Hemodynamic Factors in Atherosclerosis

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Atherosclerosis is a degenerative process of the artery wall with well-recognized systemic risk factors such as hyperlipidemia, hypertension, and cigarette smoking. However, many individuals at high risk for atherosclerosis are free of significant plaque formation, whereas others with no recognized risk factors develop extensive lesions. Furthermore, morbidity and mortality usually result from localized plaque deposition rather than diffuse disease. Certain vessels, such as the abdominal aorta, carotid arteries, coronary arteries, and peripheral arteries, are particularly susceptible to plaque formation, whereas others, such as upper extremity vessels, are rarely involved. Even in susceptible arteries, plaque deposition is focal. The distal internal carotid is almost always free of disease despite marked atherosclerosis in the adjacent carotid bifurcation.

Several hypotheses have been proposed to account for the unique and focal pattern of atherosclerotic plaque formation. The knowledge that blood flow exerts stresses on vessel walls and affects mass transport to arterial tissue has led to the hypothesis that fluid dynamic forces are localizing factors in atherogenesis. Differences in local susceptibility and reactivity of the artery wall may also play a significant role. The purpose of this chapter is to examine both hemodynamic and artery wall factors that may determine the local nature of plaque deposition and to consider the specific conditions that promote atherosclerosis in several highly vulnerable sites in the arterial tree.

Hemodynamic Factors in Plaque Localization

Blood does not flow uniformly in the arterial tree because of variations in geometric configuration and resistance to flow. Differing lumen diameters, curvatures, branchings, and angles produce local disturbances in the primary flow field, resulting in regions of altered shear stress and boundary conditions with areas of separation, secondary flow patterns, and turbulence. Characterization of these conditions at specific sites becomes much more complex when the pulsatile nature of blood flow is taken into consideration. Branch points are known to be particularly vulnerable to plaque formation and are subject to wide variation in hemodynamic conditions. Thus, it is not surprising that a wide variety of hemodynamic factors have been implicated in plaque pathogenesis, including high and low wall shear stress, flow separation and stasis, oscillation of flow, turbulence, and hypertension.

Wall Shear Stress

Wall shear stress (τw) in arteries is the tangential drag force produced by blood moving across the endothelial surface. It can be approximated by the Hagen-Poiseuille formula:

\[ \tau_w = \frac{4 \mu Q}{\pi r^3} \]

where \( \mu \) = viscosity of blood, \( Q \) = blood flow, and \( r \) = radius. Wall shear stress is a function of the velocity gradient of blood near the endothelial surface and is directly proportional to blood flow and blood viscosity and inversely proportional to the cube of the vessel radius. Thus, for a given flow rate, a small change in vessel radius has a large effect on wall shear stress.

High Shear Stress

High shear stress has been thought to potentiate plaque formation by producing endothelial injury and disruption, thereby exposing the underlying artery wall to circulating platelets and lipids. Areas of high shear stress can be produced in the aorta of experimental animals by constricting the lumen. This reduces radius and increases flow velocity and results in marked elevations in wall shear. In 1968, Fry constricted the canine aorta with a mechanical intraluminal device and increased wall shear stress to ap-
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Figure 7-1. Scanning electron micrograph of endothelial surface of a coarctate monkey aorta. Six months after coarctation, there was a 70% lumen stenosis, a 15 mm Hg pressure gradient, and high-flow velocity and shear stress within the coarctation channel. The endothelial surface in the center of the coarctation channel, as well as elsewhere in the aorta, was intact, with no evidence of endothelial disruption or damage. Direction of blood flow is indicated (arrow). (From Zarins CK, Bomberger RA, Glagov S: Local effects of stenosis: Increased flow velocity inhibits atherogenesis. Circulation 64[Suppl II]:II-221, 1981.)

approximately 400 dynes/cm². This represented a 20-fold increase above the normal level of 15 to 20 dynes/cm², and resulted in endothelial damage and an increase in endothelial permeability. Other studies reported the in vivo finding of damaged and disrupted endothelial cells in high shear stress areas such as aortic ostial flow dividers. Together, these findings were taken as evidence that high shear stress was an initiating factor in atherogenesis.

