Pulsatile Flow and Atherosclerosis in the Human Carotid Bifurcation

Positive Correlation between Plaque Location and Low and Oscillating Shear Stress

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Fluid velocities were measured by laser Doppler velocimetry under conditions of pulsatile flow in a scale model of the human carotid bifurcation. Flow velocity and wall shear stress at five axial and four circumferential positions were compared with intimal plaque thickness at corresponding locations in carotid bifurcations obtained from cadavers. Velocities and wall shear stresses during diastole were similar to those found previously under steady flow conditions, but these quantities oscillated in both magnitude and direction during the systolic phase. At the inner wall of the internal carotid sinus, in the region of the flow divider, wall shear stress was highest (systole = 41 dynes/cm², diastole = 10 dynes/cm², mean = 17 dynes/cm²) and remained unidirectional during systole. Intimal thickening in this location was minimal. At the outer wall of the carotid sinus where intimal plaques were thickest, mean shear stress was low (~0.5 dynes/cm²) but the instantaneous shear stress oscillated between ~7 and +4 dynes/cm². Along the side walls of the sinus, intimal plaque thickness was greater than in the region of the flow divider and circumferential oscillations of shear stress were prominent. With all 20 axial and circumferential measurement locations considered, strong correlations were found between intimal thickness and the reciprocal of maximum shear stress ($r = 0.90, p < 0.0005$) or the reciprocal of mean shear stress ($r = 0.82, p < 0.001$). An index which takes into account oscillations of wall shear also correlated strongly with intimal thickness ($r = 0.82, p < 0.001$). When only the inner wall and outer wall positions were taken into account, correlations of lesion thickness with the inverse of maximum wall shear and mean wall shear were 0.94 ($p < 0.001$) and 0.95 ($p < 0.001$), respectively, and with the oscillatory shear index, 0.93 ($p < 0.001$). These studies confirm earlier findings under steady flow conditions that plaques tend to form in areas of low, rather than high, shear stress, but indicate in addition that marked oscillations in the direction of wall shear may enhance atherogenesis. (Arteriosclerosis 5:293–302, May/June 1985)

The role of specific hemodynamic variables in the initiation and development of atherosclerotic plaques in human arteries can be assessed by correlating flow field measurements with the distribution of intimal lesions about branch ostia and bifurcations. At present, noninvasive methods for determining flow velocity profiles in situ do not provide sufficient spatial resolution to describe the complex flow patterns at such locations, nor are current imaging techniques adequate for precise localization of early nonstenosing lesions. With the use of appropriate geometric and scaling parameters, rigid glass or plastic models can be used to visualize flow profiles and measure flow velocities representative of those occurring in human vessels.

Postmortem human arteries are suitable for determinations of corresponding plaque location and size if appropriate pressure-fixation procedures are used. Previous comparison of steady flow measurements in scale models of the human carotid bifurcation with plaque deposition in a corresponding series of autopsy specimens revealed that early lesions occurred principally in regions of flow separation, low wall shear stress, and departure from unidirectional
flow. Specifically, plaque formation was maximal at the outer wall of the carotid sinus where flow separation and low wall shear occurred in the model studies, and it was minimal near the flow divider (inner wall) where shear stress was high and flow streamlines were mainly axially oriented. At the side walls where circumferential velocity components were present, intimal thickening was intermediate between that formed at the outer and inner walls.

To explore the effects of pulsatile flow on hemodynamic forces acting on the endothelial surface, we observed flow patterns in a glass carotid bifurcation model utilizing a pulsatile flow system that produced systolic and diastolic intervals and a pulse wave form similar to that which prevails in normal young adults. In contrast to steady flow conditions, pulsatile flow created a cyclically varying region of separation and reversal at the outer wall of the sinus and helical patterns which changed markedly in magnitude and direction. We have now measured flow velocity in a Plexiglas model of the bifurcation at several axial and circumferential stations using laser Doppler velocimetry, and we used the near wall velocity gradients to calculate values for wall shear stress. Comparisons of the pulsatile fluid dynamic measurements with the human specimens revealed a good correlation between reciprocals of maximum and mean wall shear stress and intimal plaque deposition. In addition, oscillations in wall shear stress amplitude and direction occurring mainly in systole correlated strongly with plaque thickness.

Methods

Comparisons were made between data obtained from pulsatile flow studies in a Plexiglas model and the circumferential distribution of intimal plaque thickness at five standard sampling levels in human carotid bifurcations. The five standard axial locations at which flow velocity determinations were made in the model and intimal thicknesses were measured in the specimens are shown in Figure 1.

