

The cardiovascular system in disease – diseases of the vessels

6



Objectives

You should be able to:

- Understand the pathological basis of arteriosclerosis and atherosclerosis.
- Define shock and list the main causes.
- Outline the risk factors for and complications of hypertension.
- Describe how lipids are transported and metabolized, and how this may be modified with drugs.
- Describe the main causes and types of aneurysms.
- Describe the various classifications of the vasculitides.
- Describe the common congenital abnormalities of the vessels.
- Outline the various benign and malignant lesions which affect the vessels.
- Recall the risk factors for varicose veins and deep venous thrombosis.
- Understand the causes of lymphoedema and lymphangitis and how they arise.

ARTERIOSCLEROSIS AND ATHEROSCLEROSIS

Definitions and concepts

Arteriosclerosis is a term used to describe hardening and thickening of arteries. This reduces their elastic properties.

Atherosclerosis is one of the processes that leads to arteriosclerosis, and is the main cause of both ischaemic heart disease (see p. 77) and peripheral vascular disease (see p. 108). It involves the formation of atheroma, an accumulation of lipid plaques, within the walls of a vessel.

Arteriosclerosis of small arteries and arterioles is termed arteriolosclerosis, and is predominantly caused by hypertension.

There are three main types of arteriosclerosis:

- Atherosclerosis.
- Arteriolosclerosis.
- Monckeberg's calcific medial sclerosis.

Consequences of arteriosclerosis

Arteriosclerosis results in a reduced arterial lumen with a consequent reduction in end-organ perfusion. Furthermore, due to the loss of elasticity, rupture is more likely. There is also a predisposition to thrombus formation.

Atherosclerosis

It has been said that every adult in the Western world has some degree of atheroma in their arteries. Atherosclerosis and its complications are the main cause of mortality (over 50%) in the Western world.

Risk factors

Risk factors for atherosclerosis include constitutional factors such as:

- Age. Increased age increases the number and severity of lesions.
- Male sex. Men are affected to a much greater extent than women, until the menopause when the incidence in women increases, but men continue to be predominantly affected.
- Genetic predisposition.

Strong risk factors for atherosclerosis are:

- Smoking.
- Hypertension.
- Diabetes mellitus (see below).
- Hyperlipidaemia. It is directly related to levels of cholesterol and LDL. HDL levels are protective.

Other factors involved in the development of atherosclerosis are:

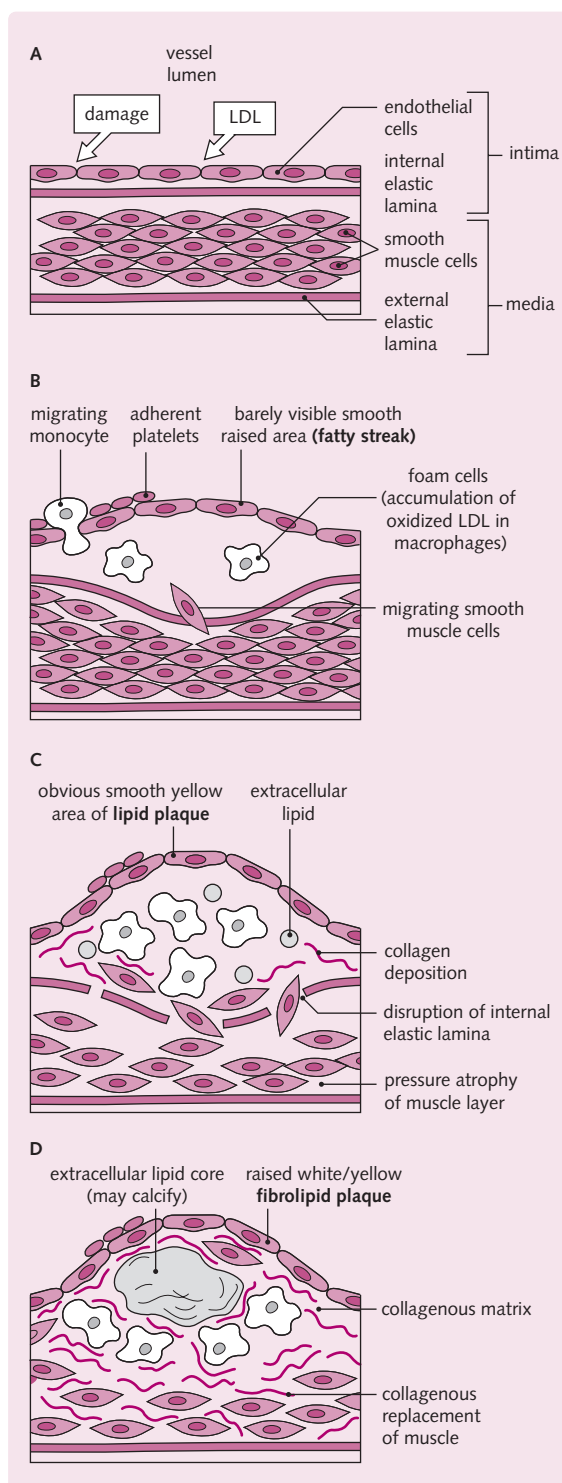
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Fig. 6.1 Stages in the formation of an atheromatous plaque. (A) Damage to the endothelium. Chronic or repeated endothelial cell (EC) injury occurs, leading to metabolic dysfunction and structural changes. EC have a major role in actively preventing thrombus formation. Damage activates EC, upregulating inflammatory adhesion molecules (e.g. ICAM-1) and promoting monocyte and platelet adhesion. Injury also increases permeability to lipids and low-density lipoprotein (LDL), allowing movement into the intima. (B) Formation of a fatty streak. Monocytes adhere to the endothelium, migrate into the intima and become macrophages. There, they take up the LDL and become foam cells as they cannot degrade lipids. Local oxidation of LDL aids uptake by, and is chemotactic for, macrophages. Platelets adhere to activated endothelial cells or areas of denuded matrix. Activated platelets, activated EC and macrophages release platelet-derived growth factor (PDGF) and induce smooth muscle migration into the intima. (C) Development of lipid plaque. Smooth muscle proliferation and an increase in extracellular matrix occur in the intima. Smooth muscle cells also take up LDL and form foam cells. Greater macrophage infiltration takes place. Lipid may also be released free into the intima. Macrophages contribute many other factors (e.g. superoxide, proteases) that increase the damage. (D) Complicated plaques. As the lesion develops, pressure causes the media to atrophy and the muscle to be replaced by collagen. A fibrous cap of collagen forms on top. There is increased free lipid in the intima. The endothelium becomes fragile and ulcerates, leading to further platelet aggregation and thrombus formation.

- Exercise – decreases the incidence of coronary heart disease; however, whether it prevents atheroma formation is unclear.
- Obesity – increases mortality, but this may only be a reflection of diet and lipid profile.
- Diet – decreased saturated fat intake has a beneficial effect, as may antioxidants (e.g. vitamin E in red wine).
- Stress and personality – certain highly stressed and type A personalities (anxious, moody and prone to worry) may have an increased tendency to atherosclerosis and coronary heart disease.

Pathogenesis

Atherosclerosis generally affects medium to large arteries. It is characterized by lipid deposition in the intima, with smooth muscle and matrix proliferation combining to produce a fibrous plaque that protrudes into the lumen (Fig. 6.1). The lesions tend to be focal, patchy, and not involve the whole circumference of the vessel.



Other theories of pathogenesis include:

- Prostaglandins. The balance between prostacyclin and thromboxane has an influence on thrombus formation and, because fibrin and platelets are important components of atheromatous lesions, this must have a strong influence on pathogenesis.
- Thrombosis is the primary event that builds up in layers and organizes to form atheromatous plaques.
- Neoplasia. An abnormal proliferation of smooth muscle occurs, caused by some as yet unidentified factor that produces uncontrolled growth.

Atherosclerosis is primarily an inflammatory process, and it is asymptomatic until it produces:

- Narrowing of the lumen – sufficient narrowing of the vessel produces symptoms of ischaemia (e.g. intermittent claudication, angina or gangrene).
- Sudden occlusion – caused by plaque rupture followed by thrombosis (e.g. in myocardial infarction).
- Emboli – these may impact in other vessels (e.g. stroke).
- Aneurysms – resulting from wall weakening.

Atheroma is a disease of the intima.



Treatment

The majority of research has looked at ways of reducing ischaemic heart disease by treating risk factors; it is not known what effect this has on the progress of atherosclerosis, but indirectly the following treatments have been used:

- Dietary control (reduced fat and sugar intake; increased amounts of fresh fruit and vegetables).
- Regular exercise and change in life-style (decrease stress).
- Stopping smoking.
- Cholesterol-lowering drugs (e.g. statins).
- Adequate blood pressure control.
- Optimal control of diabetes.

- Anti-platelet agents (e.g. aspirin and clopidogrel).

Monckeberg's medial calcific sclerosis

This is an idiopathic, degenerative disease of the elderly (aged over 50 years) characterized by focal calcifications in the media of small- and medium-sized arteries.

The femoral, tibial, radial and ulnar arteries are predominantly involved. There is little or no inflammation, and usually the calcifications do not cause either obstructions or symptoms. There is an increase in pulse pressure (isolated systolic hypertension) caused by loss of elasticity in the arteries.

Effects of diabetes mellitus on vessels

Diabetes mellitus causes a range of serious vascular complications, the severity of which is directly related to blood glucose levels. Intensive control of blood glucose (monitored long term by levels of glycosylated haemoglobin, HbA_{1c}), and treatment with ACE inhibitors can minimize these risks. Complications include:

- Microangiopathy.
- Hyaline arteriosclerosis.
- Atherosclerosis.

Type I diabetes is predominantly associated with small vessel disease (e.g. retinopathy, nephropathy, neuropathy), while type II predominantly causes large vessel disease (e.g. ischaemic heart disease and peripheral vascular disease).

Microangiopathy

Microangiopathy is diffuse thickening of the basement membranes of capillaries; paradoxically, however, they become more permeable, especially to plasma proteins. This results in specific organ damage:

- Nephropathy – glomerular involvement leads to microalbuminuria and can progress to renal failure.
- Retinopathy – degenerative changes include maculopathy and cataracts.
- Neuropathy – peripheral nerves, especially those in the lower leg, are most susceptible.

These phenomena are related to hyperglycaemia and the formation of advanced glycosylation end products.