It is now recognized that the reported in vivo endothelial abnormalities were due to experimental artifacts and that under normal circumstances there is no morphologic evidence of endothelial denudation or disruption either in high or low shear areas in the arterial tree. Furthermore, when shear stress was elevated by aortic coarctation and studied after 10 days to 9 months rather than acutely, there was no evidence of endothelial damage or denudation in the high shear coarctation channel (Fig. 7-1). Thus, if endothelial damage occurred acutely as a result of very high shear, it healed rapidly with no scarring or residual intimal thickening. Specific injury to the endothelium and aortic wall by clamping and suturing to produce a constriction also healed without evidence of endothelial abnormality or intimal thickening in the high shear stress area (Fig. 7-2).

The relationship between high shear stress and plaque formation has been studied in monkeys with aortic coarctation that were fed an atherogenic diet. Extensive intimal plaques formed in the aorta proximal to the coarctation, but within the high shear stress coarctation channel, plaque formation was inhibited (Fig. 7-3). Thus, there is no evidence that high shear stress results in endothelial damage, and rather than promoting plaque formation, high shear appears to inhibit plaque deposition. Such a feedback inhibition may serve to limit the rate of plaque deposition in developing stenoses, which produce local elevations in wall shear stress.

Low Shear Stress

The earliest atherosclerotic lesions in experimental atherosclerosis develop at the upstream rims of aortic ostia, which

Figure 7-2. Coarctation of aorta in a monkey fed an atherogenic diet for 6 months. The coarctation was produced by suture and is demonstrated by angiography (A). The excised coarcted aortic segment (B) reveals that the prior arterial wall injury has healed fully, and there is no evidence of endothelial disruption or plaque formation within the stenosis. Intimal plaque formed proximal and distal to the stenosis, suggesting that plaque formation was inhibited in the narrowed high shear stress area. (From Zarins CK, Bomberger RA, Glagov S: Local effects of stenosis: Increased flow velocity inhibits atherogenesis. Circulation 64[Suppl II]:II-221, 1981.)
are regions of low shear stress. Similar plaque localization has been noted in humans (Fig. 7-4), and Caro and associates have suggested that low wall-shear rates may retard the mass transport of atherogenic substances away from the wall, resulting in increased intimal accumulation of lipids. In addition, low shear stress may interfere with turnover at the endothelial surface of substances essential both to artery-wall nutrition and to the maintenance of optimal endothelial metabolic function.

Correlative studies of plaque localization in the human carotid bifurcation with quantitative model flow studies have shown that intimal plaques form in the low shear stress region of the carotid sinus opposite the flow divider and not in the high shear stress region along the inner wall of the internal carotid artery. Shear stress values of zero and below were recorded in the region most likely to develop plaque, and it has been suggested that a threshold value below which plaque deposition occurs may exist. Similar quantitative correlative studies of the human aortic bifurcation have also shown that plaques localize in regions of low shear stress rather than high shear stress.

**Flow Field Changes**

A number of flow field alterations other than shear stress changes occur at branch points and have been implicated in plaque localization. These changes are particularly prominent in the carotid bifurcation because of the presence of the carotid sinus and may account for the marked vulnerability of this site to atherosclerosis. The carotid sinus has twice the cross-sectional area of the distal internal carotid artery and this, together with the effects of branching and angulation, results in a large area of flow separation and stasis along the outer wall of the carotid sinus (Fig. 7-5). Flow visualization and computational fluid dynamics studies demonstrate that as flow from the common carotid artery enters the bifurcation, flow streamlines are compressed toward the flow divider and inner wall of the internal carotid artery, where flow is rapid and laminar and shear stress is high (Fig. 7-6). Plaques do not form in this area. Along the outer wall of the sinus, a large area of flow separation develops in which flow velocity and shear stress are low. The earliest intimal plaques develop in this region, as do late, complicated, and clinically significant lesions. In the region of flow separation, there is a reversal of axial flow and slow fluid movement upstream. However, the region of separation is not simply a zone of stasis and recirculation but is a zone of complex secondary flow patterns, including counterrotating helical trajectories (Fig. 7-7). Flow reattaches distally in the sinus, and the distal internal carotid, which is almost always free of plaque, has relatively rapid axial flow throughout its cross-section.

