Hemodynamics of Carotid Artery Atherosclerotic Occlusive Disease

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Hemodynamic mechanisms for the initiation and progression of carotid bifurcation atherosclerotic occlusive disease have been extensively researched during the past few decades. Attention has focused on the carotid bulb, or sinus, where most atherosclerotic plaques are found. Herein, the authors review the seminal works that have led to an understanding of not only complex local hemodynamics but also the elicited specific biologic response. In addition, new analysis of the age-dependent morphologic maturation of the human carotid bifurcation is unveiled. Understanding the role of hemodynamics in atherogenesis may lead to the improvement of minimally invasive endovascular therapy and noninvasive strategies.

MORE than 700,000 Americans experience a stroke each year; in 2000, the total associated mortality from stroke was approximately 283,000 (1). Currently, there are 4.6 million stroke survivors in the United States, where the disease is the third leading cause of death and the number one cause of major morbidity (1). Atherosclerotic disease of the carotid artery is responsible for 20%-30% of all strokes (2). It is estimated that approximately 0.5% of people older than 60 years and 10% of people older than 80 years have carotid artery stenosis. The total number of carotid endarterectomies has increased from just 13,000 in 1975 to more than 106,000 in 1995. The number is expected to rise with the increasing proportion of elderly in the population. More recently, carotid artery stent placement was introduced as an alternative to carotid endarterectomy, and since 1997 the number of cases in which stents were placed increased to more than 12,000 worldwide, with a reported success rate of more than 98% (3). In the largest review of more than 5,000 carotid artery stent placement procedures (4), only 2.1% of patients were found to have restenosis of more than 50% at 6 months. At 12 months, the restenosis rate was 3.5%. The major stroke and death rate at 1 year following stent placement was 2.4% (4).

Several factors play a role in the development of carotid artery stenosis. Nonmodifiable factors include age, race, sex, genetics, and family history. Specifically, an older age, black and Hispanic ethnicity, male sex, and positive family history are all risk factors. Modifiable risk factors include smoking, hyperlipidemia, a sedentary lifestyle, increased body mass index, use of oral contraceptives, alcohol and substance abuse, diabetes mellitus, hypertension, prior transient ischemic attack or stroke, elevated homocysteine levels, elevated anticardiolipin antibodies, presence of a carotid bruit, cardiac disease, increased fibrinogen, and low serum folate levels (5).

The geometry of the carotid bifurcation itself can also be considered a risk factor. The unique geometry of the carotid bifurcation governs the local hemodynamics, which have been implicated in carotid artery wall heterogeneity. Carotid stenosis is localized to the carotid bulb and progresses circumferentially from the outer wall of the bulb toward the carina. Several studies have defined the relationship among bifurcation anatomy, hemodynamics, and the development of atherosclerosis (6–8).

ATHEROSCLEROTIC LESIONS

Location

Carotid arterial stenosis has been observed to consistently occur where the common carotid artery bifurcates into the internal carotid artery (ICA) and external carotid artery. The carotid bulb, or sinus, appears to host a unique blood flow environment and is thought to play a role in local blood flow disturbances that lead to endothelial cell damage and subsequent plaque formation. After impinging on the carina of the bifurcation, blood flow is redirected downstream into the carotid branches. Due to the tight turn, the inertial force of the flowing blood precludes it from following the outer curvature of the carotid sinus and flow...
separates, creating local flow disturbances. The proximal segment of the ICA, where flow is separated, is the most common site for the development of plaque.

**Symptomatic and Asymptomatic Plaque**

Carotid plaques have a variety of characteristics that distinguish them, most notably as either homogeneous or heterogeneous (9–11) (Table 1, Figs 1, 2). In general, homogeneous plaques are stable, with deposition of fatty streaks and fibrous tissues. The cholesterol-rich, slightly raised fatty streaks become a fibrous plaque. Atherosclerotic changes include diffuse intimal thickening that results from the migration of medial smooth muscle cells into the subendothelial space through the fenestrations in the internal elastic lamina. Intimal growth includes increasing amounts of elastic fibers, collagen, and glycosaminoglycans (5). These plaques rarely have evidence of hemorrhage or ulcerations.

