PART I

Natural history and preoperative planning
CHAPTER 1

Etiology and pathogenesis of aortic disease

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The aorta can be affected by a variety of pathological conditions. Some of them have a clear genetic component and affect young patients or patients in the early adolescence. Most pathology is however encountered in the grown-up population and is caused by degenerative diseases. This chapter will focus on the following pathological conditions that affect the aorta: atherosclerosis, aneurysms, dissections, Marfan’s syndrome, Ehlers–Danlos syndrome, and Takayasu’s disease.

Atherosclerosis

Atherosclerosis is a systemic and generalized disease that is the main cause for premature death in the adult population in the Western world. Several vascular beds are affected simultaneously, the heart, brain, viscera, and extremities. The pathophysiology of atherosclerosis in large arteries, such as aorta, is not different from that in small vessels. The etiology of atherosclerosis is extremely complex. Despite intense research there is still a long way to go before we have a good understanding of the disease that is reflected in new preventive and therapeutic strategies. The atherosclerotic process involves predominantly the intimal and medial layers of the wall.

The response to injury hypothesis proposed by Ross has had a heavy input on atherosclerotic research [1, 2]. It has stimulated research on endothelial interaction with blood cells and signaling to smooth muscle cells. An initial event is some sort of injury to the endothelium leading to permeability alterations allowing passage of large molecules such as lipids. The injury may not be mechanical. Low-density lipoproteins in hypercholesteremic patients can in itself cause endothelial injury.

The thromboresistance is lost with increased risk for thrombosis. Platelets adhere to the site of injury. They release growth factors, e.g. PDGF (platelet-derived growth factor) which is a strong mitogen for smooth muscle cell proliferation. This local stimulus leads to accumulation of smooth muscle cells within the intima and deposition of extracellular matrix proteins. Furthermore, there is deposition of lipids and infiltration of lipid-loaded cells. A proliferative lesion has been formed.

Fatty streak and fibrous plaque

The intimal layer with the endothelial cells is the first line of defense against atherosclerosis. The very first event is the fatty streak which consists of lipid accumulation in macrophages located in and beneath the endothelium [3]. Depending on genetics and life style, the fatty streak may either regress or progress into atheroma. Progression of lipid accumulation leads to focal intimal thickenings. Formation of fibrous plaques is usually not seen until in the fourth decade. Fibrotic tissue and smooth muscle cells form a fibrous cap surrounding the lipid core. There is a necrotic center of amorphous material, extracellular proteins, matrix fibers, lipid-containing cells, cholesterol crystals, and calcium salts. The plaques are infiltrated with vasa vasorum. The lipid-rich core is extremely thrombogenic due its high content of tissue factor. An intact fibrous cap prevents release of procoagulative activity.

The lesions can be characterized as soft or hard. The soft plaques are dominated by lipid deposition in the necrotic core. They are particularly prone to rupture leading to thrombotic complications. The hard sclerotic lesions are characterized by
calcification. They cause stenosis and, depending on the degree of flow impairment, ischemia.

**Inflammation and plaque**

The involvement of inflammatory cells as well as their activation has put forward the hypothesis of inflammation as an initial event in atherosclerosis. The atheromatous plaque consists of a core of foam cells and lipids. The border regions, shoulders, of the plaque are made up of inflammatory cells such as T-cells, macrophages, and mast cells [4]. These cells produce cytokines as signs of activation [5]. The plaques are predominantly located in areas of flow disturbances such as branches. The macrophages produce PDGF as a mitogen, cytokines and growth factors. Interleukin 1 (IL-1), tumor necrosis factor α (TNF-α), transforming growth factor β (TGF-β), and several others factors are produced. Through these mediators, the macrophages can affect and regulate cellular organization in the plaque. The macrophages may be antigen presenting cells to T-lymphocytes that participate in the inflammatory process. Oxidized LDL is such an antigen that can trigger the inflammation [6].

