CHAPTER 1

Pathogenesis of Atherosclerosis and Methods of Arterial and Venous Assessment

Mario De Nunzio[1] *and Timothy J. England*[2]

[1]Derby Hospitals NHS Foundation Trust, Royal Derby Hospital, UK
[2]Division of Medical Sciences & GEM, School of Medicine, University of Nottingham, UK

OVERVIEW

- Atherosclerosis is a chronic inflammatory disorder
- The ankle–brachial pressure index (ABPI), calculated from the ratio of ankle systolic blood pressure (SBP) to brachial SBP, is a sensitive marker of arterial insufficiency in the lower limb
- Blood velocity increases through an area of narrowing. Typically, a 2-fold increase in peak systolic velocity compared with the velocity in a proximal adjacent segment of the same artery usually signifies a stenosis of 50% or more
- In detecting femoral and popliteal artery disease, duplex ultrasonography has a sensitivity of 80% and a specificity of 90–100%
- The introduction of multidetector computed tomography (MDCT) has had a dramatic effect on vascular imaging. Computed tomography pulmonary angiography (CTPA) for suspected pulmonary embolism (PE) is a good example, but computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are widely used to investigate large artery pathology
- Colour duplex scanning is both sensitive and specific (90–100% in most series) for detecting proximal deep vein thrombosis (DVT).

Pathogenesis of atherosclerosis

Atherosclerosis is a chronic inflammatory disorder that results in hardening and thickening of arterial walls. Although it inevitably accompanies aging, it is not a degenerative process. The initial insult, called a 'fatty streak', is a purely inflammatory lesion and has been observed in infants. Over many years, circulating monocyte-derived macrophages adhere to and invade the arterial wall. An inflammatory response, proliferation of vascular smooth muscle cells and deposition of cholesterol and other lipids create arterial plaques. The insult creates a prothrombotic environment and induces the release of inflammatory mediators including cytokines, growth factors and hydrolytic enzymes. Over time, the plaques narrow the arterial lumen (and at times dilate it) and subsequently rupture, causing platelet activation, aggregation and resultant thrombus and embolus formation (Figure 1.1). It remains unclear as to what causes a stable plaque to rupture but it may be due to mechanical stress (e.g. hypertension) and the large lipid core redistributing shear stress over weakened areas of a thin fibrous cap.

It is recognised that increasing age, a genetic predisposition, male sex, hypertension, lipid abnormalities (in particular, LDL-cholesterol), diabetes, chronic high alcohol intake and cigarette smoking (causing an increase in free radicals) increase the risk of atherogenesis and endothelial dysfunction. Atherosclerosis mainly affects large and medium-sized arteries at places of arterial branching (e.g. carotid bifurcation). Symptoms occur when there is insufficient blood flow to the vascular bed as a result of

1 *in situ* thrombotic arterial occlusion,
2 low flow distal to an occluded or severely narrowed artery or
3 embolism from an atherosclerotic plaque or thrombus.

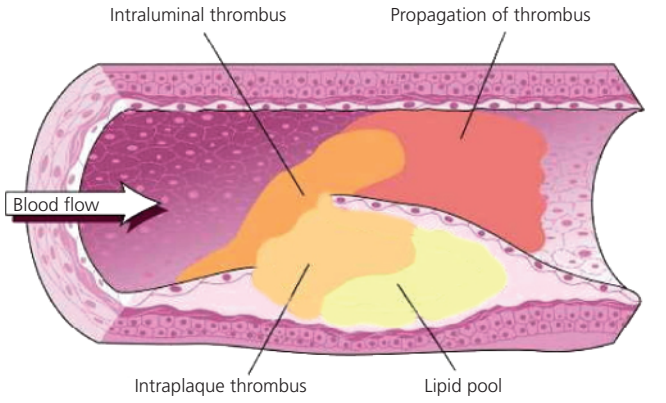


Figure 1.1 Spontaneous rupture or fissuring of an atherosclerotic plaque exposes the lipid-rich core and triggers platelet activation and platelet aggregation. The platelet GP IIb/IIIa receptor activation binds fibrinogen and leads to intravascular thrombus formation, resulting in complete or near-complete vessel occlusion. Clinically, this often presents with a life-threatening unstable event such as an acute coronary syndrome, acute limb ischaemia or stroke.

ABC of Arterial and Venous Disease, Third Edition.
Edited by Tim England and Akhtar Nasim.

Clots occurring in the venous system are often evaluated referencing the principles of Virchow's triad, the three broad categories that contribute to thrombosis: venous stasis due to prolonged immobility, endothelial and vessel wall injury, for example, due to radiation or medical devices, and hypercoagulability states such as patients with malignancy or clotting factor deficiency.

Investigating vascular disease

Diagnostic and therapeutic decisions in patients with vascular disease are guided primarily by the history and physical examination. However, the accuracy and accessibility of non-invasive investigations have greatly increased due to technological advances in computed tomography (CT) and magnetic resonance (MR) scanning. Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) continue to evolve rapidly and are best described as 'minimally invasive' techniques when used with intravenous (i.v.) contrast. This chapter describes the main investigative techniques used in arterial and venous diseases.

Principles of vascular ultrasound

In its simplest form, ultrasound is transmitted as a continuous beam from a probe that contains two piezoelectric crystals. The transmitting crystal produces ultrasound at a fixed frequency (set by the operator according to the depth of the vessel being examined), while the receiving crystal vibrates in response to reflected waves and produces an output voltage. Conventional B-mode (brightness mode) ultrasonography records the ultrasound waves reflected from tissue interfaces and a two-dimensional picture is built according to the reflective properties of the tissues.

