
The Aetiology of Vascular Disease

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Abstract

This chapter explains how and why vascular disease processes evolve into the lesions encountered by interventional radiologists.

1 Introduction

The aetiology of vascular disease describes the fundamental processes that are involved in the lesions treated by interventional radiologists. The principles that underpin the pathophysiology of these lesions also give rise to new therapeutic challenges such as treating neointimal hyperplasia and in stent restenosis which can, in turn lead to technological advances in stent and balloon design.

Before discussing these pathological processes, the normal anatomy will be briefly described.

2 Normal Arterial Structure and Physiology

The arterial system consists of three basic types of vessel.

1. The large elastic vessels in the thoracic aorta, abdominal aorta and the iliac arteries with their elasticity aid the maintenance of the diastolic blood pressure.
2. Medium-sized muscular arteries, including the superficial femoral and brachial arteries as well as visceral branches, which distribute blood to the capillary beds.
3. The smaller arterioles that modulate vascular tone and themselves have a large role in the regulation of systemic blood pressure and the delivery of oxygen and nutrients to the tissues.

The arterial wall consists of three layers; the tunica intima, tunica media and tunica adventitia. The intima is the internal layer of the artery and is formed from a single layer of mesenchymal endothelial cells, basement membrane and internal elastic lamina loosely attached to the media by

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supportive connective tissue. Endothelial cells have a complex role in the homeostasis of the vascular tree and adjacent flowing blood secreting enzymes, growth factors, immunoglobulins and anticoagulants depending on the vascular bed they serve.

The thickest layer of the arterial wall is the tunica media and consists mainly of elastic fibres and smooth muscle cells containing actin and myosin filaments which contract to varying degrees; hence the ability to modulate the arterial vascular tone and blood pressure. Pathologically the smooth muscle element of the media has an influential role to play in the development of the atherosclerotic plaque.

The adventitia comprises of loose connective tissue, lymphatics and its own nutrient arterial supply known as the vasa vasorum.

The arterial system can also be conveniently be classified into the particular vascular territories they supply such as cerebrovascular, coronary, renovascular and peripheral vascular beds.

3 The Aetiology and Pathophysiology of Atherosclerosis

The pathophysiology of atherosclerosis in the peripheral artery tree is complex, involving a disturbance of the normal homeostatic mechanisms including endothelial dysfunction (Anderson 1999), platelet activation, lipid metabolism, inflammatory response, oxidative stress, smooth muscle activation and thrombosis (Libby 2002).

3.1 Risk Factors

The main risk factors for the development of atherosclerosis are cigarette smoking, diabetes mellitus, hypertension and hyperlipidaemia. Cigarette smoking incurs the greatest risk in the initiation and development of atherosclerosis, with smokers up to five times more likely to develop the disease. The mechanisms are multifactorial involving endothelial dysfunction, increased oxidised LDL and a hypercoagulable state increasing the propensity for thrombosis.

Diabetes mellitus is an important risk factor for hyperlipidemia and atherosclerosis; it is also commonly associated with hypertension, abnormalities of coagulation, platelet adhesion and increased oxidative stress. Diabetics with poor glycaemic control are up to four times more likely to develop plaques (Fowkes et al. 1992, Kannel and McGee 1985). Stopping smoking along with good glycaemic control offers the greatest benefit in long term survival and limb salvage (Quick and Cotton 1982).

Hypertension is associated with morphologic alterations of the arterial intima and functional alterations of the

Table 1 Summary of stages of development of the atherosclerotic plaque

1. LDL absorbed into the subendothelial layer
2. LDL is oxidised
3. Macrophages are attracted into the subendothelial matrix and imbibe the oxidised LDL
4. SMCs are attracted into the matrix, proliferate and secrete glycoproteins
5. Plaque enlarges and fibroses
6. Vascular remodelling compensation
7. Loss of remodelling compensation, propensity for stenosis and occlusion
8. Unstable plaques may rupture and thrombose, leading either to vessel occlusion or distal embolisation

endothelium that are similar to the changes observed in hypercholesterolemia and established atherosclerosis. Endothelial dysfunction is also a feature of hypertension.

