternative to surgical aortic valve replacement. The native valve is not removed but is compressed by the new bioprosthetic valve, which is implanted within it. The bioprosthetic valve is mounted on a large stent-like structure and is implanted through a catheter inserted in the femoral

artery (Fig. 16.86). TAVI has several major advantages. It avoids the need for a sternotomy, is associated with a short recovery period, can be used in high-risk and otherwise inoperable patients, and is much better tolerated by older patients. Complications include stroke (2%) and heart block necessitating pacemaker implantation (5%–15%).

Prosthetic valve dysfunction

Symptoms or signs of unexplained heart failure in a patient with a prosthetic heart valve may be due to valve dysfunction, and urgent assessment is required. Metallic valves can suffer strut fracture and fail, causing catastrophic regurgitation. Alternatively, they may thrombose and cause systemic thromboembolism or valve obstruction, especially in the presence of inadequate anticoagulation. Biological valve dysfunction is usually associated with the development of a regurgitant murmur and may begin to develop 8–10 years after implantation.

Infective endocarditis

This is caused by microbial infection of a heart valve, the lining of a cardiac chamber or blood vessel, or a congenital anomaly. Both native and prosthetic valves can be affected. The most common causes of infective endocarditis are streptococci and staphylococci but other organisms may also be involved.

Epidemiology

The incidence of infective endocarditis in community-based studies ranges from 5 to 15 cases per 100 000 per annum. More than 50% of patients are over 60 years of age (Box 16.93). In a large British study, the underlying condition was rheumatic heart disease in 24% of patients, congenital heart disease in 19%, and other cardiac abnormalities such as calcified aortic valve or floppy mitral valve in 25%. The remaining 32% were not thought to have a pre-existing cardiac abnormality. Bacterial endocarditis is a serious illness; the case fatality is approximately 20% even with treatment, and is even higher in those with prosthetic valve endocarditis and those infected with antibiotic-resistant organisms.

Pathophysiology

Infective endocarditis typically occurs at sites of pre-existing endocardial damage, but infection with particularly virulent or aggressive organisms, such as *Staphylococcus aureus*, can cause endocarditis in a previously normal heart. Staphylococcal endocarditis of the tricuspid valve is a common complication of intravenous drug use. Many acquired and congenital cardiac lesions are vulnerable, particularly areas of endocardial damage caused by a high-pressure jet of blood, such as ventricular septal defect, mitral regurgitation and aortic regurgitation, many of which are haemodynamically insignificant. In contrast, the risk of endocarditis at the site of haemodynamically important low-pressure lesions, such as a large atrial septal defect, is minimal.

Infection tends to occur at sites of endothelial damage because they attract deposits of platelets and fibrin that are vulnerable to colonisation by blood-borne organisms. The avascular valve tissue and presence of fibrin and platelet aggregates help to protect proliferating organisms from host defence mechanisms. When the infection is established, vegetations composed of organisms, fibrin and platelets grow and may become large enough to cause obstruction or embolism. Adjacent tissues are destroyed and abscesses may form. Valve regurgitation may develop or increase if the affected valve is damaged by tissue distortion, cusp perforation or disruption of chordae. Extracardiac manifestations, such as vasculitis and skin lesions, may occur as the result of either emboli or immune complex deposition. Mycotic aneurysms may develop in arteries at the site of infected emboli. In fatal cases, infarction of the spleen and kidneys and, sometimes, an immune glomerulonephritis may be found at postmortem.

Microbiology

Over three-quarters of cases are caused by streptococci or staphylococci. Viridans streptococci, such as *Streptococcus mitis* and *Strep-*

16.92 Anticoagulation targets and prosthetic heart valves

Mechanical valves	Target INR
Ball and cage (e.g. Starr–Edwards)	3.0–4.0
Tilting disc (e.g. Bjork–Shiley)	
Bi-leaflet (e.g. St Jude)	2.5–3.0
Biological valves with atrial fibrillation	2.0–3.0
(INR = International Normalised Ratio)	

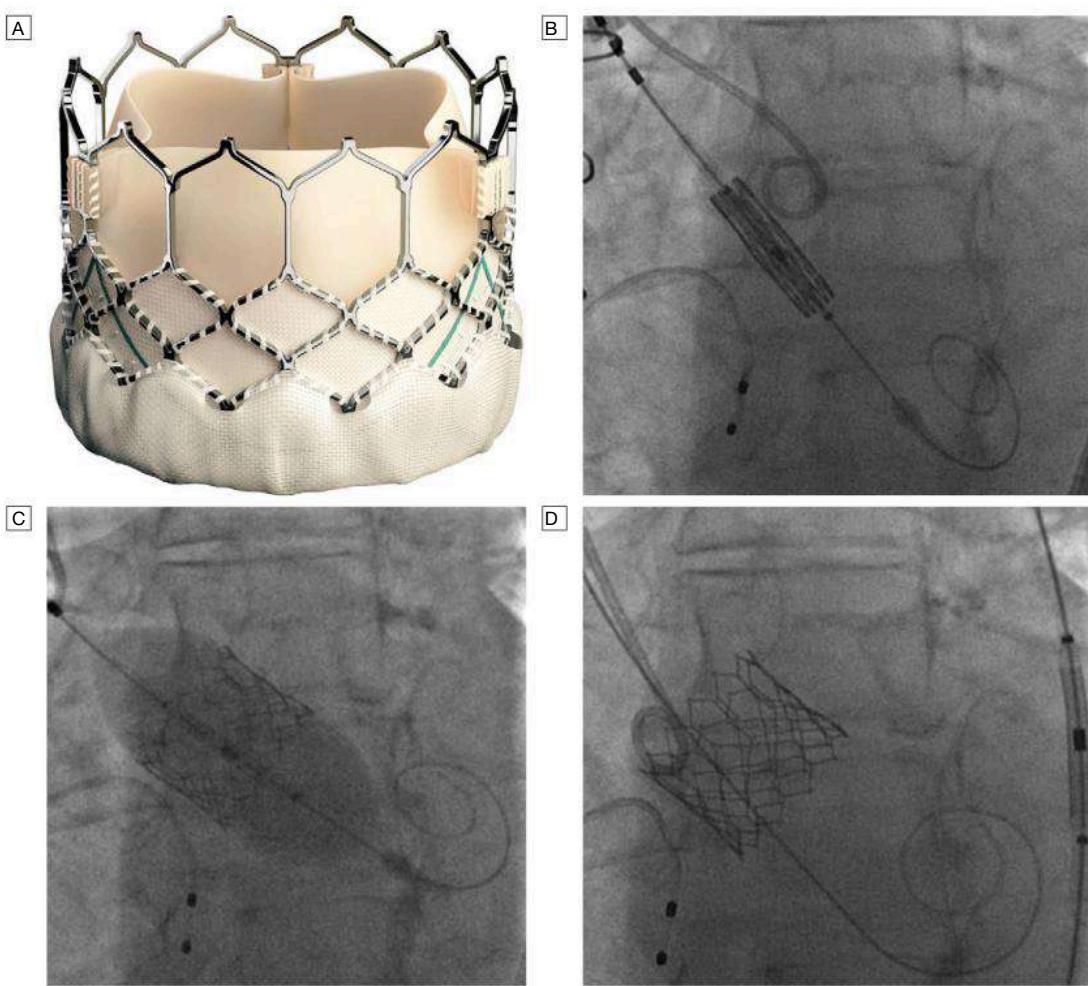


Fig. 16.86 Transcatheter aortic valve implantation (TAVI). Appearance of an expanded bioprosthetic valve **A**, which is positioned through a large femoral catheter in an unexpanded form **B**, before the valve is deployed by a balloon **C** during rapid ventricular pacing, to leave behind the fully expanded valve **D**.



16.93 Endocarditis in old age

- **Symptoms and signs:** may be non-specific, with delirium, weight loss, malaise and weakness, and the diagnosis may not be suspected.
- **Common causative organisms:** often enterococci (from the urinary tract) and *Streptococcus gallolyticus* subsp. *gallolyticus* (from a colonic source).
- **Morbidity and mortality:** much higher.

sanguis, which are commensals in the oral cavity, can enter the blood stream on chewing or tooth-brushing, or at the time of dental treatment, and are common causes of subacute endocarditis (Box 16.94). Other organisms, including *Enterococcus faecalis*, *E. faecium* and *Strep. gallolyticus* subsp. *gallolyticus* (previously known as *Strep. bovis*), may enter the blood from the bowel or urinary tract. Patients who are found to have endocarditis caused by *Strep. gallolyticus* should undergo colonoscopy, since this organism is associated with large-bowel malignancy.

Staph. aureus has now overtaken streptococci as the most common cause of acute endocarditis. It originates from skin infections, abscesses or vascular access sites such as intravenous and central lines, or from intravenous drug use. It is highly virulent and invasive, usually producing florid vegetations, rapid valve destruction and abscess formation. Other causes of acute endocarditis include *Strep. pneumoniae* and *Strep. pyogenes*.

Post-operative endocarditis after cardiac surgery may affect native or prosthetic heart valves or other prosthetic materials. The most common organisms are coagulase-negative staphylococci such as *Staph. epidermidis*, which are part of the normal skin flora. There is frequently a

history of wound infection with the same organism. Coagulase-negative staphylococci cause native valve endocarditis in approximately 5% of cases and this possibility should always be considered before they are dismissed as blood culture contaminants. Another coagulase-negative staphylococcus, *Staph. lugdenensis*, causes a rapidly destructive acute endocarditis that is associated with previously normal valves and multiple emboli. Unless accurately identified, it may also be overlooked as a contaminant.

In Q fever endocarditis due to *Coxiella burnetii*, the patient often has a history of contact with farm animals. The aortic valve is usually affected and there may also be hepatitis, pneumonia and purpura. Life-long antibiotic therapy may be required.

In about 3%–4% of cases, endocarditis may be caused by Gram-negative bacteria of the so-called HACEK group (*Haemophilus aphrophilus* – now known as *Aggregatibacter aphrophilus*–*Aggregatibacter actinomycetemcomitans*; *Cardiobacterium hominis*; *Eikenella corrodens*; and *Kingella kingae*). These are slow-growing, fastidious Gram-negative organisms that are oropharyngeal commensals. The diagnosis may be revealed only after prolonged culture and the organisms may be resistant to penicillin.

Brucella endocarditis is associated with a history of contact with goats or cattle and often affects the aortic valve.

Yeasts and fungi, such as *Candida* and *Aspergillus*, may attack previously normal or prosthetic valves, particularly in immunocompromised patients or those with in-dwelling intravenous catheters. Abscesses and emboli are common, therapy is difficult, surgery is often required and mortality is high. Concomitant bacterial infection may be present.

Pathogen	Of native valve (n = 280)	In injection drug users (n = 87)	Of prosthetic valve	
			Early (n = 15)	Late (n = 72)
Staphylococci	124 (44%)	60 (69%)	10 (67%)	33 (46%)
<i>Staph. aureus</i>	106 (38%)	60 (69%)	3 (20%)	15 (21%)
Coagulase-negative	18 (6%)	0	7 (47%)	18 (25%)
Streptococci	86 (31%)	7 (8%)	0	25 (35%)
Oral	59 (21%)	3 (3%)	0	19 (26%)
Others (non-enterococcal)	27 (10%)	4 (5%)	0	6 (8%)
<i>Enterococcus</i> spp.	21 (8%)	2 (2%)	1 (7%)	5 (7%)
HACEK	12 (4%)	0	0	1 (1%)
Polymicrobial	6 (2%)	8 (9%)	0	1 (1%)
Other bacteria	12 (4%)	4 (5%)	0	2 (3%)
Fungi	3 (1%)	2 (2%)	0	0
Negative blood culture	16 (6%)	4 (5%)	4 (27%)	5 (7%)

(HACEK = *Haemophilus aphrophilus* – now known as *Aggregatibacter aphrophilus*–*Aggregatibacter actinomycetemcomitans*; *Cardiobacterium hominis*; *Eikenella corrodens*; and *Kingella kingae*)
Adapted from Moreillon P, Que YA. Infective endocarditis. Lancet 2004; 363:139–149.

Clinical features

Endocarditis can take either an acute or a more insidious ‘subacute’ form; the latter often passes undetected initially. There is considerable overlap because the clinical pattern is influenced not only by the organism but also by the site of infection, prior antibiotic therapy and the presence of a valve or shunt prosthesis. The subacute form may abruptly develop acute life-threatening complications, such as valve disruption or emboli. The Duke criteria for diagnosis of infective endocarditis are shown in Box 16.95.

