Localization of Atherosclerosis Lesions

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Arteries are now recognized as a distinct organ system, with biosynthetic and biomechanical functions that maintain normal physiologic function across a wide range of conditions. Under certain circumstances, artery wall cellular function is altered, allowing the accumulation of atherosclerotic plaque in the intima. Characteristically, atherosclerotic plaque is not uniformly distributed throughout the vascular system, but is localized to distinct and reproducible areas such as the carotid bifurcation, the coronary arteries, the abdominal aorta, and the lower extremity arteries. Hemodynamic forces, cellular responses, and other factors are thought to play an important role in determining the location of these lesions. This chapter reviews the etiologic factors responsible for the localization of atherosclerotic lesions.

Arterial smooth muscle and endothelial cell responses to physiologic and pathologic stimuli promote the induction and progression of atherosclerotic plaque. These stimuli include (1) blood flow and wall shear stress (flow fields) in proximity to the endothelial surface; (2) blood-borne substances, particularly elevated concentrations of certain lipoprotein fractions; (3) the structure, proliferation, and biosynthetic reactivity of cells comprising the arterial wall; and (4) the reactivity of migratory cells that enter the arterial wall and participate in the evolving pathologic process. Although the relative contribution of each of these stimuli to plaque localization may vary, there is a close integration between mechanical and metabolic arterial functions such that alteration of one stimulus will affect other aspects of the pathogenetic process.

Arterial Structure and Function

INTIMA

The intima comprises the innermost arterial layer, extending from the luminal surface to the internal elastic lamina. An endothelial cell monolayer overlies the internal elastic lamina, with few leukocytes, smooth muscle cells, or connective fibers present under normal circumstances. The basal lamina provides a continuous, pliable substrate for the endothelial cell monolayer, as well as focal attachments to the internal elastic lamina. Functional overlap among adjacent endothelial cells, and cell deformability in response to pulsatile wall motion, bending, or stretching help prevent the development of discontinuities in the endothelial lining. Focal attachments to the underlying elastic lamina and adjacent cells prevent slippage, telescoping, or endothelial cell detachment by elevations of shear stress or other mechanical forces. Endothelial cells sense changes in blood flow, pressure, and ambient oxygen tension through specific, receptor-activated cellular metabolic and biosynthetic events. Agonists such as thrombin, platelet-activating factor, and bradykinin increase endothelial cell intracellular calcium through receptor-coupled changes in phosphoinositide metabolism. Activation of ion channels induces cellular events through a second messenger system that enable endothelial cells to regulate tone, inflammation, and hemostasis. In addition, endothelial cells produce biologic mediators that influence hemostasis, immunogenicity, and vascular remodeling, as well as vasoreactivity.
Response-to-Injury Hypothesis
(Endothelial Denudation)

The endothelial surface is exposed to shear stress and potential mechanical injury by the force of luminal blood flow. In vivo, experimentally induced endothelial cell denudation is transient, and is rapidly restored by regeneration. Despite this vigorous and rapid response, endothelial disruption had been proposed as a critical and essential first step in atherosclerotic plaque formation. In the response-to-injury hypothesis, the loss of endothelium, with subsequent platelet adherence, the release of platelet-derived growth factor, and the induction of smooth muscle cell proliferation is considered to be the initial step in atherogenesis. According to this hypothesis, local, repeated endothelial denudation and the ensuing response to injury determines the location of plaque formation. There is, however, little evidence to suggest that endothelial disruption or removal results in eventual sustained lesion formation, even in the presence of hyperlipidemia. Endothelial denudation and platelet adherence in an animal model have not resulted in smooth muscle proliferation or intimal lesions. Strong evidence suggests formation of intimal plaque requires the presence of an intact endothelium.