**Role of the endothelium**

The integrity of the endothelium is essential in preventing the initial developments of the plaque. Perturbation of the endothelium causes expression of growth factors that stimulate proliferation of smooth muscle cells. Likewise adhesion molecules are expressed on the endothelial surface causing cellular interactions. Platelets adhere to the endothelium through expression of their surface glycoproteins Ib and IIb/IIIa. Specific adhesion molecules such as selectins are involved in leukocyte rolling on the surface followed by sticking and extravasation of the cells. VCAM-1, vascular cell adhesion molecule, adheres monocytes and lymphocytes and is upregulated by high cholesterol levels. Activated adhering cells and cells in the vessel wall release inflammatory mediators, e.g., cytokines. Proteolytic enzymes, metalloproteinases (MMPs), and their inhibitors are activated and contribute to the development of the plaque by facilitating migration and proliferation of cells.

Recent research has demonstrated the importance of a variety of immune cells in the atherosclerotic process. T-cells activated from antigens release cytokines, which trigger activation of macrophages and other vascular cells. The process is balanced by regulatory T-cells, which produce IL-10 and TGF-β, both anti-inflammatory mediators. Release of inflammatory cytokines especially IL-6 will stimulate production of CRP in the liver. An excellent and comprehensive review of inflammation and atherosclerosis was recently published [7].

**Plaque rupture**

There is an overwhelming body of knowledge on the role of plaque rupture to initiate thrombosis and ischemia [8]. Most of the data stems from coronary arteries but the process does not differ in other parts of the vascular system.

The lipid core of the plaque is highly thrombogenic due to its content of tissue factor. When the lipid is sealed in its fibrous cap, it is harmless but when released it initiates an immediate and very strong coagulation. Activated macrophages in the plaque express tissue factor, which further enhances the thrombotic state.

The shoulders of the plaque are at risk for rupture. Cytokine-mediated cell activation leads to proteolytic degradation of the matrix particularly in the shoulder region. MMPs are key players in these events. Functional polymorphism in several MMP genes is associated with atherosclerotic manifestations and complications such as coronary thrombosis, myocardial infarction, stenosis, arterial stiffness, and blood pressure [9]. MMP genotyping can probably be of importance in the clinical management of cardiovascular patients in the future.

In small arteries such as the coronaries, plaque rupture can lead to thrombotic occlusion. In larger arteries including the aorta, this can occur as well only if there is a pronounced stenosis. More often plaque rupture will cause ulceration with thrombotic depositions and subsequent risk for embolization.

**Degeneration of the plaque**

Degeneration of the plaques can occur from necrotic changes in the plaque. Insufficient circulation through the vasa vasorum causes ischemia. Activated MMPs degrade the extracellular matrix thereby contributing to the plaque destabilization. The plaque degeneration can lead to ulceration or...
other complications such as thrombosis or embolization of thrombotic or atheromatous material.

**Plaque and flow**
The likelihood of developing atherosclerotic lesions differs between arteries at various locations. Plaques develop in relation to branches, twists, and bends. Typically they are found in the proximal, upstream part of the orifice. One common feature is flow disturbances with turbulence, flow separation, and low shear stress. Shear stress influences directly the endothelium, which leads to increased permeability and altered cellular functions such as expression of nitric oxide and adhesion molecules. Plaques localize predominantly in areas with low shear stress while areas of high shear stress are relatively spared from atherosclerosis [10].

Formation of a stenotic plaque does not initially encroach on the luminal transverse area and volume. There is a compensatory enlargement of the artery to accommodate the plaque without affecting flow. Usually the plaque is eccentric in the vessel leaving a rounded lumen but an oval vessel. This has been demonstrated in different parts of the vascular tree. Large plaques may however encircle the whole circumference and cause a stenosis [11].

Constriction and dilatation, mediated through the endothelium, are means of keeping wall shear stress constant [12].