Subacute endocarditis

This should be suspected when a patient with congenital or valvular heart disease develops a persistent fever, complains of unusual tiredness, night sweats or weight loss, or develops new signs of valve dysfunction or heart failure. Less often, it presents as an embolic stroke or peripheral arterial embolism. Other features (Fig. 16.87) include purpura and petechial haemorrhages in the skin and mucous membranes, and splinter haemorrhages under the fingernails or toenails. Osler’s nodes are painful, tender swellings at the fingertips that are probably the product of vasculitis; they are rare. Digital clubbing is a late sign. The spleen is frequently palpable; in *Coxiella* infections, the spleen and the liver may be considerably enlarged. Non-visible haematuria is common. The finding of any of these features in a patient with persistent fever or malaise is an indication for re-examination to detect hitherto unrecognised heart disease.

Acute endocarditis

This presents as a severe febrile illness with prominent and changing heart murmurs and petechiae. Clinical stigmata of chronic endocarditis are usually absent. Embolic events are common, and cardiac or renal failure may develop rapidly. Abscesses may be detected on echocardiography. Partially treated acute endocarditis behaves like subacute endocarditis.

Post-operative endocarditis

This may present as an unexplained fever in a patient who has had heart valve surgery. The infection usually involves the valve ring and may resemble subacute or acute endocarditis, depending on the virulence of the organism. Morbidity and mortality are high and revision surgery is often required. The range of organisms is similar to that seen in native valve disease, but when endocarditis occurs during the first few weeks after surgery it is usually due to infection with a coagulase-negative staphylococcus that was introduced during the perioperative period.

i 16.95 Diagnosis of infective endocarditis*

Major criteria

Positive blood culture

- Typical organism from two cultures
- Persistent positive blood cultures taken > 12 hrs apart
- Three or more positive cultures taken over > 1 hr

Endocardial involvement

- Positive echocardiographic findings of vegetations
- New valvular regurgitation

Minor criteria

- Predisposing valvular or cardiac abnormality
- Intravenous drug misuse
- Pyrexia $\geq 38^{\circ}\text{C}$
- Embolic phenomenon
- Vasculitic phenomenon
- Blood cultures suggestive: organism grown but not achieving major criteria
- Suggestive echocardiographic findings

*Modified Duke criteria. Patients with two major, or one major and three minor, or five minor have definite endocarditis. Patients with one major and one minor, or three minor have possible endocarditis.

Investigations

Blood culture (see Fig. 6.6) is the pivotal investigation to identify the organism that is the cause of the infection and to guide antibiotic therapy. Three to six sets of blood cultures should be taken prior to commencing therapy and should not wait for episodes of pyrexia. The first two specimens will detect bacteraemia in 90% of culture-positive cases. A meticulous aseptic technique is essential. Taking discrete sets of blood cultures from peripheral sites at intervals of ≥ 6 hours reduces the risk of misdiagnosis due to contamination with skin commensals. Isolation of a typical organism in more than one culture provides strong evidence in favour of the diagnosis (see Box 16.95). An in-dwelling line should not be used to take cultures. Both aerobic and anaerobic cultures are required.

Echocardiography is key for detecting and following the progress of vegetations, for assessing valve damage and for detecting abscess formation. Vegetations as small as 2–4 mm can be detected by trans-thoracic echocardiography, and even smaller ones (1–1.5 mm) can be visualised by TOE, which is particularly valuable for identifying abscess formation and investigating patients with prosthetic heart valves. Vegetations may be difficult to distinguish in the presence of an abnormal

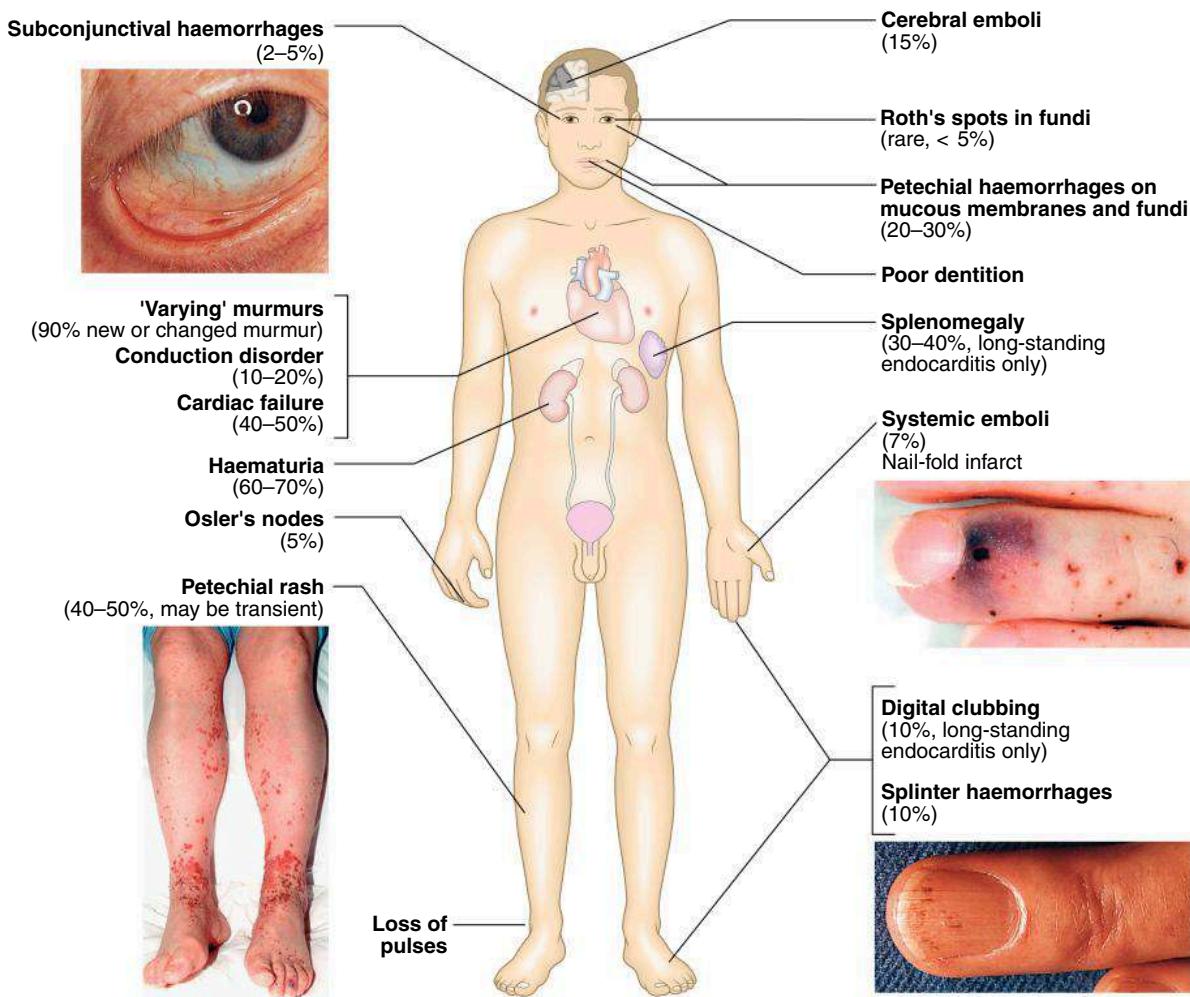


Fig. 16.87 Clinical features that may be present in endocarditis. Insets (Petechial rash, nail-fold infarct) From Newby D, Grubb N. *Cardiology: an illustrated colour text*. Edinburgh: Churchill Livingstone, Elsevier Ltd; 2005.

16

valve; the sensitivity of transthoracic echo is approximately 65% but that of TOE is more than 90%. Failure to detect vegetations does not exclude the diagnosis.

Elevation of the ESR, a normocytic normochromic anaemia, and leucocytosis are common but not invariable. Measurement of serum CRP is more reliable than the ESR in monitoring progress. Proteinuria may occur and non-visible haematuria is usually present.

The ECG may show the development of AV block (due to aortic root abscess formation) and occasionally infarction due to emboli. The chest X-ray may show evidence of cardiac failure and cardiomegaly.

Management

A multidisciplinary approach, with cooperation between the physician, surgeon and microbiologist, increases the chance of a successful outcome. Any source of infection should be removed as soon as possible; for example, a tooth with an apical abscess should be extracted, or an in-dwelling catheter or device removed.

Empirical treatment depends on the mode of presentation, the suspected organism and the presence of a prosthetic valve or penicillin allergy. If the presentation is subacute, antibiotic treatment should ideally be withheld until the results of blood cultures are available. However, if empirical antibiotic treatment is considered necessary, amoxicillin (2 g IV 6 times daily) should be considered (with or without gentamicin). If the presentation is acute, empirical therapy should be started with vancomycin (1 g IV twice daily) and gentamicin (1 mg/kg IV twice daily), with dose adjustment based on antibiotic levels. The same regimen is used in true penicillin allergy. Patients with suspected prosthetic valve

endocarditis should be treated with vancomycin and gentamicin at the above-mentioned doses, plus rifampicin orally in a dose of 300–600 mg twice daily. Following identification of the causal organism, determination of the minimum inhibitory concentration (MIC) for the organism helps guide antibiotic therapy. Recommended regimens for some of the most common scenarios are shown in Box 16.96. More detailed information can be found in the 2012 British Society for Antimicrobial Chemotherapy guidelines (see 'Further reading').

A 2-week treatment regimen may be sufficient for fully sensitive strains of streptococci, provided specific conditions are met (Box 16.97).

Cardiac surgery with débridement of infected material and valve replacement may be required in a substantial proportion of patients, particularly those with *Staph. aureus* and fungal infections (Box 16.98). Antimicrobial therapy must be started before surgery.

Prevention

Antibiotic prophylaxis is no longer routinely given to people at risk of infective endocarditis undergoing interventional procedures. It can be considered in those at the highest risk of endocarditis.

Congenital heart disease

Congenital heart disease can be the result of defects in the formation of the heart or great vessels or can arise because the anatomical changes that occur during transition between the fetus and the newborn child fail to proceed normally. Congenital heart disease usually presents in

i 16.96 Antimicrobial treatment of common causative organisms in infective endocarditis

Antimicrobial susceptibility	Antimicrobial	Dose	Duration	
			Native valve	Prosthetic valve
Streptococci				
Penicillin MIC \leq 0.125 mg/L	Benzylpenicillin IV	1.2 g 6 times daily	4 weeks ¹	6 weeks
Penicillin MIC > 0.125, \leq 0.5 mg/L	Benzylpenicillin IV and gentamicin IV	2.4 g 6 times daily 1 mg/kg twice daily ²	4 weeks 2 weeks	6 weeks 2 weeks
Penicillin MIC > 0.5 mg/L	Vancomycin IV and gentamicin IV	1 g twice daily ³ 1 mg/kg twice daily ²	4 weeks 4 weeks	6 weeks 6 weeks
Enterococci				
Amoxicillin MIC \leq 4 mg/L and gentamicin MIC \leq 128 mg/L	Amoxicillin IV and gentamicin IV ²	2 g 6 times daily 1 mg/kg twice daily ²	4 weeks 4 weeks	6 weeks 6 weeks
Amoxicillin MIC > 4 mg/L and gentamicin MIC \leq 128 mg/L	Vancomycin IV and gentamicin IV ²	1 g twice daily ³ 1 mg/kg twice daily ²	4 weeks 4 weeks	6 weeks 6 weeks
Staphylococci – native valve				
Meticillin-sensitive	Flucloxacillin IV	2 g 4–6 times daily ⁴	4 weeks	–
Meticillin-resistant, vancomycin MIC \leq 2 mg/L, rifampicin-sensitive	Vancomycin IV Rifampicin orally	1 g twice daily ³ 300–600 mg twice daily	4 weeks	–
Staphylococci – prosthetic valve				
Meticillin-sensitive	Flucloxacillin IV and gentamicin IV and rifampicin orally	2 g 4–6 times daily 1 mg/kg twice daily ² 300–600 mg twice daily	– – –	6 weeks 6 weeks 6 weeks
Meticillin-resistant, vancomycin MIC \leq 2 mg/L, rifampicin-sensitive	Vancomycin IV and rifampicin orally	1 g twice daily ³ 300–600 mg twice daily	– –	6 weeks 6 weeks

¹When conditions in Box 16.97 are met, 2 weeks of benzylpenicillin and gentamicin (1 mg/kg twice daily) may be sufficient. Ceftriaxone 2 g once daily IV/M can be used instead of benzylpenicillin for those with non-severe penicillin allergy. ²Pre-dose gentamicin level should be \leq 1 mg/L, post-dose 3–5 mg/L. Adjust dose according to levels and renal function. ³Pre-dose vancomycin level should be 15–20 mg/L. Adjust dose according to levels and renal function. ⁴Use 6 times daily if weight $>$ 85 kg.

