Vascular system 2: diseases affecting the arterial system

Key points

- In atherosclerosis, a lipid-rich plaque forms on the innermost layer of the artery wall
- Atherosclerosis plays a role in many diseases where there is narrowing or blockage of the arteries
- Modifiable risk factors for arterial disease include hyperlipidaemia, diabetes, hypertension and smoking
- In the coronary arteries ischaemia causes chest pain, while in the arteries of the lower limbs it causes claudication
- Vasculitides are diseases of blood vessels caused by immune-mediated processes

Author Selina Jarvis is a research nurse and former Mary Seacole development scholar at Kingston and St George’s University of London and King’s Health Partners (Guy’s and St Thomas’s Foundation Trust).

Abstract With its arteries and veins, the vascular system connects the heart with all other organs and tissues and circulates blood around the body. It can be affected by diseases with different pathogenic mechanisms. Many arterial diseases are underpinned by atherosclerosis, while some have genetic origins or are immune-mediated. This article, the second in a three-part series, describes the pathophysiology of the main arterial diseases. The first article in the series covered the anatomy and physiology of the vascular system, and the third will discuss diseases of the venous system.


The vascular system is a complex network of blood vessels connecting the heart with all other organs and tissues in the body via the arteries (which bring oxygenated blood to the organs and tissues) and veins (which return to the heart with deoxygenated blood). Its structure, physiology and function are described in the first article of this three-part series.

This article, the second in the series, reviews the common diseases affecting the arteries. In many of them, the underlying pathogenic process is atherosclerosis.

Atherosclerosis

The general term for the hardening of the arteries is arteriosclerosis – from the Greek arterio (artery) and skleros (hard). Arteriosclerosis can have different causes, including blood vessel calcification (more common in older people), but is most commonly due to atherosclerosis.

The disease is particularly prevalent in the Western world and is the single largest cause of arterial disease. It affects the larger and medium arteries, such as the aorta and the coronary, cerebral and peripheral arteries (Zhao, 2018). These become hardened and lined with atheroma ‘plaque’ – also known as atheroma, which restricts the supply of oxygenated blood to the organs and tissues.

The progressive formation of atheroma in the arterial vessels can begin in childhood. It is the result of endothelial cell dysfunction, lipid deposition and complex inflammatory processes.

The squamous epithelial cells that form the endothelium (innermost layer of the vessel wall) are delicate and vulnerable to hyperlipidaemia, hyperglycaemia (from diabetes), hypertension and toxins such as cigarette smoke, which culminates in low-grade inflammation. Once injured, the endothelial cells change shape and their properties are altered; they become increasingly permeable to fluids, lipids and immune cells.

Monocytes are immune cells that survey the integrity of the endothelium. If they detect damage, they go to the damaged
Atherosclerotic narrowing, and atherosclerosis is the most common cause of coronary artery disease (CAD) (Jarvis and Saman, 2017).

Narrowing or blockage of the coronary arteries causes ischaemia, which often manifests as chest pain. In stable angina, there is a fixed flow defect caused by a stable atheroma restricting blood supply to the myocardium. When a patient with stable angina undertakes exercise or is under stress, there is a mismatch between blood supply to, and blood demand of, the myocardium, which causes chest pain. Upon rest or stress reduction, the symptoms resolve.

In unstable angina (UA), which belongs to a spectrum of conditions called acute coronary syndrome, the atheroma progresses further and chest pain may also occur at rest and become more frequent and/or more severe. However, in the case of UA, there is no detectable myocardial cell necrosis when assessed using biochemical tests such as troponin levels (a myocardial protein used as a marker of damage).

Cholesterol accumulates not only in foam cells, but also in the atheroma itself, where it forms a lipid core. Lipid-rich plaques contain inflammatory cells, smooth muscle cells, cellular debris and a fibrous capsule. The plaques are prone to rupture, which can ultimately block arterial blood flow, leading to a dramatic mismatch between supply to, and demand of, the affected organs or tissues.