As the atherosclerotic plaque develops, the elicited biologic response is an attempt to cover the plaque with a fibrous cap. Unfortunately, over time the fibrous cap may rupture and release the underlying debris into the circulation. Restabilization of the ruptured plaque includes a normal cascade of wound healing responses leading to heterogeneous structure. Heterogeneous plaques are unstable, with histologic characteristics of lipid-laden macrophages, monocytes, leukocytes, necrotic debris, cholesterol crystals, and calcifications. These plaques are soft and friable but may harden with calcium, lipid, and cholesterol accumulation within the vessel wall. Surface irregularities or plaque ulceration have also been shown to be risk factors for thromboembolic events. Ulcerated plaques consist of soft, gelatinous clots that contain platelets, fibrin, white blood cells, and red blood cells. The complicated plaque may undergo rupture, intraplaque hemorrhage, extensive necrosis, calcification, and subsequent thrombosis. Infiltration of the fibrous cap by foam cells may also contribute to the rupture. The affected artery can be involved in a segmental or asymmetric manner.

Extensive studies of plaque characteristics have revealed a correlation between the histologic features of a plaque and its susceptibility to cause thromboembolic events. In general, symptomatic carotid disease is not a result of inadequate perfusion due to a high degree of stenosis. Rather, patients with symptomatic carotid disease usually have heterogeneous plaques that are the source of shed emboli. The degree of carotid artery stenosis alone may not enable an adequate prediction of which patients will suffer strokes.

Plaque characteristics have been studied not only to elucidate the cause of the disease but also in an effort to correlate them with either intravascular or perivascular findings at ultrasonography (US). However, effort is directed also toward the development of less-invasive characterization techniques, such as magnetic resonance (MR) imaging. Soft heterogeneous plaques that are more likely to be related to stroke usually have low echogenicity at US. This corresponds to the weak reflection of ultrasound and the echolucency of the lipid and hemorrhage content of the plaque (12,13).

**Angiography**

Angiography remains the “gold standard” for evaluating carotid stenosis, although various noninvasive imaging modalities are currently available. US, for example, has been widely used before carotid endarterectomy because it is noninvasive and easy to operate. Qureshi et al (14), however, reported a false-positive rate of 20% in symptomatic candidates; the rate was as high as 41% in asymptomatic patients. Angiography provides detailed information about potential associated intracranial atherosclerotic disease seen in up to 20% of patients.

Adequate evaluation of the vessel wall and plaque composition is desirable for screening, grading stenosis, performing follow-up, and avoiding complications related to angiography. Spiral computed tomographic (CT) angiography and color-coded duplex US are noninvasive techniques that could replace angiography, which is more susceptible to complications, and give detailed information about stenosis grade and plaque characteristics. Spiral CT angiography and color-coded duplex US have been used to evaluate carotid stenosis either as a stand-alone technique or as a combined method (15) (Table 2).

### HEMODYNAMICS

**Anatomy and Development of the Carotid Bulb**

A study by McGill (16) showed that atherosclerosis of the carotid sinus be-

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**Table 1** Plaque Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stable (Asymptomatic)</th>
<th>Unstable (Symptomatic)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage with plaque rupture</td>
<td>32</td>
<td>74</td>
<td>NA</td>
</tr>
<tr>
<td>Percentage with necrotic core</td>
<td>22</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>Mean distance (±SD) from necrotic core to lumen (mm)</td>
<td>0.5 ± 0.5</td>
<td>0.27 ± 0.3</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Percentage with calcification</td>
<td>7</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Mean no. of macrophages (±SD)</td>
<td>385 ± 622</td>
<td>1,114 ± 1,104</td>
<td>&lt;.009</td>
</tr>
<tr>
<td>Disruption of fibrous cap</td>
<td>+</td>
<td>++</td>
<td>NA</td>
</tr>
</tbody>
</table>

Note.—Data are from references 9–11. + = some degree of disruption; ++ = substantial degree of disruption.