(IM = intramuscular; IV = intravenous; MIC = minimum inhibitory concentration)

Adapted from Gould FK, Denning DW, Elliott TS, et al. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the working party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother* 2012; 67:269–289.

i 16.97 Conditions for the short-course treatment of endocarditis caused by fully sensitive streptococci

- Native valve infection
 - Minimum inhibitory concentration (MIC) \leq 0.125 mg/L
 - No adverse prognostic factors (heart failure, aortic regurgitation, conduction defect)
 - No evidence of thromboembolic disease
 - No vegetations $>$ 5 mm diameter
- Clinical response within 7 days

i 16.98 Indications for cardiac surgery in infective endocarditis*

- Heart failure due to valve damage
- Failure of antibiotic therapy (persistent/uncontrolled infection)
- Large vegetations on left-sided heart valves with echo appearance suggesting high risk of emboli
- Previous evidence of systemic emboli
- Abscess formation

*Patients with prosthetic valve endocarditis or fungal endocarditis often require cardiac surgery.

childhood but some patients do not present until adult life. It has been estimated that the incidence of haemodynamically significant congenital cardiac abnormalities is about 0.8% of live births (Box 16.99). Defects that are well tolerated, such as atrial septal defect, may cause no symptoms until adult life or may be detected incidentally on routine examination or chest X-ray. Congenital defects that were previously fatal in childhood can now be corrected, or at least partially, so that survival to adult life is the norm. Such patients remain well for many years but subsequently re-present in later life with related problems, such as arrhythmia or heart failure (Box 16.100).

Pathophysiology

Understanding the fetal circulation helps clarify how some forms of congenital heart disease occur. Fig. 16.88 shows the fetal circulation

and the changes that normally occur immediately after birth. In the fetus there is little blood flow through the lungs, which are collapsed because they are not required for gas exchange. Instead, oxygenated blood from the placenta passes directly from the right atrium to the left side of the heart through the foramen ovale without having to flow through the lungs, and also from the pulmonary artery into the aorta via the ductus arteriosus.

During early embryonic life, the heart develops as a single tube that folds back on itself and then divides into two separate circulations. Failure of septation can cause some forms of atrial and ventricular septal defect, whereas failure of alignment of the great vessels with the ventricles contributes to transposition of the great arteries, tetralogy of Fallot and truncus arteriosus. Atrial septal defects occur because the foramen ovale fails to close at birth, as is normal. Similarly, a persistent ductus arteriosus will

i**16.99 Incidence and relative frequency of congenital cardiac malformations**

Lesion	% of all congenital heart defects
Ventricular septal defect	30
Atrial septal defect	10
Persistent ductus arteriosus	10
Pulmonary stenosis	7
Coarctation of aorta	7
Aortic stenosis	6
Tetralogy of Fallot	6
Complete transposition of great arteries	4
Others	20

i**16.100 Presentation of congenital heart disease throughout life****Birth and neonatal period**

- Cyanosis
- Heart failure

Infancy and childhood

- Cyanosis
- Heart failure
- Arrhythmia
- Murmur
- Failure to thrive

Adolescence and adulthood

- Heart failure
- Murmur
- Arrhythmia
- Eisenmenger syndrome
- Hypertension (coarctation)
- Complications of previous cardiac surgery:
- Arrhythmia related to scarring
- Heart failure secondary to scarring

remain if it fails to close after birth. Failure of the aorta to develop at the point of the aortic isthmus and where the ductus arteriosus attaches can lead to coarctation of the aorta. Maternal infection and exposure to drugs or toxins are important causes of congenital heart disease. Maternal rubella infection is associated with persistent ductus arteriosus, pulmonary valvular and/or artery stenosis, and atrial septal defect. Maternal alcohol misuse is associated with septal defects, and maternal lupus erythematosus with congenital complete heart block. Genetic or chromosomal abnormalities, such as Down syndrome, may cause septal defects, and gene defects have also been identified as leading to specific abnormalities, such as Marfan syndrome and Turner syndrome (karyotype XO).

Clinical features

Symptoms may be absent, or the child may be breathless or fail to attain normal growth and development. Some defects are not compatible with extrauterine life and lead to neonatal death. Clinical signs vary with the anatomical lesion. Murmurs, thrills or signs of cardiomegaly may be present. In coarctation of the aorta, radio-femoral delay may be noted (Fig. 16.89) and some female patients have the features of Turner syndrome (p. 674). Features of other congenital conditions, such as Marfan syndrome or Down syndrome, may also be apparent. Cerebrovascular events and cerebral abscesses may complicate severe cyanotic congenital disease.

Early diagnosis is important because many types of congenital heart disease are amenable to surgery, but this opportunity is lost if secondary changes, such as irreversible pulmonary hypertension, occur.

Central cyanosis and digital clubbing

Central cyanosis of cardiac origin occurs when desaturated blood enters the systemic circulation without passing through the lungs (right-to-left

shunting). In the neonate, the most common cause is transposition of the great arteries, in which the aorta arises from the RV and the pulmonary artery from the LV in association with a ventricular septal defect. In older children, cyanosis is usually the consequence of a ventricular septal defect combined with severe pulmonary stenosis (as in tetralogy of Fallot) or with pulmonary vascular disease (Eisenmenger syndrome). Chronic cyanosis is associated with finger and toe clubbing.

Growth retardation and learning difficulties

These may occur with large left-to-right shunts at ventricular or great arterial level, and also with other defects, especially if they form part of a genetic syndrome. Major intellectual impairment is uncommon in children with isolated congenital heart disease but minor learning difficulties can occur. Cerebral function can also be affected after cardiac surgery if cerebral perfusion is compromised.

Syncope

In the presence of increased pulmonary vascular resistance or severe left or right ventricular outflow obstruction, exercise may provoke syncope as systemic vascular resistance falls but pulmonary vascular resistance rises, worsening right-to-left shunting and cerebral oxygenation. Syncope can also occur because of associated arrhythmias.

Pulmonary hypertension

Persistently raised pulmonary flow with a left-to-right shunt causes increased pulmonary vascular resistance followed by pulmonary hypertension. Progressive changes, including obliteration of distal arterioles, take place and are irreversible. At this stage, central cyanosis occurs and digital clubbing develops. The chest X-ray shows enlarged central pulmonary arteries and peripheral ‘pruning’ of the pulmonary vessels. The ECG shows features of right ventricular hypertrophy.

Eisenmenger syndrome

In patients with severe and prolonged pulmonary hypertension the left-to-right shunt may reverse, resulting in right-to-left shunt and marked cyanosis. This is termed Eisenmenger syndrome. The cyanosis in Eisenmenger syndrome may be more apparent in the feet and toes than in the upper part of the body, resulting in so-called differential cyanosis. Eisenmenger syndrome is more common with large ventricular septal defects or persistent ductus arteriosus than with atrial septal defects. Patients with Eisenmenger syndrome are at particular risk from abrupt changes in afterload that exacerbate right-to-left shunting, such as vasodilatation, anaesthesia and pregnancy. The long-term prognosis is poor with around 50% of young adults surviving 10 years from diagnosis.

Congenital heart disease in pregnancy

During pregnancy, there is a 50% increase in plasma volume, a 40% increase in whole blood volume and a similar increase in cardiac output, so problems may arise in women with congenital heart disease (Box 16.101). Many with palliated or untreated disease will tolerate pregnancy well, however. Pregnancy is particularly hazardous in the presence of conditions associated with cyanosis or severe pulmonary hypertension; maternal mortality in patients with Eisenmenger syndrome is more than 50%.

Persistent ductus arteriosus

Normally, the ductus arteriosus closes soon after birth but in this anomaly it fails to do so. Persistence of the ductus is often associated with other abnormalities and is more common in females.

Pathophysiology

During fetal life, before the lungs begin to function, most of the blood from the pulmonary artery passes through the ductus arteriosus into the aorta (see Fig. 16.88). Persistence of the ductus causes a continuous AV shunt from the aorta to the pulmonary artery since pressure in the aorta is higher than that in the pulmonary artery. The volume of

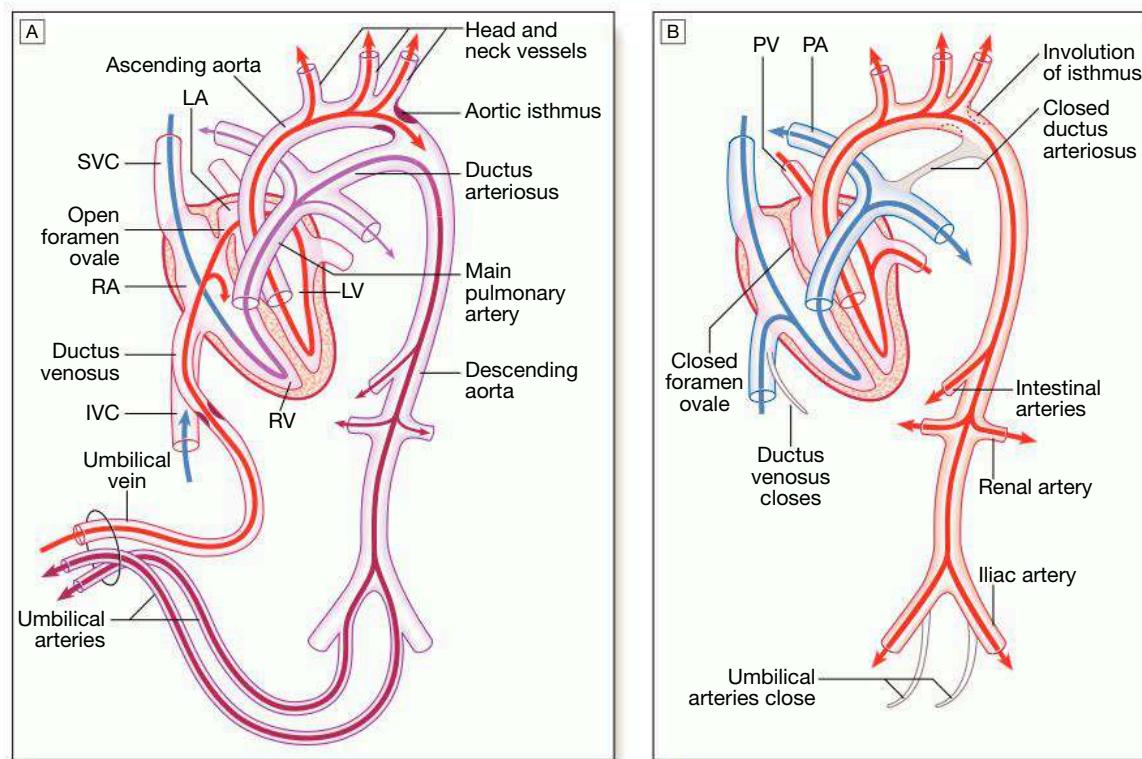


Fig. 16.88 Changes in the circulation at birth. **A** In the fetus, oxygenated blood comes through the umbilical vein where it enters the inferior vena cava (IVC) via the ductus venosus (red). The oxygenated blood streams from the right atrium (RA) through the open foramen ovale to the left atrium (LA) and via the left ventricle (LV) into the aorta. Venous blood from the superior vena cava (SVC, blue) crosses under the main blood stream into the RA and then, partly mixed with oxygenated blood (purple), into the right ventricle (RV) and pulmonary artery (PA). The pulmonary vasculature has a high resistance and so little blood passes to the lungs; most blood passes through the ductus arteriosus to the descending aorta. The aortic isthmus is a constriction in the aorta that lies in the aortic arch before the junction with the ductus arteriosus and limits the flow of oxygen-rich blood to the descending aorta. This configuration means that less oxygen-rich blood is supplied to organ systems that take up their function mainly after birth, e.g. the kidneys and intestinal tract. **B** At birth, the lungs expand with air and pulmonary vascular resistance falls, so that blood now flows to the lungs and back to the LA. The left atrial pressure rises above right atrial pressure and the flap valve of the foramen ovale closes. The umbilical arteries and the ductus venosus close. In the next few days, the ductus arteriosus closes under the influence of hormonal changes (particularly prostaglandins) and the aortic isthmus expands. (PV = pulmonary vein) Adapted from Drews U. Colour atlas of embryology. Stuttgart: Georg Thieme; 1995.

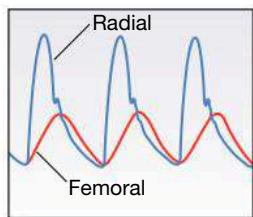


Fig. 16.89 Radio-femoral delay. The difference in pulse pressures is shown.



16.101 Pregnancy in women with congenital heart disease

- **Obstructive lesions:** poorly tolerated and associated with significant maternal morbidity and mortality.
- **Cyanotic conditions:** especially poorly tolerated. Specialised pre-conception counselling should explain the increased risks.
- **Surgically corrected disease:** patients often tolerate pregnancy well.
- **Children of patients with congenital heart disease:** 2%–5% will be born with cardiac abnormalities, especially if the mother is affected. The risk may be up to 20% in babies born of women with left-sided lesions.

the shunt depends on the size of the ductus but as much as 50% of the left ventricular output may be recirculated through the lungs, with a consequent increase in the work of the heart (Fig. 16.90). A large left-to-right shunt in infancy may cause a considerable rise in pulmonary

artery pressure and sometimes this leads to progressive pulmonary vascular damage.

