Localizing Role of Hemodynamics in Atherosclerosis in Several Human Vertebrobasilar Junction Geometries

J. Ravensbergen, J.W. Ravensbergen, J.K.B. Krijger, B. Hillen, H.W. Hoogstraten

Abstract—Atherosclerosis is a common finding in the vertebrobasilar junction and in the basilar artery. Several theories try to link the process of atherogenesis with the forces exerted by the flowing blood. An attractive relation has been found between the locations in vessels at which atherosclerotic plaques are often present and the locations in models where complicated flow patterns exist. Most of the studies provided data on bifurcations. Finding a similar relation in an arterial confluence would certainly add to the credibility of the (causal) relationship between hemodynamics and atherosclerosis. Further support can be provided if variations of the geometry result in changes of the location of the atherosclerotic lesions, corresponding to the changes of the flow force distribution. In our previous numerical and experimental work, the influence of geometric and hemodynamic parameters, such as asymmetrical inflow, confluence angle, and blunting of the apex, on the flow in vertebrobasilar junction models has been investigated in detail. Recirculation areas and distribution of the wall shear stress have been computed. In this anatomic study, the effect of modulation of these geometric and hemodynamic parameters on the flow pattern is compared with the size and location of plaques in human vertebrobasilar junctions and basilar arteries. In addition, a comparison is made between the preferential areas of atherosclerotic plaques in junctions and bifurcations to demonstrate the localizing role of hemodynamics in atherogenesis. The apex of the vertebrobasilar junction and the lateral walls of the basilar artery appeared to be prone to atherosclerosis. In 43 of 85 vertebrobasilar junctions, a plaque was found at the apex. Furthermore, the summed plaque thickness at both lateral walls differs significantly (paired t test, \( P = .03 \)) from that at the walls facing the pons and the skull base. In contrast, several authors found that the lateral walls of the mother vessel and the apex in bifurcations are often spared. Modulation of the various parameters in the models changed the size of the regions with low wall shear stress and/or recirculation areas dramatically. A comparable effect was found in the occurrence of plaques in the human vertebrobasilar junction; eg, for an atherosclerotic plaque at the apex, a predicted probability larger than 0.5 was computed for blunted apexes and for sharp-edged apexes with a confluence angle exceeding 90°. Apparently, two geometric risk factors for an atherosclerotic plaque at the apex can be distinguished: a blunted apex and a large confluence angle. (Arterioscler Thromb Vasc Biol. 1998;18:708-716.)

Key Words: atherosclerosis ■ basilar artery ■ computational hemodynamics ■ geometry

Atherosclerosis is the main cause of death in the Western world. This disease is mostly found in large arteries. One of the striking features of this disease is its patchy distribution. Atherosclerotic plaques are often present at locations where complicated flow patterns can be expected, such as bifurcations, bends, and junctions. In early studies, it was already postulated that mechanical and hemodynamic factors might be an important cause of atherosclerosis.1 Several hypotheses have been proposed to relate atherosclerosis with local hemodynamics, such as pressure-related, turbulence-related, and shear-related hypotheses. In a review article, Gessner2 commented on these theories and showed that the validity of most theories was highly questionable and that only shear-related studies showed promising results. Nowadays, the low wall shear theory (Caro et al14) is considered to be more plausible than the high wall shear theory (Fry5). Considerable attention has been paid to the distribution of atherosclerotic plaques in vessels in comparison with the characteristics of the local velocity field in numerical or experimental models, mostly concerning bifurcations.6–12

A stronger indication of a causal relationship between low wall shear stress and atherosclerosis can be provided if the same connection can be found in vessels with a totally different flow pattern. Although the overall geometry of bifurcations and junctions is similar, the flow direction is reversed, which leads to rather different flow phenomena. The basilar artery is the only large artery in humans in which two flows merge. Therefore, we felt it would be valuable to study the relation between hemodynamics and atherosclerosis in the vertebrobasilar junction and the basilar artery and to compare the results with those from studies of bifurcations.

Received April 2, 1997; revision accepted November 19, 1997.
From the Department of Functional Anatomy, Utrecht University (J.R., J.W.R., J.K.B.K., B.H.); and the Department of Mathematics, University of Groningen (H.W.H.), the Netherlands.
Correspondence to B. Hillen, Department of Functional Anatomy, Utrecht University, PO Box 80039, 3508 TA Utrecht, the Netherlands.
E-mail b.hillen@fa.ruu.nl
© 1998 American Heart Association, Inc.
The geometry of vessels influences the flow field to a large extent.\(^{13-17}\) Moreover, arterial geometry shows considerable variability. Consequently, the hemodynamic phenomena near the blood vessel wall vary between vessels, and this variation will affect the localization of atherosclerotic lesions. Striking examples of the large variations observed in human vertebrobasilar junctions are the variation of the confluence angle between 10° and 160°,\(^{18,19}\) the local geometry of the apex of the vertebrobasilar junction, which varies from smooth and blunted to very sharp (Fig 1), and the difference between the diameter of the two vertebral arteries.\(^{20,21}\)