Hyperlipidaemia is an established risk factor for atherosclerosis. Oxidised LDL is a key feature in the development of plaques and there is convincing evidence that lowering serum cholesterol reduces the risk of subsequent coronary heart disease events and overall mortality (Gaziano 1996; Haffner et al. 1999).

Atherosclerotic lesions do not occur in a random fashion and haemodynamic factors are also important. Fluid shear stresses generated by blood flow activate the endothelium and influence the phenotype of the endothelial cells by modulation of gene expression. Atherosclerotic plaques characteristically occur in regions of branching and marked curvature at areas of geometric irregularity and where blood undergoes sudden changes in velocity and direction of flow. Increased shear stress and turbulence are thought to promote atherogenesis in these vascular territories (Topper and Gimbrone 1999).

3.2 The Development of the Atherosclerotic Plaque

The stages of development of atherosclerotic plaques are summarised in Table 1 and described in more detail in the following sections.

3.2.1 The Endothelium and Endothelial Dysfunction

A thin layer of vascular endothelium separates the circulating blood volume from the subendothelial matrix and the media of the blood vessels and is the key centre for vascular arterial homeostasis (Furchgott and Zawadzki 1980), controlling the balance between vasodilation and constriction,

coagulation and anticoagulation and the modulation of the inflammatory response.

These mechanisms are maintained by vascular autocrine and paracrine feedback loops involving prostaglandins, nitrous oxide (Ludmer et al. 1986) and angiotensin II. Endothelial dysfunction caused by the risk factors described previously potentiates the development and progression of atherosclerosis (Loscalzo 2001).

The endothelium also supports the recruitment and adhesion of macrophages and their diapedesis through the endothelium into the subendothelial matrix with the production and secretion of local cytokines (Rosenfeld 1996), these take up the oxidised LDL forming the basis of the atherosclerotic plaque (Libby 2000).

3.2.2 Inflammatory Response

Circulating LDL is absorbed into the subendothelial matrix and becomes oxidised (Hansson 2001). The inflammatory response is initiated via the secretion of selectins and cytokines which attract macrophages to migrate into the matrix from the blood via diapedesis (Hansson 2001). These scavenger white cells then imbibe the oxidised LDL becoming 'Foam cells' due to their lipid laden content. Cytokines have a secondary effect of stimulating smooth muscle cell (SMC) mitosis and migration into the subendothelial layer through the internal elastic lamina (Schonbeck 2001) thus forming the lipid laden plaque.

3.2.3 Role of Smooth Muscle Cells

Smooth muscle cells change their character once stimulated by injury, growth factor or cytokines becoming migratory secretory cells capable of proliferation via the process of mitosis and secretion of matrix proteins and enzymes that become the dominant component of plaque growth (Rivard 2000). The extracellular matrix of the plaque secreted by the SMCs contains products such as proteoglycans, collagen, elastin and fibronectin (Raines 2000). SMCs control the homeostasis of collagen metabolism and when stimulated in the process of atherosclerosis, favours the deposition of collagen and through maturation and shortening of the collagen fibres resulting in fibrosis and luminal stenosis (Rekhter 1999).

3.2.4 Compensatory Vascular Remodelling

To compensate for the enlarging atherosclerotic plaque and subsequent luminal narrowing the vessel enlarges to maintain luminal patency, a process known as geometric remodelling (Glagov 1987; Pasterkamp 2000). However, once the plaque has reached a critical size (>40% of the cross sectional area) the artery can no longer enlarge and the lumen narrows as the plaque grows. The injury also initiates vasoconstriction further narrowing the lumen contributing

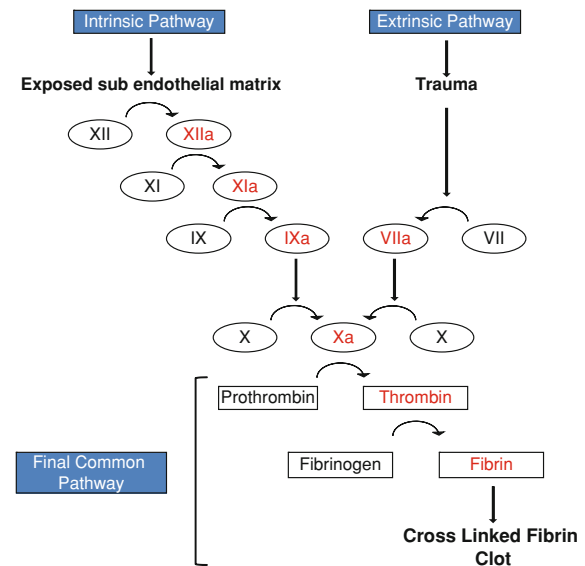


Fig. 1 Coagulation cascade

to the stenosis which can often be treated with angioplasty and stenting.