* NA = not applicable, NS = not significant.
gins during adolescence. Peterson et al (17) analyzed gross atherosclerotic lesions that progress with age and concluded that the common carotid artery proximal to the bifurcation and the ICA distal to the bifurcation showed a marked increase in size with advancing age; however, the angle of the carotid bifurcation did not appear to be directly related to age.

Recently, Seong and colleagues (18,19) investigated the morphologic changes in the carotid artery with aging (Fig 3). The most important findings when comparing morphologic images of the carotid bifurcation obtained from infancy to adulthood were the substantial growth of the ICA with...
age and the development of a carotid sinus at the root of the ICA. Initially similar in size to the external carotid artery in infancy and childhood, the ICA experiences a substantial growth at its root during adolescence. The carotid sinus that is common at adulthood can be seen with both anteroposterior and lateral angiographic projections. It appears that the carotid sinus develops in late adolescence (18,19).

Therefore, it appears that the carotid bulb in humans develops as a result of arterial remodeling that coincides with maturation and growth of the brain and occurs at approximately the same time that hormonal changes take place during puberty. Although the reasons for its appearance are unknown, it is interesting to speculate why this unique bifurcation develops in this way. Complementary hemodynamic studies about the obtained geometries may help shed light on this question.

One of the more interesting findings in the studies by Seong and colleagues is that the bifurcation angle remains virtually unchanged during the growth period and maintains a value of 73.6°–78.1° (as previously described by Peterson et al (17)). The angle split between the ICA and external carotid artery, however, relative to the common carotid artery does change. The angle of each branch relative to the line tangent to the terminus of the common carotid artery centerline at the bifurcation point was defined by the tangents to the centerlines of the daughter branches at their origin. The summation of the two angles was considered the bifurcation angle. The ICA angle increases continuously with age, with a corresponding decrease in the angle of the external carotid artery. One of the reasons that the angle of the ICA increases is the progressive increase in the diameter of the ICA. Remodeling of the common carotid artery terminus may accommodate a smooth hydraulic transition into the growing ICA with increasing perfusion demand.

Larger studies have yet to confirm these initial findings. Another limitation of the findings above is the lack of distinction between the left and right carotid bifurcation. Differences between the two carotid bifurcations do exist, as pointed out by Peterson et al (17). The left carotid artery is closer to the heart and arises directly from the aorta, whereas the right carotid artery arises from the brachiocephalic trunk. However, the question of whether these distinctions induce morphologic differences that are either random or systematic must be evaluated with a much larger database than available for previous studies.

Flow Mechanics

The hypothesis that blood flow patterns at the carotid bifurcation have a substantial bearing on the predilection of this region to atherosclerosis has led to a comprehensive investigation into the associated hemodynamics (20–22). Many factors, such as blood flow velocity, mural tensile stress, turbulence, and arterial wall shear stress (WSS), have been proposed as causative factors in the initiation of atheroma. WSS in particular has been explored and consequently implicated as an atherogenic factor by many investigators (21,23–25). Initial hypotheses involving WSS contended that atheroma formation at sites with low wall shear was due to a decreased efflux of cholesterol (23). Other studies (24) have suggested that atheroma formation occurs at sites with high WSS due to damage caused to the endothelium. Vascular zones susceptible to plaque formation have been found to experience a combination of low and oscillating shear stresses, whereas zones with high wall shear are relatively free of disease (21,25,26).

