Chapter 3

Clinical Correlation of Atherosclerosis: Aortic Disease

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Introduction

The aorta is a common site of atherosclerotic plaque formation. The infrarenal abdominal aortic segment is particularly vulnerable, whereas the thoracic aorta is relatively spared. Differences in susceptibility may be due to differences in the structure, composition, and nutrition of the aortic wall as well as differences in flow conditions and mechanical stresses which have been shown to be associated with a predisposition to atherosclerosis. Plaque deposition is associated with localized dilation in relation to erosion, atrophy, and thinning of the media, which predisposes the atherosclerosis-prone abdominal aorta to aneurysm formation with eventual fibrosis and calcification of the aortic wall. Circulating levels of elastase have been proposed as etiologic factors, but aneurysm formation in this location is regularly associated with atherosclerosis. Life-threatening rupture of an abdominal aneurysm may be quite sudden. Progressive enlargement and transverse dimensions >4.0 cm increase the probability of rupture. The role of aneurysm configuration, wall erosion, and atrophy as well as the presence of florid atherosclerosis are probable major factors in the tendency to disruption. Mural thrombus formation tends to restore normal lumen caliber and stable flow, but the contribution of mural thrombosis to the tensile strength of the wall is not clear. Plaque deposition and

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thrombosis may also occur without associated medial thinning or
dilation and result in the development of lumen stenosis, obstruction
to flow, and/or embolization to the lower extremities. The clinical
risk factors and individual tissue reactions that may determine
these differences in response remain to be defined.

Aortic atherosclerosis is characterized by the formation of intimal plaques with the usual morphological features of atherosclerosis including cellular proliferation, lipid accumulation, inflammation, necrosis, fibrosis, and dystrophic calcification. Plaque ulceration may result in embolization of plaque elements or thrombus formation. Plaque deposition is accompanied by arterial wall changes that result in artery enlargement. Erosion, atrophy, and associated weakening of the aortic wall may eventually result in aneurysm formation. In medium-sized muscular arteries with relatively small diameters, such as the coronary arteries, vessel enlargement may play an important role in maintaining lumen patency. In the large-sized aorta, atherosclerosis-associated enlargement is more likely to predispose to aneurysm formation. In the aorta, plaque deposition does not occur uniformly. The abdominal aorta is particularly susceptible to both plaque formation and aneurysmal enlargement, whereas the thoracic aorta is relatively resistant to both of these processes. In this chapter we examine the differences between the thoracic aorta and abdominal aorta, which may account for these segmental differences in vulnerability. We also consider the features of the atherosclerotic process and the associated artery wall changes that may underlie the pathogenesis of aneurysmal degeneration.

**Contrasting Susceptibility of the Thoracic and Abdominal Aortic Segments**

Although both the thoracic and abdominal aortic segments are prone to plaque formation, thoracic aortic plaques are usually less abundant, more discrete, less complicated, and less calcific than those in the abdominal aorta of the same individual. Thoracic aortic plaques tend to develop predominantly in relation to intercostal branch ostia, but occlusive or obstructive atherosclerosis is rarely seen. Infrarenal abdominal aortic plaques and thrombosis may obstruct blood flow leading to intermittent claudication and other manifestations of distal ischemia. The thoracic aorta is also less prone to developing aneurysmal disease, whereas the infrarenal abdominal aorta often becomes aneurysmal, particularly in elderly men. The different susceptibilities of the thoracic and abdominal aorta may be related to local differences in aortic flow conditions and mechanical stresses as well as to differences in aortic wall structure, composition, and nutrition.
Structural Differences

The major physical differences between thoracic and abdominal segments are shown in Figure 1. Thoracic aortic diameter is greater than that of the abdominal aorta, and accordingly, has a greater number of transmedial lamellar units. The thoracic aorta also contains relatively more elastin and less collagen than the abdominal aorta, allowing greater distensibility and pulse propagation. The abdominal aorta, which contains proportionately more collagen, is stiffer and less compliant than the thoracic segment. Each abdominal aortic lamellar unit supports approximately 3000 dynes/cm circumferential tension, whereas each thoracic lamellar unit supports about 2000 dynes/cm. The outer two thirds of the human thoracic aortic wall is supplied with intramural medial vasa vasorum, whereas the abdominal aorta is largely devoid of medial vasa vasorum. Because intramural vasa vasorum are largely absent from the abdominal aorta, nutrition is presumably dependent primarily on diffusion from the lumen. Thus, even early