Clinical features

With small shunts there may be no symptoms for years, but when the ductus is large, growth and development may be retarded. Usually, there is no disability in infancy but cardiac failure may eventually ensue, dyspnoea being the first symptom. A continuous 'machinery' murmur is heard with late systolic accentuation, maximal in the second left intercostal space below the clavicle (see Fig. 16.90). It is often accompanied by a thrill. Pulses are increased in volume.

Enlargement of the pulmonary artery may be detected radiologically. The ECG is usually normal. If pulmonary vascular resistance increases, pulmonary artery pressure may rise until it equals or exceeds aortic pressure. The shunt through the defect may then reverse, causing Eisenmenger syndrome. The murmur becomes quieter, may be confined to systole or may disappear.

Investigations

Echocardiography is the investigation of choice although the persistent ductus requires specific echocardiographic views, such as from the suprasternal notch, to reveal it. The ECG shows evidence of right ventricular hypertrophy.

Management

A persistent ductus can be closed at cardiac catheterisation with an implantable occlusive device. Closure should be undertaken in infancy if the shunt is significant and pulmonary resistance not elevated, but this

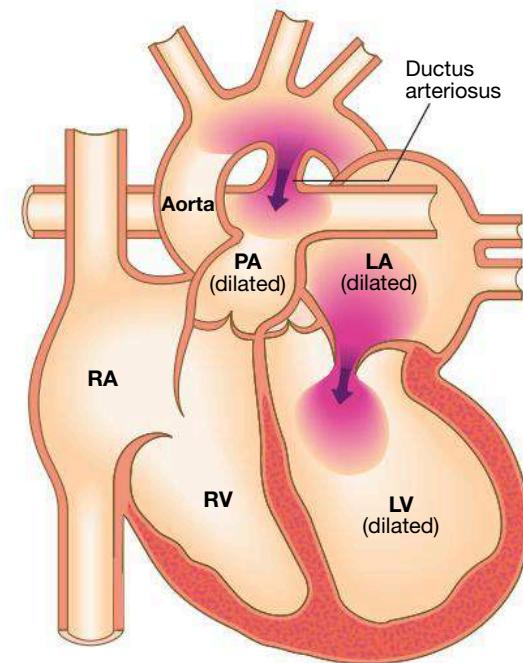


Fig. 16.90 Persistent ductus arteriosus. There is a connection between the aorta and the pulmonary artery with left-to-right shunting. (LA = left atrium; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle)

may be delayed until later childhood in those with smaller shunts, for whom closure remains advisable to reduce the risk of endocarditis. When the ductus is structurally intact, a prostaglandin synthetase inhibitor (indometacin or ibuprofen) may be used in the first week of life to induce closure. However, in the presence of a congenital defect with impaired lung perfusion, such as occurs in severe pulmonary stenosis and left-to-right shunt through the ductus, it may be advisable to improve oxygenation by keeping the ductus open with prostaglandin treatment. Unfortunately, these treatments do not work if the ductus is intrinsically abnormal.

Coarctation of the aorta

This condition is twice as common in males and occurs in 1 in 4000 children. It is associated with other abnormalities, most frequently bicuspid aortic valve and 'berry' aneurysms of the cerebral circulation. Acquired coarctation of the aorta is rare but may follow trauma or occur as a complication of Takayasu's disease.

Pathogenesis

Narrowing of the aorta occurs in the region where the ductus arteriosus joins the aorta, at the isthmus just below the origin of the left subclavian artery (see Fig. 16.88). This causes raised BP affecting vessels of the head and neck proximal to the coarctation, and reduced BP and impaired circulation distally.

Clinical features

Aortic coarctation is an important cause of cardiac failure in the newborn but symptoms are often absent in older children or in adults. Headaches may occur from hypertension proximal to the coarctation, and occasionally weakness or cramps in the legs may result from decreased circulation in the lower part of the body. The BP is raised in the upper body but normal or low in the legs. The femoral pulses are weak and delayed in comparison with the radial pulse (see Fig. 16.89). A systolic murmur is usually heard posteriorly, over the coarctation. There may also be an ejection click and systolic murmur in the aortic area due to a bicuspid aortic valve. As a result of the aortic narrowing, collaterals form; they mainly involve the periscapular, internal mammary and intercostal arteries, and may result in localised bruits.



Fig. 16.91 MRI scan of coarctation of the aorta. The aorta is severely narrowed just beyond the arch at the start of the descending aorta (arrow A). Extensive collaterals have developed; a large internal mammary artery (arrow B) and several intercostal arteries (arrows C) are shown. Unusually, in this case, there is also a coarctation of the abdominal aorta (arrow D).

Investigations

Imaging by MRI is the investigation of choice (Fig. 16.91). The chest X-ray in early childhood is often normal but later may show changes in the contour of the aorta (indentation of the descending aorta, '3 sign') and notching of the under-surfaces of the ribs from collaterals. The ECG may show evidence of left ventricular hypertrophy, which can be confirmed by echocardiography.

Management

In untreated cases death may occur from left ventricular failure, dissection of the aorta or cerebral haemorrhage. Surgical correction is advisable in all but the mildest cases. If this is carried out sufficiently early in childhood, persistent hypertension can be avoided. Patients repaired in late childhood or adult life often remain hypertensive or develop recurrent hypertension later on. Recurrence of stenosis may occur as the child grows and this may be managed by balloon dilatation and sometimes stenting. The latter may be used as the primary treatment. Coexistent bicuspid aortic valve, which occurs in over 50% of cases, may lead to progressive aortic stenosis or regurgitation, and also requires long-term follow-up.

Atrial septal defect

Atrial septal defect is one of the most common congenital heart defects and occurs twice as frequently in females. Most are 'ostium secundum' defects, involving the fossa ovalis that, in utero, was the foramen ovale (see Fig. 16.88). 'Ostium primum' defects result from a defect in the atrioventricular septum and are associated with a 'cleft mitral valve' (split anterior leaflet).

Pathogenesis

Since the normal RV is more compliant than the LV, a patent foramen ovale is associated with shunting of blood from the LA to the RA, and then to the RV and pulmonary arteries (Fig. 16.92). As a result, there is gradual enlargement of the right side of the heart and of the pulmonary arteries. Pulmonary hypertension and shunt reversal sometimes complicate atrial septal defect, but are less common and tend to occur later in life than with other types of left-to-right shunt.

Clinical features

Most children are asymptomatic for many years and the condition is often detected at routine examination or following a chest X-ray. Symptoms include dyspnoea, cardiac failure and arrhythmias, especially AF. The characteristic physical signs are the result of the volume overload of the RV:

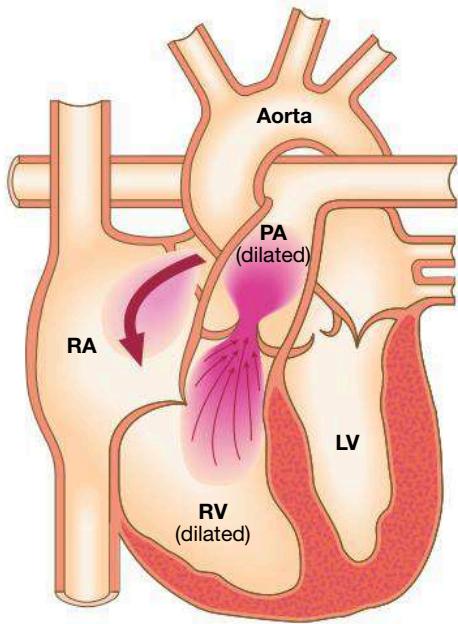


Fig. 16.92 Atrial septal defect. Blood flows across the atrial septum (arrow) from left to right. The murmur is produced by increased flow velocity across the pulmonary valve, as a result of left-to-right shunting and a large stroke volume. The density of shading is proportional to velocity of blood flow. (LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle)

- wide, fixed splitting of the second heart sound: wide because of delay in right ventricular ejection (increased stroke volume and RBBB), and fixed because the septal defect equalises left and right atrial pressures throughout the respiratory cycle
- a systolic flow murmur over the pulmonary valve.

In children with a large shunt, there may be a diastolic flow murmur over the tricuspid valve. Unlike a mitral flow murmur, this is usually high-pitched.

Investigations

Echocardiography is diagnostic. It directly demonstrates the defect and typically shows right ventricular dilatation, right ventricular hypertrophy and pulmonary artery dilatation. The precise size and location of the defect are best defined by TOE (Fig. 16.93). The chest X-ray typically shows enlargement of the heart and the pulmonary artery, as well as pulmonary plethora. The ECG usually demonstrates incomplete RBBB because right ventricular depolarisation is delayed as a result of ventricular dilatation (with a 'primum' defect, there is also left axis deviation).

Management

Atrial septal defects in which pulmonary flow is increased 50% above systemic flow (i.e. a flow ratio of 1.5:1) are often large enough to be clinically recognisable and should be closed surgically. Smaller defects may be managed conservatively and patients monitored periodically with echocardiography. Closure can also be accomplished at cardiac catheterisation using implantable closure devices (Fig. 16.94). The long-term prognosis thereafter is excellent, unless pulmonary hypertension has developed. Severe pulmonary hypertension and shunt reversal are both contraindications to surgery.

Ventricular septal defect

Ventricular septal defect is the most common congenital cardiac defect, occurring once in 500 live births. The defect may be isolated or part of complex congenital heart disease.

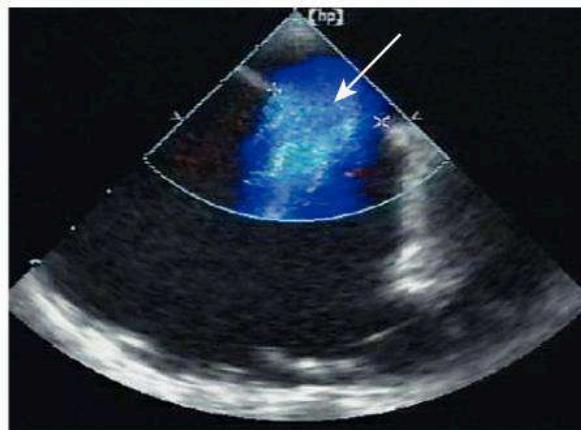


Fig. 16.93 Transoesophageal echocardiogram of an atrial septal defect. The defect is clearly seen (arrow) between the left atrium above and right atrium below. Doppler colour-flow imaging shows flow (blue) across the defect.

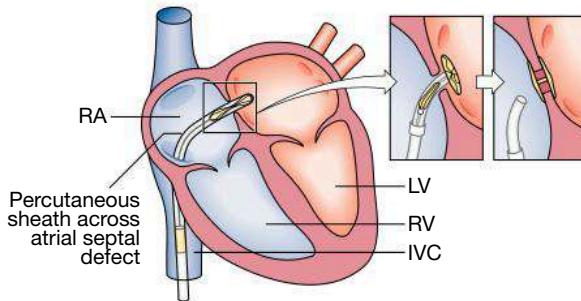


Fig. 16.94 Percutaneous closure of atrial septal defect. The closure device is delivered across the interatrial septum and a disc deployed on either side to seal the defect. (IVC = inferior vena cava; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle)

Pathogenesis

Congenital ventricular septal defect occurs as a result of incomplete separation of the ventricles. Embryologically, the interventricular septum has a membranous and a muscular portion, and the latter is further divided into inflow, trabecular and outflow portions. Most congenital defects are 'perimembranous', occurring at the junction of the membranous and muscular portions of the septum.

Clinical features

Flow from the high-pressure LV to the low-pressure RV during systole produces a pansystolic murmur, usually heard best at the left sternal border but radiating all over the precordium (Fig. 16.95). A small defect often produces a loud murmur (*maladie de Roger*) in the absence of other haemodynamic disturbance. Conversely, a large defect produces a quieter murmur, particularly if pressure in the RV is elevated. This may be found immediately after birth, while pulmonary vascular resistance remains high, or when the shunt is reversed in Eisenmenger syndrome. Congenital ventricular septal defect may present with cardiac failure in infants, as a murmur with only minor haemodynamic disturbance in older children or adults, or, rarely, as Eisenmenger syndrome. In some infants, the murmur becomes quieter or disappears due to spontaneous closure of the defect.

If cardiac failure complicates a large defect, it is usually absent in the immediate postnatal period and becomes apparent only in the first 4–6 weeks of life. In addition to the murmur, there is prominent parasternal pulsation, tachypnoea and indrawing of the lower ribs on inspiration.