Ultrasound signals reflected off stationary surfaces have the same frequency with which they were transmitted, but the principle underlying Doppler ultrasonography is that signals reflected from moving objects, e.g. red blood cells, undergo a frequency shift in proportion to the velocity of the target. The output from a continuous-wave Doppler ultrasound is most frequently presented as an audible signal (e.g. a hand-held pencil Doppler, Figure 1.2), so that a sound is heard whenever there is movement of blood in the vessel being examined. With continuous-wave ultrasonography, there is little scope for restricting the area of tissue that is being examined because any sound waves that are intercepted by the receiving crystal will produce an output signal. The solution is to use pulsed ultrasound. This enables the investigator to focus on a specific tissue plane by transmitting a pulse of ultrasound and closing the receiver except when signals from a predetermined depth are returning. For example, the centre of an artery and the areas close to the vessel wall can be examined in turn.

Examination of an arterial stenosis shows an increase in blood velocity through the area of narrowing. The site(s) of any stenotic lesions can be identified by serial placement of the Doppler probe along the extremities. Criteria to define a stenosis vary between laboratories, but a 2-fold increase in peak systolic velocity compared with the velocity in a proximal adjacent segment of the artery usually signifies a stenosis of ≥50% (Table 1.1). The normal (triphasic)

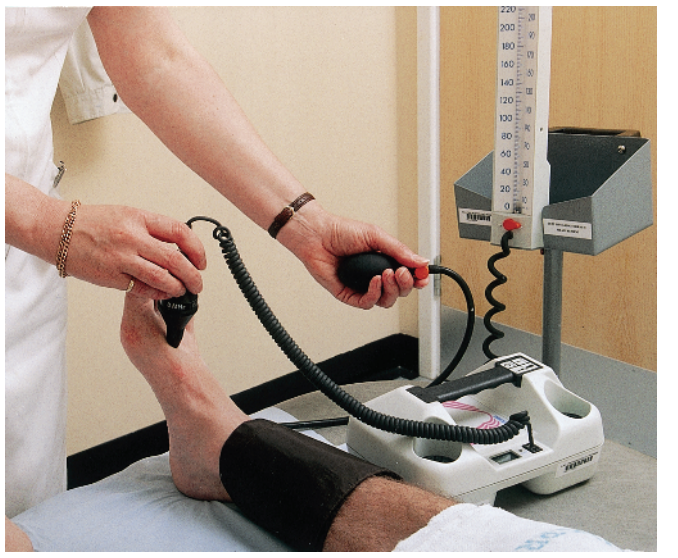


Figure 1.2 A hand-held pencil Doppler being used to measure the ankle–brachial pressure index.

Table 1.1 Relationship between increased blood velocity and degree of stenosis.

Diameter of stenosis (%)	Peak systolic velocity (m/s)*	Peak diastolic velocity (m/s)*	Internal carotid: common carotid artery ratio†
0–39	<1.1	<0.45	<1.8
4–59	1.1–1.49	<0.45	<1.8
60–79	1.5–2.49	0.45–1.4	1.8–3.7
80–99	2.5–6.1	>1.4	>3.7
>99 (critical)	Very low	NA	NA

*Measured in the lower part of the internal carotid artery.
†Ratio of peak systolic velocity in internal carotid artery stenosis relative to the velocity in the proximal common carotid artery.

Doppler velocity waveform is made up of three components that correspond to different phases of arterial flow (Figure 1.3):

- Rapid antegrade flow reaching a peak during systole
- Transient reversal of flow during early diastole
- Slow antegrade flow during late diastole.

Doppler examination of an artery distal to a stenosis shows characteristic changes in the velocity profile (Figure 1.3d):

- The rate of rise is delayed and the amplitude decreased
- The transient flow reversal in early diastole is lost
- In severe disease conditions, the Doppler waveform flattens; in critical limb ischaemia, it may be undetectable.

Investigations of arterial disease

Ankle–brachial pressure index

Under normal conditions, systolic blood pressure (SBP) in the legs is equal to or slightly greater than the SBP in the upper limbs. In the presence of an arterial stenosis, a reduction in pressure occurs