Hyaline arteriosclerosis

Hyaline arteriosclerosis is more prevalent and more severe in patients with diabetes mellitus.

Atherosclerosis

Atherosclerosis begins early during the onset of diabetes mellitus. Complicated plaques become more numerous and severe. Contributing factors include:

- Associated hyperlipidaemia and decreased HDL.
- Glycosylation of LDL and its cross-linking with collagen.
- Increased platelet adhesion caused by obesity and hypertension.

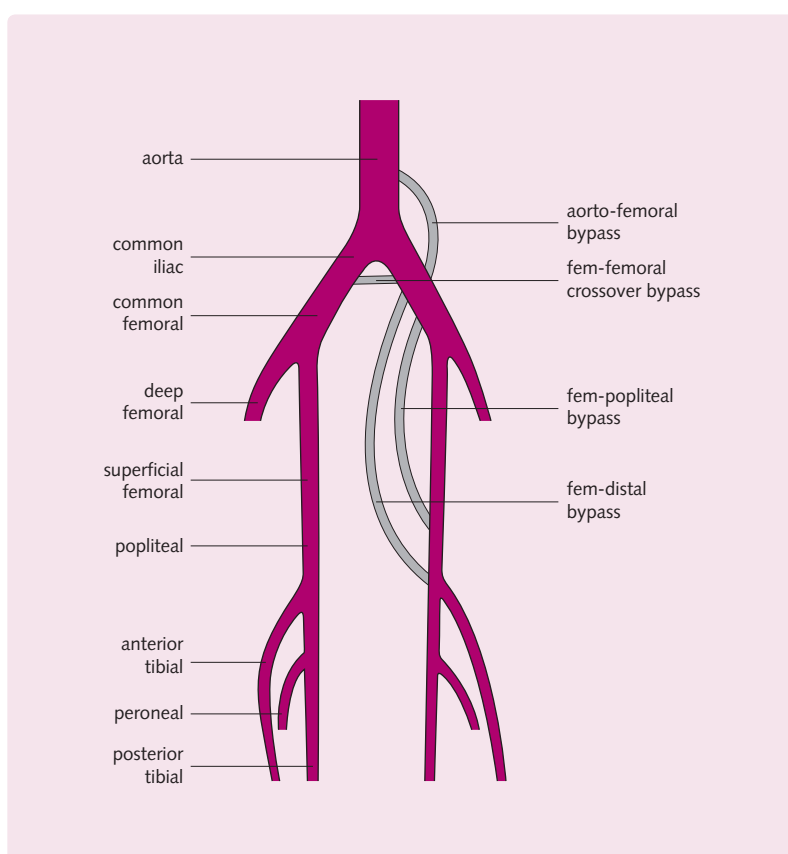
Peripheral vascular disease

Atherosclerosis and diabetes related vessel damage may commonly occur in the lower limbs. The superficial femoral artery is most commonly targeted, although the aorta, iliac and common femoral arteries may also be involved.

The most common presentation is with intermittent claudication, i.e. pain brought on by walking as the muscles become ischaemic which is relieved by rest. Treatment at this stage involves modification of cardiovascular risk factors, smoking cessation being paramount. Continuing to exercise through the pain will help to develop a collateral circulation, improving blood supply to the lower limb, and should be encouraged.

Should the ischaemia worsen, ulceration and gangrene may occur (see p. 161). Critical ischaemia, i.e. pain at rest, should be treated either with a surgical bypass procedure (Fig. 6.2), or angioplasty. If the ischaemia is so severe that the limb becomes

Fig. 6.2 Bypass procedures in peripheral vascular disease.



necrotic and non-viable, amputation should be performed.

Peripheral vascular disease is very common in diabetics and smokers. It is important to establish the claudication distance, i.e. how far the patient can walk before onset of pain. This helps determine whether the management should be conservative or surgical. 'Stop smoking, start walking' is a good starting point for treatment.

SHOCK AND HAEMORRHAGE

Shock

Definition

Shock is an acute failure of the cardiovascular system to adequately perfuse the tissues of the body. There are four major shock categories depending upon the causative factor:

- Hypovolaemic shock.
- Distributive shock.
- Cardiogenic shock.
- Obstructive shock.

Symptoms

The symptoms of shock are:

- Faintness, light-headedness, dizziness.
- Sweating, pallor.
- Reduced level of consciousness.

Signs

The classical signs of shock are:

- Pale, cold, clammy skin caused by cutaneous vasoconstriction in an effort to conserve blood flow to the vital organs and sweating caused by sympathetic stimulation.
- Rapid, weak pulse caused by tachycardia and decreased stroke volume.
- Reduced pulse pressure.
- Rapid, shallow breathing.
- Impaired urine output.
- Muscular weakness.
- Confusion or reduced awareness.

Hypovolaemic shock

This results from a fall in circulating blood volume caused by either:

- External fluid loss (e.g. vomiting, diarrhoea, haemorrhage).
- Internal fluid loss (e.g. pancreatitis, severe burns, internal bleeding).

Distributive shock

This is not due to a loss of fluid, but maldistribution of fluid as it leaves the intravascular compartment. The two main causes are:

- Sepsis.
- Anaphylaxis.

Septic shock

Septic shock is caused by toxins (e.g. endotoxin) released from bacteria during infection. The patient may have warm skin, but will have a low blood pressure due to inappropriate vasodilatation. Treatment is with fluid replacement, antibiotics and if severe can include noradrenaline and vasoconstrictors. Artificial ventilation is sometimes required for lung involvement if ARDS (adult respiratory distress syndrome) develops.

Anaphylactic shock

This is a type I hypersensitivity reaction, which is an immediate IgE-mediated immune response to an antigen in the body to which the patient is allergic. It leads to circulatory collapse, dyspnoea, and even death.

The IgE immune response consists of the activation of basophils and mast cells (basophils are mobile in the blood, mast cells are fixed in tissue). The degranulation of these cells leads to release of histamine and other factors. Prostaglandins, leukotrienes, thromboxane, and platelet activation factors are also synthesized and released. The results are as follows:

- Generalized peripheral vasodilatation, which leads to hypotension.
- Increased vascular permeability reducing plasma volume.
- Bronchial smooth muscle constriction, which leads to dyspnoea.
- Oral, laryngeal, and pharyngeal oedema.
- Urticaria and flushing.

Death may result from the circulatory collapse.

Treatment consists of immediate intramuscular adrenaline, anti-histamine (e.g. chlorpheniramine) and an infusion of hydrocortisone (a glucocorticoid).

An anaphylactoid reaction produces a similar picture to that described above, but it is caused by the direct effects of a substance on mast cells and basophils (i.e. it is not mediated by IgE). This sometimes occurs with radio-opaque contrast media.

Anaphylaxis may occur with anaesthetic gases and antibiotics. The initial treatment is Airway, Breathing, Circulation. Oxygen; fluids and adrenaline should be given immediately. Steroids and antihistamines should be given shortly after. The patient should be referred to an immunologist, and carry an alert bracelet if appropriate.

Cardiogenic shock

This is caused by an interruption of cardiac function such that the heart is unable to maintain the circulation, i.e. pump failure. It usually has an acute onset, but it may be a result of worsening heart failure. Causes include:

- Myocardial infarction.
- Arrhythmia.
- Myocarditis.

Valve failure, caused by infective endocarditis or mitral valve prolapse for example, may also result in shock.

Obstructive shock

In obstructive shock there is a direct obstruction to blood leaving the heart or great vessels, for example:

- Cardiac tamponade.
- Pulmonary embolism.
- Tension pneumothorax.

Haemorrhage

A 10% blood loss produces no change in blood pressure. A 20–30% blood loss may cause shock, but it is not usually life threatening. A 30–40% blood loss produces severe or irreversible shock

(50–70 mmHg fall in blood pressure). Respiratory rate is a much more sensitive indicator of blood loss than pulse rate or blood pressure, as Fig. 6.3 shows. Hypotension is an indirect result of blood loss. It is caused by a decreased blood volume, reducing venous return to the heart. A reduced end-diastolic volume reduces the strength of contraction and, therefore, stroke volume.

The body responds in different ways to rectify the loss of pressure and volume. The response is often subdivided into:

- An immediate response occurring within seconds (Fig. 6.4).
- An intermediate response occurring within minutes or hours (Fig. 6.5).
- A long-term response occurring within days or weeks (Fig. 6.6).

Treatment is to prevent further blood loss and volume expansion with intravenous fluids. Haemorrhage differs from other causes of hypovolaemia however as red cells, clotting factors and other components of plasma are also lost.

HYPERTENSION

Current World Health Organization (WHO) recommendations define hypertension as a resting blood pressure above 140 mmHg systolic and/or 90 mmHg diastolic in those under 50 years, and 160 mmHg systolic and/or 95 mmHg diastolic in older patients, although these criteria are somewhat arbitrary. Cardiovascular disease risks increase with blood pressure even within the normal range. Using the WHO criteria, up to 25% of the population may have hypertension.

Classification

Hypertension is classified according to both underlying cause and clinical progression. Primary (essential) hypertension accounts for 90% of hypertensive patients; the precise aetiology is unknown, but it is probably multifactorial. Predisposing factors include:

- Age (blood pressure rises with age).
- Obesity.
- Excessive alcohol intake.
- High salt intake.
- Genetic susceptibility.

Adaptations to acute haemorrhage				
Parameter	Class I	Class II	Class III	Class IV
Blood loss (%)	0–15	15–30	30–40	>40
Blood loss (mL)	0–750	750–1500	1500–2000	>2000
Pulse rate	↔	↑	↑	↑↑
Respiratory rate	↔	↑	↑↑	↑↑
Capillary refill time	↔	↔	↑	↑↑
Blood pressure	↔	↔	Narrowing of pulse pressure	↓

Fig. 6.3 Physiological adaptations to acute haemorrhage.

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Fig. 6.4 Immediate response to haemorrhage (ADH, antidiuretic hormone; BP, blood pressure; CO, cardiac output; HR, heart rate; SV, stroke volume; TPR, total peripheral resistance).