Results of flow visualization studies in which in vitro models of the carotid bifurcation were used (20,27,28) revealed a complex flow field that is due predominantly to the atypical geometry that develops at this branch site. Under steady flow condi-
tions, flow separates near the outer corner (away from apex) at the junction of the ICA and common carotid artery, which gives rise to secondary flow patterns at the outer wall of the carotid sinus (Figs 4, 5). The size of the separated region and its flow characteristics are dependent on the flow rate through the common carotid artery, the flow division between the ICA and external carotid artery, and the geometric configuration of the bifurcation (27,29). Secondary flows in the sinus were visualized by using hydrogen bubbles and dye and consisted primarily of a pair of counter-rotating helices that were symmetric about the plane of the bifurcation, the cores of which were located toward the outer wall of the sinus. Even under the steady flow conditions, at high Reynolds numbers ($R_e > 800$), these helices underwent oscillations that increased in intensity with increasing $R_e$. Flow reversal at the junction of the external and common carotid arteries was seen only at very low flow within the external carotid artery ($< 20\%$ of total flow). Secondary flows, however, were visualized in this artery with helical streamlines that rotated counter to the corresponding helices in the ICA. The bifurcation apex was found

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**Figure 3.** Angiograms of the carotid bifurcation obtained at various stages of development. A, Left carotid bifurcation in a 1-year-old boy. Note the narrow origin of the ICA. B, Left carotid bifurcation in a 5.5-year-old boy. The root of the ICA is of uniform caliber without the familiar carotid bulb. C, Left carotid bifurcation in a 15.7-year-old boy. The carotid bulb is now visible. D, Typical disease-free right common carotid artery in a 33-year-old man.

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**Figure 4.** (a) Hydrogen bubble visualization in a glass model, with the bubble-generating wire oriented in the plane of the photograph. Flow is rapid, laminar, and longitudinal along the inner wall of the carotid sinus (black arrow), and a large area of flow separation is formed along the outer wall of the sinus (white arrows). (b) Axial velocity profiles in the carotid bifurcation model. Arrows indicate the relative magnitude and direction of velocity. Dotted lines indicate the locus of points of zero velocity. Images reprinted, with permission, from reference 6.
to be a region of relatively high shear rates, demonstrating rapid clearing of dye even at the lowest $R_e$ (400) studied. The increase in cross-sectional area at the carotid sinus sets up an adverse pressure gradient, which results in very low values of wall shear in this region. As the sinus terminates into the ICA, the reduction in area causes flow acceleration and the outer wall of the sinus begins to experience higher wall shear (28).

Flow patterns under pulsatile flow conditions were investigated by Ku and Giddens (20,30) in the same bifurcation model. In general, although overall flow patterns were similar to those of steady flow, some distinctions were apparent. Flow separation may be delayed beyond the acceleration phase of systole owing to a favorable pressure gradient. The point of flow separation near the outer wall of the common carotid artery–ICA junction migrates over a small section of the wall during the cardiac cycle. Helical secondary flow patterns at the sinus side walls underwent changes in pitch during the cycle. Low oscillating wall shear values at the outer walls of the sinus, high unidirectional shears at the inner sinus wall (flow divider wall), and intermediate WSS with a high degree of oscillation at the sinus side walls were reported (20,30). In vivo studies of human carotid bifurcations performed with various techniques ranging from pulsed Doppler US (31,32) to numeric simulations based on actual arterial geometries (33–35) reported flow fields that are in accordance with the description given earlier.

A comparison of WSS distribution in vitro in carotid bifurcation models and the distribution of intimal plaque thickness obtained at autopsy showed minimal plaque formation at the flow divider wall of the sinus (region of high shear), greater intimal thickening at sinus side walls (region with circumferential velocity components, intermediate oscillatory shear), and maximal thickening at the outer walls (region of flow separation, flow reversal, low and oscillating shear) (6,21). Strong correlations were found between intimal thickening and the reciprocals of maximum wall shear and mean wall shear and between intimal thickening and oscillating shear index (21).