The Plexiglas bifurcation model used for the fluid dynamic studies was constructed from measurements obtained from biplanar angiograms of 57 patients ranging from 34 to 77 years of age. The details of construction are provided elsewhere. The dimensions of the model were scaled upward 125 times by in vivo Doppler ultrasound measurements. The model diameters at the axial levels corresponding to the five standard axial sampling sites of the human vessels were: A. common carotid, 31.0 mm; B. proximal internal carotid, 32.3 mm; C. mid-carotid sinus, 34.4 mm; D. distal internal carotid, 22.0 mm; E. proximal external carotid, 17.6 mm. The bifurcation angle was 50°.

The carotid bifurcation specimens used to quantitate lesion location and thickness were obtained at autopsy from patients aged 27 to 73 years (mean, 53 years) with no history of symptomatic cerebrovascular disease. The common carotid, internal carotid, and external carotid were excised as a unit. Each transected vessel was then cannulated and the intact bifurcation was distended with warm (37° C), buffered formalin (3.8%) at an intraluminal pressure of 100 mm Hg. Fixation was continued for 1 hour with the distended vessels immersed in fixative. On the basis of subsequent angiograms, the first 12 specimens without stenoses were selected for sectioning at the standard axial levels. Angiograms of the fixed specimens revealed mean diameters of 6.1 mm for the standard common carotid (A); 6.0 mm for the proximal internal carotid (B); 6.2 mm for the midpoint of the sinus (C); 3.5 mm for the distal internal carotid (D); and 4.0 mm for the external carotid (E) axial levels. The mean bulb length was 13.9 mm and the mean bifurcation angle, 46°. When the dimensions of the Plexiglas model are scaled to a 6.1 mm common carotid diameter, the resulting model values are 6.3, 6.8, 4.2, and 4.2 mm for levels B, C, D and E, respectively. These compare favorably with the corresponding dimensions obtained from the cadaver specimens.

At each standard axial level, measurements were made at the outer, inner, and side walls in both the models and specimens. The circumferential locations were designated in polar coordinates with 0°...
corresponding to the inner wall or flow divider, 180° corresponding to the outer wall opposite the flow divider, and 90° or 270° corresponding to the side wall locations. For the common carotid arteries (Level A), the side corresponding to the external carotid artery was taken as the 0° index point. Because of the symmetry of the model in the plane of the bifurcation, conditions at 90° and 270° were similar. Wall shear stress and intimal thickness were therefore determined at a total of 20 sites.

**Pulsatile Flow Conditions and Fluid Dynamic Measurements**

The working fluid was a mixture of water and glycerin adjusted to yield an absolute viscosity of 0.14 g/cm/sec and a kinematic viscosity of 0.12 cm²/sec. The fluid was pumped from an upstream tank through an electronically controlled shaker valve into a straight tube 3 meters long to achieve fully developed pulsatile laminar flow at the entrance to the bifurcation. The servo-driven valve directed fluid either through the test section or through a bypass tube to create the pulsatile wave form. The pumping system could be programmed to reproduce a wide range of wave forms and had a linear frequency response up to 15 Hz. The pulsatile wave form used for the present study was a replica of a carotid flow pattern obtained by noninvasive ultrasound Doppler velocimetry in a 22-year-old man with no angiographic evidence of arterial stenosis. Fluid leaving the internal carotid branch of the model flowed directly into a low resistance, constant-head tank to be recycled, while fluid in the external carotid branch flowed into a 0.94 cm collapsible tube enclosed in a pressure chamber. The tube diameter could be controlled by varying the chamber pressure, thereby permitting adjustment of the flow division between internal and external carotid branches.

For the present study, the collapsible tube chamber was adjusted to provide 45% mass flow in the external carotid artery during peak systole and 30% mean flow over the pulsatile cycle. Electromagnetic flow meters monitored flow continuously in each branch. The wave form and amplitude were adjusted to correspond to a mean flow of 5 ml/sec (Re = 300) and a peak flow of 13 ml/sec at a Reynold's number of 800, typical conditions for a normal adult human carotid. The Reynolds number, Re = VD/ν, was derived for a common carotid artery diameter of 6.1 mm and a blood viscosity of 0.035 cm²/sec. The total mass flows for the common, internal, and external carotid arteries are illustrated in Figure 2, scaled for the in vivo conditions previously described.