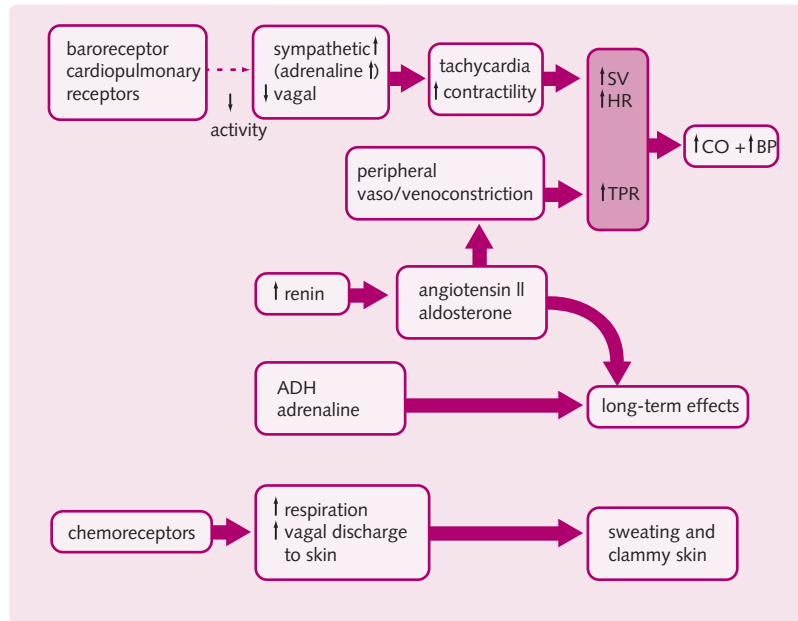


Fig. 6.5 Intermediate response to haemorrhage.

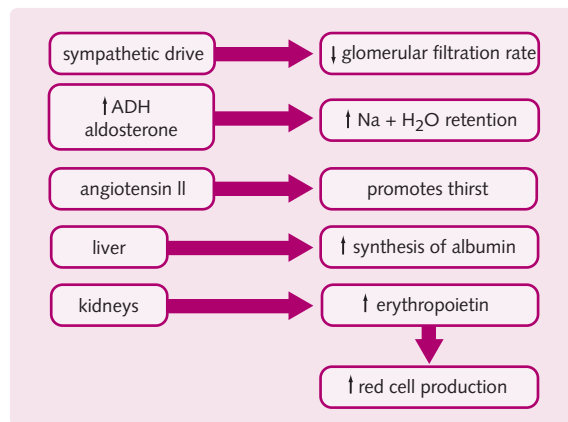
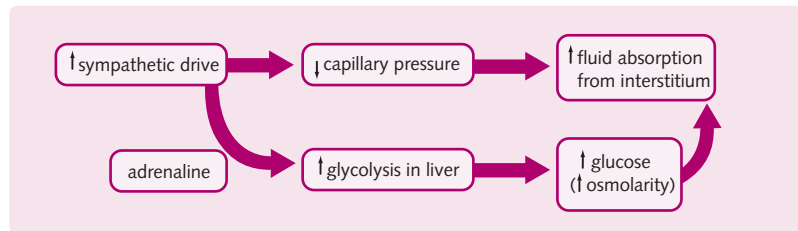


Fig. 6.6 Long-term response to haemorrhage (ADH, antidiuretic hormone).

Smoking increases cardiovascular risk in hypertensive patients. Secondary hypertension accounts for the remaining 10% of cases. Here, the hypertension arises as a result of other disease processes (see Fig. 6.7)

The clinical progression of hypertension can be classified as benign or malignant. Benign hypertension is a stable elevation of blood pressure over a period of many years (usually recognized in patients aged over 40 years). Malignant (accelerated) hypertension is an acute, severe elevation of blood pressure.

Secondary causes of hypertension				
Physiological	Renal	Drugs	Endocrine	Anatomical
Pregnancy	Renal parochymal disease Renovascular disorders Renal artery stenosis	Oral contraceptives Steroids NSAIDs	Acromegaly Cushings Conn's syndrome Pheochromocytoma Carcinoid Congenital adrenal hyperplasia	Coarctation of aorta Aortitis

Fig. 6.7 Secondary causes of hypertension (NSAIDs, non-steroidal anti-inflammatory drugs).

The distinction between primary and secondary hypertension is of great clinical significance, since only in the latter case is treatment of the underlying cause possible.



Complications

Hypertension is a major risk factor for:

- Atherosclerosis.
- Cerebrovascular disease.
- Aortic aneurysm.
- Cardiac failure (which is the cause of death in one-third of patients).
- Atrial fibrillation.
- Renal failure.
- Visual disturbance (caused by papilloedema and retinal haemorrhages).

Note that initially hypertension is usually asymptomatic, and in essential hypertension no obvious cause can be found. This can affect compliance with therapy, especially if drugs have too many side effects.

Hypertensive vascular disease

Hypertension not only accelerates atherosclerosis, but it also results in characteristic changes to arterioles and small arteries – arteriolosclerosis. All these changes are associated with narrowing of the vessel lumen. Changes in benign hypertension include:

- In arteries – muscular hypertrophy of the media, reduplication of the external lamina, and intimal thickening.
- In arterioles – hyaline arteriosclerosis (protein deposits in wall).
- In vessels of the brain – microaneurysms (Charcot–Bouchard aneurysms) can occur.

Other changes are associated with, but not restricted to, malignant hypertension. Hyperplastic arteriosclerosis, with reduplication of basement membrane and muscular hypertrophy solely within the intima, can occur in arteries and arterioles.

When these changes are associated with fibrin deposition (also known as fibrinoid changes) and necrosis of the vessel wall, the condition is known

as necrotizing arteriolitis. These changes frequently affect the renal arterioles to produce nephrosclerosis, which may impair renal function or exacerbate hypertension through the renin–angiotensin system.

Hypertensive heart disease

Systemic (left-sided) hypertensive heart disease

Criteria for diagnosis of systemic hypertensive heart disease are:

- History of hypertension ($>140/90$ mmHg).
- Left ventricular hypertrophy (wall thickness measuring >15 mm, weight >500 g, or ECG changes).
- Absence of any other causes of hypertrophy.

In hypertensive heart disease, changes that are initially adaptive lead to cardiac dilatation, congestive heart failure, and even sudden death. The heart adapts with hypertrophy of the left ventricular wall, initially without any change in ventricular volume. Histologically this is characterized by enlargement of the myocytes and their nuclei (hypertrophy). In the long term, interstitial fibrosis and myocyte atrophy occur, causing ventricular dilatation.

Pulmonary hypertensive heart disease (cor pulmonale)

Pulmonary hypertensive heart disease can be defined as right ventricular hypertrophy (wall thickness measuring >4 mm) as a result of hypertension in the pulmonary circulation caused by a primary lung pathology.

Pulmonary hypertension can be classified as:

- Right ventricular hypertrophy and failure (also known as chronic pulmonary hypertension or cor pulmonale).
- Acute pulmonary hypertension (a sudden onset usually after a large pulmonary embolism).

Right ventricular hypertrophy and failure is a chronic disease of right ventricular pressure load (e.g. pulmonary vasoconstriction in hypoxia caused by high altitude or in chronic obstructive airways disease). Right ventricular dilatation may cause tricuspid regurgitation.

Pulmonary artery hypertension may be caused by heart disease (left ventricular failure, mitral valve disease, cardiac shunts) or lung disease (primary pulmonary hypertension, interstitial fibrosis, pulmonary emboli).

Antihypertensive drugs

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors (e.g. captopril, enalapril, perindopril) inhibit the conversion of angiotensin I to angiotensin II by ACE (Fig. 6.8). They also inhibit bradykinin (a vasodilator) breakdown by ACE. They are now becoming a first-line treatment, but they should not be used to treat patients with severe renal artery stenosis as this predisposes to flash pulmonary oedema, renal ischaemia and subsequent failure.

The side effects are:

- First-dose hypotension.
- Skin rash.
- Coughing.
- Renal impairment.

There are a number of once-a-day preparations (e.g. lisinopril and ramipril) which have a lower incidence of first-dose hypotension.

Angiotensin II receptor antagonists

Angiotensin II receptor antagonists (e.g. losartan) inhibit the angiotensin II receptor and prevent the action of angiotensin II (Fig. 6.8). They are useful when ACE inhibitors have produced an intolerable cough (possibly caused by elevated bradykinin).

Diuretics

Usually a thiazide-type diuretic is used (e.g. bendrofluzide). These drugs inhibit sodium reabsorption in the distal renal tubule, which causes increased salt and water excretion, decreasing blood volume and decreasing blood pressure. Side effects in high doses are:

- Hypokalaemia (low K^+) leading to arrhythmia and muscle fatigue.
- Hyperuricaemia (high uric acid) causing gout.
- Hyperglycaemia (raised blood glucose).
- Increased low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) leading to atherosclerosis.

Other diuretics may also occasionally be used, see p. 85.

Beta-blockers

Beta-blockers are antagonists of β -adrenoceptors. They block sympathetic activity in the heart (β_1), peripheral vasculature (β_2), and other tissues including the bronchi (β_2).

In the heart, this results in a decrease in heart rate and myocardial contractility. Renin release from the juxtaglomerular cells is reduced and there is a central action, reducing sympathetic drive. These effects combine to lower blood pressure, but only in hypertensive patients.

The effect of β -blockers on the peripheral vasculature leads to a loss of β -mediated vasodilatation causing an unopposed α -vasoconstriction. This may initially cause an increase in vascular resistance, elevating blood pressure, but, in long-term use, the vascular resistance returns to pretreatment levels. However, peripheral blood flow may still be reduced, leading patients to complain of cold extremities.

Some β -blockers can preferentially act on β_1 -adrenoceptors, being more cardioselective; however, even these drugs have some blocking effect on the β_2 -adrenoceptor, and they should be given to asthmatic patients with extreme caution.

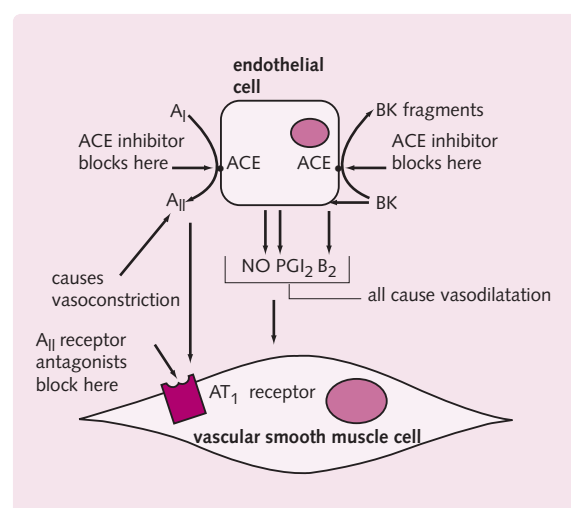


Fig. 6.8 Action of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (A_{II}) receptor antagonists (A_I , angiotensin I; A_{II} , angiotensin II; AT_1 , angiotensin II receptor type 1; B_2 , activated bradykinin-activated by endothelial cell; BK, bradykinin; NO, nitric oxide; PGI_2 , prostacyclin).