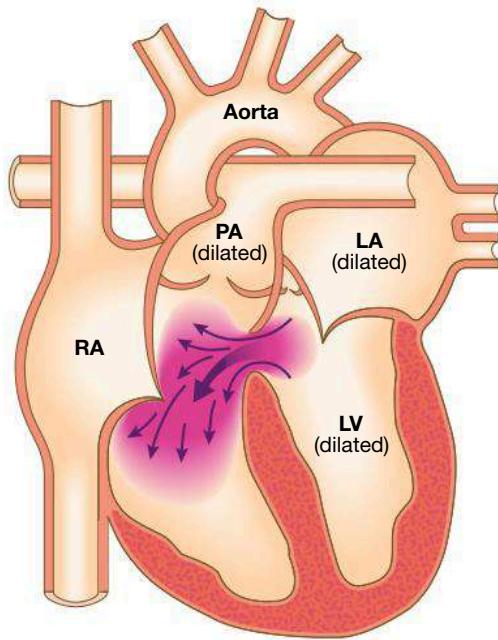


Fig. 16.95 Ventricular septal defect. In this example, a large left-to-right shunt (arrows) has resulted in chamber enlargement. (LA = left atrium; LV = left ventricle; PA = pulmonary artery; RA = right atrium)

Investigations

Echocardiography should be performed since it helps to identify the small septal defects that are not haemodynamically significant and are likely to close spontaneously. Patients with larger defects should be monitored by serial echocardiography to check for signs of pulmonary hypertension. With larger defects, the chest X-ray shows pulmonary congestion and the ECG shows bilateral ventricular hypertrophy.

Management

Small ventricular septal defects require no specific treatment. If there is cardiac failure in infancy, this should initially be treated with digoxin, diuretics and sometimes ACE inhibitors. Persisting failure is an indication for surgical repair of the defect. Percutaneous closure devices are under development.

If serial ECG and echocardiography suggest that pulmonary hypertension is developing, surgical repair should be performed. Surgical closure is contraindicated in Eisenmenger syndrome, and heart-lung transplantation is the only effective treatment. The long-term prognosis is generally very good unless Eisenmenger syndrome develops, when death occurs in the second or third decade of life, but a few individuals survive to the fifth decade without transplantation.

Tetralogy of Fallot

This is a complex defect consisting of right ventricular outflow tract obstruction and right ventricular hypertrophy, a large ventricular septal defect and an overriding aorta that, when combined with the septal defect, allows blood to be pumped directly from the RV into the aorta. It occurs in about 1 in 2000 births and is the most common cause of cyanosis in infancy after the first year of life.

Pathogenesis

Tetralogy of Fallot occurs as the result of abnormal development of the bulbar septum that separates the ascending aorta from the pulmonary artery, and which normally aligns and fuses with the outflow part of the interventricular septum. The right ventricular outflow obstruction is most often subvalvular (muscular) but may be valvar, supravalvular or a combination of these (Fig. 16.96). The subvalvular component of the right

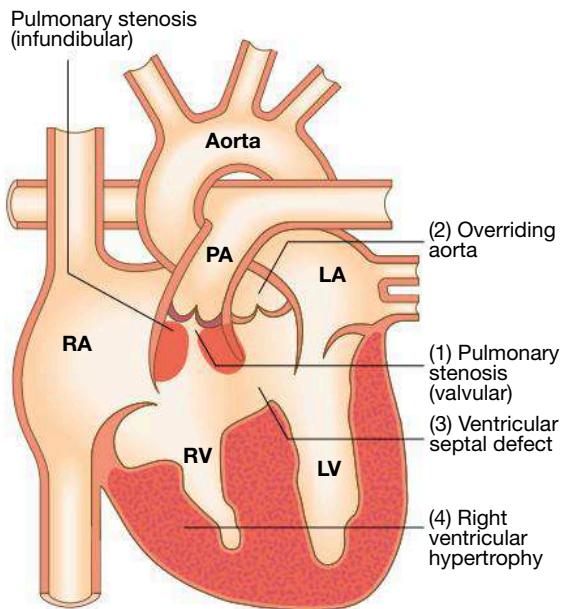


Fig. 16.96 Tetralogy of Fallot. The tetralogy comprises (1) pulmonary stenosis, (2) overriding of the ventricular septal defect by the aorta, (3) a ventricular septal defect and (4) right ventricular hypertrophy. (LA = left atrium; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle)

ventricular outflow obstruction is dynamic and may increase suddenly with sympathetic stimulation. The ventricular septal defect is usually large and similar in aperture to the aortic orifice. The combination results in elevated right ventricular pressure and right-to-left shunting of cyanotic blood across the ventricular septal defect into the aorta.

Clinical features

Children are usually cyanosed but this may not be the case in the neonate because it is only when right ventricular pressure rises to equal or exceed left ventricular pressure that a large right-to-left shunt develops. The affected child may suddenly become increasingly cyanosed, often after feeding or a crying attack, and may become apnoeic and unconscious. In older children, cyanotic spells are uncommon but cyanosis becomes increasingly apparent, with stunting of growth, digital clubbing and polycythaemia. Some children characteristically obtain relief by squatting after exertion, which increases the afterload of the left heart and reduces the right-to-left shunting. This is called Fallot's sign. The natural history before the development of surgical correction was variable but most patients died in infancy or childhood.

On examination, the most characteristic feature is the combination of cyanosis with a loud ejection systolic murmur in the pulmonary area (as for pulmonary stenosis). Cyanosis may be absent in the newborn or in patients with only mild right ventricular outflow obstruction, however. This is called acyanotic tetralogy of Fallot.

Investigations

Echocardiography is diagnostic and demonstrates that the aorta is not continuous with the anterior ventricular septum. The ECG shows right ventricular hypertrophy and the chest X-ray shows an abnormally small pulmonary artery and a 'boot-shaped' heart.

Management

The definitive management is total correction of the defect by surgical relief of the pulmonary stenosis and closure of the ventricular septal defect. Primary surgical correction may be undertaken prior to the age of 5 years. If the pulmonary arteries are too hypoplastic for surgical repair, then palliation in the form of a Blalock-Taussig shunt may be performed, where an anastomosis is created between the pulmonary artery and

16.102 Other causes of cyanotic congenital heart disease	
Defect	Features
Tricuspid atresia	Absent tricuspid orifice, hypoplastic RV, RA-to-LA shunt, ventricular septal defect shunt, other anomalies Surgical correction may be possible
Transposition of the great arteries	Aorta arises from the morphological RV, pulmonary artery from LV Shunt via atria, ductus and possibly ventricular septal defect Palliation by balloon atrial septostomy/ enlargement Surgical correction possible
Pulmonary atresia	Pulmonary valve atretic and pulmonary artery hypoplastic RA-to-LA shunt, pulmonary flow via ductus Palliation by balloon atrial septostomy Surgical correction may be possible
Ebstein's anomaly	Tricuspid valve is dysplastic and displaced into RV, RV 'atrialised' Tricuspid regurgitation and RA-to-LA shunt Wide spectrum of severity Arrhythmias Surgical repair possible but significant risk

(LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle)

subclavian artery. This improves pulmonary blood flow and pulmonary artery development, and may facilitate later definitive correction.

The prognosis after total correction is good, especially if the operation is performed in childhood. Follow-up is needed to identify residual shunting, recurrent pulmonary stenosis and arrhythmias. An implantable defibrillator is sometimes recommended in adulthood.

Other causes of cyanotic congenital heart disease

Other types of cyanotic congenital heart disease are summarised in Box 16.102.

Grown-up congenital heart disease

There are increasing numbers of children who have had surgical correction of congenital defects and who may have further problems as adults. The transition period between paediatric and adult care needs to be managed in a carefully planned manner, addressing many diverse aspects of care (Box 16.103). Those who have undergone correction of coarctation of the aorta may develop hypertension in adult life. Those with transposition of the great arteries who have had a 'Mustard' repair, in which blood is redirected at atrial level leaving the RV connected to the aorta, may develop right ventricular failure in adult life. This is because the RV is unsuited for function at systemic pressures and may begin to dilate and fail when patients are in their twenties or thirties.

Those who have had surgery involving the atria may develop atrial arrhythmias, and those who have VSD repair (and consequent ventricular scar) may develop ventricular arrhythmias. Anti-arrhythmic drugs and an ICD may be required. Such patients require careful follow-up from adolescence throughout adult life, so that problems can be identified early and appropriate medical or surgical treatment instituted. The management of patients with grown-up congenital heart disease (GUCH) is complex and has developed as a cardiological subspecialty.

16.103 Congenital heart disease in adolescence

- **Patients:** a heterogeneous population with residual disease and sequelae that vary according to the underlying lesion and in severity; each patient must be assessed individually.
- **Management plan:** should be agreed with the patient and include short- and long-term goals and timing of transition to adult care.
- **Risks of surgery:** non-cardiac surgery for associated congenital abnormalities carries increased risks and needs to be planned, with careful pre-operative assessment. Risks include thrombosis, embolism from synthetic shunts or patches, and volume overload from fluid shifts. Operative approaches should address cosmetic concerns, such as site of implantation of abdominal generator.
- **Exercise:** patients with mild or repaired defects can undertake moderately vigorous exercise but those with complex defects, cyanosis, ventricular dysfunction or arrhythmias require specialist evaluation and individualised advice regarding exercise.
- **Genetics:** Between 10% and 15% have a genetic basis and this should be assessed to understand the impact it may have for the patient's own future children. A family history, genetic evaluation of syndromic versus non-syndromic disorders and, sometimes, cytogenetics are required.
- **Education and employment:** may be adversely affected and occupational activity levels need to be assessed.
- **End of life:** some adolescents with complex disorders may misperceive and think they have been cured; transition to adult services may be the first time they receive information about mortality. Expectations on life expectancy need to be managed and adolescents are often willing to engage with this and play a role in decision-making.

Diseases of the myocardium

The myocardium can be injured secondary to ischaemia in CAD and to pressure or volume overload in hypertension or valvular heart disease. The heart muscle can be directly affected by primary heart muscle diseases.

Myocarditis

This is an acute inflammatory condition that can have an infectious, toxic or autoimmune aetiology (Box 16.104). Myocarditis can complicate many infections in which inflammation may be due directly to infection of the myocardium or the effects of circulating toxins. Viral infections are the most common causes, such as Coxsackie (35 cases per 1000 infections), influenza A and B (25 cases per 1000 infections) and, more recently, SARS-CoV-2 infection. Myocarditis may occur several weeks after the initial viral symptoms, and susceptibility is increased by glucocorticoid treatment, immunosuppression, radiation, previous myocardial damage and exercise. Some bacterial and protozoal infections may be complicated by myocarditis; for example, approximately 5% of patients with Lyme disease (*Borrelia burgdorferi*) develop myopericarditis, which is often associated with AV block. Toxins such as alcohol and drugs such as cocaine, lithium and doxorubicin may directly injure the myocardium. Other drugs, including penicillins and sulphonamides, and poisons such as lead and carbon monoxide, may cause a hypersensitivity reaction and associated myocarditis. Occasionally, autoimmune conditions, such as systemic lupus erythematosus and rheumatoid arthritis, are associated with myocarditis.

Clinical features

Myocarditis may present in one of four ways:

- *Fulminant myocarditis* follows a viral prodrome or influenza-like illness and results in severe heart failure or cardiogenic shock.
- *Acute myocarditis* presents over a longer period with heart failure; it can lead to dilated cardiomyopathy.

- *Chronic active myocarditis* is rare and associated with chronic myocardial inflammation.
- *Chronic persistent myocarditis* is characterised by focal myocardial infiltrates and can cause chest pain and arrhythmia without necessarily causing ventricular dysfunction.

Myocarditis is self-limiting in most patients and the immediate prognosis is good. Death may, however, occur due to a ventricular arrhythmia.



16.104 Some causes of myocarditis

Infections

Viral

- Coxsackie
- Adenovirus
- Influenza A
- Human immunodeficiency virus (HIV)
- Influenza B
- SARS-CoV-2

Bacterial

- *Borrelia burgdorferi* (Lyme disease)
- *Mycoplasma pneumoniae*

Protozoal

- *Trypanosoma cruzi* (Chagas' disease)
- *Toxoplasma gondii*

Fungal

- *Aspergillus*

Parasitic

- *Shistosoma*

Drugs/Toxins

- Alcohol
- Anthracyclines
- Clozapine
- Cocaine
- Lithium

Autoimmune

- Systemic lupus erythematosus
- Systemic sclerosis
- Rheumatoid arthritis
- Sarcoidosis
- Hypersensitivity reaction to penicillins, sulphonamides, lead, carbon monoxide

or rapidly progressive heart failure. Myocarditis has been reported as a cause of sudden and unexpected death in young athletes. Some forms of myocarditis may lead to chronic low-grade myocarditis or dilated cardiomyopathy (see below). For example, in Chagas' disease, the patient frequently recovers from the acute infection but goes on to develop a chronic dilated cardiomyopathy 10 or 20 years later.

Investigations

The diagnosis of myocarditis is often made after other more common causes of cardiac dysfunction have been excluded. Echocardiography should be performed and may reveal left ventricular dysfunction that is sometimes regional (due to focal myocarditis). Cardiac MRI is also useful since it may show diagnostic patterns of myocardial inflammation or infiltration. The ECG is frequently abnormal but the changes are non-specific. Blood should be taken to assess for cardiac troponin I or T which can be used to monitor severity and progression of cardiac injury and myocarditis. Occasionally, endomyocardial biopsy may be required to confirm the diagnosis.