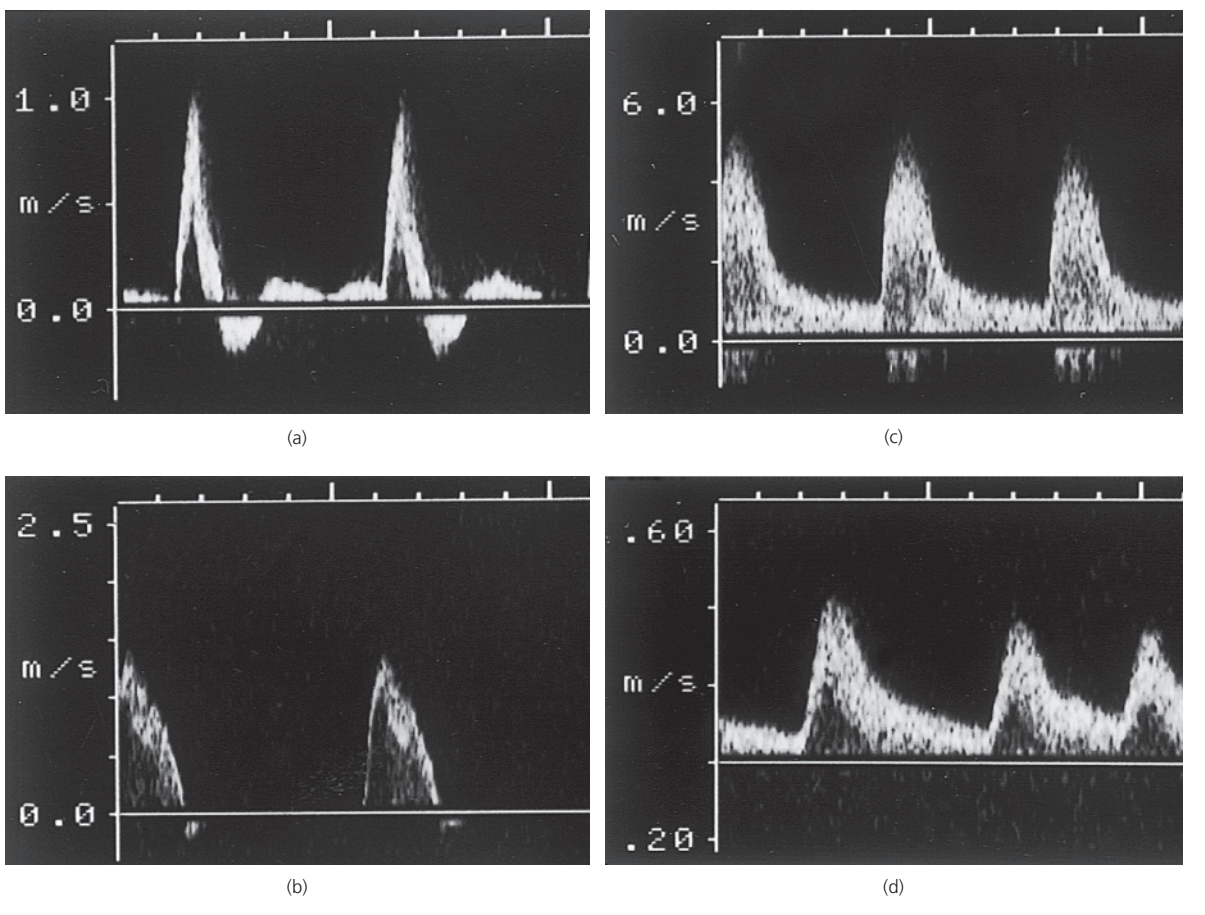


Figure 1.3 Doppler velocity waveforms: (a) a triphasic waveform in a normal artery; (b) a biphasic waveform, with increased velocity, through a mild stenosis; (c) a monophasic waveform, with a marked increase in velocity, through a tight stenosis; and (d) a dampened monophasic waveform, with reduced velocity, recorded distal to a tight stenosis.

distal to the lesion. The ankle–brachial pressure index (ABPI), calculated from the ratio of ankle SBP to brachial SBP, is a sensitive marker of arterial insufficiency in the lower limb. The highest pressure measured in any ankle artery is used as the numerator in the calculation of the ABPI. An ABPI of ≥1.0 is normal and a value <0.9 is abnormal. Patients with claudication tend to have ABPIs in the range 0.5–0.9, while those with critical ischaemia usually have an index of <0.5. In patients with diabetes (in whom distal vessels are often calcified and incompressible), SBP measured in the lower limbs may be less reliable, which can result in falsely high ankle pressures and a falsely elevated ABPI.

Exercise testing will assess the functional limitations of arterial stenoses and differentiate occlusive arterial disease from other causes of exercise-induced lower limb symptoms, e.g. neurogenic claudication secondary to spinal stenosis. A limited inflow of blood in a limb with occlusive arterial disease results in a fall in ankle SBP during exercise-induced peripheral vasodilatation. Patients can exercise for 5 min, ideally on a treadmill, but walking in the surgery or marking time on the spot are perfectly adequate. ABPI is measured before and after exercise. A pressure drop of ≥20% indicates significant arterial disease (Figure 1.4). If there is no drop in ankle SBP after a 5-min brisk walk, the patient does not have occlusive arterial disease proximal to the ankle in that limb.

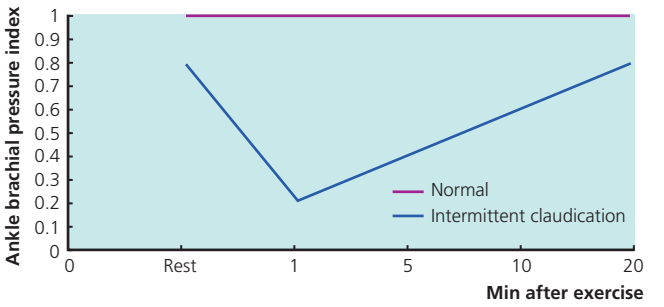


Figure 1.4 The fall in ABPI with exercise in a patient with intermittent claudication.

Duplex scanning

By combining the pulsed Doppler system with real-time B-mode ultrasound imaging of vessels, it is possible to examine (or 'sample') Doppler flow patterns in a precisely defined area within the vessel lumen. This combination of real-time B-mode sound imaging with pulsed Doppler ultrasound is called duplex scanning. The addition of colour frequency mapping makes the identification of arterial stenoses even easier and reduces scanning time (Figure 1.5).