**Flow Velocity**

Flow velocity was measured with a DISA 55L Mark II laser Doppler anemometer system with a sample volume of 1.08 mm in length and 0.12 mm in diameter as described in detail elsewhere. This method of velocity detection is noninvasive and can distinguish between negative and positive velocities. Two velocity components (axial and circumferential) were measured both in the plane of the bifurcation and perpendicular to this plane. At the walls, the two velocity components were combined to yield the magnitude and direction of velocity parallel to the wall, i.e., the velocity that induces wall shear stress. The velocity measurements indicated that the circumferential velocity component very near the walls in the plane of the bifurcation, i.e., the inner (θ = 0°) and outer (θ = 180°) walls, was negligible; and hence the wall shear stress vectors at these locations were defined by the axial components.

**Wall Shear Stress**

Stress was calculated as a function of time during the cycle at each location using a least-squares fit of three radial stations measured very close to the wall according to the defining relationship:

$$\tau_w = \mu \frac{\Delta \bar{V}}{\Delta r} \tag{1}$$

where $\tau_w$ is the wall shear stress, $\mu$ is the absolute viscosity, $\bar{V}$ is the velocity parallel to the wall, and $r$ is the radial distance from the wall. From this result for $\tau_w$, it was possible to determine various shear stress indices such as maximum, minimum, and mean wall shear stress. To correlate the excursion of shear stress over the cardiac cycle with lesion thickness, *pulse shear stress*, defined as maximum-minimum shear stress, was also calculated for each axial and polar location. Previous studies in steady flow showed that the method for estimating wall shear stress from the measured velocity profiles gave values within 15% of the theoretical Poiseuille result in the common carotid artery proximal to the bifurcation.
Oscillatory Shear Index

An oscillatory shear index (OSI) was formulated to account for the cyclic departure of the wall shear stress vector from its predominant axial alignment (see Appendix A). The rationale for development of the OSI is as follows. In the common carotid artery, flow velocity near the wall, while pulsatile, is continually directed forward or cephalad, resulting in wall shear stress that acts in the positive axial direction. This is also true along the inner wall (0°) at the flow divider, although the magnitude of the shear stress at this level is much higher than at the common carotid level. A different wall shear stress behavior was, however, observed at the outer (180°) and side (90°, 270°) walls of the bifurcation branches, particularly in the internal carotid sinus. At the 180° position for example, the near wall velocity in the sinus was found to be negative during segments of the cycle, leading to a wall shear stress vector that transiently alternated between the positive and negative axial directions.

At the side walls of the branches (90° and 270°), helical flow patterns developed and resulted in a stress vector in which the direction changed with time. Thus, to provide an index which describes the degree of deviation of the wall shear stress from its average direction, we defined the OSI as follows:

\[
OSI = \frac{\int_0^T | \tau^+ | \, dt}{\int_0^T | \tau^- | \, dt}
\]

where \( T \) is the duration of the cycle, \( \tau^+ \) is the total, instantaneous wall shear stress vector and \( \tau^- \) is the stress component acting in the direction opposite to that of the temporal mean shear stress for the inner (0°) and outer (180°) walls, and the component acting at 90° to the angular orientation of this mean shear stress vector for the side walls (0°, 90°, 270°). This index represents a measure of the shear stress acting on the luminal surface due to either "cross-flow" or reverse flow velocity components occurring during pulsatile flow.

Quantitation of Intimal Plaque Thickness in Human Specimens and Comparison with Shear Stress Data

Before sectioning the arteries at the standard axial levels, sutures were sewn into the adventitia over the full length of the specimen to mark the location of the center of the flow divider and the center of the medial side wall. This established the 0° and 90° circumferential positions for polar coordinate mapping of lesion thickness on histologic sections (Figure 3). Transverse rings were then removed at the standard levels and processed for light microscopy. Paraffin-embedded tissues were sectioned at 7 µm and were stained with hematoxylin and eosin. The Gomori trichrome-aldehyde fuchsin method was used to stain connective tissue fibers. Images of the histological sections were projected onto a digitizing tablet and the contours of the lumen, the internal elastic lamina, and the outer limit of the media were traced as described previously. The resulting data were stored and processed in a microcomputer and the intimal thickness at the four circumferential locations (0°, 90°, 180°, 270°) was computed for each section. Correlations were calculated between intimal thickness at each standard location in the cadaver bifurcations and the measured and computed hemodynamic variables in the model carotid bifurcations. Statistical analysis of the correlations was performed using the method of least squares with a two-sided t test for significance levels.