**Infection and atherosclerosis**
The strong inflammatory components of the disease have put forward the intriguing question of an infectious etiology to atherosclerosis. Virus and bacteria have been found in diseased vessel wall. Until now a causative role has not been established. *Chlamydia pneumoniae* is found in a large number of patients with atherosclerosis. About 60% of these patients are seropositive. No relations have been found between symptoms, degree of atherosclerosis, and extent of *C. pneumoniae* involvement [13]. Similarly, no correlation was found between plaque destabilization and herpes simplex or cytomegalovirus seroreactivity.

A few studies have been published on effects of antibiotics against *C. pneumoniae* for prevention of coronary events and with negative results [14, 15]. *Chlamydia* may not be the cause of atherosclerosis but can speed up the development and progression of the disease [16], perhaps by enhancing the inflammatory reaction. Much of this basic research will of course have implications on the future therapeutic strategy.

**Atherosclerosis in different parts of the aorta**
The manifestations of atherosclerosis differ not only in different vascular regions such as carotid, coronary, and femoral arteries but also in various parts of the aorta.

The infrarenal abdominal aorta is a frequent site of plaques with or without ulcerations. Ulcerated areas are covered by thrombotic material. Embolization from these areas can cause focal ischemia in the lower extremities. Often there is a heavy calcification. The stenotic lesions can develop into total occlusions. The atherosclerotic process causes medial degeneration with risk for dilatation while the thoracic aorta is relatively spared these severe manifestations.

These findings could be due to different architecture in the thoracic and the abdominal aorta. The vascular nutrition differs in these two regions of the aorta. In the thoracic aorta, the main part of the vessel wall is supplied by vasa vasorum. The abdominal aorta lacks vasa vasorum and relies on diffusion of oxygen and nutrients from the lumen. The likelihood of ischemia in this part of the aorta is thus greater and this can contribute to the degeneration of the wall.

**Risk factors for atherosclerosis**
Several risk factors for atherosclerosis have been identified. Most are associated with the metabolic syndrome and they are all lifestyle associated. The metabolic syndrome is already a widespread condition affecting 10–25% of western populations and its prevalence is increasing. Adipositas, hypertension, hyperlipidemia, and type-2 diabetes are dominating components of this syndrome. The attractiveness of the metabolic syndrome as an entity lies in the assumption that the syndrome has greater power to predict morbidity and mortality than individual components themselves.

Smoking initiates the atherosclerotic process at an earlier stage and accelerates its progression. Smoking is probably the most important factor in the development of atherosclerosis. The mechanistic
details are still unknown but it is likely that oxygen-free radicals play a role. Cessation of smoking decreases the risk for clinical manifestations of atherosclerosis probably by arresting the progression of the lesions.

The role of lipids
Disturbances in lipid metabolism have since long been associated with atherosclerosis. High cholesterol levels lead to accumulation of cholesterol esters in macrophages, which are turned into foam cells. High levels of LDL can change the endothelial barrier, particularly oxidized LDL can be noxious to the endothelium. Modified LDL can via scavenger receptors be taken up by macrophages leading to formation of foam cells.

The hydroxymethylglutaryl-coenzyme A (HMG-CoA) reducta inhibitors (statins) are effective in LDL lowering. The enzyme is the rate-limiting step in the cholesterol synthesis. Another action, probably of equal importance, is its anti-inflammatory effect. Through this mechanism, the very early events in atherogenesis can probably be prevented.

Another exciting approach to treat atherosclerosis is by using recombinant Apo-AI Milano that in animal experiments can cause regression of atherosclerosis. It is a variant of apolipoprotein A-I identified in an Italian subpopulation characterized by low HDL and low incidence of atherosclerosis. The drug was recently found to reduce the atheroma volume in coronary arteries in a controlled randomized trial in humans [17].

Aneurysms
Aneurysms develop in the degenerated aorta. Atherosclerosis is the most common cause for degeneration of the wall. Genetic components have been identified in Marfan's syndrome and Ehlers-Danlos disease. Even in the most common, degenerative, form of aortic aneurysms there is a genetic component. There is a clear familiar occurrence with a risk of about 25% for first-degree probands [18].