Endothelium and Atherogenesis

The endothelial lining regulates the movement of cells from the arterial lumen to sites within the artery wall and into the surrounding tissues. Adherence of circulating cells to the endothelium and passage through the vessel wall are functions of cell surface receptors and matrix proteins. These include the antigen-specific receptors of T and B lymphocytes, the selectins, and the integrins. Selectins control lymphocyte and neutrophil interactions with the endothelium. Integrins are responsible for platelet adhesion and cell migration. Inflammatory chemotactic factors such as platelet-activating factor, leukotriene B₄, complement C5a, and formyl-methionyl-leucyl-phenylalanine stimulate inflammatory cell binding to endothelial cells via altered expression of the CD11/CD18 integrins. The cytokines interleukin-1 and tumor necrosis factor increase leukocyte-endothelial binding by upregulating surface expression of the intracellular cell adhesion molecule and the endothelial leukocyte adhesion molecule. Specific receptor interactions also regulate lymphocyte binding (via so-called addressins).

Monocyte adhesion and infiltration into the vessel wall may play a significant role in atherogenesis. Several specialized receptors control monocyte-endothelial cell adhesion. The early development of atherosclerosis (as induced by hypercholesterolemia) is associated with the expression of adhesion molecules on endothelial cells that specifically promote monocyte adhesion. Basic endothelial cell biology, shear stress, and atherogenesis are reviewed extensively in a monograph by Dzau and colleagues. Knowledge of endothelial cell function and receptor-mediated changes in vitro and in vivo is rapidly accumulating. Evidence clearly linking in vitro endothelial cell functional alterations with in vivo plaque induction in humans is lacking, however. The precise role of the endothelial cell in the pathogenesis of plaque formation remains to be determined.

MEDIA

The media extends from the internal elastic lamina to the adventitia. Although an external elastic lamina demarcates the boundary between the media and adventitia in many vessels, a distinct external elastic lamina may not be present, particularly in vessels with a thick media and a fibrous adventitial layer. The media represents closely packed layers of smooth muscle cells in association with elastin and collagen fibers (Fig. 10-1). Groups of similarly oriented cells are surrounded by a common basal lamina of type IV collagen, and closely associated, interlacing type III collagen fibrils. Mechanical stretch, with cyclic or sudden changes in diameter, reinforces fascicle cohesion. Each cellular subgroup or fascicle is surrounded by similarly oriented elastic fibers. Abundant, focal, tight attachment sites exist between smooth muscle cells and elastic fibers, evenly distributing tension and recoil, and preventing disruption.

The musculoelastic fascicles are the structural units of the media (see Fig. 10-1). The fascicles vary in size, orientation, and matrix composition depending on location within the arterial vasculature, the transmural distribution of tension, and redistribution of tensile stress about zones of transition at branches and bifurcations. On transverse section of larger vessels, this structure appears as a series of layers. Thick, undulating collagen bundles (type I) are distributed among adjacent fascicles, and provide the major tensile support in large vessels, preventing overdilation at elevated pressures.

Axial gradients of matrix composition exist along the aorta, and vary with media penetration by vasa vasorum, wall thickness, and architecture. Acute luminal pressure elevation may disrupt fascicles, fracturing cell bodies and interrupting the basal lamina sheaths, whereas the tight cell insertions on elastic fibers tend to resist disruption. Gradual increases in mural tension, such as those associated with growth, result in increased cellular biosynthesis, with proportional increases in collagen and elastin accumulation.
ADVENTITIA

The adventitia is a framework of fibrocellular connective tissue. This framework contains a network of vasa vasorum and nerves that mediate smooth muscle tone and contraction. In smaller arteries, the adventitia is indistinct or poorly developed. In large visceral arteries, the adventitia is a layered composition of collagen and elastic fibers. The adventitia in these vessels may be more prominent than the associated media. In atherosclerotic arteries, increasing intimal plaque thickness is associated with underlying medial atrophy and adventitial thickening. Under these circumstances, the adventitia may provide considerable tensile support for the vessel wall. Indeed, after carotid or aortic endarterectomy, removal of the entire intima and most or all of the media leaves only the adventitia to maintain integrity of the arterial wall.

Physiologic Adaptation of the Arterial Wall

The arterial wall adjusts to changing hemodynamic conditions with alterations in the dimensions, structure, and composition of the arterial wall. Arterial wall tension is distributed closely by the product of the lumen radius and the distending intraluminal pressure. This tension is distributed and supported by the full thickness of the vessel wall. Chronic changes in tangential vessel wall tension significantly influence arterial wall thickness and composition.