Management

Treatment of myocarditis is primarily supportive. Treatment for cardiac failure or arrhythmias should be given and patients should be advised to avoid intense physical exertion because there is some evidence that this can induce potentially fatal ventricular arrhythmias. There is no evidence of benefit from treatment with glucocorticoids and immunosuppressive agents.

Specific antimicrobial therapy may be used if a causative organism has been identified but this is rare. Patients who do not respond adequately to medical treatment may temporarily require circulatory support with a mechanical ventricular assist device. Rarely, cardiac transplantation may be required.

Cardiomyopathy

Cardiomyopathies are primary diseases of the myocardium, which are classified according to their effects on cardiac structure and function (Fig. 16.97). They can be inherited or be caused by infections or exposure to toxins. In some cases no cause is identified.

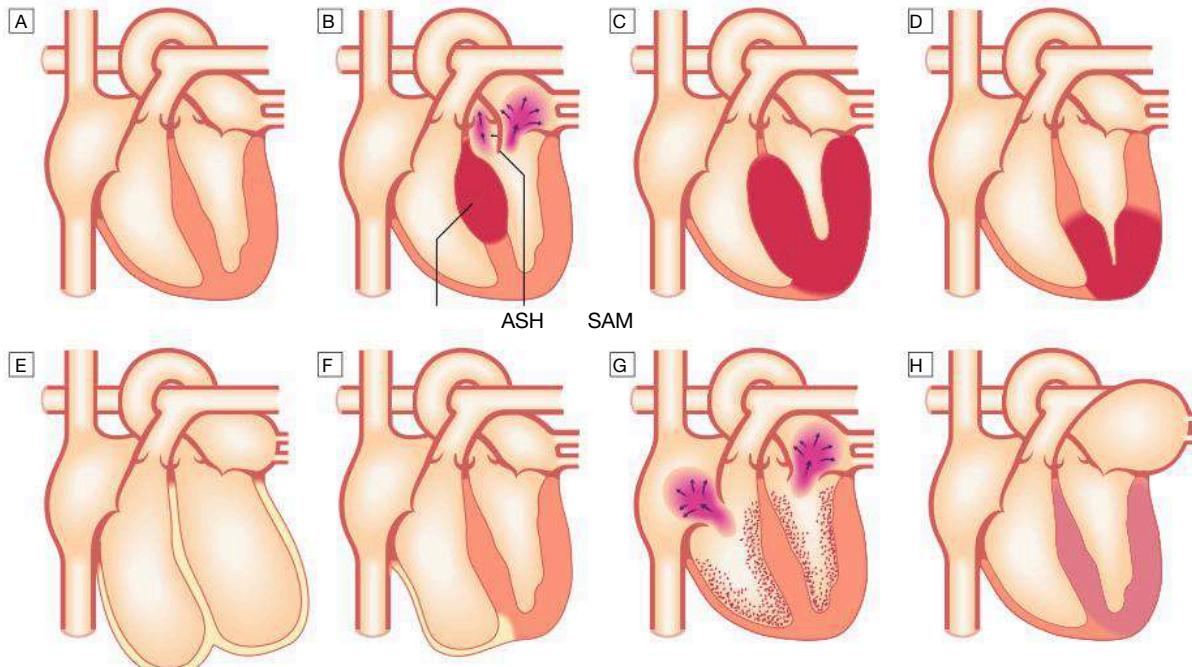


Fig. 16.97 Types of cardiomyopathy. **A** Normal heart. **B** Hypertrophic cardiomyopathy: asymmetric septal hypertrophy (ASH) with systolic anterior motion of the mitral valve (SAM), causing mitral reflux and dynamic left ventricular outflow tract obstruction. **C** Hypertrophic cardiomyopathy: concentric hypertrophy. **D** Hypertrophic cardiomyopathy: apical hypertrophy. **E** Dilated cardiomyopathy. **F** Arrhythmogenic right ventricular cardiomyopathy. **G** Obliterative cardiomyopathy. **H** Restrictive cardiomyopathy.

Dilated cardiomyopathy

In North America and Europe, symptomatic dilated cardiomyopathy has an incidence of 20 per 100 000 and a prevalence of 38 per 100 000. Men are affected more than twice as often as women.

Pathogenesis

Cardiomyopathy is characterised by dilatation and impaired contraction of the LV and often the RV. Left ventricular mass is increased but wall thickness is normal or reduced (see Fig. 16.97). Dilatation of the valve rings can lead to functional mitral and tricuspid incompetence. Histological changes are variable but include myofibrillary loss, interstitial fibrosis and T-cell infiltrates. The term 'dilated cardiomyopathy' encompasses a heterogeneous group of conditions. Alcohol may be an important cause in some patients. At least 25% of cases are inherited as an autosomal dominant trait and a variety of single-gene mutations have been identified. Most of these mutations affect proteins in the cytoskeleton of the myocytes, such as dystrophin, lamin A and C, titan, emerin and metavinculin. Many are also associated with abnormalities of skeletal muscle. The X-linked inherited skeletal muscular dystrophies, such as Becker and Duchenne, are also associated with cardiomyopathy. Finally, a late autoimmune reaction to viral myocarditis is thought to be the cause in a substantial subgroup of patients with dilated cardiomyopathy; a similar mechanism is believed to be responsible for the myocardial involvement that occurs in up to 10% of patients with advanced human immunodeficiency virus (HIV) infection.

Clinical features

Most patients present with heart failure or are found to have the condition during routine investigation. Arrhythmia, thromboembolism and sudden death may occur at any stage but these are more common in advanced disease; non-exertional chest pain is surprisingly common. The differential diagnosis includes ventricular dysfunction due to CAD, and a diagnosis of dilated cardiomyopathy should be made only when this has been excluded.

Investigations

Echocardiography and cardiac MRI are the most useful investigations. Although ECG changes are common, they are non-specific. Genetic testing is indicated if more than one family member is diagnosed with the condition.

Management

The focus of management is to control heart failure using the strategies described earlier in this chapter. Although some patients remain well for many years, the prognosis is variable and cardiac transplantation may be indicated. Patients with dilated cardiomyopathy and moderate or severe heart failure are at risk of sudden arrhythmic death and this can be reduced by rigorous medical therapy with β -blockers and either ACE inhibitors or ARBs. Some patients may be considered for implantation of a cardiac defibrillator and/or cardiac resynchronisation therapy.

Hypertrophic cardiomyopathy

This is the most common form of cardiomyopathy, with a prevalence of approximately 100 per 100 000. It is characterised by inappropriate left ventricular hypertrophy with malalignment of the myocardial fibres and myocardial fibrosis. The hypertrophy may be generalised or confined largely to the interventricular septum (asymmetric septal hypertrophy, see Fig. 16.97) or other regions of the heart. A specific variant termed apical hypertrophic cardiomyopathy is common in the Far East.

Pathogenesis

Hypertrophic cardiomyopathy is a genetic disorder, usually with autosomal dominant transmission, a high degree of penetrance and variable expression. In most patients, it is due to a single-point mutation in one of the genes that encode sarcomeric contractile proteins. There are three common

groups of mutation with different phenotypes. Beta-myosin heavy-chain mutations are associated with marked ventricular hypertrophy. In contrast, troponin mutations are associated with little, if any, hypertrophy but are characterised by marked myocardial fibre disarray, exercise-induced hypotension and a high risk of sudden death. Myosin-binding protein C mutations tend to present late in life and are often associated with hypertension and arrhythmia. In all subtypes, heart failure may develop because the stiff, non-compliant LV impedes diastolic filling. Septal hypertrophy may also cause dynamic left ventricular outflow tract obstruction (hypertrophic obstructive cardiomyopathy, HOCM) and mitral regurgitation due to abnormal systolic anterior motion of the anterior mitral valve leaflet.

Clinical features

Effort-related symptoms, such as angina, breathlessness, arrhythmia and sudden death, are the dominant clinical presentations. The symptoms and signs are similar to those of aortic stenosis, except that, in hypertrophic cardiomyopathy, the character of the arterial pulse is jerky (Box 16.105). The annual mortality from sudden death is 2%–3% among adults and 4%–6% in children and adolescents (Box 16.106). Sudden death typically occurs during or just after vigorous physical activity and is thought to be due to ventricular arrhythmias. Hypertrophic cardiomyopathy is the most common cause of sudden death in young athletes. In patients who do not suffer fatal arrhythmias, the natural history is variable but clinical deterioration is often slow.

Investigations

Echocardiography is the investigation of choice and is usually diagnostic. Sometimes the diagnosis is more difficult when another cause of left ventricular hypertrophy is present but the degree of hypertrophy in hypertrophic cardiomyopathy is usually greater than in physiological hypertrophy and the pattern is asymmetrical. The ECG is abnormal and shows features of left ventricular hypertrophy with a wide variety of often bizarre abnormalities, including deep T-wave inversion. Genetic testing can be performed and is helpful in screening relatives of affected individuals.

Management

Beta-blockers, rate-limiting calcium antagonists and disopyramide can help to relieve symptoms and prevent syncopal attacks. Arrhythmias often respond to treatment with amiodarone. No pharmacological

16.105 Clinical features of hypertrophic cardiomyopathy	
Symptoms	<ul style="list-style-type: none"> • Angina on effort • Dyspnoea on effort • Syncope on effort • Sudden death
Signs	<ul style="list-style-type: none"> • Jerky pulse* • Palpable left ventricular hypertrophy • Double impulse at the apex (palpable fourth heart sound due to left atrial hypertrophy) • Mid-systolic murmur at the base* • Pansystolic murmur (due to mitral regurgitation) at the apex
<small>*Signs of left ventricular outflow tract obstruction may be augmented by standing up (reduced venous return), inotropes and vasodilators</small>	

16.106 Risk factors for sudden death in hypertrophic cardiomyopathy

- A history of previous cardiac arrest or sustained ventricular tachycardia
- Recurrent syncope
- An adverse genotype and/or family history
- Exercise-induced hypotension
- Non-sustained ventricular tachycardia on ambulatory ECG monitoring
- Marked increase in left ventricular wall thickness

treatment has been identified that can improve prognosis, however. Outflow tract obstruction can be improved by partial surgical resection (myectomy) or by iatrogenic infarction of the basal septum (septal ablation) using a catheter-delivered alcohol solution. An ICD should be considered in patients with clinical risk factors for sudden death (see Box 16.106). Digoxin and vasodilators may increase outflow tract obstruction and should be avoided.

Arrhythmogenic ventricular cardiomyopathy

Arrhythmogenic ventricular cardiomyopathy (AVC) predominantly affects the myocardium of the right ventricle. It is inherited in an autosomal dominant manner and has a prevalence of approximately 10 per 100 000. The genetic defect involves desmosomal protein genes, most commonly plakophilin 2 (*PKP-2*), although current genetic testing protocols will not identify the culprit gene in many cases. It is characterised by replacement of patches of the right ventricular myocardium with fibrous and fatty tissue (see Fig. 16.97). In some cases, the LV is also involved and this is associated with a poorer prognosis. The diagnosis is based on a complex set of criteria that take account of the ECG, structural assessment, genetics and arrhythmias. The dominant clinical problems are ventricular arrhythmias, sudden death and right-sided cardiac failure. The ECG typically shows a slightly broadened QRS complex and inverted T waves in the right precordial leads. MRI is a helpful diagnostic tool and is used, along with the 12-lead ECG and ambulatory ECG monitoring, to screen the first-degree relatives of affected individuals. Management is based on treating right-sided cardiac failure with diuretics and cardiac arrhythmias with β -blockers or, in patients at high risk of sudden death, an implantable defibrillator can be offered.

Restrictive cardiomyopathy

In this rare condition, ventricular filling is impaired because the ventricles are ‘stiff’ (see Fig. 16.97). This leads to high atrial pressures with atrial hypertrophy, dilatation and, later, AF. Amyloidosis is the most common cause in the UK, although other forms of infiltration due to glycogen storage diseases, idiopathic perimyocyte fibrosis and a familial form of restrictive cardiomyopathy can also occur. The diagnosis can be difficult and requires assessment with Doppler echocardiography, CT or MRI, and endomyocardial biopsy. Treatment is symptomatic but the prognosis is usually poor and cardiac transplantation may be indicated.

Obliterative cardiomyopathy

This is a rare form of restrictive cardiomyopathy, involving the endocardium of one or both ventricles; it is characterised by thrombosis and

fibrosis, with gradual obliteration of the ventricular cavities by fibrous tissue (see Fig. 16.97). The mitral and tricuspid valves become regurgitant. Heart failure and pulmonary and systemic embolism are prominent features. It can sometimes be associated with eosinophilia and can occur in eosinophilic leukaemia and eosinophilic granulomatosis with polyangiitis (formerly known as Churg–Strauss syndrome). In tropical countries, the disease may be responsible for up to 10% of cardiac deaths. Prognosis is poor, with a 50% mortality within 2 years of diagnosis. Anticoagulation and antiplatelet therapy are used to reduce the risk of embolism, and diuretics to treat heart failure. Surgery (tricuspid and/or mitral valve replacement with decortication of the endocardium) may be helpful in selected cases.