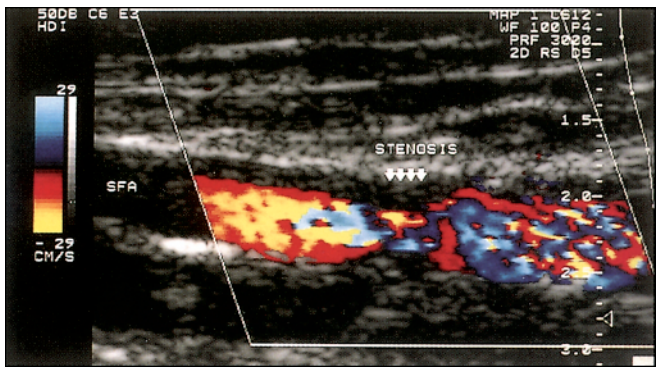


Figure 1.5 Colour duplex scanning of blood flow through a stenosis of the superficial femoral artery (SFA). The colour assignment (red or blue) depends on the direction of blood flow, and colour saturation reflects velocity of blood flow. Less saturation (mixed red and blue) indicates regions of higher blood flow, and deeper colours indicate slower flow; the absence of flow is coded as black.

Table 1.2 Uses of colour duplex scanning.

Arterial	Venous
Identify obstructive atherosclerotic disease: • Carotid • Peripheral arteries	Diagnosis of deep vein thrombosis above the knee
Surveillance of infrainguinal bypass grafts	Assessing competence of valves in deep veins
Surveillance of lower limb arteries after angioplasty	Superficial venous reflux: • Assessing patient with recurrent varicose veins • Identify and locate reflux at saphenopopliteal junction
	Pre-operative mapping of saphenous vein

In detecting femoral and popliteal disease, duplex ultrasonography has a sensitivity of 80% and a specificity of 90–100%, but ultrasound is less reliable for assessing the severity of stenoses in the tibial and peroneal arteries (Table 1.2). The National Institute of Clinical Excellence (NICE) advises the use of duplex scanning as first-line imaging to all people with suspected lower limb peripheral arterial disease for whom revascularisation is being considered (Box 1.1). Duplex scanning is especially useful for assessing the carotid arteries and for routine surveillance of infrainguinal bypass grafts where sites of stenosis can be identified before complete graft occlusion occurs and before there is a significant fall in ABPI. The normal velocity within a graft conduit ranges between 50 and 120 cm/s. As with native arteries, a 2-fold increase in peak systolic velocity indicates a stenosis of ≥50%. A peak velocity of <45 cm/s occurs in grafts at high risk of failure.

Box 1.1 **NICE recommended imaging in patients with peripheral arterial disease in whom revascularisation is being considered**

1. Duplex U/S for first-line imaging
2. Contrast-enhanced MRA – if further imaging is required after initial U/S before considering revascularisation
3. CTA – if further imaging is required after initial U/S, if contrast-enhanced MRA is contraindicated or not tolerated, before considering revascularisation.

Computed tomography angiogram

CTA is a technique that allows rapid and continuous acquisition of data during the first pass of a bolus of i.v. contrast through the arterial tree. The data can be reconstructed at any slice level, reformatted into different planes and processed into high-quality two- or three-dimensional images of vessels. The introduction of multidetector computed tomography (MDCT) has had a dramatic effect on CT imaging, and, in particular, imaging of the cardiovascular system. The development of MDCT has led to a much higher speed of data acquisition (0.37-s rotation speed versus 1-s rotation speed for conventional CT), and, secondly, MDCT acquires volume data instead of individual slice data. Thus, MDCT (without increasing the radiation dose) has led to faster scanning, improved contrast resolution and better spatial resolution. The effect of movement artefacts is also minimised.

The time taken to complete the procedure is determined by practicalities such as transferring the patient and gaining venous access, but the scan acquisition time for the entire arterial system (aortic arch to pedal vessels) is <15 s for CTA compared with ~10–15 min for MRA (Table 1.3).

Magnetic resonance angiography

Certain MR scanning techniques allow the use of a pulse sequence that images moving blood, thus showing arteries or veins without the use of an injected contrast agent or exposure

Table 1.3 Advantages and limitations of CT and MR angiographies.

CTA	MRA (enhanced)
Rapid data acquisition; less prone to movement artefact	Slower acquisition; more prone to movement artefact
High resolution, providing anatomical images of the vessel lumen and wall	Lower resolution but dependent on technique and location
Loss of accuracy with circumferential calcification	May overestimate degree and length of stenosis due to signal dropout in areas of turbulence
Ease of access, especially in emergencies, and acutely ill patients can be supported during scan	Contraindicated by need for intensive patient support Contraindications include implants such as pacemakers, defibrillators, cochlear implants and spinal cord stimulators Small scanner tunnel not tolerated by some patients due to claustrophobia or body habitus
Less expensive	More expensive
Radiation exposure	No radiation
Iodinated contrast – risk of contrast nephropathy and allergy (effective hydration helps prevent nephropathy)	Gadolinium contrast used for MRA has been associated with nephrogenic systemic fibrosis (in patients with severe renal impairment)

to ionising radiation. Non-contrast MRA therefore has substantial safety advantages but is characterised by flow dependence. Contrast-enhanced MRA using an i.v. bolus of gadolinium contrast can cover a larger area, allows more rapid data acquisition and higher resolution and gives a more direct image of the vascular lumen. Therefore, contrast-enhanced MRA is more commonly used. A variety of imaging sequences are used depending on the vessels being studied and the field strength of the machine. Information is obtained from both the axial images and the vessel reconstructions (Figures 1.6 and 1.7).