The relationship between human arterial wall thickness and tangential wall tension is demonstrated effectively during the early postnatal period. Under normal circumstances, blood pressure in the pulmonary trunk and ascending aorta are very nearly equal at birth, as at about half the normal adult value. At this time, the length, radius, wall thickness, and morphology of the pulmonary trunk and ascending aorta are similar. At birth, aortic blood pressure rises to approximately twice the prenatal value, whereas pulmonary pressure falls by half. This results in a marked increase in tangential tension in the aorta and stimulates a corresponding increase in aortic wall thickness (Fig. 10-2). Matrix fiber accumulation for the aorta and the pulmonary trunk vessels parallels the increase in wall tensile stress, and the rate of production of matrix per cell is markedly different for the two artery segments. This accumulation accounts for the difference in wall thickness between the two vessels. Despite differences in tension and matrix fiber content between the two vessels, cell proliferation continues at the same rate in each. This phenomenon...
Figure 10-2  Relation between tension, age, and elastin and collagen deposition in the ascending aorta (AA) and pulmonary trunk (PT) in a rabbit model. Aortic wall tension rises rapidly after birth with increasing blood pressure, and is accompanied by a significant increase in elastin and collagen. (From Leung DYM, Glagov S, Mathews MB. Elastin and collagen accumulation in rabbit ascending aorta and pulmonary trunk during postnatal growth: correlation of cellular synthetic response with medial tension. Circ Res 1977;41:316.)

demonstrates the capability of smooth muscle cells to modulate their biosynthetic metabolism in response to alterations in imposed tensile stress.

A smooth muscle cell biosynthetic response to cyclic stretch also has been demonstrated in cell culture.[59] Rabbit aortic smooth muscle cells were grown on purified elastin membranes, then subjected to cyclic stretching at 52 cycles/min for 4 to 8 days. Compared to cells grown without stretching, cells on cyclically stretched the fourth decade. Fibrous plaques usually are eccentric, and are covered by an intact endothelial surface. Although considerable variation exists in plaque composition and configuration, a characteristic architecture prevails.

The immediate subendothelial region of the plaque consists of a compact and well organized, stratified layer of smooth muscle cells and connective tissue fibers known as the fibrous cap. This structure may mimic medial architecture, including the formation of a subendothelial elastic lamina, which may function to sequester the underlying necrotic and thrombogenic plaque core from the luminal surface. This surface usually is regular, with a concave contour corresponding to the circular or oval cross-sectional lumen of the uninvolved vessel wall segment. The stable necrotic core occupies the deeper plaque. The core contains amorphous, crystalline, and droplet forms of lipid. Cells of undetermined origin, with morphologic, functional, and cell surface receptor characteristics of smooth muscle cells or macrophages are noted beneath the core. These cells also may contain lipid vacuoles. Calcium and myxoid deposits, collagen and elastin matrix fibers, basal lamina, and amorphous ground substance also are evident. Atherosclerotic plaques grow in an episodic fashion, demonstrating dense fibrocellular regions adjacent to organizing thrombus and atheromatous debris. Intermittent ulceration and healing occur, with thrombi being incorporated into the lesion.

Vasa vasorum may nourish the plaque, facilitating the organization of thrombotic deposits and the remodeling of the plaque and artery wall.[60] Attenuation of the subadjacent media promotes outward bulging of the plaque toward the adventitia. Although this attenuation sequesters plaque, enlarges the artery, and stabilizes the wall, a predominant lytic reaction may result in excessive arterial dilation or aneurysmal degeneration. Experimental evidence suggesting such a mechanism for aneurysm formation has been obtained in nonhuman primates in our laboratory[61] and by other investigators.[62]

Tissue between the necrotic core and the media, however, usually is densely fibrotic. Arterial wall support may thus be maintained by the integrity of fibrous cap or thickened adventitia. Advanced lesions, particularly those associated with aneurysms, may appear to be atrophic and relatively acellular, consisting of dense fibrous
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tissue and a minimal necrotic center. Calcification is a prominent feature, involving the superficial and deeper layers. Terms such as fibrocalcific, lipid-rich, fibrocellular, necrotic, and myxomatous describe various predominant aspects of advanced plaques. Calcific deposits are most prominent in plaques in older people and in the abdominal aorta or coronary arteries, where the earliest plaques form in animal models and in humans.49