Particles of dye are carried rapidly along the inner wall but are cleared very slowly from the outer region of flow separation and low flow velocity. Particles in the region of flow separation have an increased residence time and would have greater opportunity to interact with the vessel wall. Time-dependent lipid particle-vessel wall interactions...
Figure 7-5. Hydrogen bubble flow visualization studies in a glass model human carotid bifurcation under steady flow conditions. Flow is rapid, laminar, and longitudinal along the inner wall of the carotid sinus (black arrow). Along the outer wall, there is a large area of flow separation (white arrows). A-E, Refer to tissue sections taken in a corresponding human carotid bifurcation that demonstrated that early intimal plaques formed in the area of flow separation. (From Zarins CK, Giddens DP, Bharadvaj BK, et al: Carotid bifurcation atherosclerosis: Quantitative correlation of plaque localization with flow velocity profiles and wall shear stress. Circ Res 53:502, 1983.)

Figure 7-6. Surfaces of constant velocity magnitude for pulsatile flow in a carotid artery model calculated using Computational Fluid Dynamics at A, peak systole and B, mid-diastole. Surfaces depict range from 0 cm/sec along the vessel wall to 20 cm/sec in the vessel interior in increments of 5 cm/sec. Half of the model is removed for visualization purposes. The maximum value of velocity magnitude is approximately 60 cm/sec in the carotid artery, so a surface of 5 cm/sec represents relatively slow blood flow. Note that along the outer wall of the carotid sinus region, there is a large separation between the zero velocity surface, representing the vessel wall, and the 5 cm/sec surface. This separation corresponds to a low-velocity region and is observed at all times during the cardiac cycle. Also note that the flow surfaces are close together along the inner wall of the bifurcation near the flow divider, as well as in the proximal common carotid and distal internal carotid arteries, corresponding to steep gradients of velocity and high shear stress. (From Taylor CA, Hughes TJR, Zarins CK: Computational investigations in vascular disease. Comp Phys 10:224, 1996.)
During early systole, the region of flow separation disappears with forward flow throughout the cross-sectional area of the sinus. During late systole, however, the region of separation and flow reversal becomes prominent along the outer wall, and there is a reversal in the shear stress direction vector. During diastole, conditions are similar to those seen under steady flow conditions. The magnitudes of velocity and shear are low in this region and correlate strongly with plaque localization. Alternating positive and negative shear stress vectors (oscillations) along the outer wall of the carotid sinus have also been shown to correlate strongly with early plaque deposition.

Particle tracking studies reveal increased residence time along the outer wall, which is caused by oscillation of fluid velocity about a mean value close to zero. This delays the convection of fluid and traps fluid elements near the outer wall for several cycles despite the absence of a clear region of stasis or of an area of permanent boundary layer separation. Increased residence time increases the duration of exposure of the lumen surface to circulating atherogenic agents and favors time-dependent transendothelial diffusion as well as intimal entrapment of atherogenic particles.

Thus, variations in shear stress direction associated with pulsatile flow may lead to increased endothelial permeability, whereas even relatively high shear stresses that remain unidirectional may not be injurious. The oscillating shear stress pattern may cause an increased ingress of plasma constituents through the endothelial monolayer by effects on the stability of intercellular junctions. Endothelial cells normally align in the direction of flow in an overlapping arrangement. Changing shear stress may cause cyclic shifts in the relationship between shear stress direction and the orientation of intercellular overlapping borders. This hypothesis agrees well with reports of increased permeability of cultured, confluent endothelial cells subjected to changes in shear stress and increased Evans blue dye uptake.

Oscillation of Flow

Under conditions of pulsatile flow, the flow field considerations are more complex. Conditions along the inner wall of the carotid sinus are similar to those seen under steady flow conditions. Flow velocity and shear stress are high, and flow remains laminar. There are fluctuations in magnitude of velocity and shear but no change in velocity or shear stress direction.

Along the outer wall, where plaque forms, pulsatile flow produces an oscillating shear stress pattern (Fig. 7-8).

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Along the outer wall, where plaque forms, pulsatile flow produces an oscillating shear stress pattern (Fig. 7-8).
Flow field disturbances such as flow separation, recirculation, and vortex formation may occur in various regions of the arterial tree under normal and abnormal conditions. However, turbulence does not develop in the absence of abnormal geometry such as stenoses or shunts. Experimentally induced arteriovenous anastomoses, stenoses, or aneurysms can produce intimal thickenings with some features of atherosclerosis. However, regions immediately distal to severe stenoses, where significant turbulence has been demonstrated, are free of atherosclerotic lesions.