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FIGURE 1. Comparison of human thoracic and abdominal aortic segments. The thickness of the media of the abdominal aorta is appropriate for its diameter, but the number of its mediam lamellar units is relatively low for the diameter compared with the thoracic aorta. Media total tension of the abdominal aorta is appropriate for its diameter, but tension per lamellar unit is higher than in the thoracic portion. Furthermore, the abdominal aortic media, only 29 lamellar units thick, is avascular. None of the the avascular aortic medias or avascular zones of vascular aortic medias of mammals studied are as thick as the abdominal aorta of humans. Other mammals aortas that have comparably elevated tensions per lamellar unit have more than 29 lamellae and vasa vasorum. LU indicates lamellar unit.
intimal plaque deposition may augment the barrier to diffusion, rendering the abdominal aortic media vulnerable to ischemic degeneration and atrophy. Intimal plaque formation would also be expected to increase the diffusion distance across the wall, predisposing to processes that may promote inflammatory cell infiltration, lipid accumulation, and further plaque formation. Extension into the plaque of reactive vasa vasorum may help to clear lipid from the intimal lesion, but this may also induce further proliferation and plaque enlargement. Conversely, failure of vasa vasorum ingrowth may result in arterial wall atrophy and promote aneurysm formation. Thus, differences in structure and nutrition would appear to be associated with the differing vulnerabilities of the thoracic and abdominal aorta.

**Flow Conditions**

Hemodynamic factors are important in plaque localization, particularly at branch points, bends, and bifurcations. Detailed quantitative correlative studies of the carotid bifurcation reveal that plaques tend to form in regions of reduced wall shear stress and flow separation and where wall shear stress oscillates in direction in the course of the cardiac cycle. The thoracic aorta is exposed to relatively high flow rates, with outflow through the cerebral, upper extremity, and visceral artery branches. The renal arteries alone account for approximately 25% of the cardiac output. In contrast, the infrarenal abdominal aorta supplies mainly the lower extremities, where flow is quite variable depending on exercise conditions. In our increasingly sedentary society, walking and lower extremity exercise is diminished and the abdominal aorta is likely exposed to relatively low flow rates and oscillating wall shear stress over prolonged periods of time. In addition, flow reverses direction during the cardiac cycle in the abdominal aorta, as it is in vulnerable regions at the carotid bifurcation. Therefore, the abdominal aorta would be subjected to the adverse hemodynamic effects associated with low wall shear stress and oscillation of shear stress direction, which favor plaque formation. In contrast, the thoracic aorta is not subjected to these flow-related predisposing hemodynamic risk factors. Experimental model flow studies of the abdominal aorta reveal, however, that the adverse hemodynamic conditions can be eliminated or minimized by simulating the high flow conditions that prevail during exercise.
Atherosclerotic Arterial Enlargement

Arterial enlargement during atherogenesis may compensate for increasing plaque size and prevent or retard the development of lumen stenosis. This process may occur as a result of local increases in flow associated with periodic temporary narrowing of the lumen produced by an encroaching intimal plaque. The increase in wall shear stress may be expected to stimulate endothelial release of nitric oxide and/or other factors resulting in smooth muscle relaxation in the media and artery dilation. Ongoing increases in radius would be expected to cease when baseline wall shear stress is restored, which has been noted in arteries proximal to arteriovenous fistulas. Alternatively, the plaque may induce direct proteolytic or involutional changes in the media underlying the plaque with resulting dilation. Thinning of the media is commonly seen beneath atherosclerotic plaques regardless of location, with associated eccentric outward bulging of the underlying artery wall. Compensatory enlargement has been demonstrated in human coronary arteries, carotid arteries at the bifurcation, and in the superficial femoral arteries as well as in experimental atherosclerosis in primates in coronary, carotid, and superficial femoral artery sites. Enlargement accompanied by increasing atherosclerotic plaque formation has also been demonstrated in our own recent studies of the human thoracic and abdominal aorta. We have found that abdominal aortic enlargement is closely related to the degree of atherosclerotic plaque deposition, whereas thoracic aorta enlargement is more closely linked to increasing age.