Angiographic luminal narrowing often is perceived as plaque protrusion into the lumen. This perception is supported by gross observations of vascular surgeons and pathologists who examine collapsed atherosclerotic arteries en face or on cross section. Without distending intraluminal pressure, elastic recoil causes the eccentric plaque to appear as a protrusion or bulge. Pressure fixation47 restores the cross-sectional luminal contour to its usually regular, round, or oval configuration, even with large and extensive raised atherosclerotic lesions.31 Fixed in this manner, the usual eccentric atherosclerotic plaque bulges outward from the lumen; the external cross-sectional contour of an atherosclerotic artery becomes oval while retaining a circular lumen. This characteristic also is demonstrated in vivo in aortic cross-sectional images obtained by computed tomographic aortography. Protrusion of plaque or its contents into the membranes produced two to four times more collagen. Cell proliferation was not differentially altered by any of these procedures. Furthermore, the cyclically stretched cells showed fewer degenerative changes, and their cytoplasmic features confirmed the proposed level of biosynthesis.48

Chronically elevated adult arterial transmural tension increases the cross-sectional area of the media without a significant structural change in the lamellar architecture. Matrix protein deposition increases, with a proportionally greater increase in collagen compared to elastin fibers.30 In patients with hypertension, arterial and intimal intimal thickening also may develop as an adaptive response to the increase in wall tension.49

Adaptive changes in artery luminal diameter are determined by changes in blood flow. During embryologic growth and development, lumen diameter is determined by the volume of blood flow. After birth, increases in artery diameter continue as a response to increases in blood flow.50 This phenomenon also is demonstrated in mature arteries after cessation of growth, with enlargement of arteries proximal to arteriovenous fistulas, and a decrease in the size of arteries proximal to amputated limbs.51

Luminal diameter adaptation is responsive to wall shear stress, as determined by the effective velocity gradient at the endothelial-blood interface.42 In mammals, wall shear stress normally ranges between 10 and 20 dynes/cm² at all locations throughout the arterial vasculature. In arteriovenous fistulas, the afferent artery enlarges enough to restore shear stress to this physiologic range.43 This response depends on the presence of an intact endothelial surface,44 and may be mediated by the release of endothelial-derived relaxing factors, including nitric oxide, or other vasoactive agents55 (Ying H, Harris EJ Jr, Dalman RL, unpublished observations, 1992).

Human Atherosclerotic Plaque Morphology

Although atherosclerotic plaques are distinguished by the presence of lipid, it is unclear whether all lesions containing lipids are necessarily precursors of clinically significant atherosclerotic plaques. A prime example of this uncertainty is demonstrated by the questionable significance of the so-called fatty streak lesion. This term describes a flat, yellow, focal luminal patch or streak, representing an accumulation of lipid-laden foam cells in the intima, evident in most people older than 3 years of age. They are identified with increasing frequency between the ages of 8 and 18 years, after which many apparently resolve, despite the frequent presence of matrix materials among the characteristic cells. Fatty streaks exist at any age, often adjacent to or even superimposed on advanced atherosclerotic plaques. Fatty streaks and atheromas, however, do not have identical patterns of localization, and fatty streaks do not compromise the lumen or ulcerate.56 In experimental animals, diet-induced lesions resembling fatty streaks occur early, before characteristic atherosclerotic lesions prevail. Although this subject remains controversial, the link and transition between fatty streak and fibrous plaque formation remains to be clarified.

The term fibrous plaque identifies the characteristic and unequivocal atherosclerotic lesion. These intimal deposits appear in the second decade of life, becoming predominant or clinically significant only during or after lumen after pressure fixation signifies plaque ulceration, hemorrhage, dissection, or thrombosis.

Mechanical Determinants of Plaque Localization

Near-wall properties of arterial flow fields and the distribution of mural wall shear stress correspond closely to atherosclerotic plaque localization.57-59 Plaques develop where shear stress is reduced,54,59 not elevated, with an intact endothelial surface, even in the absence of platelet
deposition. 

The revised response-to-injury hypothesis now stresses metabolic or functional changes sustained by intact endothelial cells that alter binding or metabolism of lipid molecules or modify transendothelial transport, rather than denudation of the endothelium itself.