In the human carotid bifurcation, in the region where plaques form, although there is a zone of complex secondary and tertiary flow patterns (including counterrotating helical trajectories), there is no turbulence. This is true under a wide range of Reynolds numbers and flow conditions, including both steady and pulsatile flow. Furthermore, in vivo noninvasive pulsed Doppler ultrasound studies of carotid arteries in normal human subjects do not exhibit turbulence. Thus, although it is clear that strong secondary flow patterns exist in the normal carotid bifurcation in areas of early plaque formation, turbulence does not. Turbulence may develop late, however, as a result of severe carotid stenosis and thus would be a result, rather than a cause, of atherosclerotic plaques.

**Hypertension**

Postmortem studies have revealed that hypertension is associated with an increase in both the extent and severity of atherosclerosis. Numerous epidemiologic studies have identified hypertension as an important risk factor for the development of clinical complications of atherosclerosis, such as myocardial infarction and stroke. Yet, clinical data comparing the development of myocardial infarction or stroke in persons with and without control of mild to moderate hypertension revealed no significant difference, suggesting that other factors, possibly interacting with hypertension, may be important.

Thus, the effects of hypertension may be different in different portions of the arterial tree as a result of other local hemodynamic variables. It is well known, for example, that hypertension is a more important factor in cerebrovascular disease and stroke than in coronary artery or peripheral occlusive disease. The occurrence of severe atherosclerosis in clinically normotensive individuals and the sparing of vessels distal to stenoses, even in the presence of elevated blood pressure, indicate that although hypertension may potentiate or enhance atherogenesis, it may not be in itself a necessary atherogenic factor.

Experimentally, hypertension has been implicated as an important etiologic factor in plaque pathogenesis. When hypertension was induced by midthoracic aortic coarctation in atherosclerotic primates, there was increased plaque deposition in the aorta proximal to the coarctation. However, other hemodynamic conditions also existed in the region proximal to the coarctation, including decreased flow velocity, decreased shear stress, increased pulse pressure and wall motion, and increased wall tension. In the aorta distal to the coarctation, mean blood pressure was also elevated because of the presence of renovascular hy-
pertension, but plaque deposition in the distal aorta was almost entirely absent (Table 7–1). Inhibition of plaque deposition, despite the presence of hypertension and marked hyperlipidemia, was associated with decreased pulse pressure, decreased wall motion, and decreased arterial wall metabolism. Hypertension enhanced experimental plaque formation but inhibited plaque regression and enhanced plaque progression, despite reduction of hypercholesterolemia. These observations suggest that factors other than blood pressure per se may be of primary importance in atherogenesis. Thus, although hypertension is important in the clinical complication of atherosclerosis, the nature of its role in plaque pathogenesis remains unclear.

**TABLE 7–1**

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>Proximal Aorta</th>
<th>Distal Aorta</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Stenosis</td>
<td>50.0 ± 7.0</td>
<td>74.0 ± 5.0</td>
</tr>
<tr>
<td>70% Stenosis</td>
<td>91.1 ± 4.1</td>
<td>97.5 ± 1.7</td>
</tr>
</tbody>
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* Significant statistically different.


E. **Artery Wall Susceptibility**

In addition to the interaction of intraluminal hemodynamic conditions with the systemic and lipid environment, local susceptibility and responses of the artery wall are important in the development of atherosclerotic lesions. The artery wall is composed of the intima, which is covered on the luminal surface by a monolayer of endothelial cells; the media, which contains smooth muscle cells, collagen, and elastin; and the adventitia, which contains a network of vasa vasorum.

**Endothelial Injury**

Endothelial injury and the response to endothelial injury have been implicated in plaque pathogenesis. According to this hypothesis, the endothelial lining of arteries is damaged by one of several factors, including mechanical forces such as shear stress and hypertension, chemical agents such as hyperlipidemia or homocysteine, immunologic reactions, or hormonal dysfunction. The injury hypothesis also encompasses the response to such injury, including platelet deposition, release of platelet-derived growth factor, leukocyte adhesion and diapedesis, cellular proliferation, and lipid deposition. Focal, repeated endothelial injury would account for the localized nature of plaque deposition.

Although widely quoted, direct evidence for this hypoth-

**Medial Functional State and Metabolism**

The functional state of the media appears to be important in plaque pathogenesis. Under conditions in which there is increased pulse pressure, increased wall motion, and increased wall tension, such as exist proximal to aortic coarctation, there is smooth muscle cell proliferation, increased biosynthetic activity, and plaque formation. Similar increases in metabolic activity of medial smooth muscle cells can be demonstrated in vitro. Cyclic stretching of elastin membranes on which were grown smooth muscle cells resulted in increased biosynthesis of collagen, hyaluronate, and chondroitin 6-sulfate. Thus, plaques form readily in areas where medial smooth muscle cells are metabolically active.