Types of β -blockers include:

- Propranolol, atenolol (act on β_1 , β_2).
- Metoprolol, bisoprolol (selective β_1 -blockers).

The main side effects of β -blockers are:

- Bronchoconstriction, leading to worsening asthma or chronic obstructive airways disease.
- Bradycardia.
- Hypoglycaemia.
- Fatigue and lethargy.
- Impotence.
- Sleep disturbance, nightmares, and vivid dreams (particularly propranolol).
- Rebound hypertension if stopped suddenly.

Alpha-blockers

Alpha-blockers (e.g. prazosin and doxazosin) are antagonists of α -adrenoceptors. There is postsynaptic block of α_1 -adrenoceptors, which prevents sympathetic tonic drive and leads to vasodilatation. Therefore, there is a decrease in total peripheral resistance and thus a decrease in blood pressure. Doxazosin is often used for labile (catecholamine-mediated) hypertension.

Side effects of α -blockers are:

- Postural hypotension caused by loss of sympathetic vasoconstriction.
- First-dose phenomenon of rapid hypotension when initially administered.

Other sympatholytics

Adrenergic neuron blockers (e.g. guanethidine) prevent the release of noradrenaline from postganglionic neurons. They are rarely used now because they affect supine blood pressure control, and they may cause postural hypotension. They may be useful with other therapy in resistant hypertension.

Centrally acting α_2 -agonists (e.g. methyldopa) decrease central sympathetic drive by displacing noradrenaline with a false transmitter (e.g. methylnoradrenaline from methyldopa). Release of the false transmitter is more active on α_2 pre-synaptic negative feedback receptors than on α_1 , reducing transmitter release and ultimately blood pressure. They are used to treat hypertension in pregnancy because more modern drugs have never been tested in pregnancy.

Calcium antagonists

Calcium antagonists (e.g. verapamil, nifedipine, amlodipine, diltiazem) block voltage-gated calcium channels in myocardium and vascular smooth muscle. This causes a decrease in myocardial contractility, electrical conductance and vascular tone.

Calcium antagonists interfere with the action of various vasoconstrictor agonists (e.g. noradrenaline, angiotensin II, thrombin). All may precipitate heart failure (but this risk is reduced with nifedipine and nifedipine-like drugs, e.g. amlodipine).

Verapamil and diltiazem decrease heart rate by causing an inhibition of conduction through the AV node. They should be used only very cautiously with β -blockers as this may lead to heart block. The main side effect of these drugs is constipation.

Nifedipine and amlodipine relax vascular smooth muscle, dilating arteries. The main side effects are headache and ankle oedema.

Diltiazem also decreases vascular tone, hence its use as an anti-anginal. Its main side effect is bradycardia.

Potassium channel agonists

Potassium channel agonists (e.g. nicorandil) open ATP-dependent K^+ channels. Opening of K^+ channels hyperpolarizes vascular smooth muscle cells, thereby making depolarization harder to achieve. This reduces the stimulation by vasoconstricting agonists on the muscle cells.

Potassium channel agonists are used only in severe hypertension when other methods have failed (diazoxide is used in hypertensive emergencies). They are usually used with a β -blocker and thiazide diuretic to counteract side effects.

Side effects of potassium channel agonists are:

- Increased hair growth (with minoxidil).
- Salt and water retention, leading to oedema (use thiazide).
- Reflex sympathetic activation causing tachycardia (use β -blocker).

Combinations

ACE inhibitors are being used increasingly as a first-line treatment for hypertension as they carry a reduced risk of side effects. They can be combined with thiazide treatment, but caution should be used

with existing diuretic treatment due to the risk of a collapse in blood pressure in volume depleted patients. β -Blockers have traditionally been used with a thiazide if a thiazide has not been effective alone.

After these options have failed or are contraindicated, calcium antagonists should be tried. Diuretics may be used in addition, but verapamil should not be combined with β -blockers.

In severe hypertension where the above therapies have been tried or are contraindicated, then the vasodilators, α -blockers, and centrally acting drugs may be used. They may be used in conjunction with an ACE inhibitor, or a thiazide and a β -blocker, although doxazosin is being used more frequently in preference to diuretics and β -blockers because of its vasodilator effect and minimal side effects.

LIPIDS AND THE CARDIOVASCULAR SYSTEM

Lipid transport and metabolism

The insolubility of lipids in plasma means a special transport mechanism is required. This is provided by lipid-protein complexes known as lipoproteins, while the individual proteins are known as apolipoproteins. The apolipoproteins also act as receptors for cell surface proteins, which determine the destination of different lipoproteins. Low-density lipoprotein (LDL) is the main lipoprotein involved in the transport of cholesterol. Fig. 6.9 shows the main transport pathways for lipids from the diet (exogenous) and for lipids from the body's stores (endogenous).

It is thought that lipoprotein A is a prothrombotic lipoprotein that is particularly involved in coronary disease, while high levels of high-density lipoprotein (HDL) are protective. The classification of lipoproteins is outlined in Fig. 6.10.

Hyperlipidaemia

Hyperlipidaemia (Fig. 6.11) can be classified as hypertriglyceridaemia (raised triglycerides – also called triacylglycerides), hypercholesterolaemia (raised cholesterol), or hyperlipoproteinaemia (raised lipoproteins).

Effects of hyperlipidaemia

Atherosclerosis

There is a strong correlation between cholesterol levels and death rates from ischaemic vascular disease. There is an even stronger correlation between fibrinogen levels and ischaemic vascular disease. It must, therefore, be remembered that atherosclerosis is a multifactorial disease.

It is thought that LDL damages the arterial wall by producing oxygen radicals, or exacerbates wall injury from other causes. Atheromatous plaques may develop in this damaged arterial wall. HDL however is protective against atherosclerosis.

Acute pancreatitis

Acute pancreatitis can result from hypertriglyceridaemia.

Subcutaneous deposits

Subcutaneous deposits of lipids are often painful, and can be found in the skin usually around the eyes (xanthelasma) and in tendons (tendon xanthomas). They are usually diagnostic of hyperlipidaemia.

Treatment of hyperlipidaemia

Hyperlipidaemia can be treated by diet or drugs.

Dietary treatment involves reduction of calorific intake, saturated fats, cholesterol, and alcohol; supplements of omega-3 fats (present in fish oils) are given, increasing HDL levels, which is beneficial.

Indications for drug therapy are:

- High LDL levels, which must be treated if arterial disease is present.
- High triglycerides, which need to be treated only if symptomatic (e.g. causing xanthomas or pancreatitis).
- Low HDL levels.

Drugs used to lower cholesterol

Statins (e.g. simvastatin, atorvastatin)

Statins are β -hydroxy- β -methylglutaryl coenzyme A (HMG CoA) reductase inhibitors. The liver compensates for the decreased cholesterol synthesis by increasing LDL receptors, which decreases plasma levels of LDL-cholesterol. They are used to treat most hypercholesterolaemias, and they are very

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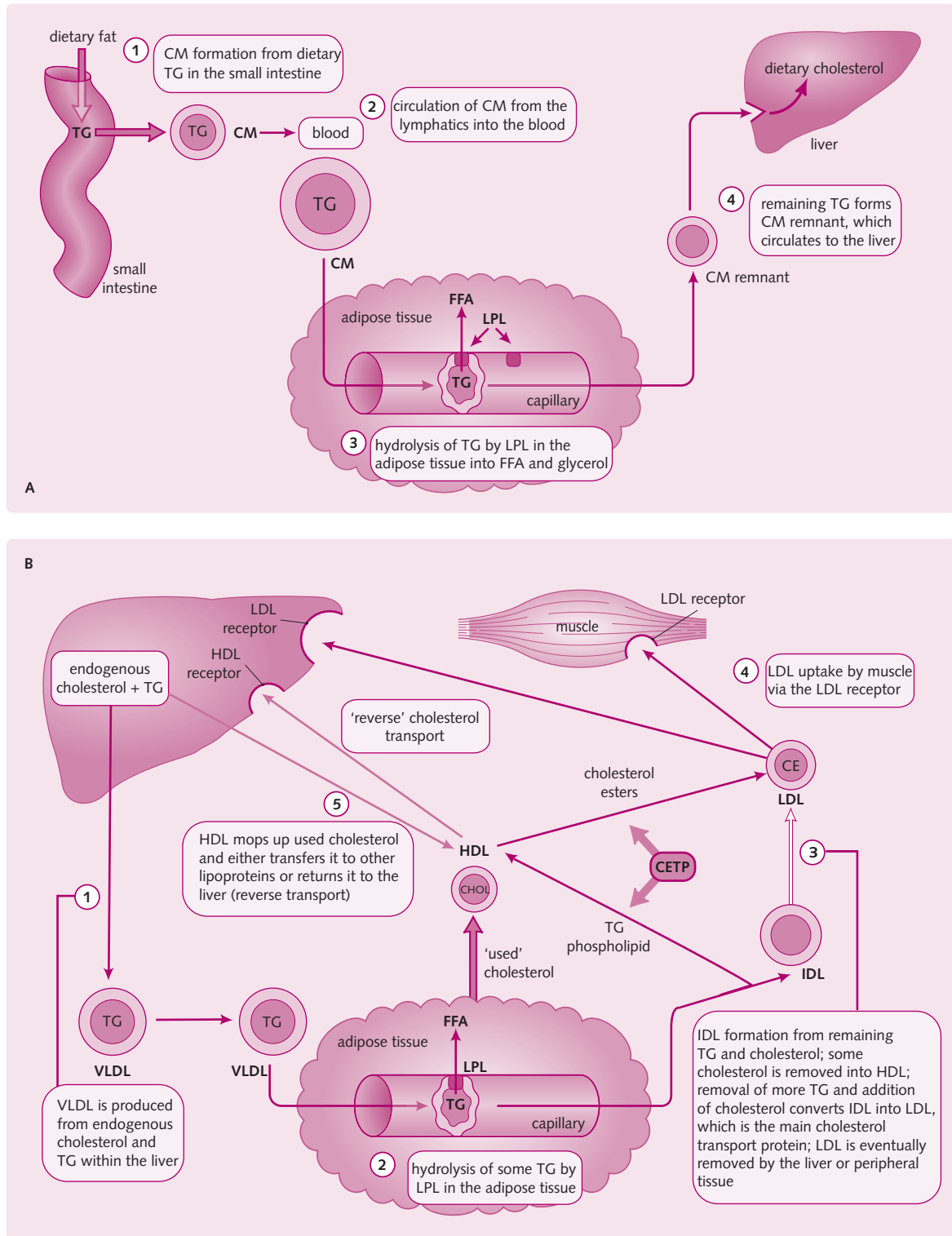


Fig. 6.9 (A) Exogenous and (B) endogenous lipid transport pathways (CE, cholesterol esters; CETP, cholesterol ester transfer protein; CM, chylomicron; FFA, free fatty acid; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; TG, triacylglycerol; VLDL, very low-density lipoprotein).