Results

Common Carotid Artery

Wall shear stress in the common carotid artery (Level A) ranged from 3 to 28 dynes/cm² with a mean of 7 dynes/cm² and was the same at all points about the circumference (Table 1). The shear stress vector was aligned in the forward axial direction throughout the pulse cycle, and the oscillatory shear index was zero. Intimal thickness ranged from 0.10 ± 0.02 mm to 0.15 ± 0.03 mm with no differences in thickness among the four measurement sites about the circumference.
Table 1. Pulsatile Shear Stress and Intimal Dimensions at the Carotid Bifurcation

<table>
<thead>
<tr>
<th>Level</th>
<th>Intimal thickness (mm)</th>
<th>Pulsatile shear stress (dynes/cm²)</th>
<th>Model flow results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Max</td>
<td>Min</td>
</tr>
<tr>
<td>A. Common carotid</td>
<td>0.10 ± 0.02</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>270</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td>B. Proximal internal carotid</td>
<td>0.14 ± 0.05</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>4</td>
<td>-7</td>
</tr>
<tr>
<td></td>
<td>270</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>C. Midpoint carotid sinus</td>
<td>0.19 ± 0.07</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>6</td>
<td>-13</td>
</tr>
<tr>
<td></td>
<td>270</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>D. Distal internal carotid</td>
<td>0.07 ± 0.02</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>70</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>49</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>270</td>
<td>70</td>
<td>23</td>
</tr>
<tr>
<td>E. External carotid</td>
<td>0.27 ± 0.15</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>73</td>
<td>5</td>
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<td>180</td>
<td>35</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>270</td>
<td>73</td>
<td>5</td>
</tr>
</tbody>
</table>

*OSI = oscillatory shear index; see text.

Proximal Internal Carotid

In the proximal internal carotid (Level B) there were marked differences in both magnitude and direction of shear stress at different locations about the circumference of the vessel as well as at different times during the pulse cycle. Along the inner wall (0°), shear stress was high, reaching a maximum of 50 dynes/cm² at peak systole and decreasing gradually to an end-diastolic value of 17 dynes/cm². The mean value was 26 dynes/cm², three times higher than in the common carotid artery (Table 1). Shear stress was unidirectional throughout the cardiac cycle (Figure 4), and the oscillatory shear index was zero. Intimal thickness was 0.14 ± 0.05 mm and did not differ significantly from thickness in the common carotid artery.

Along the outer wall (180°) of the carotid sinus, as well as along the zones of transition between the common and internal carotid artery and between the common and external carotid artery, wall shear stress values were of low magnitude and oscillated between positive and negative values during systole but remained relatively constant during diastole. The circumferential component of velocity was negligible throughout the cycle at both inner and outer walls of the bifurcation.

The maximum positive shear stress was 4 dynes/cm² in early systole, and flow velocity and shear stress direction were axially aligned in the forward direction throughout the acceleration phase. During midsystole, shear stress reversed direction sharply and became negative in direction, reaching a magnitude of -7 dynes/cm². Oscillations between forward and reverse shear stress diminished in magnitude during late systole and during diastole had a mean value very close to zero (Figure 5). The magnitude of shear stress during diastole was similar to the value...
The wall shear stress at the outer wall of the carotid sinus (Level B). This curve was derived from near-wall velocity data such as that shown in Figure 6. The shear stress oscillation from positive to negative values systole is characteristic of locations along the outer wall of the sinus.

Figure 5.

The axial velocity component measured very near (1.5 mm) to the outer wall of the proximal internal carotid sinus (Level B) in the model. The velocity during early systole was initially forward. During the time for which the flow in the common carotid and its branches was high, however, the near-wall velocity shown here reversed sharply. During diastole, the velocity at the outer wall was very nearly zero.

Figure 6.

Shear stress at the side wall (90° and 270° with respect to the flow divider) exhibited a complex pattern of directional changes reflecting the evolving vortex structures in the flow field described earlier. The wall shear stress vector rotated through 70° of arc during systole as shown in Figure 7. The vector was inclined 15° to the longitudinal axis in early systole, but rotated to a position nearly perpendicular to this axis at the peak of systole. During diastole, the shear stress vector stabilized at a mean value inclined approximately 33° to the axis. The magnitude of shear stress at the side walls was less than along the inner wall and changed during the pulse cycle from a maximum of 11 dynes/cm² to a minimum of 1 dyne/cm² with a mean of 3 dynes/cm². The oscillatory shear index was 0.07 and intimal thickness was greater than at the inner wall or in the common carotid artery (Table 1).