Conversely, distal to severe aortic coarctations, despite an increase in mean pressure, pulse pressure is decreased and aortic wall motion is diminished. This is accompanied by atrophy of the media with loss of smooth muscle cells and a significant reduction in DNA content (see Table 7–1). Metabolic function is diminished, with decreased glycolysis and decreased collagen synthesis. Under these conditions, intimal plaque does not form despite a high mean blood pressure and marked hypercholesterolemia, with total serum cholesterol levels of 700 to 900 mg/dL.

Further evidence for the importance of the media in plaque formation can be found in the healing of arterial injuries in the presence of marked hypercholesterolemia. Standard, focal, transmural necrotizing injuries were produced in hypercholesterolemic rabbits. Despite endothelial sloughing at the time of injury, the endothelium was completely regenerated after 4 days. After 30 days, however, in many instances the media had not healed. Those injury sites with a healed, intact media developed intimal thick-
en at the site of injury. However, those in which the media failed to heal and became atrophic had no intimal thickening but rather became aneurysmal. These observations suggest that an intact, metabolically active media is necessary for intimal plaque formation.

**ARTERY WALL ADAPTATION**

Artery walls can adapt to enlarging intimal plaques by dilating to maintain a normal lumen diameter. Hemodynamic forces appear to be important in this adaptation. Vessels in high-flow positions, such as arteries feeding an arteriovenous fistula, autogenous aortorenal bypass grafts, and collateral arteries carrying increased flow around an obstruction, tend to enlarge. Conversely, lumen diameter is reduced in arteries with low flow, distal to arteriovenous fistulas, in arteries supplying atrophic or amputated extremities, or in vascular bypass grafts that are too large in relationship to the runoff bed.

Arteries proximal to a chronic arteriovenous fistula have markedly increased blood flow and flow velocity. However, there is no increase in wall shear stress due to artery dilatation and increase in lumen radius. Kamiya and Togawa have suggested that shear stress acts to regulate lumen diameter through an alteration in protein flux in the artery wall. Guyton and Hartley have suggested that arteries dilate as a result of an increase in flow pulsatility and peak velocity, which are sensed by endothelial cells and signaled to medial smooth muscle cells. The response appears to be dependent on the presence of an intact endothelial surface and may be mediated through endothelial-derived vasoactive agents.

**Atherosclerotic Artery Enlargement**

In experimental diet-induced atherosclerosis in monkeys, coronary arteries and carotid arteries have been noted to enlarge as intimal plaques increase in size. Atherosclerotic artery enlargement has also been demonstrated in human coronary, carotid, and superficial femoral arteries, as well as in the abdominal aorta. Artery enlargement can compensate for the enlarging intimal plaque and prevent lumen encroachment or stenosis (Fig. 7–10). However, this compensatory mechanism appears to be effective in preventing stenosis for relatively small plaques that occupy less than 40% of internal elastic lamina cross-sectional area. Larger plaques result in lumen encroachment and stenosis. Compensatory enlargement in response to intimal plaques can be excessive in certain arterial segments, resulting in a larger than normal caliber. This may predispose to aneurysmal enlargement. Thus, the development of stenosis may be a balance between plaque deposition on the one hand (which tends to narrow the lumen) and artery enlargement on the other (which can maintain a normal lumen caliber or predispose to aneurysm formation). Hemodynamic forces may play a role in the size regulation of atherosclerotic arteries through normal endothelial-dependent artery wall responses or through direct effects of the plaque on the underlying artery wall.