In the heart, aberrations in arterial blood flow can lead to myocardial infarction (MI). In the arteries supplying the brain, atherosclerosis can lead to a cerebrovascular accident (stroke), either because the arteries have become stenotic or due to atherosclerotic plaque rupture and formation of a new thrombus, which migrates and affects cerebral blood flow. Blockage of the arteries supplying the lower limbs has similar effects, causing peripheral arterial disease (PAD).

The atheroma tends to form at sites where arteries bend, branch off or bifurcate (for example, where the two common carotid arteries divide into the two internal and external carotid arteries).

Conversely, stretches of straight blood vessel often remain atheroma free, compared with areas where there is disturbed blood flow. Such sites are characterised by alterations in blood flow and shear stresses (caused by frictional forces by the blood flow) on the endothelium, which plays a role in atherosclerosis (Zhao, 2018).

**Coronary artery disease**

The coronary arteries provide oxygenated blood to the heart (myocardium). The right and left coronary arteries and their branches are easily affected by atherosclerotic narrowing, and atherosclerosis is the most common cause of coronary artery disease (CAD) (Jarvis and Saman, 2017).

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Clinical Practice

Systems of life

Complete abrogation of the coronary blood supply can result in irreversible damage to the region of the myocardium supplied by the affected artery. This often occurs due to the rupture of an atheroma in the vessel wall, which triggers the formation of a thrombus.

The thrombus causes acute ischaemia, which, if left untreated, can lead to myocardial cell necrosis and MI involving either the whole thickness of the heart muscle (ST elevation MI) or only part of the cardiac wall (non-ST elevation MI). In case of ST elevation MI, without reperfusion within 6-12 hours, there will be irreversible damage, cardiac remodeling, arrhythmias, heart failure and a high risk of death (Jarvis and Saman, 2017).

Cerebrovascular disease

The brain receives blood from two main paired arteries; the internal carotid and vertebral arteries, and where their branches terminate (at the base of the brain) form the anastomotic Circle of Willis supplying different regions of the brain (Fig 2).

Cerebrovascular disease (CVD) includes events, such as cerebrovascular accidents (strokes), in which brain tissue becomes starved of oxygen and risks permanent damage. This can occur either due to a vessel occlusion that alters the intracerebral blood supply or haemorrhage caused by vessel rupture.

Causes of CVD can be further described as:

- Intrinsic blood vessel defect secondary to atherosclerosis, inflammation or malformation, or due to aneurysm (abnormal widening of an artery) or dissection (tear in the intimal layer of an artery wall);
- Blockage of an intracranial blood vessel by an embolus that has migrated from extracranial vessels after – for example, clot formation in the heart due to atrial fibrillation or atheromatous plaque rupture and thrombus formation in the carotid arteries;
- Inadequate cerebral blood flow and decreased perfusion due to an injury or hyper-viscosity of the blood (for example, in polycythaemia);
- Blood vessel rupture causing haemorrhage.

Around 20% of strokes are caused by brain haemorrhage (haemorrhagic stroke), while 80% are due to a blockage from thromboembolic disease (ischaemic stroke) (Caplan, 2018). Table 1 lists the different types of stroke and the risk factors.

In acute cerebral infarction, there is neuronal cell necrosis, which can cause permanent damage unless reperfusion with thrombolytics (‘clot-busting’ drugs) is undertaken urgently.

In transient ischaemic attack (TIA), there is transient ischaemia usually lasting two to three hours; however this can last up to 24 hours. TIAs can be a predictor of future strokes, especially if risk factors are not managed. It was previously thought that TIAs did not cause any lasting neurological damage, however, neuroimaging has shown that, in 50% of patients, there are micro-infarctions associated with cognitive decline (Bivard et al, 2018; Ay and Koroshetz, 2006).

One cause of haemorrhagic stroke is intracranial aneurysm, which results from a weakness of the vascular wall, ballooning and becoming prone to rupture. Intracranial aneurysm causes most cases of subarachnoid haemorrhage (SAH); 75% of patients with SAH are under 65 years of age. Berry aneurysms are responsible of 85% of cases of SAH; they are referred to as berry aneurysms because the dilated vessel resembles a ‘berry on a stem’ and these may occur in the Circle of Willis (Fig 2) (Newby et al, 2014).