Figure 7.

The shear stress vector at the side walls of the carotid sinus (Level B) changed in both magnitude and direction during the flow cycle. The upper curve illustrates the rapid increase and decrease in the magnitude of the wall shear stress occurring with each systole, and the relatively constant value during diastole. The lower curve gives the variation in the shear stress vector direction. 0° is taken to be aligned along the axis of the internal carotid artery. The vector changed direction sharply during systole over a range from 15° to 82° before attaining a constant angle during the latter half of the cycle.

In this location previously reported for steady flow at a comparable Reynolds number (0 dynes/cm²). The corresponding variation in flow velocity during the pulse cycle at a luminal position 1.5 mm from the outer wall of the model proximal carotid sinus is shown in Figure 6. The oscillatory shear index was high (0.32) at this location as was intimal thickness (0.63 ± 0.17 mm) (Table 1).

Shear stress at the side wall (90° and 270° with respect to the flow divider) exhibited a complex pattern of directional changes reflecting the evolving vortex structures in the flow field described earlier. The wall shear stress vector rotated through 70° of arc during systole as shown in Figure 7. The vector was inclined 15° to the longitudinal axis in early systole, but rotated to a position nearly perpendicular to this axis at the peak of systole. During diastole, the shear stress vector stabilized at a mean value inclined approximately 33° to the axis. The magnitude of shear stress at the side walls was less than along the inner wall and changed during the pulse cycle from a maximum of 11 dynes/cm² to a minimum of 1 dyne/cm² with a mean of 3 dynes/cm². The oscillatory shear index was 0.07 and intimal thickness was greater than at the inner wall or in the common carotid artery (Table 1).

Midpoint of Carotid Sinus

Measurements of shear stress at the midpoint of the internal carotid sinus (Level C) revealed a more limited range of variation in direction and magnitude but showed characteristics similar to those at the proximal internal carotid level (Level B). At the inner wall (0°), shear stress at the mid-sinus level varied between 10 and 41 dynes/cm² with mean of 17 dynes/cm². The oscillatory shear index was zero, and intimal thickness was no different from the thickness in the common carotid artery. Along the outer wall
wall, shear stress was low, ranging between +6 and −13 dynes/cm² during systole before returning to an end-diastolic value of −0.7 dynes/cm². The oscillatory shear index was high (0.35) and the intima was thickened (0.49 ± 0.10 mm) compared to the inner wall and common carotid. The orientation of the side wall shear stress vector alternated over a range of 40° with an average angle of 46° with respect to the longitudinal axis of the internal carotid artery.

**Distal Internal Carotid**

Shear stress increased markedly in the distal internal carotid (Level D) at all points about the circumference as flow accelerated into the smaller diameter vessel from larger carotid sinus. Shear stress reached a maximum value of 109 dynes/cm² at the inner wall and had a mean value over the cycle of 45 dynes/cm². At the outer wall, shear also increased to a maximum of 49 dynes/cm² with a mean value of 20 dynes/cm². Flow was unidirectional, flow disturbances were absent or minimal, and intimal thickness was minimal, ranging from 0.06 ± 0.01 mm to 0.09 ± 0.04 mm.

**External Carotid**

The external carotid (Level E) was also a site of high, unidirectional wall shear stresses, but changes during the cycle were not large. There was a suggestion of increased intimal thickness along the inner wall relative to the outer wall, but this was not statistically significant (Table 1).

**Correlation of Shear Stress With Intimal Thickness**

When all 20 measurement locations were considered, intimal thickness bore an inverse relationship to both maximum shear stress (r = −0.69) and minimum shear stress (r = −0.63), but these results were not statistically significant. Intimal thickening did, however, correlate strongly with the reciprocal of the maximum shear stress attained during the cycle (r = 0.90, p < 0.0005) and with the reciprocal of the mean shear stress averaged over the cycle (r = 0.82, p < 0.001), indicating that intimal thickening does not occur in areas of high wall shear stress but develops in regions with a very low magnitude of maximum shear or time-averaged mean shear (Table 2). Pulse shear stress (maximum-minimum shear) had an inverse relationship with lesion thickness (r = −0.61), but the result was not statistically significant. The oscillatory shear index, however, yielded a significant correlation with intimal thickness (r = 0.82, p < 0.001). When only the inner and outer wall measurement locations were considered, i.e., the locations where lesions were maximal and minimal (Table 2), correlations between intimal thickness and the reciprocals of wall shear were especially striking: reciprocal of maximum shear stress, r = 0.94 (p < 0.001); reciprocal of mean shear stress, r = 0.95 (p < 0.001); oscillatory shear index, r = 0.93 (p < 0.001). The close correspondence among intimal thickness, 1/maximum shear, 1/mean shear and oscillatory shear index is represented graphically in Figure 8.