Degradation of elastin has been associated with dilatation while rupture of the wall is related to collagen degradation [19]. MMP-9 (gelatinase B) that degrades elastin, collagen type IV, fibronectin, and other matrix proteins has been linked to aneurysmal disease. High levels of MMP-9 and MMP-3 have been found in abdominal aortic aneurysmal tissue [20, 21]. Levels of MMP-9 are associated with aneurysmal size [22].

Of particular interest is the importance of mutations in the genes coding for MMPs. Single nucleotide polymorphism in the MMP-9 gene at location-1562 (1562 bases from the start of the gene) has been associated with atherosclerosis and intracranial aneurysms. The latter is however controversial [23]. This mutation has been linked to aortic aneurysms in one study [24] while this was not confirmed in another investigation [25]. The latter study furthermore indicated that genetic variations in inhibitors of MMPs, TIMPs, were involved in aneurysm formation. More research is clearly needed to establish details of the genetic interplay in aortic aneurysms.

The aneurysmal pathology is characterized by a chronic inflammation with destruction of the extracellular matrix, remodeling of the wall layers, and reduction in number of smooth muscle cells. The smooth muscle cells are essential for production of extracellular matrix proteins. Less supportive scaffold enhances the degradation. The balance between MMPs and their inhibitors, TIMPs, is pivotal in the degradation of the wall. As the process progresses, dilatation occurs. This leads to flow disturbances, changes in wall tension with reduced tensile strength, and finally rupture. Therapeutic trials with doxycycline, a MMP inhibitor, are ongoing and preliminary results are encouraging with less progression of aneurysmal size in treated patients [26].

Dissections
Acute dissection can occur following degeneration with weakening of the wall. The most common form is the atherosclerotic variety typically seen in hypertensive patients. Lipid deposition, intimal thickening, fibrosis, and calcification are seen. The extracellular matrix is degraded with lysis of elastin, collagen breakdown, and cellular apoptosis. Through the action of MMPs the intima and vessel wall become fragile. The elastin synthesis may be inefficient. Macrophages, which express the elastin gene and produce tropoelastin, may play an important role by producing a defective elastin [27]. The histology is characterized by media necrosis, scarcity of smooth muscle cells, and loss of elastin [28].
The polymerization of elastin is a very complicated process. Fibulin-5 is an extracellular protein expressed in the basement membrane in blood vessels. It is a key player in the synthesis of elastin. Patients with dissection in the thoracic aorta were recently found to have reduced levels of fibulin-5 [29]. This means that a low content of elastin in patients with dissection could be due to reduced synthesis, increased degradation or both.

Familial dissection in the ascending aorta (type A) was recently linked to a genetic mutation involving dysregulation TGF-\(\beta\) signaling. This suggests that TGF-\(\beta\) may have a critical role in this condition [30].

Obstruction of the vasa vasorum can cause local ischemia in the wall. The burden of mechanical stress in the hypertensive patient facilitates disruption.

The intramural hematoma is regarded as a special variety of a localized dissection even if this concept has been disputed recently [31]. The etiology may be disruption of a medial vasa vasorum causing a localized bleeding with hematoma. The intramural hematomas are particularly hazardous since approximately half of these patients go on to dissection or rupture [32].

Localized ulcers can occur in all parts of the aorta. They develop from plaque rupture and constitute weak points in the wall where a dissection can start.

There has been an interesting discussion on seasonal variation and the influence of atmospheric conditions on thoracic dissections. There seems to be a peak in wintertime [33, 34]. Atmospheric pressure and temperature seemed to be unrelated to aortic dissection in another recent study [35].

**Marfan’s syndrome**

Marfan’s syndrome is an autosomal dominant trait with main manifestations from the connective tissue with degeneration of the elastic fibers. The incidence is about 1/5000 inhabitants. Typically the main abnormalities are found in the cardiovascular, skeletal, and ocular systems.

Apart from mitral valve prolapse, dilatation of the aorta is typical for the cardiovascular involvement. The aortic dilatation is progressive and starts with enlargement of the sinuses of Valsalva. All parts of the aorta can be affected as the disease progresses distally. The most serious complications are dissection of the aorta or aneurysm formation with rupture. The patients are typically long and slender with arachnodactyly (long fingers). They have pectus excavatus, flat feet, and scoliosis. The ocular abnormalities are mainly lens luxation and myopia.