Classification of lipoproteins		
Particle	Source	Predominantly transports
Chylomicron (CM)	Gut	Triacylglycerol
Very low-density lipoprotein (VLDL)	Liver	Triacylglycerol
Intermediate-density lipoprotein (IDL)	Catabolism	Cholesterol
Low-density lipoprotein (LDL)	Catabolism	Cholesterol
High-density lipoprotein (HDL)	Catabolism	Cholesterol
Lipoprotein A	Liver, gut	—

Fig. 6.10 Classification of lipoproteins.

effective if used in conjunction with a resin (up to 50% reduction in cholesterol levels). They are currently the only lipid-lowering treatment for which there is good evidence for reduced mortality.

The main side effects include reversible myositis and disturbed liver function tests.

Hyperlipidaemias must be remembered as controllable causes of coronary heart disease, especially in young adults.



Bile acid binding resins (e.g. colestipol and cholestyramine)

Colestipol and cholestyramine inhibit reabsorption of cholesterol in the gut. They bind to bile salts in the gut and stop their reabsorption. This leads to increased excretion and decreased absorption of cholesterol. To compensate, the liver increases cholesterol conversion into bile salts and also increases LDL receptors. This removes LDL-cholesterol from circulation. They can aggravate hypertriglyceridaemia.

Ezetimibe

This is a novel, orally acting selective inhibitor of dietary and biliary absorption of cholesterol. It may

be used alone, or in combination with a statin to further lower cholesterol.

Probucol

Probucol causes a 10% reduction in LDL-cholesterol, but it also lowers HDL and remains in the body for months. It has some antioxidant activity, which may reduce atherosclerosis formation.

Drugs used to lower triglyceride levels

Nicotinic acid

Nicotinic acid inhibits VLDL synthesis by the liver, leading to a decrease in intermediate density lipoprotein (IDL) and LDL. It also increases lipoprotein lipase (LPL) activity.

Nicotinic acid can be used for most types of hyperlipidaemia, usually in conjunction with a resin (see above). Its main side effects are rashes, nausea, abnormal liver function, and a prostaglandin-mediated cutaneous reaction.

Fibrates

Gemfibrozil reduces lipolysis of triglycerides in adipose tissue, leading to decreased hepatic production of VLDL. Bezafibrate increases LPL activity, which leads to decreased VLDL and decreased triglycerides, but it may increase LDL.

Fibrates are used mainly in familial hyperlipidaemia. Gemfibrozil is the better drug as it does not increase LDL. The main side effects include nausea, abdominal discomfort and flu-like symptoms.

ANEURYSMS

Definitions and concepts

An aneurysm is an abnormal, focal, permanent dilatation of an artery or part of the heart (Fig. 6.12). It is caused by a weakening of the wall:

- A true aneurysm is surrounded by all three layers of the arterial wall.
- A false aneurysm occurs when there is an actual hole in all or part of the arterial wall, which causes blood to move extravascularly, producing a haematoma.
- A dissecting aneurysm occurs when the blood is contained between the internal layers of the arterial wall and progresses by splitting the muscular layers (Fig. 6.13).

Classification of hyperlipidaemias					
Condition	Elevated lipoprotein	Elevated lipid	Biochemical defect	Drug therapy	Prevalence
Single gene defect					
Familial lipoprotein lipase (LPL) deficiency (type I)	CMs	Triacylglyceride	Low or absent LPL activity	Diet alone	Rare
Familial hypercholesterolaemia (type IIa)	LDL	Cholesterol	Deficiency of LDL receptors (none in homozygotes)	Statin, resin	Common
Familial combined hyperlipidaemia (type IIb)	VLDL, LDL	Triacylglyceride, cholesterol	Overproduction of apo-B	Fibrate	Common
Familial hyperlipoproteinaemia (type III)	CM remnants, IDL	Triacylglyceride, cholesterol	Abnormal apo-E	Fibrate	Rare
Familial hypertriglyceridaemia (type IV)	VLDL	Triacylglyceride	Overproduction of VLDL by the liver	Fibrate	Common
Familial hypertriglyceridaemia (type V)	VLDL, CMs	Triacylglyceride, cholesterol	Overproduction of VLDL by the liver	Fibrate	Rare
Multifactorial					
Hypertriglyceridaemia	VLDL	Triacylglyceride	Unknown	Fibrate	Common
Hypercholesterolaemia	LDL	Cholesterol	Unknown	Statin, resin	Common

Fig. 6.11 Classification of hyperlipidaemias. Familial, heritable abnormalities of lipid metabolism are classified according to Fredrickson type (types I–V) on the underlying genetic mutations. Hyperlipidaemia may also be multifactorial or idiopathic, without a currently identified or discrete genetic basis. These are clinically the most common in older patients. (CM, chylomicron; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.)

Aneurysms are caused by:

- Atherosclerosis. Plaque formation causes medial destruction and wall thinning. This commonly occurs in the abdominal aorta.
- Cystic medial degeneration – mucinous degeneration of the media with fragmentation of the elastic tissue. This is often seen in dissecting aortic aneurysms.
- Syphilis.
- Trauma.
- Vasculitides (especially polyarteritis nodosa).
- Congenital defects (e.g. berry aneurysms).
- Infections (mycotic aneurysms).

Aneurysms are often described by their shape. They are either fusiform (spindle shaped, being tapered at either end) or saccular (sac-like).

Mycotic aneurysms are aneurysms caused by infection. Bacteria within septic emboli that lodge in arteries may cause destruction of the arterial wall.

Turbulence of blood within an aneurysm frequently leads to the formation of a thrombus, increasing the risk of rupture.

Abdominal aortic aneurysm

The prevalence of abdominal aortic aneurysms is 3% in men aged over 50 years.

The aneurysm is usually found proximal to the iliac bifurcation of the abdominal aorta. The patient may be asymptomatic or have abdominal/back pain if there is compression of retroperitoneal structures.

Leaking and rupture with resultant haemorrhage is the most serious complication; the patient may present acutely shocked. Fistulae into the gut or vena cava may rarely occur.

Hypertension increases the risk of rupture, which occurs in approximately 30% of patients. The risk of rupture increases with the size of the aneurysm, hence all those >5 cm are considered suitable for surgery.

Surgery aims to prevent rupture. Elective surgery has an operative mortality of 5%, rising to 50% if the aneurysm ruptures. Treatment aims to replace the aneurysm with a synthetic graft, and is increasingly performed as an endovascular procedure in contrast to the conventional open repair.

Postoperative complications include myocardial infarction and renal failure.

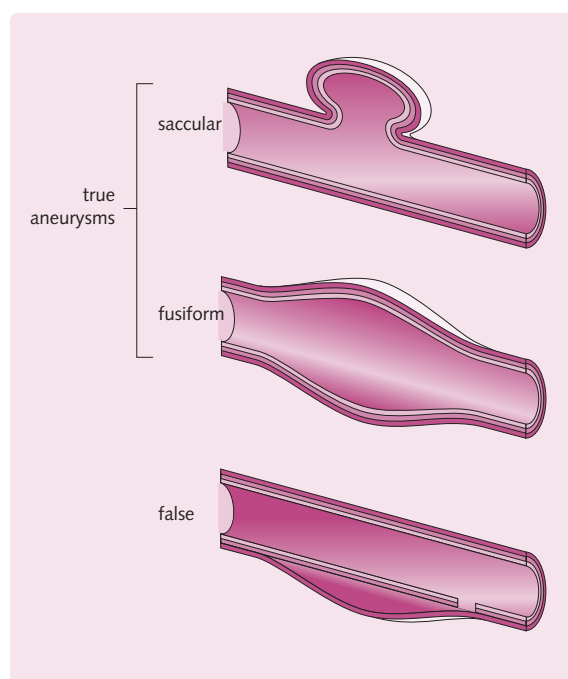


Fig. 6.12 Types of aneurysm: saccular, fusiform, and false.

Abdominal aortic aneurysm is very common, especially in hypertensive male smokers. Treatment is initially conservative by monitoring of the aneurysm with ultrasound. Surgery, either open or endovascular repair, should only be considered when the risk of the aneurysm rupturing exceeds the risks of surgery. This is thought to be at a size >5 cm.

Syphilitic (luetic) aneurysm

Syphilitic (luetic) aneurysms can occur in the thoracic aorta of patients with tertiary syphilis.

There is inflammation of the adventitia, especially the vasa vasorum (endarteritis). This causes ischaemia and loss of muscle and elastic tissue, which leads to weakening of the arterial wall.

Microscopically the vasa vasorum have thickened walls, and they are surrounded by inflammatory cells. The aneurysm may extend backwards along the aorta to the aortic valve leading to valve regurgitation.