Applications of CTA and MRA

CTA and MRA are both widely used to investigate large artery pathology (Figures 1.8 and 1.9). Each technique has different advantages and disadvantages (Table 1.3). CTA has the major advantage of speed, but local preferences and availability often determine which technique is used. Computed tomography pulmonary angiography (CTPA) for suspected pulmonary embolism (PE) is probably the most commonly used computerised angiographic investigation (Figure 1.10). CTPA is now recommended by NICE guidance as the first-line investigation for patients with a high risk of PE after clinical evaluation.

In the investigation of abdominal aortic aneurysm (AAA) and aortic dissection, CTA is the preferred investigation because it images the vessel wall and can provide information about mural thrombus, inflammatory changes and rupture. Software reconstructs hundreds of images and displays them in two- or three-dimensional planes (Figure 1.11). This becomes an important tool for pre-operative planning and post-operative follow-up, especially in regard to use of endovascular stent grafts for AAA repair. CTA is more sensitive and specific than conventional angiography in detecting the presence of endoleaks.

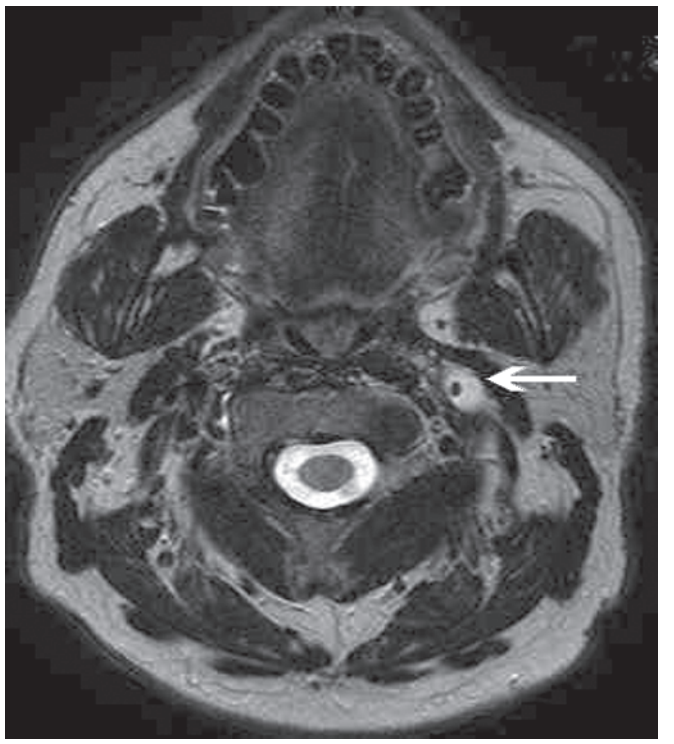


Figure 1.6 T2-weighted axial MR scan of the neck showing a left internal carotid artery dissection, with thrombus in the vessel wall producing a high signal (arrow).

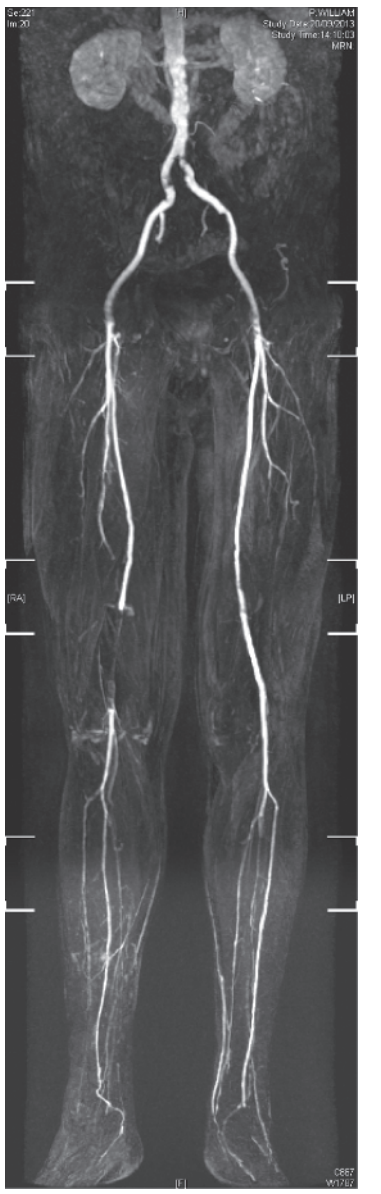


Figure 1.7 Contrast-enhanced MRA of the peripheral arteries showing bilateral common iliac stenosis and right superficial femoral artery occlusion.

Contrast-enhanced MRA is recommended in the investigation of suspected lower limb peripheral arterial disease for patients who need further imaging after initial duplex ultrasound before considering revascularisation. If MRA is contraindicated or not tolerated, patients should be offered CTA (Box 1.1).

MDCT angiography and MRA have equally high sensitivity and specificity for the detection of renal artery stenosis, but CTA is often preferred in order to avoid gadolinium administration, especially in patients with severe renal impairment (Figure 1.9). MDCT can also be used post stenting to assess for recurrent renal artery stenosis.