Takotsubo cardiomyopathy

Takotsubo cardiomyopathy (Takotsubo syndrome) is a form of acute left ventricular dysfunction characterised by dilatation of the left ventricular apex and adjacent myocardium, with associated left ventricular impairment. The mechanism is poorly understood. It is often associated with acute environmental or emotional stress (such as a bereavement) and presents with chest pain, breathlessness and sometimes cardiac failure. It occurs more frequently in women than in men and there is a high prevalence of neurological and psychiatric disorders. The symptoms and ECG often mimic acute ST elevation acute coronary syndrome. The diagnosis is usually made at coronary angiography, when CAD is found to be absent or minimal. Echocardiography or left ventriculography then shows characteristic ‘apical ballooning’ of the LV. The dilated apex and narrow outflow of the LV resemble a Japanese octopus trap, or takotsubo (Fig. 16.98).

Left ventricular ejection fraction returns to normal within days to weeks. Although commonly thought to be a benign condition, it is associated with a recurrence rate of 10% and a mortality of 20% at 5 years. There are no known treatments that have been shown to influence clinical outcome.

16

Secondary causes of cardiomyopathy

Many systemic conditions can produce a picture that is indistinguishable from dilated cardiomyopathy, including connective tissue disorders, sarcoidosis, haemochromatosis and alcoholic heart muscle disease (Box 16.107). In contrast, amyloidosis and eosinophilic heart disease produce symptoms and signs similar to those found in restrictive or obliterative cardiomyopathy, whereas the heart disease associated with Friedreich’s ataxia can mimic hypertrophic cardiomyopathy.

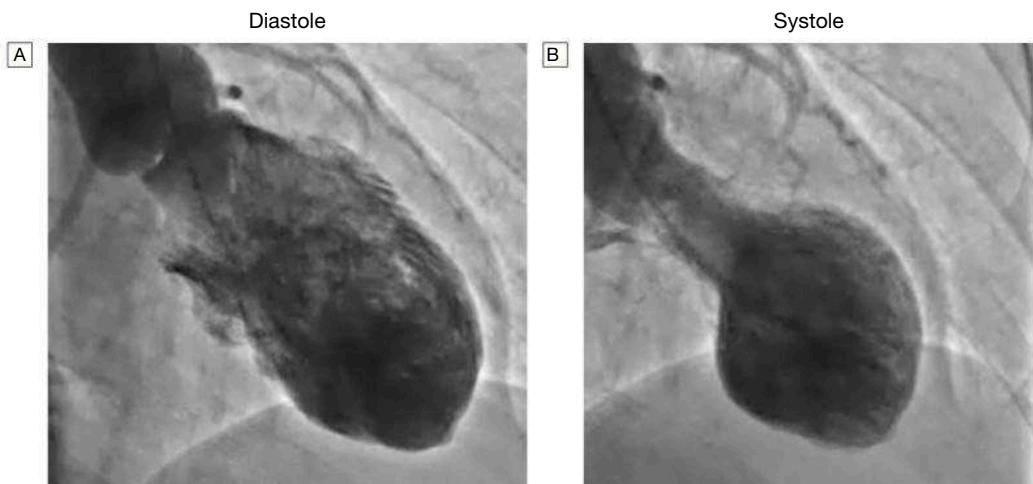


Fig. 16.98 Left ventriculograms in diastole **A** and systole **B** in a patient with Takotsubo cardiomyopathy. Note the ballooning of the left ventricular apex in systole which is characteristic of this condition (compare with Fig. 16.16).

16.107 Specific diseases of heart muscle	
Infections	
Viral	<ul style="list-style-type: none"> • Coxsackie A and B • Influenza • HIV • SARS-CoV-2
Bacterial	<ul style="list-style-type: none"> • Diphtheria • <i>Borrelia burgdorferi</i>
Protozoal	<ul style="list-style-type: none"> • Trypanosomiasis • <i>Toxoplasma gondii</i>
Endocrine and metabolic disorders	
<ul style="list-style-type: none"> • Diabetes • Hypo- and hyperthyroidism • Acromegaly 	<ul style="list-style-type: none"> • Carcinoid syndrome • Phaeochromocytoma • Inherited storage diseases
Connective tissue diseases	
<ul style="list-style-type: none"> • Systemic sclerosis • Systemic lupus erythematosus 	<ul style="list-style-type: none"> • Polyarteritis nodosa
Infiltrative disorders	
<ul style="list-style-type: none"> • Haemochromatosis • Haemosiderosis 	<ul style="list-style-type: none"> • Sarcoidosis • Amyloidosis
Toxins	
<ul style="list-style-type: none"> • Doxorubicin • Alcohol 	<ul style="list-style-type: none"> • Cocaine • Irradiation
Neuromuscular disorders	
<ul style="list-style-type: none"> • Dystrophia myotonica 	<ul style="list-style-type: none"> • Friedreich's ataxia

Treatment and prognosis are determined by the underlying disorder. Abstention from alcohol may lead to a dramatic improvement in patients with alcoholic heart muscle disease.

Cardiac tumours

Primary cardiac tumours are rare (<0.2% of autopsies) but the heart and mediastinum may be the sites of metastases. Most primary tumours are benign (75%) and, of these, the majority are myxomas. The remainder are fibromas, lipomas, fibroelastomas and haemangiomas.

Atrial myxoma

Myxomas most commonly arise in the LA as single or multiple polypoid tumours, attached by a pedicle to the interatrial septum. They are usually gelatinous but may be solid and even calcified, with superimposed thrombus.

On examination, the first heart sound is usually loud, and there may be a murmur of mitral stenosis with a variable diastolic sound (tumour 'plop') due to prolapse of the mass through the mitral valve. The tumour can be detected incidentally on echocardiography, or following investigation of pyrexia, syncope, arrhythmias or emboli. Occasionally, the condition presents with malaise and features suggestive of a connective tissue disorder, including a raised ESR.

Treatment is by surgical excision. If the pedicle is removed, fewer than 5% of tumours recur.

Diseases of the pericardium

The normal pericardial sac contains about 50mL of fluid, similar to lymph, which lubricates the surface of the heart. The pericardium limits distension of the heart, contributes to the haemodynamic interdependence of the ventricles, and acts as a barrier to infection. Nevertheless, congenital absence of the pericardium does not result in significant clinical or functional limitations.

16.108 Causes of acute pericarditis and pericardial effusion	
Infection	<ul style="list-style-type: none"> • Viral • Bacterial
	<ul style="list-style-type: none"> • Tuberculosis
Inflammatory	<ul style="list-style-type: none"> • Rheumatoid arthritis • Systemic lupus erythematosus
Other	<ul style="list-style-type: none"> • Post-myocardial infarction • Uraemia • Malignancy • Trauma

Acute pericarditis

This is due to an acute inflammatory process affecting the pericardium, which may coexist with myocarditis.

Pathogenesis

A number of causes are recognised (Box 16.108), but in some cases the cause is unclear. All forms of pericarditis may produce a pericardial effusion that, depending on the aetiology, may be fibrinous, serous, haemorrhagic or purulent. A fibrinous exudate may eventually lead to varying degrees of adhesion formation, whereas serous pericarditis often produces a large effusion of turbid, straw-coloured fluid with a high protein content. A haemorrhagic effusion is often due to malignant disease, particularly carcinoma of the breast or bronchus, and lymphoma. Purulent pericarditis is rare and may occur as a complication of sepsis, by direct spread from an intrathoracic infection, or from a penetrating injury.

Clinical features

The typical presentation is with chest pain that is retrosternal, radiates to the shoulders and neck, and is typically aggravated by deep breathing, movement, a change of position, exercise and swallowing. A low-grade fever is common. A pericardial friction rub is a high-pitched, superficial scratching or crunching noise, produced by movement of the inflamed pericardium, and is diagnostic of pericarditis; it is usually heard in systole but may also be audible in diastole and frequently has a 'to-and-fro' quality.

Investigations

The diagnosis can often be made on the basis of clinical features and the ECG; the latter shows ST elevation with upward concavity (Fig. 16.99) over the affected area, which may be widespread. PR interval depression is a very specific indicator of acute pericarditis. Later, there may be T-wave inversion, particularly if there is a degree of myocarditis. Echocardiography may be normal or may reveal pericardial effusion, in which case regular echocardiographic monitoring is recommended.

Management

The pain usually responds to aspirin (600mg 6 times daily) but a more potent anti-inflammatory agent, such as indometacin (500mg 3 times daily), may be required. Colchicine is very effective at relieving symptoms and also prevents relapsing episodes if taken for 3 months from symptom onset. Glucocorticoids are no longer recommended for this condition. In viral pericarditis, recovery usually occurs within a few days or weeks but there may be recurrences (chronic relapsing pericarditis). Purulent pericarditis requires treatment with antimicrobial therapy, pericardiocentesis and, if necessary, surgical drainage.

Pericardial effusion

Pericardial effusion often accompanies pericarditis and can have a number of causes, as shown in Box 16.108.

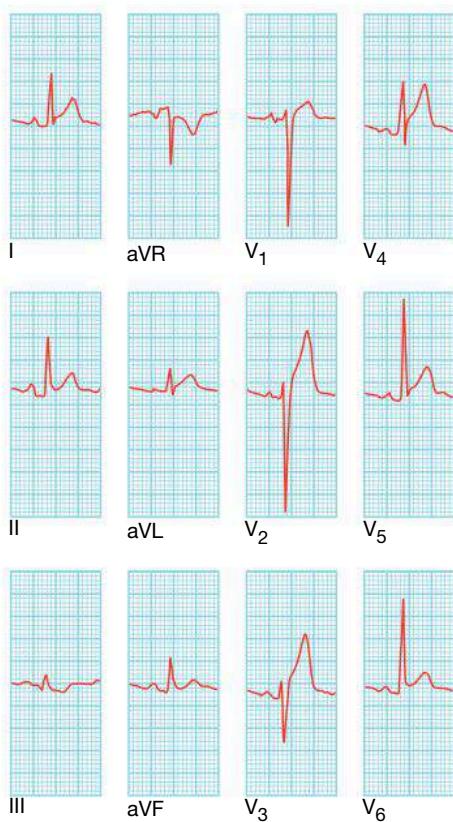


Fig. 16.99 ECG in viral pericarditis. Widespread ST elevation (leads I, II, aVL and V₁–V₆) is shown. The upward concave shape of the ST segments (see leads II and V₅) and the unusual distribution of changes (involving anterior and inferior leads) help to distinguish pericarditis from acute myocardial infarction.

Clinical features

With the onset of an effusion the heart sounds may become quieter, and a friction rub, if present, may diminish in intensity but is not always abolished. Larger effusions may be accompanied by a sensation of retrosternal oppression. While most effusions do not have significant haemodynamic effects, large or rapidly developing effusions may cause cardiac tamponade. This term is used to describe acute heart failure due to compression of the heart and is described in detail below. Typical physical findings are a markedly raised JVP, hypotension, pulsus paradoxus and oliguria. Atypical presentations may occur when the effusion is loculated as a result of previous pericarditis or cardiac surgery.

Investigations

Echocardiography is the definitive investigation and is helpful in monitoring the size of the effusion and its effect on cardiac function (Fig. 16.100). The QRS voltages on the ECG are often reduced in the presence of a large effusion. The QRS complexes may alternate in amplitude due to a to-and-fro motion of the heart within the fluid-filled pericardial sac (electrical alternans). The chest X-ray may show an increase in the size of the cardiac silhouette and, when there is a large effusion, this has a globular appearance. Aspiration of the effusion may be required for diagnostic purposes and, if necessary, for treatment of large effusions, as described below.

Management

Patients with large effusions that are causing haemodynamic compromise or cardiac tamponade should undergo aspiration of the effusion. This involves inserting a needle under echocardiographic guidance medial to the cardiac apex or below the xiphoid process, directed upwards towards the left shoulder. The route of choice will depend on

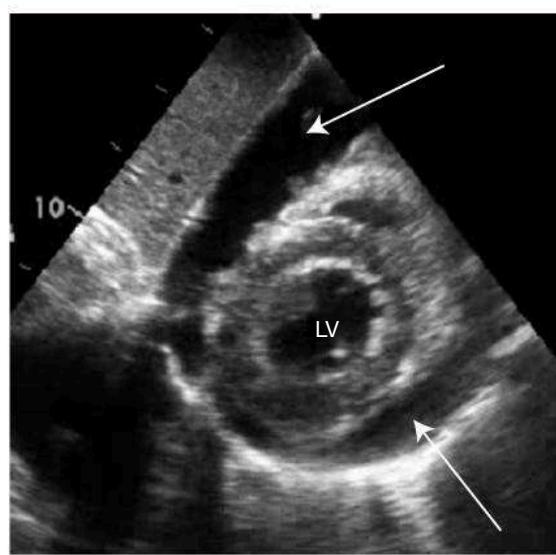


Fig. 16.100 Pericardial effusion: echocardiogram (apical view). Short-axis view of the heart showing a large circumferential pericardial effusion (arrows). (LV = left ventricle)

the experience of the operator, the shape of the patient and the position of the effusion. A pericardial drain may be placed to provide symptomatic relief. Complications of pericardiocentesis include arrhythmias, damage to a coronary artery and bleeding, with exacerbation of tamponade as a result of injury to the RV. When tamponade is due to cardiac rupture or aortic dissection, pericardial aspiration may precipitate further potentially fatal bleeding and, in these situations, emergency surgery is the treatment of choice. A viscous, loculated or recurrent effusion may also require formal surgical drainage.