3.2.5 Unstable Plaques

Plaques susceptible to rupture have been shown to have a lipid laden core with a thin fibrous cap and inflammatory macrophages at the cap surface (Davis 1993). Enzymes secreted by the macrophages breakdown the thin cap eventually leading to plaque rupture (Galis 2002), and exposure of the underlying proteins e.g. Von Willebrand Factor initiating platelet aggregation and thrombosis (see Sect. 3.2.6) that can critically stenose or occlude the lumen causing acute symptoms (Makin 2002). This pathophysiological event is important in the acute presentation of Peripheral vascular disease, coronary thrombosis, and also has a role in carotid artery platelet emboli and transient ischaemic attack.

3.2.6 Thrombosis

The process of thrombosis begins with primary haemostasis, whereby platelets adhere to the damaged endothelium. This is followed by platelet granule release and platelet aggregation.

Secondary haemostasis involves the coagulation cascade (Fig. 1) which comprises the extrinsic pathway [now called the tissue coagulation pathway (TCP)] and the intrinsic pathway [now known as the contact activation pathway (CAP)]. The final common pathway links the TCP and CAP resulting in the conversion of prothrombin to thrombin and fibrinogen to fibrin the cross linked clot.

Thrombolytic agents e.g. Alteplase (rt-PA tissue type plasminogen activator) are employed in arterial and venous

thrombosis. These reverse the final common pathway activating plasminogen to form plasmin which degrades fibrin into soluble fragments and breaks up the clot.

During plaque rupture the underlying 'naked' lipid core and subendothelial proteins such as von Willebrand factor become exposed to the circulating blood volume which bind and activate platelets, secreting a host of factors including platelet activating factor (PAF) and Thromboxane A₂ (TxA₂). This in turn causes further platelet aggregation in the exposed tissue (primary haemostasis) and launches the TCP (formerly the extrinsic pathway) resulting in thrombosis within the ruptured plaque. (MacFarlane 1964). Usually the vessel wall remodels into a stenosis at this level with the inflammatory response (see Sect. 3.2.2) but occasionally platelets may embolise resulting in trash foot or the fibrin cross linked clot is released causing acute ischemia in the vascular bed it serves (Rauch et al. 2001).

3.2.7 Embolic Phenomenon

Types

1. Thromboembolic
2. Fat e.g. during orthopaedic procedures or after fractures of long bones
3. Amniotic Fluid
4. Talc e.g. intravenous drug abuse
5. Therapeutic e.g. Uterine artery embolisation

Peripheral vascular disease exhibits a more chronic progression with claudication, rest pain and ulceration and the gradual build up of a collateral circulation embolic phenomena typically present acutely with pain, pallor, paraesthesia, pulselessness and paralysis due to a poor collateral circulation and the abrupt occlusion of the vessel.

It is worth noting that 80% of peripheral vascular emboli originate from cardiac pathology such as untreated arrhythmias (atrial fibrillation especially) and myocardial infarcts. Disruption of the normal cardiac cycle in vivo initiates the clotting cascade via the TCP and the fragmented thrombus is ejected into the vascular tree. The majority of the rest are migrated in situ thromboemboli.

4 Neointimal Hyperplasia

One of the complications of peripheral bare metal stent deployment for arterial stenosis and occlusive disease is restenosis due to neointimal hyperplasia (NIH). Restenosis after successful angioplasty, as well as after surgical bypass grafting may also be caused by NIH. Finally it can be seen at the ends of endovascular stent grafts. Stent insertion disrupts the endothelium exposing the subendothelial tissues to the circulating blood volume causing platelet adhesion and aggregation to the underlying thrombogenic proteins e.g. von Willebrand factor. Activated platelets

secrete growth factors such as platelet derived growth factor (PDGF) which stimulate the migration of SMCs and the remodelling process is activated (Richter et al. 2000) (see Sect. 3.2.4). Nitrous oxide plays a role in stimulating SMC proliferation and with the changes in sheer stress within the stented section are thought to be the cause of in stent restenosis. In effect the stimulus for remodelling and SMC proliferation is not switched off (Richter et al. 2000).