Overall flow characteristics in planar bifurcation models with rigid and compliant arterial walls are found to be similar, with lower WSS induced in the compliant models (34,36). Approximately 30% reduction in mean shear stress and 100% variation in peak...
shear stress have been reported with laser Doppler anemometry measurements in an in vitro elastomer model (36). Results of numeric analyses coupling the flow field and arterial wall motion by mathematically modeling the arterial wall by means of shell mechanics showed a general reduction in shear stress values (34) and a 25% reduction in high values of shear (37,38) compared with rigid models. Simulation of arterial compliance by using intravascular US measurements of variation in artery diameter to define moving boundaries resulted in a 4%–17% decrease in wall shear (compared with rigid models) if the wall motion was greater than 10% and a negligible decrease in wall shear if the wall motion was less than 6% (39). The region of reversed axial flow in the carotid sinus increased temporally and spatially in compliant models compared with rigid models, with the flow separation point moving upstream (34,36).

Although planar bifurcation models provide vital information about the prevalent hemodynamics of the human carotid bifurcation, nonplanar curvature, and variations in geometry from individual to individual may introduce substantial changes to these observed flow patterns (27,40–42). Advances in medical imaging, image processing techniques, and computational abilities have facilitated numeric analysis studies that incorporate morphologically realistic arterial geometries from in vivo data (22,40). Skewing of velocity profiles due to curvature of the common carotid artery (resulting in asymmetric wall shear) or different wall shear maps of the anterior and posterior aspects of the carotid sinus due to out-of-plane curvature of this section can be ascertained with such combined approaches (33,40,42). Investigators comparing flow fields in carotid bifurcation models measured directly with MR imaging and the corresponding flow patterns obtained with numeric simulations reported general agreement between the two techniques (33,43,44) (Fig 6). The inability of MR imaging to provide velocity data with adequate spatial and temporal resolution, thereby introducing errors in quantitating secondary flow velocities and centerline flow in the carotid sinus, was noted (33,43,44).

Endothelial and Plaque Reaction to Hemodynamics

Atherosclerotic plaques are located in defined regions of the vasculature, specifically at branching points, at bifurcations, and within curves. As previously discussed, these locations show a strong correlation to areas of disturbed flow with the common feature of low and oscillatory WSS. This phenomenologic observation has spurred an extensive body of research into the response of the endothelium to the hemodynamic environment and its potential role in atherogenesis.

The endothelial cell monolayer serves as the communicating medium between the flowing blood and the arterial wall. It provides a protective barrier to arterial damage; disruption to this barrier in a given hemodynamic environment could contribute to atherogenesis (45). Beginning with the seminal work by Fry (46), it was observed that endothelial cells that had been surgically oriented in the perpendicular direction to flow eventually realign in the direction of the flow. This finding demonstrates the dynamic response of the endothelium to mechanical stimuli. It is now clear that focal ulcerations of the lumen or removal of the endothelial cells by shear forces do not evoke initiation of atherosclerotic disease (47). Rather, vasoactive and toxic substances produce modifications of endothelial reactivity and metabolism (48). The dynamic response of the endothelial cells include changes in permeability; oxidative modification of low-density lipoproteins; and the release of chemoattractants, mitogens, and growth factors that produce alterations in the smooth muscle cells of the media (48).

In the outer wall of the carotid bifurcation, a common location for the development of atherosclerotic plaques, there is flow separation and secondary vortex formation characterized by a reversal of the flow direction. Just beyond peak systole there is a reversal of the direction of WSS (25). Under these conditions, the endothelial cells are not predominantly aligned in the downstream direction (49). Moreover, there is an increased particle residence time, which implies