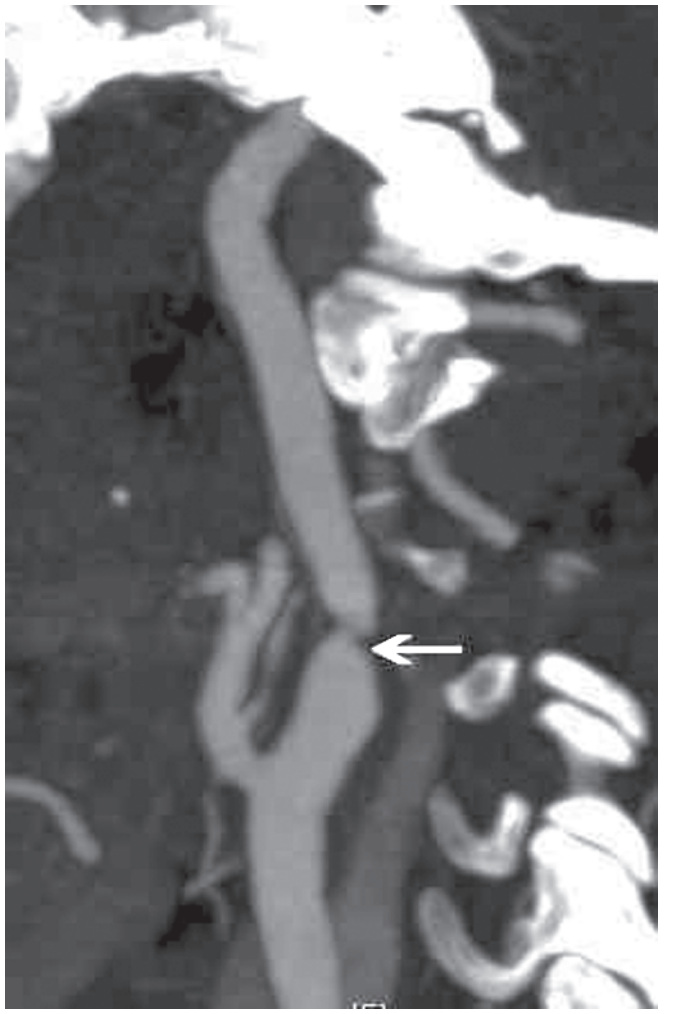


Figure 1.8 CT angiogram showing a tight stenosis of the right internal carotid artery (arrow).

Technical advances in both CT and MRI, with increased speed and resolution of imaging, coupled with data acquisition synchronised with respiratory and cardiac cycles, has led to their increased use in non-invasive cardiac imaging. Initial non-contrast CT is recommended to quantify calcification in the coronary arteries in patients with chest pain in whom clinical assessment and 12-lead ECG alone cannot diagnose angina and the likelihood of coronary artery disease (CAD) is low. The presence of calcium is a marker of atherosclerosis and there is a direct correlation between the extent of calcification of the coronary arteries and the risk of future cardiac events. If the 'calcium score' on CT is moderately elevated, contrast CTA of the coronary arteries is recommended and significant stenoses can be detected with a sensitivity of 95% or higher (Figure 1.12). MRI provides excellent anatomical and

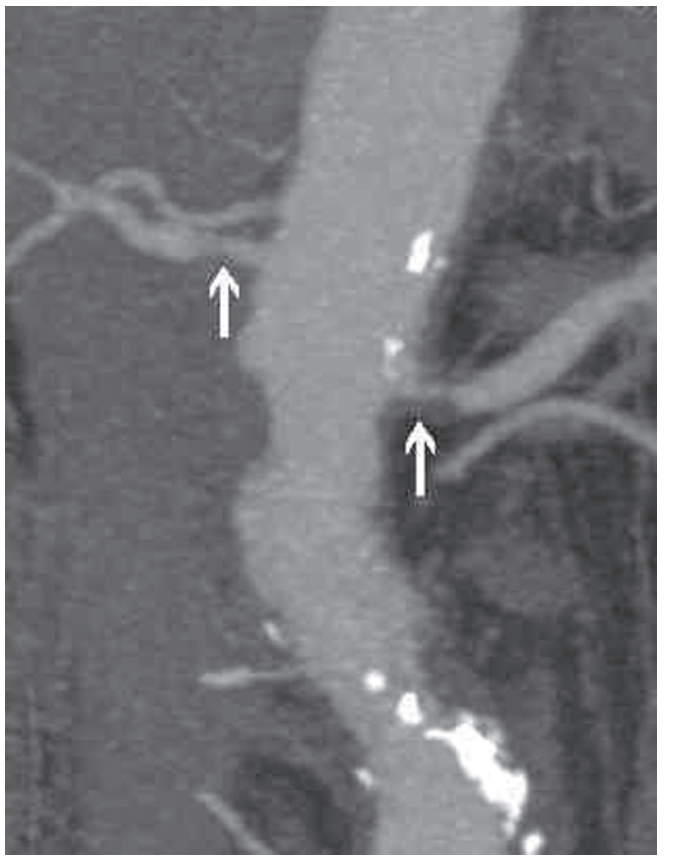


Figure 1.9 CT angiogram showing bilateral renal artery stenoses (arrows).