The pathophysiology of neointimal hyperplasia has given rise to novel innovations in intervention including drug eluting balloons and stents after the success of similar therapeutic agents in the coronary arteries. The cost/benefit remains to be proven in the peripheral arteries.

Drug eluting technology aims to interrupt one part of the restenosis mechanism either being antithrombotic (Heparin coated), anti-inflammatory (corticosteroid) or antiproliferative (chemotherapeutic agents such as methotrexate and paclitaxil) thus increasing the longevity of the angioplasty or stent.

5 The Aetiology of Arterial Aneurysms

The incidence of abdominal aortic aneurysms (AAAs) in post mortem studies from Sweden found AAA's in 4.7% of men and 1.7% of women aged 56–74 years old (Bengtsson et al. 1992). This was correlated in a prospective screening study of more than 125,000 patients aged 50–79 years old with the definition of an aneurysm given as an aortic diameter of >3 cm (Brady et al. 2001).

5.1 Types

The majority of aneurysms seen in modern practice are due to vascular degeneration and dilation of the large elastic vessels. Mycotic aneurysms are rare and are caused by destruction of the media by bacteria in infected thrombus and represent a significant clinical challenge (Johnson et al. 1983).

Intracranial 'Berry' aneurysms, can be congenital in origin with defects in the elastic lamina/media of the vessel wall but also environmental e.g. hypertension. Endovascular treatment of these has revolutionised practice in recent years.

Pseudoaneurysms (false aneurysms) are specific entities consisting of a haematoma that communicates with the arterial wall. Usually iatrogenic, they are also seen associated with pancreatitis where the extra visceral enzymes erode the splenic artery wall and may also occur after trauma. These types of aneurysm complicate 0.2% of diagnostic catheter aneurysms and up to 2.2% of arterial interventional procedures (Messina et al. 1991).

5.2 True Arterial Aneurysms

The tensile strength of the artery is determined mainly by the structure of the media and the elastin and collagen fibres within it. In aneurysmal disease the homeostatic balance between the elastase proteolytic enzyme and alpha 1 anti-trypsin (elastase inhibitor) is disrupted, often by an environmental factor such as cigarette smoking resulting in a generalised increase in elastase (Campa 1987; Cohen 1991; Tilson 1988).

Abdominal aortic aneurysms have been attributed to a weakening of the arterial wall as a result of atherosclerotic vascular disease caused by the atheromatous lesions. Recent evidence supports a multifactorial process in which atherosclerosis is involved, but is not the only causative factor. Other aetiological factors include changes in the matrix of the aortic wall with age, proteolysis, metalloproteinase changes, inflammation, infectious agents (e.g. syphilis, bacterial infections) and a genetic predisposition (e.g. Marfan syndrome; Ehlers-Danlos syndrome).

The development of atherosclerotic plaques within the aorta and the inherent repair mechanism that surrounds this initial insult renders the media subject to neutrophil infiltration and as such the potential for elastase and collagenase secretion. This, combined with an increase in diastolic blood pressure, weakens the tensile strength of the aorta and it gradually dilates. Environmental and genetic factors have a large role in aneurysm development and make it difficult to predict who may be prone to the disease (Rehm 1998).

True aneurysms involve dilation of all three layers of the vessel wall, whereas false aneurysms are caused by the disruption of one or more layers of the vessel wall and are usually either iatrogenic or post traumatic. Elastin and collagen are the primary structural elements of the aortic wall. The distribution of elastin and collagen fibres are lowest in the infrarenal aorta and hence, with their proteolytic destruction, dilatation of the aorta ensues, often resulting in rupture, unless there is early open surgical or endovascular management. Once an aneurysm diameter is more than 6 cm there is a 25% annual rupture risk. The risk of cardiac related mortality has also been shown to be proportional to aneurysm size.