Tuberculous pericarditis

Tuberculous pericarditis may complicate pulmonary tuberculosis but may also be the first manifestation of the infection. In Africa, a tuberculous pericardial effusion is a common feature of AIDS. The condition typically presents with chronic malaise, weight loss and a low-grade fever. An effusion usually develops and the pericardium may become thick and unyielding, leading to pericardial constriction or tamponade. An associated pleural effusion is often present.

The diagnosis may be confirmed by aspiration of the fluid and direct examination or culture for tubercle bacilli. Treatment requires specific antituberculous chemotherapy (p. 522); in addition, a 3-month course of prednisolone (initial dose 60 mg a day, tapering down rapidly) improves outcome.

Chronic constrictive pericarditis

Constrictive pericarditis is due to progressive thickening, fibrosis and calcification of the pericardium. In effect, the heart is encased in a solid shell and cannot fill properly. The calcification may extend into the myocardium, so there may also be impaired myocardial contraction. The condition often follows an attack of tuberculous pericarditis but can also complicate haemopericardium, viral pericarditis, rheumatoid arthritis and purulent pericarditis. It is often impossible to identify the original insult.

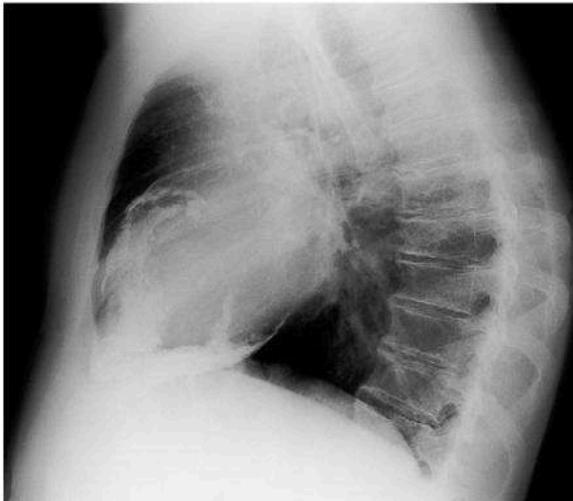
Clinical features

The symptoms and signs of systemic venous congestion are the hallmarks of constrictive pericarditis. AF is common and there is often dramatic ascites and hepatomegaly (Box 16.109). Breathlessness is not a prominent symptom because the lungs are seldom congested. The condition is sometimes overlooked and should be suspected in any patient

**16.109 Clinical features of constrictive pericarditis**

- Fatigue
- Rapid, low-volume pulse
- Elevated JVP with a rapid y descent
- Loud early third heart sound or 'pericardial knock'
- Kussmaul's sign
- Hepatomegaly
- Ascites
- Peripheral oedema
- Pulsus paradoxus

(JVP = jugular venous pressure)

**Fig. 16.101 Lateral chest X-ray from a patient with severe heart failure due to chronic constrictive pericarditis.** There is heavy calcification of the pericardium.

with unexplained right heart failure and apparently normal heart size and function on echocardiography.

Investigations

A chest X-ray, which may show pericardial calcification (Fig. 16.101), and echocardiography often help to establish the diagnosis. CT scanning is useful for imaging the pericardial calcification. Constrictive pericarditis is often difficult to distinguish from restrictive cardiomyopathy and in such cases complex echo-Doppler studies and cardiac catheterisation may be required.

Management

The resulting diastolic heart failure is treated using loop diuretics and aldosterone antagonists, such as spironolactone. Surgical resection of the diseased pericardium can lead to a dramatic improvement but carries a high morbidity, especially if performed late in the disease course, as the pericardium becomes heavily bound to the myocardium.

Cardiac tamponade

This term is used to describe acute heart failure due to compression of the heart as the result of a large pericardial effusion. Tamponade may complicate any form of pericarditis but can be caused by malignant disease, by blood in the pericardial space following trauma, or by rupture of the free wall of the myocardium following MI.

**16.110 Clinical features of cardiac tamponade**

- Dyspnoea
- Collapse
- Tachycardia
- Hypotension
- Gross elevation of the JVP
- Soft heart sounds with an early third heart sound
- Pulsus paradoxus (a large fall in BP during inspiration, when the pulse may be impalpable)
- Kussmaul's sign (a paradoxical rise in JVP during inspiration)

(JVP = jugular venous pressure)

Clinical features

Patients with tamponade are unwell, with hypotension, tachycardia and a markedly raised JVP. Other clinical features are summarised in Box 16.110.

Investigations

The pivotal investigation is echocardiography, which can confirm the diagnosis and also helps to identify the optimum site for aspiration of the fluid. The ECG may show features of the underlying disease, such as pericarditis or acute MI. When there is a large pericardial effusion, the ECG complexes are small and there may be electrical alternans: a changing axis with alternate beats caused by the heart swinging from side to side in the pericardial fluid. A chest X-ray shows an enlarged globular heart but can look normal.

Management

Cardiac tamponade is a medical emergency. When the diagnosis is confirmed, percutaneous pericardiocentesis should be performed as soon as possible, which usually results in a dramatic improvement. In some cases, surgical drainage may be required.

Further information**Journal article**

Gould FK, Denning DW, Elliott TS, et al. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the working party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother*. 2012;67:269–289.

Websites

acc.org American College of Cardiology (ACC): free access to guidelines for the evaluation and management of many cardiac conditions.

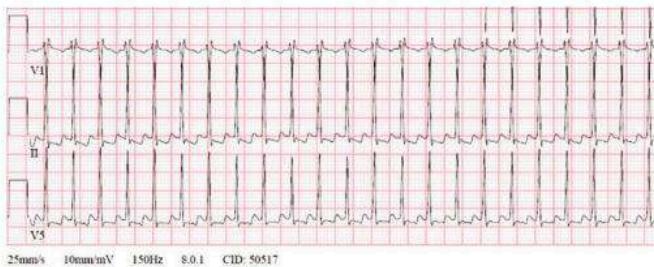
americanheart.org American Heart Association (AHA): free access to all the ACC/AHA/ESC guidelines, AHA scientific statements and fact sheets for patients.

americanheart.org European Society of Cardiology (ESC): free access to guidelines for the diagnosis and management of many cardiac conditions, and to educational modules.

jbs3risk.com Joint British Societies for the Prevention of Cardiovascular Disease: risk calculator.

Multiple Choice Questions

- 16.1. A 24-year-old woman presents at the emergency department with an episode of sudden-onset rapid regular palpitation of one hour's duration. She has no previous cardiovascular history. On examination, heart rate is 180 beats/min and regular, blood pressure 104/68mmHg. Examination is otherwise unremarkable. The ECG shows a regular, narrow QRS tachycardia (see figure).



Which of the following is the most appropriate initial management for this rhythm?

- A. Intravenous adenosine
- B. Oral beta-blocker
- C. Valsalva manoeuvre with or without leg raising
- D. Bilateral carotid sinus pressure
- E. Intravenous atropine

Answer: C.

The diagnosis is supraventricular tachycardia (SVT), based on the sudden onset, the regular nature of the tachycardia, and the absence of obvious P waves on the ECG. SVT is usually caused by a re-entrant mechanism involving the atrioventricular node (see p. 415). Treatments that cause transient AV nodal block interrupt the tachycardia and restore sinus rhythm. Intravenous adenosine is usually effective but is not normally given until after vagal manoeuvres have been tried. The Valsalva manoeuvre is often effective and can be enhanced by leg raising after breath-holding is released (the 'REVERT' manoeuvre). Carotid sinus pressure may also be effective but should never be applied to both carotid arteries simultaneously. Atropine is an anticholinergic drug which is used to treat symptomatic bradycardia, not tachycardia.

- 16.2. A 77-year-old diabetic woman presents to her general practitioner because of fatigue and breathlessness. She is found to have an irregular pulse at 74 beats/min. An ECG confirms atrial fibrillation with good heart rate control. An echocardiogram is performed showing left atrial enlargement but no other abnormality. What is the most appropriate strategy to reduce this patient's risk of a future stroke?
- A. Oral aspirin, 75mg once daily
 - B. Oral clopidogrel, 75mg once daily
 - C. Immediate DC cardioversion
 - D. Oral digoxin
 - E. Oral anticoagulation with warfarin or a direct oral anticoagulant

Answer: E.

This woman has atrial fibrillation and a relatively high CHA₂DS₂-VASc score of 4 points (1 point each for gender and diabetes mellitus, and 2 points for age greater than 75 years). She has an annual stroke risk

of around 4% which would be reduced to 1% with oral anticoagulation using a direct oral anticoagulant such as apixaban or edoxaban, or with warfarin (target International Normalised Ratio 2–3). Oral antiplatelet drugs such as aspirin or clopidogrel are ineffective for stroke prevention in atrial fibrillation. Immediate cardioversion would increase stroke risk because a prior period of oral anticoagulation is required to make the procedure safe. Digoxin is used for heart rate control but has no impact on stroke risk. (For more on stroke prevention in atrial fibrillation see page 414.)

- 16.3. A fit 25-year-old man presents to the emergency department with an episode of syncope while running a half-marathon. He had a few seconds warning with lightheadedness, was syncopal for around 15 seconds, and made a rapid recovery. His father had died suddenly age 54 years with no cause determined. On examination the patient appeared well, pulse 50 and regular, BP 110/62mmHg. Precordial examination revealed a forceful apical impulse and an ejection systolic murmur loudest in the aortic area. What is the most likely diagnosis?
- A. Hypertrophic obstructive cardiomyopathy
 - B. Aortic stenosis
 - C. Mitral regurgitation
 - D. Long QT syndrome
 - E. Dilated cardiomyopathy

Answer: A.

This patient presents with symptoms and signs of hypertrophic obstructive cardiomyopathy. Syncope is a common symptom and is caused either by left ventricular outflow tract obstruction during exercise, or by ventricular arrhythmia. The patient presents with typical cardiac syncope – a short prodrome, brief syncope and a rapid recovery. The family history of sudden death raises suspicion of an inherited cardiac condition. While aortic stenosis is a possibility, it is not likely in such a young patient and is rarely inherited. Hypertrophic cardiomyopathy is inherited with an autosomal dominant pattern and the murmur is caused by left ventricular outflow obstruction. Mitral regurgitation does cause a systolic murmur but it is usually pansystolic, and there is no association with syncope. Long QT syndrome can cause sudden death and is inherited, but is not associated with any structural abnormality or murmur. Dilated cardiomyopathy is sometimes inherited but does not commonly cause syncope or a murmur.

- 16.4. A 30-year-old woman presents with a 2-week history of fever and malaise, and develops sharp left-sided chest pain, worse on inspiration and on leaning forward. The pain radiates to her left shoulder. On examination pulse is 100 beats/min and regular, blood pressure 104/66mmHg. The jugular venous pulse is not elevated. The apex beat is not displaced and feels normal. First and second are both present, with a harsh to-and-fro sound audible in systole and diastole. An echocardiogram shows a small pericardial effusion and no other abnormality. The 12-lead ECG is shown in the figure.



Which of the following treatments is most appropriate?

- A. Oral ibuprofen, 400mg three times daily
- B. Oral prednisolone, initially 40mg daily and reducing dose over 2 weeks
- C. Pericardiocentesis
- D. Oral colchicine 500 µg twice daily for 3 months
- E. Percutaneous coronary intervention

Answer: D.

The diagnosis is acute pericarditis, probably of viral aetiology because of the prodromal symptoms. Examination reveals a pericardial rub, and the ECG shows widespread saddle-shaped ST segment elevation

without reciprocal ST segment depression. The most effective treatment for symptoms and to prevent recurrence is colchicine. Non-steroidal anti-inflammatory drugs such as ibuprofen may also help acute symptoms, but oral corticosteroids are not effective. Pericardiocentesis would only be indicated if there was a large pericardial effusion and compromise (hypotension, pulsus paradoxus, elevated jugular venous pulse, oliguria). Percutaneous coronary intervention is not appropriate as the pattern of ST segment elevation suggests pericarditis and not ST elevation myocardial infarction.