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**Figure 6.** Diagrams illustrate axial velocity profiles in the branching plane at peak systolic flow \( t_{\text{tp}} = 0.1 \), systolic deceleration \( t_{\text{tp}} = 0.14 \), minimum flow at the beginning of diastole \( t_{\text{tp}} = 0.36 \), and at diastolic flow \( t_{\text{tp}} = 0.8 \). The quantity \( t_{\text{tp}} \) represents normalized time with respect to the duration of the cardiac pulse. Reprinted, with permission, from reference 38.
that exposure to atherogenic agents is prolonged (50). This flow-induced phenomenon may favor transendothelial diffusion or intimal entrapment of the atherogenic particles. In addition, this flow environment may lead to disadvantageous changes to endothelial cell metabolism by increasing the duration of luminal contact with catalytic bolic products while at the same time decreasing the replenishment of nutritive substances (25,50,51). Production of nitric oxide and superoxide anion ($O_2^-$) by the endothelial cells is variable and dependent on time-varying patterns of WSS (52). Peroxynitrite, a reaction product of these radicals, is a powerful oxidant, and its toxic effects are implicated in vascular dysfunction associated with hypercholesterolemia, hypertension, and diabetes (53). Endothelial nitric oxide synthase (eNOS) and superoxide dismutase, an antioxidant defense enzyme that counters superoxide anion, are produced by endothelial cells exposed to WSS that is uniform in magnitude and direction (52). This realization poses another mechanism by which low values of oscillatory WSS could contribute to the initiation and development of atherosclerotic disease.

Despite large changes in cardiac output—as much as a fivefold increase during maximum exercise—the time-averaged WSS remains relatively constant in magnitude in large arteries (between 10 and 30 dyne/cm²) (52,54–56). This control over WSS values imposed on the endothelium is afforded by the change of vessel diameter. The conformational changes of the endothelial membrane and membrane cytoskeletal proteins brought on by fluid forces leads to downstream cell activation (45). The WSS acting on the luminal surface of the endothelium is also relayed throughout the cell by the cytoskeleton to sites that convert this mechanical signal into electrophysiologic, biochemical, and genetic responses (57). Davies et al (57) studied 15,000 differentially profiled endothelial genes that had been isolated from two regions of pig aorta (one region prone to atherosclerotic disease and disturbed flow, and the other resistant to plaque formation being exposed to laminar, unidirectional flow) and determined that less than 200 (1.5%) of these genes were differentially expressed. Such studies can provide the determination of atheroprotective and atheropermissive gene expression. One drawback to the genomics approach for elucidating endothelial response to regions of disturbed flow is the inability to obtain gene expression of a few cells, which leads to the spatial and temporal averaging of a larger region. The use of techniques such as atomic force microscopy and scanning confocal microscopy provides information about structural and biochemical responses of the endothelium on a subcellular level.

Plaque composition and structural integrity are highly variable, being not only patient specific, but site specific as well. Glagov and colleagues (25) proposed that the initial formation of plaques occurs in faintly disrupted luminal surfaces, the irregularities of which are imposed by the shape of the subendothelial foam cells. These areas of focal flow disturbance are associated with foam cell penetration of the endothelium, fiber exposure, and platelet deposition (58). Plaque modeling continues with the accumulation of thrombocytes and monocytes in the interrupted sites of the endothelium (25). This process, a combination of destructive and defensive healing, is complex, and for further study the reader is referred to more complete literature reviews by Glagov and colleagues (25,48). In the absence of plaque disruptions, fissuring, hemorrhage, or thrombus deposition, the luminal aspect of mature lesions remains smooth, with a relatively circular cross-section so as to preserve laminar flow (48). Fluid mechanics play a role not only in the production and organization of the plaque modeling, but also in the eventual advent of plaque complications, such as the rupture of the fibrous cap, which potentiates the onset of clinical symptoms.