**PLAQUE LOCALIZATION**

**Carotid Bifurcation**

Carotid bifurcation atherosclerosis occurs primarily along the outer wall of the internal carotid artery in the area of the carotid sinus. This has been noted on postmortem specimens, angiograms of patients with severe carotid stenosis, in carotid bifurcation plaques removed during carotid endarterectomy, and in experimental carotid plaques. Angiographic studies in patients have demonstrated static zones and boundary layer separation at the outer wall of the carotid sinus in the region where plaques form, and Doppler spectrum analyses have confirmed flow separation and stasis in this area of the carotid bifurcation in patients. Quantitative correlative studies demonstrate that the earliest carotid plaques form in the area subjected to low shear stress, oscillating shear stress, flow separation, and flow stasis. Late, complex lesions and ulcerations also occur in this region, and it is possible that the hemodynamic conditions may promote not only plaque formation but also plaque complication, ulceration, and thrombosis (Fig. 7–11).
the remainder of systole as intramyocardial pressure increases the resistance to flow.\textsuperscript{85} Flow reversal during systole has been demonstrated with tachycardia and in concentric left ventricular hypertrophy. During isovolumetric relaxation, as intramyocardial and intraventricular pressures decline, coronary flow accelerates rapidly, then decreases slowly as aortic pressure falls and intraventricular pressure builds again late in diastole.

If other determinants of coronary flow are held constant, net coronary flow is directly proportional to heart rate.\textsuperscript{85} Conversely, the diastolic time interval is inversely related to heart rate.\textsuperscript{84} As heart rate increases, the time spent in diastole when flow is greatest decreases markedly. Because phasic fluctuation in coronary flow is predominantly a systolic occurrence, both the frequency and magnitude of oscillations in shear stress direction should be directly dependent on heart rate. Thus, the frequent preferential localization of plaques in the coronary arteries compared with the renal or other peripheral arteries may be related to the fact that the coronary arteries experience at least twice as many oscillations of flow velocity over time as other major arteries. Thus, during a 1-year period, a resting heart rate of 80 results in 10.5 million more systoles than a resting heart rate of 60, emphasizing the remarkable cumulative effect of a modest change in heart rate on flow conditions in the coronary arteries.

To test the hypothesis that heart rate is an important risk factor in coronary atherosclerosis, we produced sinoatrial node ablation in cynomolgus monkeys. This resulted in a 20% reduction in mean heart rate and a reduction in the magnitude of heart rate fluctuation. After 6 months on an atherogenic diet, animals with a low heart rate had a 50% reduction in intimal plaque area, a 50% reduction in maximum lesion size, and a 50% reduction in percentage stenosis.\textsuperscript{85} Similarly, there was a significant reduction in carotid bifurcation atherosclerosis.\textsuperscript{82} Thus, heart rate reduction had a protective effect on both coronary and carotid atherosclerosis in monkeys.

Heart rate has also been directly implicated as an independent risk factor in human coronary atherosclerosis. A number of major prospective clinical studies have found high heart rates in men at rest to be predictive of future manifestations of coronary heart disease.\textsuperscript{86, 87} Conversely, low heart rates are thought to protect against the development of coronary atherosclerosis.\textsuperscript{88} Although increased resting heart rate seems to correlate significantly with an atherogenic lipid profile in sedentary men, suggesting a possible metabolic pathway for the effect of heart rate on coronary artery disease,\textsuperscript{89} both theoretical and experimental evidence suggests that hemodynamic factors associated with cyclic myocardial contraction predispose the coronary arteries selectively to atherosclerosis. Hemodynamic factors such as hypertension, altered shear stress, and flow disturbances have also been implicated in plaque localization and progression in several locations in the coronary arteries,\textsuperscript{90} but a selective effect in the coronary tree has not been emphasized.

### Abdominal Aorta

Human and experimental atherosclerotic lesions are prone to localize in regions of the arterial tree exposed to rela-
tively low flow rates. The human abdominal aorta may be particularly vulnerable to early and rapid development of atherosclerosis because of relatively low flow velocities compared with the remainder of the aorta. One fourth of the cardiac output is delivered to the renal arteries at rest. Renal artery flow, together with celiac and superior mesenteric artery flow, thus ensures a relatively constant high-volume flow through the proximal aorta. In contrast, the volume of flow in the aorta below the renal arteries is greatly dependent on the muscular activity of lower extremities. The infrarenal abdominal aorta may be the appropriate size for a physically active bipedal existence, but with an increasingly sedentary lifestyle, the infrarenal human abdominal aorta may be subjected to relatively slower flow velocities than the suprarenal aorta during a major portion of the day. This effect may be further accen-
tuated by the tendency of the aorta to dilate with age. Thus, a slower flow pattern in the abdominal aorta may tend to favor intimal proliferation and the ingress of lipids, with the formation of atherosclerotic plaques. It is hypothesized that the beneficial effect of exercise in retarding the progression of cardiovascular disease is due, at least in part, to the elimination of adverse hemodynamic conditions, including high particle residence time and low wall shear stress.