Atherosclerosis tends to occur principally in three locations within the arterial vasculature: the carotid–cerebral (Fig. 10-3), coronary, and aortic–peripheral systems. Within these predisposed regions, lesions form in predictable geometric configurations, demonstrating the influence of shear stress and flow patterns. Size, as well as localization, closely correlate with low wall shear stress and departures from unidirectional flow. Plaque initiation and localization is the result of low, rather than high, shear stress, low flow velocity, flow separation, and oscillation in wall shear direction.

Regions of increased mural tensile stress about branches, pulsatile wall motion, and wall thickness and density also are associated with selective plaque localization. Conversely, regions of relatively elevated wall shear or reduced tensile stress, at flow dividers and along the outer or convex aspects of curved arterial segments, generally are spared. Hemodynamics and tensile influences also are important in plaque progression and evolution, and influence potential plaque regression. As an example of this influence on regression, hypertension was found to sustain experimental plaque progression in a hypercholesterolemic cynomolgus monkey model, despite a reduction in serum cholesterol level. Reduced flow and consequent reduction in wall shear stress also tend to induce intimal thickening. An increase in wall volume, including cell enlargement, cell proliferation, and net matrix accumulation is demonstrated in long-term reactions.

A sieving effect related to these changes in wall composition and porosity has been proposed. Wall thickening, including intimal thickening, may retard transmural mass transport, providing the basis for intimal lipid deposition. The accumulation of matrix fibers with affinity for lipid molecules and the fusion or accretion of lipid particles on these components also may be responsible.

Susceptible Regions of the Arterial Vasculature

CAROTID ARTERY BIFURCATION

The carotid bifurcation is particularly prone to plaque formation, with focal plaque deposition occurring principally at the origin of the internal carotid artery (Fig. 10-4). The proximal common and distal internal carotid arterial segments are relatively spared. Plaque formation is thought to be the result of hemodynamic conditions created by the geometry of the bifurcation region. The cross-sectional area of the sinus is twice that of the immediately distal internal carotid segment. This relationship, in addition to the branching angle, results in a large area of flow separation and low shear stress along the outer wall of the sinus. Wall shear stress in this region oscillates in both magnitude and direction during the cardiac cycle. A region of laminar flow and high unidirectional shear stress exists along the relatively spared, flow-divider side inner wall of the sinus (Fig. 10-3).

The oscillations in flow direction in the region of greatest plaque formation occur primarily during the downstroke of systole. If low and oscillating wall shear stresses favor atherogenesis, then modification of heart rate could affect atherogenesis, particularly in the proximal segments of the coronary arteries, as well as the carotid bifurcation.

Outer wall plaque enlargement at the carotid bifurcation modifies the geometric configuration of the lumen, favoring subsequent plaque formation on the side and

![Cross section of carotid sinus](image-url)
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inner walls. In its most advanced and stenotic form, carotid bifurcation atherosclerotic disease thus involves the entire circumference of the sinus, including the region of the flow divider (Fig. 10-5). Nonetheless, carotid bifurcation plaques remain largest and most complicated at the outer and side walls of the sinus. Characteristic hemodynamic conditions at the carotid bifurcation, including the turbulence responsible for the characteristic bruit, also may compromise integrity of existing carotid plaques and contribute to their tendency to fissure, ulcerate, and form thromboemboli.

Previous studies of hemodynamic factors in the region of plaque formation in the carotid bifurcation were characterized in a glass model of the carotid bifurcation. More recent studies of plaque localization, the extent of compensatory artery enlargement, and plaque progression was retarded by a lowered heart rate. The finding that heart rate correlated positively with plaque formation in experimental atherosclerosis at the carotid bifurcation lends further support to a role for heart rate as a determinant of the severity of experimental atherogenesis, as we have demonstrated previously in the coronary arteries. These observations are in agreement with the experimental findings of others, and are in accord with epidemiologic reports that elevated heart rate is associated with an increased occurrence of clinical cardiovascular events.