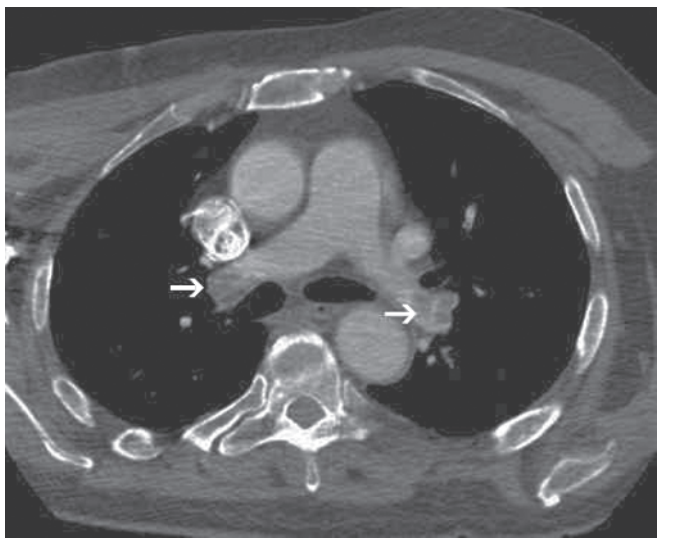
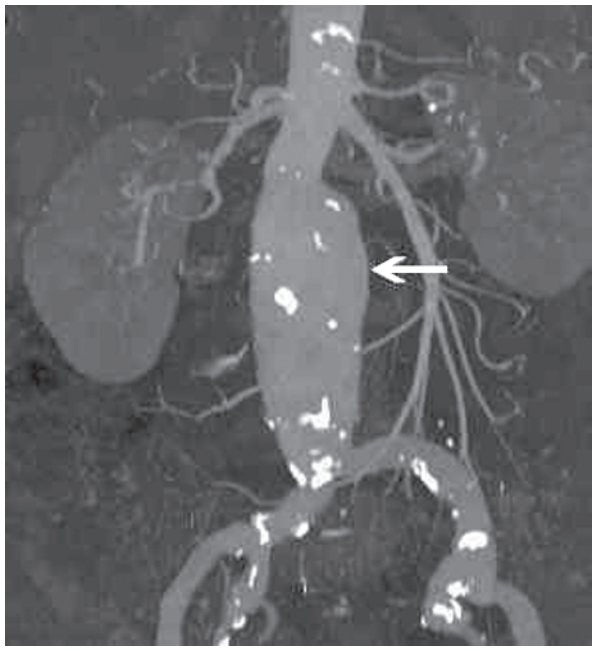
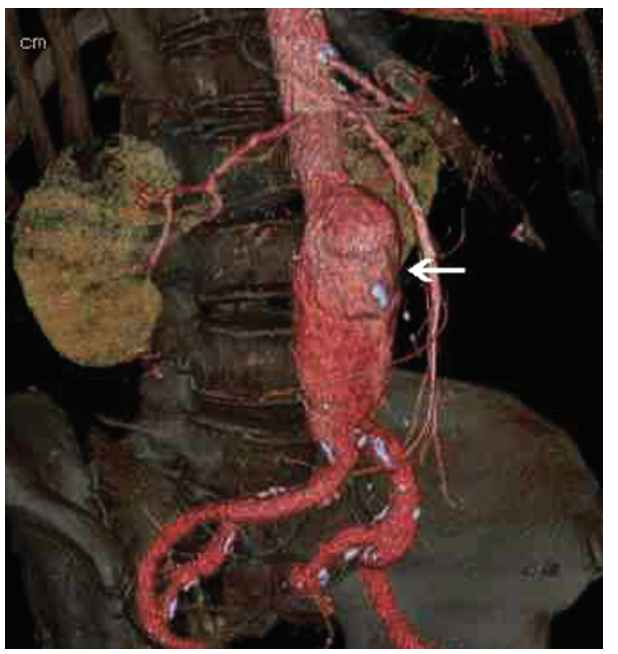


Figure 1.10 CT pulmonary angiogram showing a clot displacing contrast in both main pulmonary arteries (arrows).



(a)



(b)

Figure 1.11 (a) CT angiogram showing an abdominal aortic aneurysm (arrow) and (b) the volume-rendered reconstruction of the CT angiogram in the same patient.

functional cardiac detail. It can be used to characterise congenital heart disease, assess ventricular mass and function and differentiate forms of cardiomyopathy. Non-invasive functional cardiac MRI is recommended as an alternative to stress echocardiography or myocardial perfusion scintigraphy in the assessment of myocardial ischaemia using contrast-enhanced perfusion or stress-induced wall motion abnormality techniques.