Table 1. Stroke types and risk factors

<table>
<thead>
<tr>
<th>Stroke types and risk factors</th>
<th>Risk factors</th>
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<tbody>
<tr>
<td>Haemorrhagic stroke</td>
<td>Hypertension, trauma, vascular malformations, bleeding diatheses, illicit drug use</td>
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<tr>
<td>Intracerebral haemorrhage</td>
<td>Smoking, hypertension, genetic susceptibility, cocaine use</td>
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<tr>
<td>Subarachnoid haemorrhage</td>
<td>Atherosclerotic risk factors (for example, age, gender, smoking and diabetes); history of stroke or transient ischaemic attack</td>
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<tr>
<td>Ischaemic stroke</td>
<td>History of heart disease, atrial fibrillation, valvular disease, endocarditis</td>
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<tr>
<td>Ischaemic (thrombosis)</td>
<td>Atherosclerotic risk factors (for example, age, gender, smoking and diabetes); history of stroke or transient ischaemic attack</td>
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<tr>
<td>Ischaemic (embolic)</td>
<td>Atherosclerotic risk factors (for example, age, gender, smoking and diabetes); history of stroke or transient ischaemic attack</td>
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</table>

Source: adapted from Caplan, 2018
Clinical Practice

Systems of life

Some cases cases of berry aneurysm occur in association with adult polycystic kidney disease or with other genetic diseases such as Ehlers-Danlos syndrome (a collagen disorder). In the remaining cases, 5% may be due to an arterio-venous malformation and 10% of cases of SAH may be due to non-aneurysmal causes.

Aortic disease

Diseases that affect the aorta – the largest artery in the body – can lead to aneurysm or dissection or can cause aortitis – inflammation of the aorta. In many cases a decision must be made for patients to have either active surveillance or prompt intervention. In some of these diseases, atherosclerosis is the key underlying process, but the aorta is also affected by many diseases with a completely different pathogenesis.

An aortic aneurysm refers to abnormal widening of the aorta, which makes the vessel prone to rupture. An anortic dissection is when there is a tear in the tunica intima (innermost layer) of the vessel wall which allows blood to track between the tunica intima and tunica media. Both can affect either the thoracic aorta, or the abdominal aorta – or both.

Aortic aneurysm

An aorta with an aneurysm is more than 1.5 times the anteroposterior diameter expected for the patient's age and gender (Sheehan, 2017). Although aortic aneurysms can occur in the thoracic segment of the aorta, in 90% of cases they are abdominal and situated below the renal arteries.

Most aortic aneurysms are secondary to atherosclerosis, but they can also be due to cystic medial necrosis (CMN), a completely different process involving cyst-like lesions and the accumulation of a basophilic ground substance.

In CMN, the aorta shows signs of collagen and elastin loss from its tunica media and tunica externa (external layer of the vessel wall), as well as marked smooth muscle loss. The aorta becomes vulnerable and, in case of abdominal aortic aneurysm (AAA), is at risk of rupture. Without prompt diagnosis and intervention, a ruptured AAA will lead to massive haemorrhage and death.

Some genetic connective tissues disorders, such as Marfan syndrome or Ehlers-Danlos syndrome, can affect the elasticity of the aorta, leading to CMN and putting patients at risk of aortic aneurysm (and aortic dissection). Other genetic diseases may also be implicated. Aortic aneurysms are sometimes caused by aortitis linked to conditions such as syphilis, or by diseases such as Takayasu’s arteritis, Reiter’s syndrome, giant cell arteritis and ankylosing spondylitis (Newby et al, 2014).

Aortic dissection

The aorta is exposed to high pulsatile blood pressures and shear stresses, and so may be more vulnerable to rupture than any other blood vessel. A tear in its intimal layer can cause aortic dissection, the majority of which occur within 10cm of the aortic valve.

The tear in the intimal layer is the initial insult. As blood flows through it, there is subsequent degeneration of the medial layer and creation of a false lumen alongside the true lumen of the aorta.