We have also suggested that the combination of flow separation, low wall shear stress, and oscillation in shear stress direction during the cardiac cycle, which occurs at the lateral wall opposite the flow divider about the carotid bifurcation, results in regions of recirculation and increased particle residence time. Affected regions, such as the lateral wall of the internal carotid artery at the carotid bifurcation, are therefore subjected to delayed clearance of putative blood-borne atherogenic factors, and are thereby predisposed to atherogenesis.

ABDOMINAL AORTA

Clinically significant aortic plaque generally is most prominent below the level of the renal arteries. Plaque complications include obstruction, ulceration, thrombus formation, and, potentially, aneurysmal degeneration. Putative explanations for the focal nature of these complications include flow differences in the infrarenal compared to the suprarenal aorta, differences in mural archi-
ture, or vasa vasorum distribution and aortic wall nutrition. Reduced physical activity results in an overall reduction in flow volume and velocity in the infrarenal segment, whereas suprarenal flow volume is largely independent of skeletal muscular activity. The long-term effect of reduced flow velocity may be accentuated by the tendency of the aorta to enlarge with age. The frequency of vasa vasorum present within the media drops precipitously from the thoracic to abdominal and infrarenal segments of the aorta, potentially contributing to the relatively avascular nature of the abdominal aorta.

Relative flow disturbances within the infrarenal aorta due to discrepancies between iliac artery flow volumes also may contribute to plaque and aneurysmal degeneration. A recent review of German World War II veterans compared those with and without traumatic above-knee amputation at least 40 years after limb removal. An abdominal aortic aneurysm was six times more likely to be identified in the amputee group compared to the age, sex, and risk factor-matched controls. Of the patients who underwent aortography, 84% of the amputees but none of the control group demonstrated axial shifting of the infrarenal aorta toward the patent iliofemoral artery. The 12 patients with left leg amputation demonstrated a leftward convexity of the terminal aorta, and the 4 with right-sided amputation demonstrated rightward convexity (Fig. 10-6). The common iliac artery contralateral to the side of amputation was pathologically dilated in all patients who underwent aortography. This study suggests that unilateral flow reduction after above-knee leg amputation, and resultant asymmetrical flow fields within the infrarenal aorta and at the aortic bifurcation, may precipitate aneurysmal degeneration of this area and an ipsilateral shift of the axis of the infrarenal aorta.

**SUPERFICIAL FEMORAL ARTERY**

No widely accepted explanation for the discrepancy between the incidence of upper and lower extremity atherosclerotic plaque exists. Recognized differences in the two areas include hydrostatic pressure and activity-dependent variations in volume flow. As in the abdominal aorta, relative inactivity, and subsequently diminished shear stress may lead to increased rates of plaque deposition in these arteries.

Cigarette smoking and diabetes mellitus are the risk factors most closely associated with atherosclerotic disease of the lower extremities. The specific mechanism through which these risk factors act is unknown. Lower extremity arterial medial density, however, may be augmented by the chronically increased smooth muscle tone characteristic of nicotine use, interfering with the transmural transfer of materials entering the intima. Speculation on the etiology of the predominant incidence of occlusive plaque of the superficial femoral artery at the adductor canal has centered on the likelihood of repeated mechanical trauma, limitations on vessel compliance, or restrictions on compensatory enlargement due to the closely applied adductor magnus tendon (Fig. 10-7). Despite these observations, the mechanism of the pervasive and highly predictable localization of peripheral vascular occlusive disease in the lower extremities remains to be determined.

**Conclusion**

Arterial structural characteristics, the response of endothelial and smooth muscle cells to tensile and shear stress, the infiltration of monocytes and other inflammatory cells, physiologic adaptation and remodeling, in addition to pathogenic attenuation and plaque formation, all play an important role in the localization of atherosclerotic plaque to a few widely recognized areas of the arterial system. Although the molecular mechanisms responsible for this localization remain obscure, much has been learned about the physical and cellular forces responsible for this phenomenon. Further investigations using real-time flow and plaque imaging modalities in vivo, smooth muscle cell culture and proliferation studies in vitro, and the development of sophisticated in vivo models of flow separation, wall shear stress, and particle residence time promise to provide more specific mechanistic clues regarding the phenomenon of arterial
atherosclerotic plaque localization, as well as the related clinical problems of anastomotic fibrointimal hyperplasia and vein graft stenosis.

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