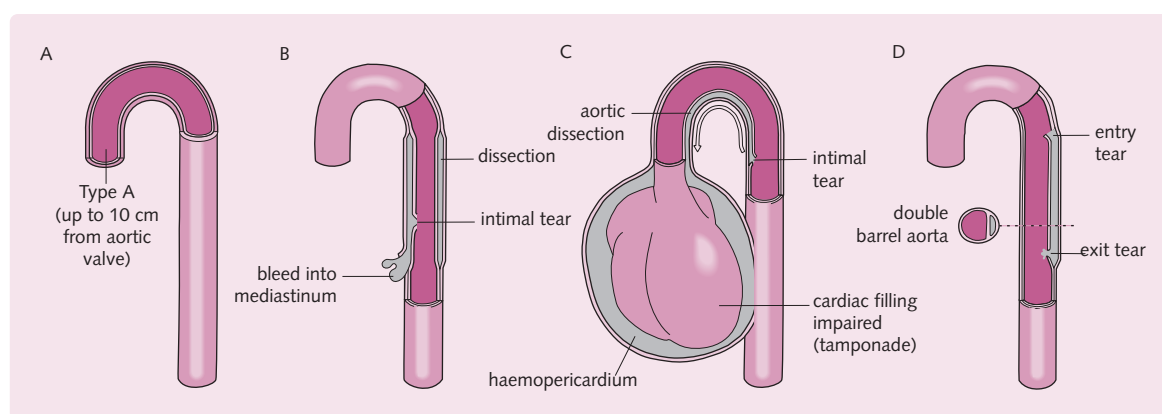


Fig. 6.13 Dissecting aortic aneurysm. (A) Type A and B dissections. Type A are within 10 cm of the aortic valve; type B are beyond this. (B) Rupture into the mediastinum. (C) Rupture into the pericardium. (D) Rupture into the aorta.

Sequelae include syphilitic heart disease, compression of adjacent structures, and rupture.

Aortic dissection

In this condition, blood in the aorta is dissected into two flows: one in the normal lumen and another in one of the layers of the media (Fig. 6.13). There are two main types:

- Stanford type A involves an intimal tear in the ascending aorta within 10 cm of the aortic valve. This aneurysm can be treated by surgical replacement of the aortic arch.
- Stanford type B involves the descending thoracic aorta. As surgery here is more complex, management is medical with careful reduction in blood pressure.

Aortic dissection is seen predominantly in men aged 40–60 years with systemic hypertension, particularly in Marfan syndrome where cystic medial degeneration occurs. It may also occur as a result of trauma, especially iatrogenic (e.g. during arterial cannulation).

Clinical features include sudden onset of severe chest pain radiating to the back and downwards. Sequelae of dissection include:

- Rupture into the thorax or abdomen.
- Occlusion of aortic branches, especially coronary, cerebral, and renal arteries.
- Extension along the aorta to include other arteries or disruption of the aortic valve.
- Cardiac tamponade caused by proximal extension and subsequent haemopericardium.

Other causes of aneurysms

Congenital causes

Berry aneurysms in the circle of Willis can be caused by focal weakness in the arterial wall of the cerebral vessels. In contrast to aortic aneurysms, they are saccular. Rupture of these occasionally occurs leading to subarachnoid haemorrhage.

Vasculitides

Two forms of vasculitis may cause aneurysm (see p. 119):

- Polyarteritis nodosa – aneurysms may form in any organ with vessels affected by the disease.

- Kawasaki syndrome – dilatation of the coronary arteries associated with arteritis is a complication of the disease.

Myocardial ischaemia

Myocardial ischaemia may lead to dilatation and aneurysm of the ventricle, which may later rupture. A similar aneurysm may also occur in Chagas' disease (trypanosomiasis).

INFLAMMATORY VASCULAR DISEASE

Concepts and classification

The vasculitides are a group of conditions characterized by vasculitis (inflammation and damage of the vessel walls), categorized in Fig. 6.14. They may be classified by pathogenesis (infective, immune-mediated, or idiopathic) or by the size of the vessel affected (large, medium, or small).

Most systemic vasculitides probably involve an immunological process. Many different processes have been described. There may be deposition of circulating antigen–antibody complexes in conditions such as systemic lupus erythematosus. Antibodies may react with fixed tissue antigens as in Kawasaki syndrome. Temporal arteritis involves delayed-type hypersensitivity reactions with granuloma formation.

Vessels affected by vasculitides		
Vessel size	Arteries	Disease
Large/ medium	Aorta Carotid Temporal	Giant cell arteritis, Takayasu's arteritis
Medium/ small	Coronary Mesenteric	Polyarteritis nodosa, Kawasaki disease
Small/ arteriole	Glomeruli and arterioles	Wegener's granulomatosis, microscopic polyarteritis nodosa
Arteriole/ capillary	—	Henoch–Schönlein purpura, cutaneous leucocytoclastic
Veins	—	Buerger's disease

Fig. 6.14 Vessels affected by vasculitides.

The presence of anti-neutrophilic cytoplasmic autoantibodies (ANCA), which react with antigens in the cytoplasm of neutrophils, can be seen in many vasculitides. The antigen may be perinuclear (p-ANCA) or cytoplasmic (c-ANCA).

Infectious vasculitides

The causes of infectious vasculitides may be:

- Bacterial (e.g. *Neisseria*).
- Viral (e.g. herpes).
- Other infectious causes such as *Rickettsia* (Rocky Mountain spotted fever), spirochaetes (syphilis), or fungi (*Aspergillus*).

Immunological vasculitides

The immunological vasculitides can be classified as:

- Immune complex – Henoch–Schönlein purpura, systemic lupus erythematosus.
- Direct antibody – Goodpasture's syndrome (anti-basement membrane antibodies), Kawasaki disease.
- ANCA associated – Wegener's granulomatosis, microscopic polyarteritis.
- Cell mediated – organ rejection.

Idiopathic vasculitides

Giant-cell (temporal) arteritis

Giant-cell arteritis is the most common of the vasculitides, occurring in the elderly and being rare in those younger than 55 years of age. There is focal granulomatous inflammation of medium and small arteries, especially the cranial vessels. It usually presents with headache and facial pain, or polymyalgia rheumatica (flu-like aches and fever). The erythrocyte sedimentation rate (ESR) and/or C reactive protein (CRP) are usually raised. Visual disturbances develop in about half affected individuals and may lead to blindness without prompt intervention. Diagnosis is by temporal artery biopsy; microscopically, the following signs are seen:

- Granulations with giant cells.
- General leucocytic infiltrate.
- Fibrosis of the intima and stenosis.

There is often associated thrombosis. Diagnosis is by biopsy, which may be negative in one-third of cases. Treatment is with high doses of corticosteroids.



Giant cell arteritis commonly affects the temporal arteries and is important as it is an easily preventable cause of blindness.

Takayasu's disease (aortic arch syndrome)

Takayasu's disease typically affects females in the 20–40-year-old age group. It is most common in Asia. It is a granulomatous vasculitis of medium-to-large arteries, especially the aorta and the great vessels. Patients present with visual disturbances, neurological deficits, and diminished upper pulses ('pulseless disease'). If the renal arteries are involved, hypertension may result. There is thickening of the aortic wall with mononuclear cell infiltrates. Fibrosis and granulomas may result.

Polyarteritis nodosa

Polyarteritis nodosa is twice as common in males as in females, usually occurring in the middle aged. It is associated with the hepatitis B surface (s) antigen. p-ANCA is usually elevated.

Fibrinoid necrosis of medium-to-small arteries occurs, especially of the main viscera (e.g. coronary, renal and hepatic arteries). The pulmonary arteries are not usually affected. Presenting features can be general (e.g. fever) or relate to the specific system involved:

- Renal – hypertension, renal failure.
- Cardiac – myocardial infarction, heart failure.
- Central nervous system – hemiplegia, psychoses.
- Gastrointestinal – abdominal pain, melaena.

Segmental lesions occur, with fibrinoid necrosis of the wall and a neutrophil infiltrate. Healing results in thickening and often aneurysmal dilatation. A type of polyarteritis nodosa known as Churg–Strauss is an eosinophilic syndrome which affects the lungs. Diagnosis is by biopsy; treatment is with anti-viral therapy for hepatitis B associated polyarteritis or immunosuppression.

Kawasaki syndrome (mucocutaneous lymph node syndrome)

Kawasaki syndrome is an acute febrile illness of young children. Patients present with lymphadenopathy, rash, erythema, peeling skin, and (in 20% of those affected) coronary arteritis with aneurysms, which may lead to myocardial infarction or sudden cardiac death.

Similar lesions occur to those seen in polyarteritis nodosa. Aspirin and γ -globulin therapy is thought to prevent cardiac complications.

Microscopic polyarteritis (leucocytoclastic angiitis)

Microscopic polyarteritis is a fibrinoid necrosis of the smallest vessels, and it is thought to be a form of hypersensitivity reaction. Typically, there is an acute onset with a precipitating agent (e.g. bacteria) and involvement of the skin or viscera. There may be little neutrophilic infiltrate.

Wegener's granulomatosis

The majority of cases are in patients aged over 50 years. The condition consists of a triad of symptoms:

- Necrotizing vasculitis of the lung and upper respiratory tract.
- Granulomas of the respiratory tract.
- Glomerulonephritis of the kidneys.

c-ANCA type autoantibodies are usually present. Lesions are similar to those of polyarteritis nodosa, but granulomas also occur. Treatment is by immunosuppression (using prednisolone and cyclophosphamide).

Thromboangiitis obliterans (Buerger's disease)

Thromboangiitis obliterans is typically found in male smokers aged less than 35 years. It is twice as common in Jews as in non-Jews. It involves inflammation of the vessels of the lower limbs. Nodular phlebitis (inflammation of veins) and ischaemia of the extremities results. There is neutrophilic infiltration with thrombi and giant-cell formation.

Frequently, the condition is painful and leads to gangrene if smoking is not stopped.

Vasculitis in systemic disease

Many diseases have vasculitis as a component.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) affects capillaries, arterioles, and venules. An inflammatory vasculitis is predominant; neutrophils are more common than lymphocytes. Vasculitic lesions on the skin, muscle, and brain are common. Raynaud's phenomenon may also be present. A similar pathology exists in other connective tissue disorders (e.g. scleroderma, cryoglobulinaemia).

Henoch–Schönlein purpura

This is a hypersensitivity reaction that is often preceded by infection. Purpuric rashes caused by inflammation of capillaries and venules are present on the legs and buttocks. Abdominal pain, arthritis, haematuria, and nephritis may also occur.

Rheumatoid vasculitis

Vasculitis is one of the extra-articular features of rheumatoid arthritis.