The aortic wall is thin with fragmentation of the elastic fibers in the medial layer. There is also defective synthesis and crosslinking of elastin. Collagen metabolism is affected as well with signs of increased collagen turnover (elevated hydroxyproline secretion in the urine and low proline/hydroxyproline ratio) [36].

The genetic defect responsible for Marfan’s syndrome has been localized to the fibrillin gene (FBN1) on chromosome 15. Fibrillin is a glycoprotein about 350 kD. A large number of mutations (>500) in the gene are found in Marfan patients. In the connective tissue there is a reduced fibrillin-1 deposition. This leads to defect fibrillin aggregation and crosslinking of elastin. Extracellular microfibrils are mainly made up of fibrillin. The defective microfibrils impair anchoring and structural maintenance in various tissues. The elastin formed is more easily degraded by MMPs. The weakness in the wall leads to aneurysmal dilatation and/or dissection.

**Ehlers–Danlos syndrome**

The Ehlers–Danlos syndrome is a genetically determined disease of the connective tissue. The main abnormalities are found in the described skin, joints, and arteries. Of all the 11 types of Ehlers–Danlos syndrome described, number IV is of particular interest from a cardiovascular point of view. This form is an autosomal dominant or recessive trait. The arterial manifestations make type IV particularly serious. The major cutaneous symptom is echymoses. Collagen type III synthesis is reduced in the arterial system. This renders the vessels thin and fragile. Especially the medial layer is thin with fragmentation of the internal elastic membrane.

**Takayasu’s disease**

Takayasu described this disease in 1908 [37]. It is characterized by a chronic inflammation that is predominantly localized to the arch. Synonymous names are “pulseless disease” or “aortic arch syndrome,” names that are quite descriptive of the nature of the disease. However, the disease is not
limited to the aortic arch but is found in most other large vessels. Women are much more frequently affected than men with a ratio of 4:1. The disease always starts before 40 years of age with a mean onset around 30. The incidence is 2–3 per million inhabitants in the USA.

Macroscopic findings
Stenotic processes that can involve all parts of the aorta and its main branches characterize the disease. The walls are thickened with perivascular sclerosis. The external diameter of the vessel is not affected. The stenotic process intrudes into the lumen and reduces the luminal surface area. In advanced cases, there may be complete occlusion. Typically there is a poststenotic dilatation in Takayasu’s disease. Aortic aneurysms or dissection are not features of the disease. The supra-aortic branches are involved in 50% of the cases. The clinical symptoms depend on the extent and location of the lesions.

The typical lesions are usually seen in the arch and its branches but changes can occur in all other branches such as the visceral and the iliac vessels.

Microscopic findings
The most characteristic finding is that of a chronic inflammation. The most pronounced changes are seen in the adventitial and medial layers. The adventitia is site for a sclerotic collagenous dense tissue and with thickening of the vasa vasora. The media show breakage of the elastic fibers and with signs of neovascularization. The vessel wall is infiltrated with inflammatory cells, lymphocytes, histiocytes, and sometimes giant cells. The intima is grossly thickened with a loose connective tissue. The intimal changes are secondary to the pathological processes in the outer layers. Sometimes frank deposition of atherosclerotic material can be seen in the stenotic lesions. The histopathological changes can be related to the clinical stage. In the active phase, the findings of granulomas and infiltration with inflammatory cells are common. Later during the occlusive stage, the chronic inflammation with scarring is predominant.

The granulomatous appearance in the chronic stage has initiated speculations on tuberculosis being of etiological importance. Antigens from mycobacteria can cause granuloma. In recent clinical surveys, tuberculosis was found in 20% of the patients [38] and tuberculin test was positive in 47% [39]. The inflammatory component of the disease is further stressed by a correlation between IL-8 levels in plasma and degree of disease activity [40].

References
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