Blood flows between the tunica intima and media eventually separating these layers causing a false lumen. This diversion of blood flow from its normal course means that, eventually, blood flow through some branches of the aorta may be reduced. This leads to reduced blood flow in the coronary, brachiocephalic, intercostal, visceral, renal and iliac vessels (Safi, 2017).

Aortic dissection may be congenital or acquired, and is more common in people with hypertension. As mentioned above, genetic connective tissue disorders such as Marfan syndrome and Ehlers-Danlos syndrome can increase the risk of aortic dissection. Patients with congenital aortic stenosis and metabolic disorders such as homocystinuria are also at increased risk. Pregnancy may be a risk factor in women presenting with aortic dissection before the age of 40.

Aortic dissection can be categorised based on whether it affects the ascending or the descending aorta – or both.

Peripheral arterial disease

Peripheral arterial disease (PAD) refers to arterial syndromes caused mainly by atherosclerotic obstruction in the arteries of the lower limbs. Risk factors for PAD are therefore similar to those for atherosclerosis (smoking, diabetes, hypertension and hyperlipidaemia). Causes of PAD are listed in Box 1.

PAD can be classified according to disease severity; its prevalence increases from the age of 40 and is highest in people with a history of CAD and/or CVD (Armstrong, 2017).

Over time, PAD causes luminal narrowing of the blood vessels, limiting blood flow to the tissues and leading to chronic ischaemic pain in the lower limbs. More advanced PAD can lead to arterial obstruction resulting in pain at rest, ulceration and compromised tissue viability.

Ischaemic leg pain that is relieved by rest (usually resolving within around 10 minutes) and occurs at particular walking distances is referred to as intermittent claudication. Patients with PAD may experience pain in the feet, calves, thighs or buttocks, according to which part of the peripheral arterial blood supply is affected:

- Buttock or hip claudication is due to PAD in the aortoiliac vessels;
- Thigh claudication is due to PAD in the common femoral artery;
- Calf claudication is due to PAD in the superficial femoral artery (upper two-thirds of the calf) and popliteal artery (lower third of the calf);
- Foot claudication is due to PAD in the tibial and peroneal arteries.

Persistent ischaemia can damage the peripheral nerves, which can in turn lead to neuropathic pain and/or loss of sensation – potentially causing functional impairment, infections and foot ulceration (McDermott, 2015). PAD is more common in people with diabetes than in those without it (9.5% and 4.5%, respectively), with PAD exacerbating peripheral neuropathies, which are also more common in people with diabetes.

Patients who already have stenotic arteries in the limbs are at risk of developing acute limb ischaemia, which may be caused by a clot (thrombus) in the stenotic vessel, trauma or thromboembolism and this is a surgical emergency.

The clinical features of acute and chronic limb ischaemia are shown in Box 2.

Vasculitides

This refers to inflammatory diseases affecting the arteries and capillaries.
Vasculitides are a heterogeneous group of diseases driven by autoimmune processes. Often associated with rheumatological diseases, they include a broad range of diseases, some of which have a predilection for either a particular size of blood vessel or a particular organ. Classification of the vasculitides is based on the predominant size of the vessel affected but there may be some overlap with certain vasculitides (Merkel, 2018).

Table 2 lists the main types of systemic vasculitides. Their consequences depend on the size of the blood vessels they affect, how many vessels are involved, and/or the target organ. In many diseases that cause vasculitis, it remains unclear what the trigger is or why there is a predilection for a particular blood vessel or organ but these diseases have the common feature in that in most cases they occur due to an immune-mediated process.

**“Atherosclerosis is the often underlying process in the main arterial diseases”**

### Conclusion
Atherosclerosis is the often underlying process in the main arterial diseases (coronary artery, cerebrovascular, aortic and peripheral arterial disease). The rarer vasculitides have a different pathogenesis but potentially similar clinical manifestations. The incidence of arterial diseases is growing due to unhealthy lifestyles and the ageing of the population, increasing the burden on the healthcare system. Since many of them are due to atherosclerosis, active primary and secondary prevention through the management of modifiable risk factors is a priority. In some cases of arterial disease, prompt recognition of emergencies and referral for multidisciplinary care are needed. **NT**

### References