**Table 2. Correlation of Shear Stress Variables with Intimal Thickness at the Human Carotid Bifurcation**

<table>
<thead>
<tr>
<th>Hemodynamic variable</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All data points (n = 20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum shear</td>
<td>−0.69</td>
<td>NS</td>
</tr>
<tr>
<td>Mean shear</td>
<td>−0.63</td>
<td>NS</td>
</tr>
<tr>
<td>1/Maximum shear</td>
<td>0.90</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>1/Mean shear</td>
<td>0.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse shear</td>
<td>−0.61</td>
<td>NS</td>
</tr>
<tr>
<td>Oscillatory shear index (OSI)</td>
<td>0.82</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outer and inner wall only</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1/Maximum shear</td>
<td>0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1/Mean shear</td>
<td>0.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oscillatory shear index (OSI)</td>
<td>0.93</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*The correlation technique used here assumes a linear association and normally distributed variables. To study these assumptions, a residual analysis was performed. The information obtained from scatter plots of residuals versus the independent variables and from normal probability plots indicate that the above assumptions are valid. Plots of intimal thickness versus each of the independent variables also support the assumptions. Therefore, a correlation analysis appears to be appropriate for these experimental data. Since the correlations are based on averages, the strength of associations could be overestimated.

**Figure 8.** Graphical representation of the relative changes in intimal thickness of the internal carotid artery along the outer wall of the carotid bifurcation compared with the relative changes in the hemodynamic variables of 1/maximum shear stress, 1/mean shear stress, and oscillatory shear index at the five levels of the section as defined in Figure 1. All values were normalized to the maximum value as measured at the proximal internal carotid outer wall.
Discussion

Under conditions of pulsatile flow, the inner wall of the carotid bifurcation in the region of the flow divider and the distal internal carotid artery are subjected, on the average, to relatively high shear stress, while the outer wall of the carotid sinus is a region of relatively low shear stress. The side walls of the sinus, as well as of the common carotid artery, are exposed to intermediate levels of shear stress magnitude, but the carotid bulb shows large regions with helical flow patterns and oscillations in shear stress direction. Although the distribution of mean wall shear stress under conditions of pulsatile flow is consistent with expectations extrapolated from previous steady flow studies, pulsatile flow results in unsteady fluid dynamic behavior that may be important in atherogenesis.

For example, pulsatility generates a changing region of flow reversal and separation that disappears during early systole but redevelops during late systole into a separation region larger than that predicted by steady flow modeling. The magnitudes of wall shear stresses measured late in diastole are in agreement with those measured under conditions of steady flow at corresponding Reynolds numbers. During systole, however, pulsatile flow causes significant fluctuations in the magnitude of wall shear stress. Maximum shear stress in the common carotid artery during the peak of systole was approximately twice as large as that measured during steady flow at Re = 800, due in large part to the fact that unsteady velocity profiles under these flow conditions are characteristically blunt during acceleration. Although the mean shear was low at the outer wall of the sinus, the pulsatile maximum wall shear stress at this location was considerably greater than with steady flow, transiently reaching the same magnitude as the mean wall shear stress in the common carotid artery.

Our finding that intimal thickness bears an inverse relationship to the magnitude of shear stress is consistent with our previous studies in the carotid bifurcation using steady flow as well as with studies by Friedman, et al., of the human aortic bifurcation using pulsatile flow. These authors measured axial velocity in a cast of a human aortoiliac bifurcation and found a negative correlation between intimal thickness and maximum, mean, and pulse shear with correlation coefficients ranging from -0.628 and -0.685. These values compare well with our negative correlations of -0.61 to -0.69 for the same measures of shear. Our finding of a much stronger correlation between intimal thickness and the reciprocal of maximum and mean shear suggests that a threshold value of shear stress magnitude may be important in plaque development.