Infectious vasculitis

Systemic infections can result in a vasculitis. These often produce a purpuric rash due to a hypersensitivity reaction.

Raynaud's disease

Raynaud's disease is not strictly a vasculitis, but it is worth considering here as it has some features in common with those of other vasculitides.

Primary Raynaud's disease affects 5% of the population, and it is mainly found in young healthy women. There is pallor and cyanosis caused by vasospasm of the small arteries/arterioles in the hands and feet. The exact aetiology is unknown, but it is thought to be due to increased vasomotor responses to cold or emotion.

Secondary Raynaud's phenomenon refers to the decrease in blood flow that occurs secondary to the narrowing of the arteries that supply the extremities. It implies a known aetiology; this can be atherosclerosis, systemic lupus erythematosus, scleroderma, or Buerger's disease.

CONGENITAL ABNORMALITIES OF THE VESSELS

Vascular anatomy is complex, and it undergoes considerable remodelling during embryological development. There are many areas where alterations from the usual development can occur. These do not necessarily produce deficiencies in the flow of blood; rather, most represent an alternative supply and drainage of the same tissue. For example, errors in the remodelling of the great vessels may give rise to double inferior and superior venae cavae; this is caused by a failure of regression of a primitive element.

A vascular ring may form around the oesophagus and trachea, causing difficulty in swallowing and breathing. This is caused by a persistent right dorsal aorta or it may result from other problems in aortic arch development.

Primary lymphoedema may result from hypoplasia of the lymphatic system.

Abnormalities in the coronary circulation may sometimes be normal (e.g. when branches of the left coronary artery arise directly from the aorta), or they may lead to ischaemia and infarction of the myocardium.

Some abnormalities may even be protective. For example, sometimes the kidney has a double renal arterial supply, protecting it from under-perfusion in hypovolaemia.

Two important anomalies of the circulation are:

- Arteriovenous fistulae.
- Berry aneurysms.

Arteriovenous fistula

An arteriovenous fistula is an abnormal communication between an artery and a vein. This may be congenital in origin or secondary to trauma, inflammation, or a healed ruptured aneurysm. Fistulae may cause shunting of blood, bypassing circulations and increasing venous return, thereby increasing cardiac output. This may predispose to heart failure.

Fistulae may be seen in Paget's disease of the bone, where the increased blood flow through the affected bones may eventually lead to heart failure.

Arteriovenous fistulae are used in haemodialysis for renal patients. Artificial arteriovenous fistulae can be surgically placed between the radial artery and cephalic vein (Fig 6.15). This causes the vein to distend and thicken, enabling large bore needles to be inserted. These take blood to and from the dialysis machine.

Berry aneurysm

Berry aneurysms are found in about 2% of post mortem examinations, and they are the most common intracranial aneurysm. They are small sacular aneurysms in the cerebral vessels. They can measure about 0.2–3.0 cm in diameter, but are usually around 1.0 cm. They frequently occur at branch points in the circle of Willis (Fig. 6.16). These aneurysms are commonly seen in patients with coarctation of the aorta and polycystic renal disease.

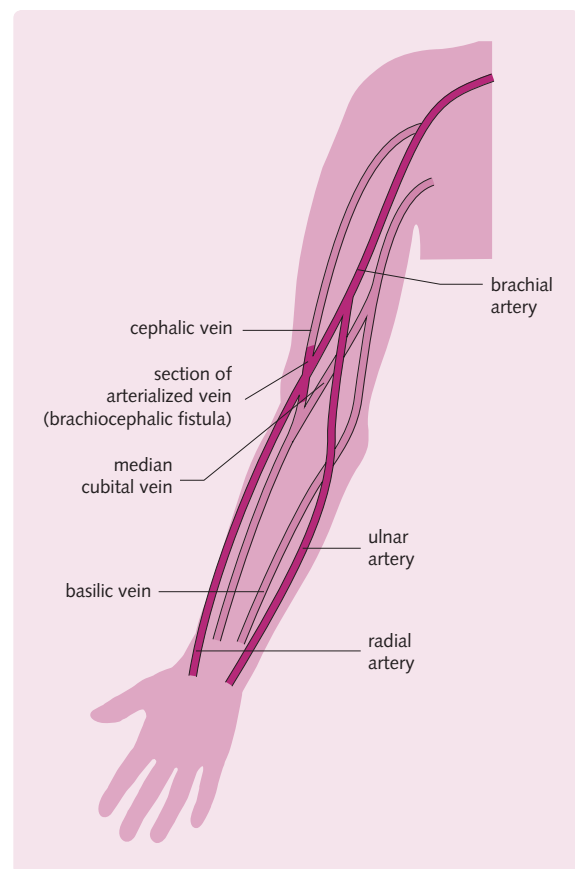


Fig. 6.15 Surgically created arteriovenous fistula.

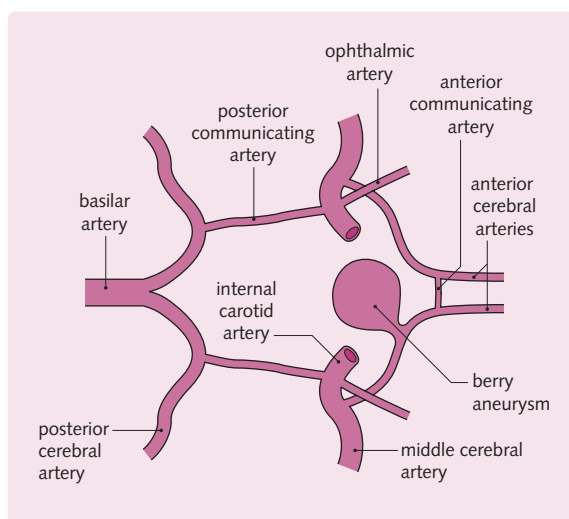


Fig. 6.16 Berry aneurysm in the circle of Willis.

Berry aneurysms are asymptomatic until they rupture (usually when the patient is aged between 40 and 60 years). Rupture is more common in males. Predisposing factors to rupture include smoking, hypertension, and atheroma. The original outpouching is caused by local focal wall weakness. This then gets larger as a result of the haemodynamics in the lumen. Eventually rupture may occur. Rupture of berry aneurysms results in a subarachnoid haemorrhage, presenting with a sudden-onset severe headache which may be fatal.

Berry aneurysms are common and can be corrected surgically, so it is important to remember this as a cause of acute severe headache.



into capillary haemangioma, juvenile capillary haemangioma, cavernous haemangioma and granuloma pyogenicum.

Capillary haemangioma

Capillary haemangiomas occur mostly in skin and mucous membranes. These are well-defined, encapsulated aggregates of capillaries. They may be thrombosed.

Juvenile capillary ('strawberry') haemangioma

Juvenile capillary haemangiomas are present at birth on the face and scalp of infants. They grow rapidly for the first few months then regress and disappear by the age of 5 years.

Cavernous haemangioma

Cavernous haemangiomas are large, cavernous, vascular channels that are not encapsulated. They involve skin, mucous membranes, the central nervous system, and the liver.

Granuloma pyogenicum

Granuloma pyogenicum is an ulcerated version of capillary haemangioma, often caused by trauma. Typically, it is composed of capillaries with oedema, inflammatory cells, and granulation tissue. Granuloma gravidum occurs in the gum of up to 5% of pregnant women.

Glomangioma

Glomangiomas are painful tumours of the glomus body (a receptor in the smooth muscle of arteries that is sensitive to temperature; i.e. at arteriovenous anastomoses in the skin). Glomangiomas are usually found in fingers or nail beds. They are branching vascular channels with aggregates of glomus bodies.

Telangiectasia

Telangiectasias are aggregations of prominent small vessels in the skin or mucous membranes. They are probably not a true neoplasm, but are either congenital or an exaggeration of existing vessels.

Naevus flammeus (ordinary birthmark)

Naevus flammeus is a macular lesion with vessel dilatation. Most regress, except the 'port-wine stain'

NEOPLASTIC VASCULAR DISEASE

Benign tumours and related conditions

Haemangioma

Haemangiomas are common, especially in children; they make up approximately 7% of all benign tumours. Haemangiomas are usually subdivided

naevi, which persist and are a sign of the Sturge–Weber syndrome (neurocutaneous angiomas).

Spider naevi

Spider naevi are minute, often pulsatile arterioles occurring around a central core, usually above the waist. They are associated with hyperoestrogen states (e.g. cirrhosis and pregnancy).

Osler–Weber–Rendu disease (hereditary haemorrhagic telangiectasia)

This disease is a rare autosomal dominant condition, characterized by multiple, small aneurysms on the skin and mucous membranes. Patients present with bleeding usually from the nose, mouth or rectum.

Bacillary angiomatosis

Bacillary angiomatosis is a fatal disease caused by Rickettsia-like bacteria. There is proliferation of blood vessels in the skin, lymph nodes, and organs of immunocompromised patients. Treatment with erythromycin is curative.

Intermediate-grade tumours

Haemangioendothelioma

Haemangioendotheliomas are neoplasms that show both benign and malignant characteristics (i.e. some are benign, others are malignant). They consist of vascular channels with masses of spindle-shaped plump cells of endothelial origin.

Malignant tumours

Angiosarcoma (haemangiosarcoma)

Angiosarcomas are rare, but very aggressive tumours that metastasize widely. They are found in skin, breast, liver, and spleen, especially in the elderly. There are small, discrete, red nodules that change into large, white masses, in which cells of all differentiations are found.

Haemangiopericytoma

Haemangiopericytoma is a malignant tumour of pericytes occurring in the lower extremities or in the retroperitoneum. About half of all these tumours metastasize.

Kaposi's sarcoma

Kaposi's sarcoma is a malignant tumour of unknown origin, but probably from lymphatic endothelium. Purple papules/plaques are found in the skin, mucosa, or viscera. Microscopically, it is composed of sheets of spindle-shaped plump cells with intermingled red blood cells and vascular channels.

There are four types of this disease:

Classic Kaposi's sarcoma

Classic Kaposi's sarcoma affects mainly elderly Eastern European men, especially Ashkenazi Jews. Multiple red plaques occur on the lower extremities. The disease is rarely fatal.

African Kaposi's sarcoma

African Kaposi's sarcoma affects mainly younger men in equatorial Africa. Clinically, it is similar to classic Kaposi's sarcoma.