Atherosclerotic Medial Thinning

Thinning of the media with loss of normal structure and composition is a common feature in atherosclerosis and is a constant feature in abdominal aortic aneurysm formation. Human aortic aneurysms are characterized by extensive atrophy of the media with almost total loss of normal lamellar architecture (Figure 2). The media is usually almost totally devoid of the usual elastin layers and is converted into a narrow and calcific fibrous band. In nonaneurysmal aortas, recent morphological studies show that the abdominal aorta is much more prone to media atrophy beneath atherosclerotic lesions than is the thoracic aorta. The microanatomic features of abdominal aortic structure and the susceptibility of this region to atherosclerosis and to the resulting...
erosive effects on the media are the main features that correspond to the special susceptibility of this aortic segment to aneurysm formation. Experimental studies confirm the importance of the destruction of the medial lamellar architecture in the pathogenesis of aneurysms and reveal that diet-induced atherosclerosis may result in the thinning of the media and aneurysm formation. A controlled trial of cholesterol-lowering therapy in monkeys revealed plaque regression, thinning of the media, and aneurysmal dilation of the abdominal aorta. These observations suggest that aneurysm formation is mainly a manifestation of atherosclerotic artery wall degeneration. Thus, observations of the atherosclerotic process in humans and experimental animals suggest possible mechanisms for aneurysm formation related directly to erosion of the artery wall by plaque components.

Although intimal plaque deposition is accompanied by compensatory arterial enlargement and is often associated with atrophy of the underlying media, stable early atherosclerotic plaques may actually lend structural tensile support to the artery wall, particu-
Corresponding atherosclerosis in an abdominal aneurysm forms atherosclerotic plaques, the degree of which may remain constant or increase. A computerized tomography scan shows the aneurysm containing the thrombus (T) and a lumen (L) of almost normal caliber. The thrombus consists of layers of compressed fibrin (double arrow) and a superficial layer of fresh thrombus (white arrows). There is no evidence of fibrous cap formation or endothelium at the lumen side of such thrombi.

FIGURE 3. A typical mural thrombus in an abdominal aortic aneurysm. (a) A computerized tomography scan shows the aneurysm containing the thrombus (T) and a lumen (L) of almost normal caliber. (b) The thrombus consists of layers of compressed fibrin (double arrow) and a superficial layer of fresh thrombus (white arrows). There is no evidence of fibrous cap formation or endothelium at the lumen side of such thrombi.
larly when fibrogenesis is a principle feature of plaque formation.\textsuperscript{14} During progression of the disease process, however, or during plaque regression, proteolytic enzymes such as matrix metalloproteinases are released, and aortic wall thickness and plaque composition are altered, resulting in insufficient tensile and structural support of the aortic wall.\textsuperscript{22,23} Progressive aneurysmal enlargement would then be expected to occur, accounting for the localized and selective nature of aneurysm formation in the most atherosclerosis-prone segment of the human aorta. During the dilational reaction, the enlarged lumen tends to be partially filled by mural thrombus. The residual lumen is usually maintained at nearly normal caliber, and the thrombus is often compact and stable, tending to prevent distal embolization (Figure 3).\textsuperscript{24} Presumably, flow rate at the thrombus surface associated with the persistence of near-normal lumen caliber prevents further platelet adhesion and thrombus accretion, thus avoiding the progression to occlusion. The role of mural thrombus in providing tensile support to the thinned wall is not yet clear.

**Conclusion**

Aneurysms appear at a relatively late phase of plaque evolution when plaque and media atrophy predominate, rather than at earlier phases when cell proliferation, fibrogenesis, and lipid accumulation characterize plaque progression. The major late complication of abdominal aortic aneurysm formation is sudden life-threatening rupture. Rapid progression in aneurysm diameter and diameters exceeding 4.0 cm have been found to increase the probability of disruption and have been considered as indications for preventive surgical intervention. Macrophages involved with repair processes and resorption or alteration of lipids during evolution and regression of atherosclerotic lesions are likely to be important sources of the proteolytic enzymes, which appear to be involved in aneurysmal enlargement. Although circulating proteolytic enzymes such as elastase may play some role in abdominal aortic aneurysm formation,\textsuperscript{25} morphologically, abdominal aortic aneurysms are closely associated with atherosclerosis and the clinical risk factors associated with atherosclerosis. Aneurysms rarely occur at this site in the absence of atherosclerosis and there is abundant evidence to indicate that the underlying changes in the aortic wall are associated with the metalloproteinases that are demonstrable in atheromatous plaques.
References


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