The quantitative measurements reported here help to explain some of the features of pulsatile flow demonstrated in our previous qualitative studies. Visualization of flow in a glass model by means of hydrogen bubbles showed strong variations in the extent of the separation region and sharp changes in the vortex structures within the sinus. Bubbles at the outer wall of the sinus tended to remain in this location for several cycles, indicating an increased fluid residence time. The present laser Doppler velocimeter studies in the Plexiglas model indicate that the increased residence time of bubbles at the outer wall is caused by the oscillation of fluid velocity about a mean value close to zero, thereby delaying the convection of fluid and trapping fluid elements near the outer wall for several cycles despite the absence of a region of stasis or permanent boundary layer separation.

The outer wall, where atherosclerosis is most prominent initially, is thus a site of low, time-averaged, mean shear stress and oscillatory shear stress. Both low mean shear stress and oscillatory shear stress contribute to an increased fluid residence time in the carotid sinus. The increased fluid residence time may result in modification of the mass transport of atherogenic substances between lumen and wall or in interference with endothelial metabolism by mechanisms suggested by Caro et al. and Robertson. In addition, blood-borne cellular elements such as platelets and macrophages, said to play a role in atherogenesis, would be expected to have an increased probability of deposition or adhesion in regions of increased residence time.

The oscillating shear stress pattern in areas distant from the flow divider in the carotid sinus may in itself cause an increased ingress of plasma constituents through the endothelial monolayer by effects on the stability of intercellular junctions. Since endothelial cells normally align with assumed unidirectional flows in an overlapping arrangement, increases in permeability with changing shear stress may be caused by cyclic shifts in the relationships 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 staining in relation to differences in endothelial organization that may be attributable to changing flow patterns.

There are at least two differences between in vivo blood flow and conditions in the Plexiglas model used in these experiments. First, the bifurcation model is rigid, while blood vessels are viscoelastic. Although the deformable nature of the vessel may be important in wave reflection and propagation, the effects of vessel compliance on local velocity profiles are very much smaller than the effects of branch angle, flow pulse shape, and flow partition ratio.

Second, the fluid used in the model experiments is Newtonian as compared with the non-Newtonian properties of blood. Since the diameter of a typical medium-sized artery is 1000 times that of the red blood cell and the transient shear rates are sufficiently high to disrupt rouleaux formation, the use of a Newtonian fluid would not contribute to a misinterpretation of the major findings. The 125:1 scaling of
our model assured sufficient accuracy of the shear stress estimations since the ratio of velocity measurement volume to tube diameter was small. Changes in flow partitioning between the two branch vessels during the cardiac cycle, a factor that has been shown to strongly affect the flow field, was also incorporated into our model, and the reproduction in the carotid model of a physiologic flow pulse was made possible through the use of a programmable pump. The recent, noninvasive detection of a transient region of separated, reverse flow in young normal adults gives strong confirmation to the accuracy of the modeled hemodynamics.16

Since our model was based on average dimensions of a large number of human carotid bifurcations, the data presented here should be more widely applicable to further anatomic studies than information obtained from models of individual artery specimens. Individual models may tend to reproduce special flow characteristics that may not correlate well with the usual distribution of atherosclerotic plaques in the region under study. Nevertheless, several of the factors that influence internal carotid velocity profiles should show marked individual variations that could affect both the location and the severity of disease. One variation is the branch angle, which showed a large standard deviation around the mean value.3 Model studies of flow in idealized branches indicate that greater angles produce larger separation regions. Thus, carotid bifurcations with relatively large branch angles would have larger outer wall areas subjected to nonaxial shear stresses and possibly more extensive intimal plaque formation.

The carotid pulse wave form could also be a significant contributing factor. Different pulse shapes would affect the formation and size of the separation region, the extent of flow reversal, and the size and position of the zone of increased residence time. The pulse shape is determined by wave reflections, speed of propagation, anatomic tapering of the blood vessels, and cardiac output.15

Elevated heart rates should increase exposure of the outer and side walls of the sinus to oscillatory flow fields, for increased heart rate would increase the relative time spent in systole, as compared to diastole, time during each cardiac cycle. The degree to which any of these factors could be modified by therapeutic intervention in order to affect the onset and progression of carotid bifurcation atherosclerotic disease remains to be explored.

In conclusion, comparison of detailed pulsatile hemodynamic measurements with quantitative morphologic studies of the distribution of atherosclerosis in the human carotid bifurcation revealed that low mean shear stress and marked oscillations in the direction of wall shear stress may be critical factors in the development and localization of atherosclerotic plaques. Since turbulence was not observed with flow visualization2 nor detected in the present velocity measurements, we suggest that turbulence is not a prominent feature at sites of early plaque formation. Furthermore, the results imply that high unidirectional shear stress may exert a protective effect against the induction of lesions. Hypotheses regarding relationships between shear stress or other hemodynamic variables and the pathogenesis of atherosclerosis should be tested in accurate models of vessel geometry and corresponding pressure-fixed specimens.