**Damage of the Endothelium**

Desquamation of the endothelial cells has been identified at WSS levels exceeding 300 dyne/cm² (24). Such a WSS value, however, is not physiologically relevant, because the time-averaged shear stress in large arteries is between 10 and 30 dyne/cm². Nonetheless, there are other mechanisms of endothelial damage that merit due consideration, as it is well accepted that mechanical or biochemical injury to the endothelium is a crucial initiating event of atherosclerotic disease (45). Turbulence is seldom realized in physiologic flows not pertaining to pathologic states, with the exception of flow in the ascending aorta. In the scenario of extreme stenosis, however, transition to local turbulence, characterized by the stochastic generation of three-dimensional vortices, may occur (45). Endothelial cells that experience turbulent flow with a mean WSS of 1.2 dyne/cm² proliferate at a high rate, with no cell-to-cell contact (59). The turbulent forces are sufficient to eliminate intracellular connections of the endothelium. The random WSS acting across the cell junctions leads to the isolation of the individual cells, which results in migration and mitosis of the endothelial cells. It is interesting that endothelium exposed to laminar flow (ie, preconditioned endothelium) resists the adverse effects of turbulent shear stresses (59). Decreased endothelial cell proliferation by preconditioning in an environment of turbulent shear stress may be due to the protection afforded by increased rigidity of the cytoskeleton, hence resisting the disruption of intracellular bonds (45). The discontinuous endothelial layer initiated by turbulent stresses may facilitate the transendothelial migration of leukocytes, an event thought to contribute to atherosclerosis.

Tensile stress, which is the stress exerted on the arterial wall by hydrodynamic pressure, has also been shown to have a potential correlation with atherosclerosis. Hypertension is a known risk factor for the development of atherosclerotic disease. However, the precise mechanisms by which hypertension induces the formation of plaque are ambiguous. One proposed mechanism is that increased arterial pressure imparts damage to the endothelium (60). Physical injury of the endothelium by increased tensile stress would lead to smooth muscle cell proliferation and endothelial cell dysfunction, which causes the adhesion of platelets and monocytes to the endothelial surface (60).

**Poststenotic Dilatation and Narrowing**

Poststenotic dilatation (PSD) is a well-documented observation, de-
scribed as early as 1842 (61). Experimentally induced stenosis of the rabbit and canine carotid arteries has been shown to induce PSD (62,63). Characteristics of the vessel wall during PSD include a decrease in the density of smooth muscle cells and elastin content as well as an increase in collagen and the presence of collagenase (64,65).

It is well established that WSS that stretches the endothelial cells leads to the production of nitric oxide (NO). The production of NO is associated with elevated levels of eNOS, messenger RNA, and protein, which results in local dilation of the vessel. The poststenotic region, however, is exposed to complex flow patterns that include recirculation zones and points of reattachment. During the pulsatile cycle, the disturbed fluid flow in the poststenotic area imposes oscillatory magnitude and direction of WSS, which consequently leads to nonuniform hemodynamic forces on the endothelium.

Calvo and colleagues (66) proved conclusively that NO is the essential mediator in the phenomenon of PSD. In this series of experiments, stenoses of 70% were formed in rabbit femoral arteries by using partial ligation. Arteries that were coated with a suspension of the NO synthase inhibitor NG-nitro-l-arginine methyl ester (L-NAME) had minimal PSD 3 days after the induction of the stenosis. The maximal poststenotic increase in diameter was approximately 7%. Sham studies showed an increase in the diameter of the artery of nearly 30% distal to the stenosis. These experiments clearly demonstrate the fundamental role of NO in PSD. Because of the inability of the stenotic throat to dilate in response to the high shear, the concentration of NO in the poststenotic region is increased, leading to PSD. The authors further illustrated that the inhibition of cyclooxygenase activity with indomethacin offered no substantial deterrent to the development of PSD. Poststenotic collapse of the ICA is seen clinically, and has been explained in the literature, as a consequence of the hemodynamics associated with a vascular constriction. In fluid mechanics, the law of conservation of energy, applied under specific conditions such as inviscid flow (having no or negligible viscosity), requires that as fluid velocity increases, pressure decreases. This is expressed in the famous Bernoulli equation. The convergent flow through a stenosis due to atherosclerotic plaque accelerates, and thus the lateral pressure diminishes. The peak velocity will occur at the point of maximum stenosis, or the throat, which will consequently be the point of minimum pressure. It has been proposed that this hemodynamic effect could produce “systolic wall collapse” distal to the stenosis (67). The details of flow through a stenosis in a collapsible tube have been studied extensively by using numeric techniques, with the complexity of the problem culminating in the solution for three-dimensional flow of a viscous fluid in stenotic tubes with large wall deformation (68–72).