Increased concentrations of several proteases capable of degrading collagen and/or elastin have been found in the walls of AAAs and in aortic occlusive disease; both are also associated with atherosclerosis.

An immunologic component to atherosclerotic vascular disease has been recognised and is characterised by infiltration of the aortic wall by macrophages, T lymphocytes, and B lymphocytes; these are known to activate proteolytic activity. The nature of this response has led researchers to investigate an autoimmune role in the pathogenesis of AAA.

Recent reports describe *Chlamydia pneumoniae* antigens, in contrast to active infection, in the walls of AAA. After the infectious agent is cleared, an antigenic stimulus remains, stimulating proteolytic activity with weakening of the vessel wall and aneurysm formation. Inflammatory aneurysms, once believed to be distinct entities, are currently considered one extreme in the spectrum of aneurysms; these account for 3–10% of all AAAs (Rasmussen 1997).

The familial pattern of AAA has long been recognized with a 15–19% incidence among first-degree relatives (Salo 1999). This observation suggests that one or more genes are related to AAA and atherosclerosis. The identification of these genes may ultimately enable the early detection and prevention of AAA in high-risk patients (Hirose 1998).

6 Dissection

Aortic Dissection is associated with hypertension, connective tissue disease and trauma. Hypertensive dissection can arise anywhere from the aortic root propagating proximally and distally for a variable distance. The highest incidence of aortic dissection occurs in the 50–70 year age group with a significant proportion of dissections in young people and during pregnancy. From a flap in the intima blood penetrates the tunica media and cleaves between the laminated outer 2/3 and inner 1/3 of the media, usually in a spiral fashion, down the aorta forming both true and false lumens. As the false lumen is pressurised this often compresses the true lumen (Hagan et al. 2000; Meszaros et al. 2000).

Connective tissue disease e.g. Ehler-Danlos syndrome and Marfans syndrome, can be the initiating factor due to degeneration in the collagen and elastin causing cystic medial necrosis. This tends to be encountered in a younger cohort of patients

7 Fibromuscular Dysplasia

7.1 Background

Fibromuscular dysplasia (FMD) is a non atherosclerotic, noninflammatory vascular disease that was first reported by Leadbetter and Burkland in 1938, and described originally as a disease of the renal arteries. However it has subsequently been shown that it can affect virtually any vascular arterial bed.

Fibromuscular dysplasia is an angiopathy that affects medium-sized arteries predominantly in young women of childbearing age. It most commonly affects the renal arteries and is a cause of refractory renovascular hypertension. Of patients with identified FMD, renal involvement

occurs in 60–75%, cerebrovascular involvement occurs in 25–30%, visceral involvement occurs in 9%, and arteries of the limbs are affected in about 5% (Luscher et al. 1987; Gray et al. 1996).

In patients identified with cephalic FMD, 95% have internal carotid artery involvement and 12–43% have vertebral artery involvement. Although FMD can affect arteries of any size (Hill and Antonius 1965), involvement of smaller ones, including intracranial vessels, is rare.

7.2 Types

These are related to the three layer structure of the artery: Intimal fibroplasia: <1%—Long smooth narrowing which appears radiologically similar to vasculitis (Harrison and McCormack 1971).

Medial fibroplasias: Commonest—‘String of Beads’ in middle section of the artery (Begelman and Olin 2000).

Adventitial fibroplasias: Rarest—Peri arterial hyperplasia, a collar of elastic tissue causing short tight stenosis (McCormack et al. 1966).

7.3 Aetiology

The aetiology of FMD is not known, however a variety of genetic, mechanical and hormonal factors have been proposed. The strongest link is genetic as the disease is more common in first-degree relatives of patients with FMD of renal origin (Pannier-Moreau et al. 1997).

Several other associated vascular pathologies have been identified, including aneurysms 7.3% (Cloft et al. 1988) and arterial dissection. For example, it is a predisposing factor in 15% of spontaneous cervical carotid artery dissections (Arunodaya et al. 1997; Eacahempati et al. 1998).

The increased incidence of FMD in women as compared with men suggests a possible hormonal or genetic influence. Some authors have proposed the sex difference to be related to immune system functioning, but overt inflammation, as is observed in most classic autoimmune diseases, is histologically lacking.