Model flow and computational fluid dynamics studies of the aorta have provided qualitative information on abdominal aorta hemodynamics and confirm that under resting and postprandial conditions, the infrarenal aorta experiences velocity direction oscillation, vortex formation, and increased fluid residence time, whereas the suprarenal aorta has laminar flow. Recent computational fluid dynamics investigations to quantify hemodynamic conditions in the abdominal aorta demonstrate that under resting conditions the infrarenal aorta experiences slow wall shear stress and flow reversal during most of the cardiac cycle, with the effects being most pronounced during diastole. However, the complex, recirculating flow patterns present at rest disappeared under simulated moderate levels of lower limb exercise (Fig. 7-12). Mean shear stress below the level of the renal arteries was less than 1 dyne/cm² under simulated resting conditions but increased by over 400% under simulated moderate exercise conditions to values above those in the lesion-resistant suprarenal aorta. Particle residence time, defined by the time it took 90% of instantaneously released particles to clear the infrarenal aorta, was reduced by a factor of 3 under moderate exercise conditions. These investigations support the body of evidence that moderate levels of exercise have a beneficial effect on limiting atherosclerosis. Further studies are needed to examine the duration of exposure to exercise conditions needed to achieve benefit.

Aneurysm Formation

Hemodynamic factors are important in both plaque localization and adaptive enlargement of atherosclerotic arteries. These processes may also play a role in aneurysm formation. The association between atherosclerosis and abdominal aortic aneurysms has long been recognized, and it is well-known that patients undergoing operation for aortic aneurysmal disease are generally 8 to 10 years older than patients undergoing operation for aortoiliac occlusive disease. This suggests that aortic aneurysm formation may be a later stage of atherosclerotic aortic degeneration. Intimal plaque formation in the aorta stimulates adaptive enlargement of the aorta and is usually associated with atrophy and degeneration of the aortic wall underlying the plaque. If plaque degeneration, ulceration, or atrophy were to subsequently develop, this would leave an enlarged thin-walled aorta prone to progressive aneurysmal enlargement. Experimental studies from our laboratory have demonstrated that aneurysms form in diet-induced atherosclerosis with prolonged atherogenic regimens associated with plaque and artery wall atrophy. A controlled trial of lesion regression by lowering of serum cholesterol in experimental animals resulted in aneurysmal enlargement of the abdominal aorta. These findings suggest that the interaction between the plaque and artery wall and evolution of the plaque over time may be important in the pathogenesis of aneurysms.

Alterations in blood flow in the aorta may also influence aneurysm pathogenesis by local alterations in wall shear. An increased incidence of abdominal aortic aneurysms as a very late finding in World War II amputees supports this hypothesis.
POTENTIAL ROLE OF HEMODYNAMICS IN SURGICAL PLANNING

Investigations into hemodynamic factors in atherosclerosis generally use idealized models representing the average anatomy of a group of individuals. These idealized models can be modified in a systematic fashion to investigate the effect of variations in anatomy on flow conditions and are useful for quantifying hemodynamic factors in blood vessels prone to vascular disease. However, to determine the exact flow conditions in a given individual's vascular system for clinical diagnosis or surgical planning, models that more faithfully represent individual anatomic features and flow conditions are necessary. Patient-specific computer models have been created by extracting anatomic information from imaging sources, including computed tomography (CT) and magnetic resonance imaging (MRI). These models are then discretized into a finite element mesh to obtain a finite number of points where the hemodynamic variables of velocity and pressure are computed from appropriate input conditions (Fig. 7-13). Adverse hemodynamic conditions, including recirculating flow, low shear stress, and high particle residence times, can be identified, and alternative surgical procedures to minimize these adverse conditions can be evaluated (Fig. 7-14).

As our knowledge of the importance of hemodynamic factors in atherosclerosis increases, the possibility of using this information to improve patient care will emerge. New, predictive methods using hemodynamic computer modeling hold the potential to enable the evaluation of the long-term efficacy of surgical procedures and vascular prostheses. These new computational methods can provide a means to augment the information that can be obtained from medical imaging studies. In the coming years, surgeons could decide which procedure to perform based on not only diagnostic information provided by medical imaging data sources but also predictive physiologically based computer models using knowledge of the role of hemodynamic factors in atherosclerosis.