Acknowledgments
The authors thank Regina Stankunavicius for assistance with the statistical analyses, Jacqueline Jordan for technical assistance, and Althea Zmuidzinas for preparation of the manuscript.

References
4. Ku DN. Hemodynamics and atherogenesis at the human carotid bifurcation [Dissertation]. Atlanta, Georgia: Georgia Institute of Technology, 1983
5. Bloch KE. Quantifizierung der Blutstromung im Bereiche der Carotisbifurcation mittels Ultraschall [Dissertation]. Zurich, University of Zurich, 1981
Appendix A

Oscillatory Shear Index

The purpose of the oscillatory shear index (OSI) is to provide a numerical parameter for the shear stress imposed on the arterial wall in pulsatile flow, and specifically to provide an index which describes the shear stress acting in directions other than the direction of the temporal mean shear stress vector. In view of the fact that our velocity profile measurements were taken only at the inner, outer, and side walls (θ = 0°, 180° and 90° or 270°, respectively), we defined the OSI by the relation

\[ \text{OSI} = \frac{\int_{\Delta t} f_l^* | f_l^* | dt}{\int_{\Delta t} f_l^* | f_l^* | dt} \]  
(A-1)

where \( f_l^* \) is the instantaneous wall shear stress vector and \( f_l^* \) is either the wall shear stress component acting in the direction opposite to the temporal mean wall shear stress vector for the case of inner and outer walls or the component acting at 90° to \( f_l^* \) or the case of the side walls. In the cases we studied, the \( f_l^* \) contribution is thus due either to a "locally reversed" wall shear stress direction for \( \theta = 0° \) and 180° or to a cross-flow component for \( \theta = 90° \) and 270°.

In general, however, a point along the arterial wall may experience both reverse and cross-flow shear stress components simultaneously. For such cases, we propose that the appropriate definition of OSI is

\[ \text{OSI} = \frac{\int_{\Delta t} \delta_1(\phi) f_l^* | f_l^* | \sin^2 \phi + \delta_2(\phi) f_l^* | f_l^* | \cos^2 \phi \sin | \phi | dt}{\int_{\Delta t} f_l^* | f_l^* | dt} \]  
(A-2)

where \( \phi \) is defined as the angle between the instantaneous wall shear stress vector \( f_l^* \) and the temporal mean wall shear stress vector, and \( \delta_1(\phi) \) and \( \delta_2(\phi) \) are defined by

\[ \delta_1(\phi) = \begin{cases} 1 & , 0° \leq \phi \leq 180° \\ 0 & , \text{otherwise} \end{cases} \]

\[ \delta_2(\phi) = \begin{cases} 1 & , 90° \leq \phi \leq 270° \\ 0 & , \text{otherwise} \end{cases} \]

This formula reduces to Equation (A-1) for the special cases of inner, outer, and side walls, as follows:

1. Inner wall = neither circumferential nor reverse components are present so that \( \phi = 0° \) for all values of time and \( \delta_2(\phi) = 0 \), yielding OSI = 0

2. Outer wall = no circumferential components are present but reverse components exist, so that either \( \phi = 0° \) or 180° and the equation becomes

\[ \text{OSI} = \frac{\int_{\Delta t} \delta_2(\phi) f_l^* | f_l^* | \sin \phi \cos \phi \ | | \phi | \ dt}{\int_{\Delta t} f_l^* | f_l^* | dt} \]

3. Side walls = no reverse components were present in our measurements, only cross-flow components for which \( | \phi | < 90° \) and the equation becomes

\[ \text{OSI} = \frac{\int_{\Delta t} \delta_1(\phi) f_l^* | f_l^* | \sin \phi \ | | \phi | \ dt}{\int_{\Delta t} f_l^* | f_l^* | dt} \]

It should be noted that if the wall shear stress at a point is purely oscillatory, i.e., equal excursions of \( f_l^* \) but in opposite directions, the OSI \( \rightarrow \frac{1}{2} \).
Pulsatile flow and atherosclerosis in the human carotid bifurcation. Positive correlation between plaque location and low oscillating shear stress.

D N Ku, D P Giddens, C K Zarins and S Glagov

Arterioscler Thromb Vasc Biol. 1985;5:293-302
doi: 10.1161/01.ATV.5.3.293

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