The Ehlers–Danlos syndrome (type IV) has been associated with medial fibroplasia. This syndrome should be suspected in patients with multiple aneurysms in addition to the typical angiographic findings of fibromuscular dysplasia (Schievink and Limburg 1989).

In case reports, FMD has been associated with mutations in collagen (Tromp et al. 1993), and with alpha1-antitrypsin deficiency (Schievink et al. 1998). Associations with neurofibromatosis, Alport syndrome, and pheochromocytoma have also been suggested (Gray et al. 1996).

8 Venous Disease

8.1 Normal Anatomy

Macro- and microscopically venous anatomy mirrors the arterial system with an intima, media and adventitia. The intima is composed of endothelial cells overlying a basement membrane and elastic lamina. In tunica media consists of inner and outer smooth muscle cells linked by an extra cellular matrix and the adventitia, irregular layers of collagen, fibroblasts and the vasa vasorum. The media in the arterial system is a much thicker layer and as described earlier controls the vascular resistance and blood pressure whereas the thinner veins act as capacitance vessels.

8.2 Venous Disorders

The key venous disorders encountered clinically are thromboembolic phenomena (deep vein thrombosis and pulmonary emboli) and varicose veins.

8.3 Thromboembolic Phenomena

The aetiology of venous thromboembolic disease is eloquently described and easily remembered by Virchow’s Triad:

1. Venous stasis: e.g. Extrinsic compression, diseased valves, surgery,
2. Hypercoagulability: e.g. Smoking, pregnancy, Anti-thrombin III, Protein C & S deficiency,
3. Endothelial injury: e.g. Trauma, Hypertension.

Any or all three of the triad can predispose the vein to a thrombosis (see Sect. 3.2.6) via initiation of the coagulation cascade resulting in the conversion via the common clotting pathway of prothrombin to thrombin and fibrinogen to fibrin dislodging this thrombus results in the formation of a pulmonary embolus. Once the risk of venous thromboembolism has been assessed there are many medical and interventional strategies to control the thrombotic process whilst trying to elucidate the cause.

In the acute phase of DVT catheter directed thrombolysis can dissolve the deep vein thrombus and reveal the underlying cause, usually a venous stricture e.g. May Thurner syndrome which can then be stented. Treating the thrombus in the acute phase can often avoid symptoms of post phlebitic limb which can be both debilitating for the patient and long term health care.

In the chronic phase anticoagulation to prevent thrombus progression is the mainstay of treatment but in certain circumstances insertion of an inferior vena caval (IVC) filter is necessary to avoid the consequences of a pulmonary

embolus especially if the patient has a contraindication to anticoagulation or requires a surgical procedure.

8.4 Varicose Veins

8.4.1 Aetiology

Varicose veins may be familial, and may also be seen secondary to venous obstruction due to previous DVT. They are also more common in pregnancy and may be seen in the presence of pelvic mass lesions.

Histological a varicosity is characterised by disruption of the normal venous architecture with asymmetrical areas of fibrosis causing localised thickening, remodelling of SMCs in the media and intimal thrombosis in various stages of organisation.

Several theories aim to explain the underlying mechanisms from incompetent valves, disturbance of the SMCs in the media creating a weakness in the venous wall to oestrogen-related hormonal changes during pregnancy. They may all have a contributory effect in the development of varicose veins. (Somers and Knappen 2006)

Peripheral varicosities of the long saphenous and short saphenous system can occur due to failure of the valve at the sapheno-femoral junction.

Varicoceles and pelvic congestion syndrome are similar conditions with damaged abnormal valves causing venous congestion however a varicocele can be associated with a renal tumour and this should be excluded before treatment.

9 Conclusion

The most common vascular diseases encountered by Interventional Radiologists are due to atherosclerosis and aneurysmal disease. Although with public health measures such as a reduction in smoking, the incidence of atherosclerosis may decline in the future, it currently represents a significant public health issue. In addition, the increasing prevalence of diabetes within the population would suggest that atherosclerosis will not disappear altogether. The very fact that we intervene can throw up new challenges such as neointimal hyperplasia. Endovascular techniques will therefore remain at the forefront of the management of peripheral vascular disease for the foreseeable future.

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