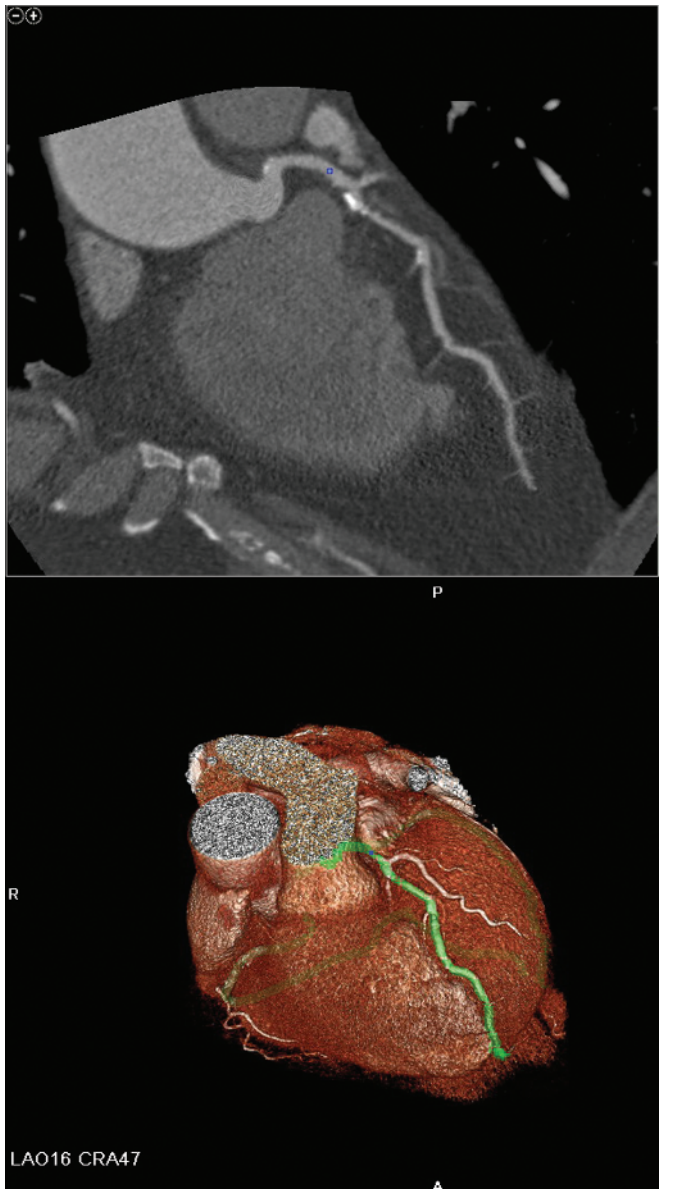


Figure 1.12 Calcified stenosis (arrow) of the proximal anterior descending branch of the left coronary artery.

Investigations in venous disease

Venous thrombosis

Colour duplex scanning is both sensitive and specific (90–100% in most series) for detecting proximal deep vein thrombosis (DVT).

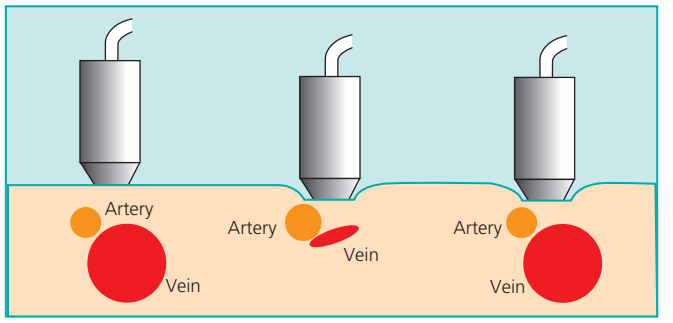


Figure 1.13 Ultrasound detection of a DVT. The probe is held lightly on the skin and advanced along the course of the vein (left). Pressure is applied every few centimetres by compressing the transducer head against the skin. The vein collapses during compression if no thrombus is present (middle) but not if a DVT is present (right).

Deep veins and arteries lie together in the leg, and the normal vein appears as an echo-free channel and is usually larger than the accompanying artery. Venous ultrasound has proved to be a very accurate method of identifying DVTs from the level of the common femoral vein at the groin crease to the popliteal vein, but the technique is much less reliable for diagnosing calf vein thrombosis (Figure 1.13). Approximately 40% of calf DVTs resolve spontaneously, 40% become organised and 20% propagate. Propagating DVT can be excluded by serial duplex scanning with an interval of 1 week.

Unenhanced or contrast magnetic resonance venography (MRV) is useful for examining the intracranial venous system, particularly in evaluating suspected dural venous sinus thrombosis. MRV and conventional enhanced (portal venous phase) CT can also be used to diagnose thrombus in intra-thoracic and abdominal veins.

Venous reflux

Colour duplex has revolutionised the investigation of the lower limb venous system because it allows instantaneous visualisation of blood flow and its direction. Thus, reflux at the saphenofemoral junction, saphenopopliteal junction and within the deep venous system, including the popliteal vein beneath the knee and the gastrocnemius veins, can be demonstrated non-invasively. Although a limited assessment of venous reflux can be undertaken using a pencil Doppler, compared with colour duplex the pencil Doppler misses ~12% of saphenofemoral and ~20% of saphenopopliteal junction reflux.

Further reading

Burrill J, Dabbagh Z, Gollub F, *et al*. Multidetector computed tomographic angiography of the cardiovascular system. *Postgrad Med J* 2007;**83**:698–704.

Chest Pain of recent onset; assessment and diagnosis of recent chest pain or discomfort of suspected cardiac origin NICE clinical guideline 95 March 2010.

Layden J, Michaels J, Bermingham S, and Higgins B, (on behalf of the clinical guideline development group). Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance. *BMJ* 2012;**345**:42–43.

Orbell JH, Smith A, Burnand KG, *et al*. Imaging of deep vein thrombosis. *Br J Surg* 2008;**95**:37–136.

Ross R. Atherosclerosis – an inflammatory disease. *NEJM* 1999;**340**(2): 115–126.

Sheikh S, Gonzalez RG, Lev MH. Stroke CT angiography. In: Gonzalez RG, Hirsch JA, Koroshetz WJ *et al*., eds. *Acute ischaemic stroke – imaging and intervention*. Springer, Berlin, 2006.

Stein PD, Hull RD. Multidetector computed tomography for the diagnosis of acute pulmonary embolism. *Curr Opin Pulm Med* 2007;**13**:384–388.

Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing NICE clinical guideline 144 June 2012.