Transplant-associated Kaposi's sarcoma

Transplant-associated Kaposi's sarcoma occurs in immunosuppressed patients. It involves the skin and viscera. Lesions regress when immunosuppression is stopped.

HIV-associated Kaposi's sarcoma

HIV-associated Kaposi's sarcoma may occur in the skin, mucous membranes, lymph nodes, viscera, or gastrointestinal tract. This is an AIDS-defining illness, and it often responds to cytotoxic drugs or α -interferon.

DISEASES OF THE VEINS AND LYMPHATICS

Varicose veins

Varicose veins are tortuous, distended superficial veins, usually of the lower limbs, caused by a persistent increased intraluminal pressure. They occur in 10–20% of the normal population, with women being more affected than men. Risk factors include:

- Pregnancy.
- Obesity.
- Prolonged standing.
- Previous deep vein thrombosis.
- Familial tendency.
- Tumours compressing the deep veins.

Aetiology

There are superficial and deep veins in the lower limb, which are interconnected by perforating veins (Fig. 6.17). Blood is returned mainly through the deep veins to the thoracic compartment by the skeletal pumping effect of the calf muscles. If there is a blockage of the deep veins (e.g. by thrombosis) or there are faulty valves in the perforating veins, then blood will move from the deep veins into the superficial veins. This will lead to distension and further valvular incompetence, resulting in stasis of blood. Oedema and changes in the skin take place (e.g. ulceration, see p. 161) which fail to heal because there is an impaired circulation.

Histologically, the venous walls will become thin where there is dilatation. Thrombosis may be seen in the superficial vein walls, but this rarely causes emboli.

Sequelae

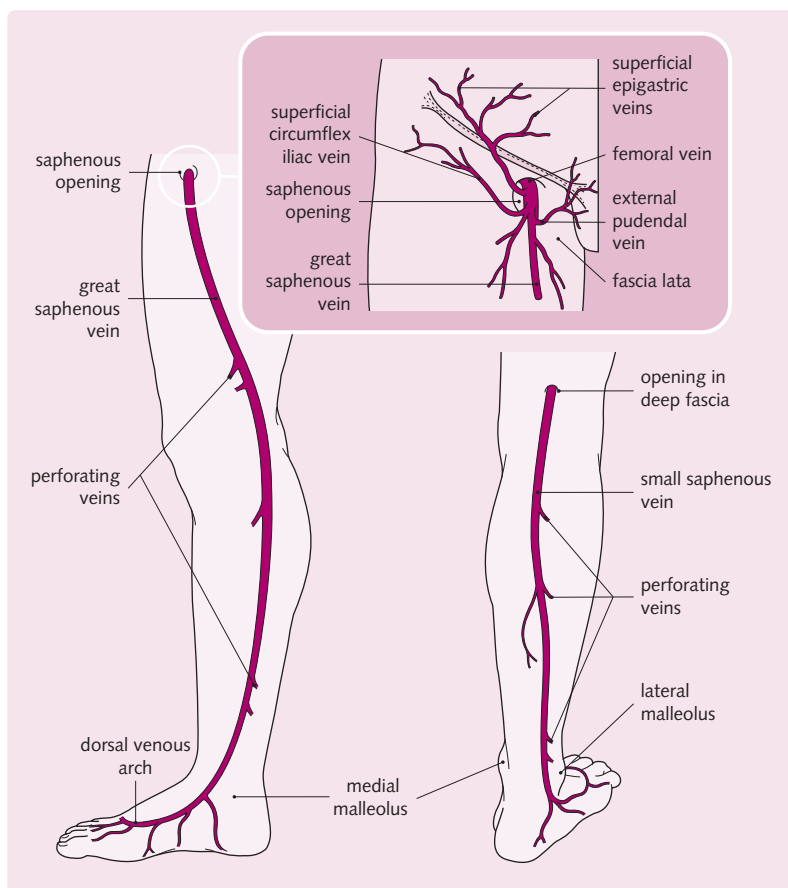
Sequelae of varicose veins include:

- Varicose ulcers.
- Dermatitis.
- Thromboemboli.

Varicose veins do not always require treatment. Occasionally, patients complain of a dragging sensation, bleeding or are disturbed by the appearance of their legs. In these patients, surgery may be appropriate to remove the distended veins. Recurrence is a significant risk.

Varicose veins affect a large number of people, those who stand for long periods of time, e.g. teachers, being particularly at risk. Treatment may be conservative, i.e. compression bandaging, or surgical. Surgical treatment may be local, e.g. injection of sclerosant into the dilated vein, or generalized, e.g. tying off the incompetent valve and stripping out the dilated vein.

Fig. 6.17 Perforating veins of the lower limbs.



Other sites of varicosities

These are as follows:

- Haemorrhoids (piles) are distended submucosal veins in the anal canal that may protrude through the anus. Bleeding and pain may result from trauma, protrusion, or spasm of the anal sphincter.
- Varicocele is a distension of the veins of the pampiniform plexus in the spermatic cord.
- Oesophageal varices are distended veins at the oesophageal–gastric junction. They are caused by portal hypertension, usually as a result of liver cirrhosis.

Deep vein thrombosis and thrombophlebitis

Thrombosis within a vein is termed phlebothrombosis – the term ‘deep vein thrombosis’ is more specific. Phlebothrombosis usually causes inflammation in the wall of the vein, which is then termed thrombophlebitis. Risk factors for thrombosis are used to formulate a Well’s score (Fig 6.18).

Thrombosis mainly affects the following:

- Deep leg veins (90% of thromboses; most commonly in the thigh). Commonly they throw off emboli that impact in the pulmonary circulation.
- Periprostatic plexus in men.
- Ovarian and pelvic veins in women.

Clinical features of thrombosis vary:

- It may be asymptomatic.
- It may present with pulmonary emboli (hypoxia, chest pain, dyspnoea or collapse).
- It may cause calf pain, with swelling, redness, and distended superficial veins. The affected calf is warmer, and there may be ankle oedema.
- If severe, occlusion may lead to cyanosis of the limb, severe oedema, and gangrene.

Investigation is with Doppler ultrasonography or venography. D-dimers (fibrin degradation products) may be non-specifically raised. Initial treatment is anticoagulation with heparin. The patient is mobilized and advised to wear support stockings.

In late pregnancy, phlegmasia alba dolens (painful white ‘milk leg’) may occur because of thrombosis of the iliofemoral veins.

Thrombophlebitis migrans (Trousseau’s syndrome) refers to multiple thrombi occurring in one place and then vanishing only to occur somewhere else. It is caused by hypercoagulability states associated with malignancy (usually adenocarcinoma of the pancreas).

Lymphangitis

Lymphangitis is inflammation of the lymphatic vessels. It is frequently found in lymphatic vessels that drain a source of infection. It often presents as a cluster of red painful streaks in the skin close to an infected site. Lymphangitis very often occurs as a result of bacterial infections (especially streptococcal). If untreated with antibiotics, it may progress to involve the lymph nodes (lymphadenitis), and it may eventually lead to septicaemia.

Histologically, the wall of the lymph vessels is infiltrated by inflammatory cells. This may spread to involve surrounding structures leading to cellulitis or an abscess.

Lymphoedema

Lymphoedema is an accumulation of interstitial fluid caused by obstruction of the draining lymphatics. The oedema is usually non-pitting (pitting oedema being suggestive of hypoproteinaemia and cardiac failure). Primary lymphoedema is a result of agenesis of the lymphatic system. Secondary lymphoedema may be caused by:

- Recurrent cellulitis.
- Malignancy.
- Surgical resection of lymph nodes.
- Radiotherapy causing fibrosis.
- Filariasis – nematode worm infection that leads to elephantiasis (gross enlargement of the skin and connective tissue).
- Post-inflammatory thrombosis leading to scarring.
- Congenital abnormal lymphatics.

If lymphoedema is prolonged, fibrosis of the interstitium occurs, leading to skin thickening and permanent oedema. The skin appears to take on an orange-peel appearance (peau d’orange). Associated ulcers and brawny hardening of the skin may also take place.

If the dilated obstructed lymphatics rupture, then chyle (lymph with digested fats) may accumulate in parts of the body cavity. Chylous ascites,

Well's risk factors for DVT	
Criteria	Score
<ul style="list-style-type: none"> • Lower limb trauma, surgery, or immobilization in a plaster cast 	+1
<ul style="list-style-type: none"> • Bedridden for more than three days or surgery within last four weeks 	+1
<ul style="list-style-type: none"> • Tenderness along line of femoral or popliteal veins 	+1
<ul style="list-style-type: none"> • Entire limb swollen 	+1
<ul style="list-style-type: none"> • Calf more than 3cm greater in circumference, measured 10 cm below tibial tuberosity 	+1
<ul style="list-style-type: none"> • Pitting oedema 	+1
<ul style="list-style-type: none"> • Dilated collateral superficial veins 	+1
<ul style="list-style-type: none"> • Past history of DVT (confirmed) 	+1
<ul style="list-style-type: none"> • Malignancy 	+1
<ul style="list-style-type: none"> • Intravenous drug use 	+3
<ul style="list-style-type: none"> • Alternative diagnosis more likely than DVT 	-2
DVT 'likely' if Well's >1 DVT 'unlikely' if Well's <2	

Fig. 6.18 Well's score showing risk factors for deep venous thrombosis (DVT).

chylothorax, and chylopericardium refer to the accumulation of chyle in the abdomen, thorax, and pericardium, respectively.

Neoplasms of the lymphatics

Lymphangioma

Lymphangiomas are benign tumours of the lymphatic capillaries. They are analogous to haemangiomas. There are two types: simple and cavernous.

Simple lymphangioma

Typically, a simple lymphangioma occurs on the head, neck, or axilla. It can also occur on the trunk and in viscera.

Simple lymphangiomas are cutaneous or pedunculated nodules made up of endothelium-lined spaces in a network. No blood cells are present.

Cavernous lymphangioma (cystic hygroma)

Cavernous masses are usually present in the neck or axilla in children. They are not encapsulated and they are poorly defined – and so are difficult to resect. Cavernous lymphangiomas tend to recur. There are dilated cystic spaces lined by endothelium.

Lymphangiosarcoma

Lymphangiosarcoma is a rare malignant tumour of the lymphatics with a poor prognosis. Prolonged lymphoedema is usually associated with the condition.

The tumour comprises multiple confluent nodules of vascular channels lined with endothelium.