In vitro experiments using a latex tube with a stenosis were conducted to demonstrate hemodynamic induction of poststenotic arterial collapse (67). In these experiments, pulsatile flow was created with a systolic/diastolic pressure input of 100/60 mm Hg. The pressure at the output ranged from 0 to 25 mm Hg; these values were chosen on the basis of carotid stump pressure measurements obtained during carotid endarterectomy procedures in humans (73). It is important to note that carotid stump pressures of less than 25 mm Hg were recorded in less than 19% of the patients and that half of these patients required the use of a shunt during the procedure, which indicates that there was insufficient collateral flow to the brain. The results of the latex tube experiments demonstrated collapse of the tube distal to a stenosis of 68% with a stenopressure of 7 mm Hg. In the case of 81% stenosis, the tube collapsed with a stenopressure of 13 mm Hg. In both cases the external pressure within the Starling resistor, representing the pressure within the carotid sheath, was 25 mm Hg. This extramural pressure was higher than that typically measured within tissue but was justified by the authors due to the anatomic arrangement of the internal jugular vein within the carotid sheath. Volume changes of the vein result in pressure exerted on the adventitial surface of the carotid. For example, during the Valsalva maneuver the venous pressure can increase to more than 50 mm Hg. These experiments demonstrate that poststenotic collapse occurs if the pressure decrease across the stenosis is 93 and 87 mm Hg, with an external pressure of 25 mm Hg in the cases of 68% and 81% stenosis, respectively. Such decreases in pressure may not be realized in actual human cases of carotid atherosclerotic disease. Perhaps the only instance in which such decreases in pressure are realized would be when the blood supply to the circle of Willis via the basilary and contralateral ICAs is severely compromised. Because the circle of Willis serves as a manifold, pressure is transmitted to the diseased artery from the other main arterial feeders. The question looms regarding the possibility of having such a large pressure drop across a carotid stenosis and the patient being able to receive sufficient cerebral perfusion.

It has been proposed that poststenotic collapse may be a possible mechanism for plaque rupture with the potential to lead to subsequent thrombosis or distal embolization (67,68). A recent report in a large patient sample (74), however, has shown that the ischemic stroke rate in patients with poststenotic narrowing was significantly lower than that in those without. The 5-year risk of ipsilateral carotid territory ischemic stroke in patients medically treated with a stenosis of 70%–99% and poststenotic narrowing was 8%. The rate for patients who did not show poststenotic narrowing was 25%. These data showed that poststenotic narrowing is associated with a lower risk of stroke. The authors postulated that the neuroprotection offered by narrowing of the ICA after a stenosis may be due to the low flow not propagating emboli into the distal cerebral territories.

Other possible mechanisms of poststenotic reduction in arterial diameter may lie in endothelial dysfunction interfering with NO production. In addition, it has been demonstrated that low shear stress can accelerate intimal thickening in grafts (75). Intimal thickening is also observed at the lateral wall of the carotid bifurcation, which is a region of low, oscillatory WSS (25). Intimal thickening may explain the observed diameter reduction distal to a stenosis.
CONCLUSION

The carotid bifurcation with the age-related development of the carotid sinus creates a unique geometric environment for a complex, nonstratified blood flow field in this region. Low and oscillatory WSS has been shown to occur with specific endothelial cell responses. Although many factors play a role in the development of carotid stenosis, it is clear that the hemodynamic environment is a contributing factor that sets a cascade of events in motion that leads to the development of atherosclerotic plaques.

References
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