CLINICAL IMPLICATIONS

Clinical efforts to control systemic risk factors such as hyperlipidemia, smoking, and hypertension have been shown to be effective in limiting morbidity and mortality due to atherosclerotic plaques. Control of localizing hemodynamic factors is also possible and may be important in inhibiting plaque formation, enhancing artery wall adaptation, and, perhaps, promoting regression of established plaques. Increased cardiac output and blood flow brought on by increased flow velocity and increased wall shear stress would tend to limit plaque formation and promote artery lumen dilatation. Experimental as well as clinical evidence supports the beneficial effects of exercise on coronary atherosclerosis. Increased flow with exercise serves to limit flow stasis and particle residence time, thus limiting
time-dependent lipid-wall vessel interaction. Significant benefit in coronary atherosclerosis can also be anticipated by reduction in heart rate by exercise, modification of psychosocial stress, and drug therapy. Indeed, exercise programs that improve fitness levels can result in a 44% lower risk of all causes of mortality and a 52% lower risk of cardiovascular-related mortality in men. Thus, a comprehensive approach to controlling clinical complications of atherosclerosis should address not only systemic but also local factors in plaque pathogenesis.

References

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Questions

1. Wall shear stress is affected most by a change in the
   (a) viscosity of blood
   (b) flow rate
   (c) vessel radius
   (d) blood pressure
   (e) cardiac output

2. The earliest atherosclerotic lesions in experimental atherosclerosis develop
   (a) at the upstream rims of aortic ostia
   (b) in regions of high shear stress
   (c) in regions of turbulent flow
   (d) in the common carotid artery
   (e) in the renal arteries

3. Low wall shear rates
   (a) may retard the mass transport of atherogenic substances away from the wall
   (b) may result in increased intimal accumulation of lipids
   (c) may interfere with turnover at the endothelial surface of substances essential to artery wall nutrition
   (d) are observed in the carotid sinus opposite the flow divider
   (e) all of the above

4. Which of the following is false?
   (a) the carotid sinus has twice the cross-sectional area of the distal internal carotid artery
   (b) the outer wall of the carotid sinus is an area of flow separation and stasis
   (c) flow visualization studies demonstrate that flow in the carotid artery is turbulent
   (d) shear stress is low along the flow divider of the carotid artery bifurcation
   (e) all of the above

5. Pulsatile flow results in
   (a) less complex flow fields
   (b) turbulent flow along the inner wall of the carotid sinus
   (c) high shear stress along the outer wall of the carotid sinus
   (d) alternating positive and negative shear stress vectors along the outer wall of the carotid sinus
   (e) all of the above

6. Hypertension is
   (a) associated with a decrease in the severity of atherosclerosis
   (b) the primary risk factor for the development of clinical complications of atherosclerosis
   (c) the result of elevated shear stress
   (d) a more important factor in coronary artery disease than in cerebrovascular disease
   (e) an important etiologic factor in plaque pathogenesis

7. Which of the following is true?
   (a) endothelial injury is the primary factor in plaque pathogenesis
   (b) the endothelial lining of arteries is observed to be damaged in vivo by shear stress
   (c) focal, repeated endothelial injury accounts for the localized nature of plaque deposition
   (d) there is no direct evidence that experimentally induced endothelial damage or removal results in eventual sustained lesion formation
   (e) there is no evidence that the formation of experimental intimal plaques requires the presence of a continuous endothelial covering

8. The functional state of the media
   (a) appears to be important in plaque pathogenesis
   (b) is unaffected by increased pulse pressure
   (c) is unrelated to wall tension
   (d) is unimportant for plaque formation
   (e) none of the above

9. Artery walls can adapt in response to
   (a) enlarging intimal plaques
   (b) increased flow
   (c) decreased flow
   (d) hypertension
   (e) all of the above

10. The human abdominal aorta
    (a) experiences high shear stress along the posterior wall below the renal arteries
    (b) may be particularly vulnerable to early and rapid development of atherosclerosis because of relatively low flow velocities compared with the remainder of the aorta
    (c) experiences relatively minor changes in flow with lower limb exercise
    (d) flow patterns are observed to be undisturbed under resting conditions in model flow and computational fluid dynamics studies
    (e) is observed to have velocity direction oscillation, vortex formation, and increased fluid residence time in the infrarenal portion relative to the suprarenal portion

Answers

1. c  2. a  3. e  4. c  5. d  6. e  7. e  8. a  9. e  10. e