The influence of several geometric and hemodynamic parameters on the flow in vertebrobasilar junction models has been investigated by us in detail in earlier work.\(^{19,22,23}\) It was found that the flow is highly three dimensional, with a strong secondary flow field consisting of four vortexes, leading to a specific distribution of the wall shear stress with regions of low wall shear stress near the apex and on both lateral walls. With asymmetrical inflow, the fluid with the highest velocity crosses the junction, changing this distribution of the wall shear stress. The angle of confluence determines the structure and strength of the secondary flow field near the apex with a long-lasting effect on the flow downstream. The blunting of the apex has only a local effect on the size of and velocities within the recirculation areas. Both geometric parameters exert a strong influence on the size of the regions with low wall shear stress and the size of the recirculation areas near the apex.

The aim of this study was to relate the presence of atherosclerotic plaques to the local hemodynamics in a more quantitative way. We compared the effect of modulation of geometric and hemodynamic parameters on the flow in vertebrobasilar-junction models with the effect on the size and localization of atherosclerotic plaques in human vertebrobasilar junctions and basilar arteries. In addition, the relation between hemodynamics and atherosclerosis for the case of a bifurcation was compared with that for the vertebrobasilar junction.

**Methods**

**Study of Atherosclerotic Plaques in Human Basilar Arteries**

Basilar arteries, including the vertebrobasilar junctions, were obtained from 17 human cadavers at the dissecting room. The mean age was 81 years. These cadavers had all been fixated under physiological pressure (Pa = 120 mm Hg) with a solution with 4% formalin. The infusion catheter (2 mm diameter) was placed in the femoral artery. Control pressure measurements in the carotid artery revealed a pressure of 120 mm Hg. In this way, arteries (especially arteries with dimensions comparable to the basilar artery or smaller) become rather rigid and the arterial geometry is preserved as much as possible (see Kratky et al\(^{24}\)). Afterward, the brain was excised and the vertebral arteries were cut as proximal as possible (in the foramen magnum). The basilar arteries were dissected and pressure filled with carboxymethyl cellulose (CMC). During the pressure filling, the outlet of each basilar artery was attached to the CMC delivery system. In this way, no external forces (except for the gravity) are working on the vessel, and no change of the geometry was observed during this procedure. The side vessels were carefully ligated. Next, they were pressure filled (Pa = 120 mm Hg) with a 1% solution of CMC. The specimens were frozen at a temperature of \(-70^\circ\)C, maintaining the internal pressure, and embedded afterward in the same solution of CMC and at the same temperature of \(-70^\circ\)C, directly on the microtome stage. Care was taken to keep the axis of the basilar artery as perpendicular as possible to the microtome stage. Four parallel reference lines were supplied around each vessel. Serial
sections of 50 μm were cut by using a sledge cryomicrotome (PMV 450MP). Histological on-tape sections, according to the procedure of van Leeuwen et al., were taken at 500-μm intervals and colored with Weigert’s elastic stain and van Gieson’s background staining.

Only the sections of the basilar artery proper, ie, between the origin and the outlet of the basilar artery, were used. In general, cross-sections of the basilar artery are circular and the diameter decreases downstream. We defined the origin of the basilar artery as the first circular cross-section (Fig 2a). Upstream from the origin, the cross-sections are ellipses. The outlet of the basilar artery is defined as the section at which the diameter of the basilar artery reaches its minimum (Fig 2a). Downstream from the outlet, the basilar artery widens to form the bifurcation of the posterior cerebellar and cerebral arteries.

The thickness of the atherosclerotic lesions was measured in each section of all basilar arteries, using the lamina elastica interna as a baseline. The measurements were made at 12 points distributed around the circumference at regular intervals of 30°; see Fig 2b. For all sections, the first measurement, ie, at 0°, was made at the middle of the wall facing the skull base. All sections of the basilar artery were used, ie, from the origin to the outlet. For an average basilar artery, measurements (12 per section) were done in 40 to 60 sections. Since a certain plaque thickness has more (pathological) effect in small vessels than in large ones, all local plaque thicknesses were normalized by dividing them by the diameter of the specific section. For slightly oblique sections, the smallest diameter was used.

To assess the longitudinal distribution of the plaques in the basilar artery, the sum of the plaque thicknesses at the 12 measure points around the circumference of each section was determined. Of all 17 vessels, these sums for cross-sections at the same distance from the origin were added. The results were plotted with respect to the distance (z) from the vessel origin. To quantify the circumferential distribution of the plaques, the plaque thicknesses at comparable measure points on all circumferences were summed for each vessel. These sums were added for all 17 vessels and plotted with respect to their location around the circumference.

To demonstrate an effect of asymmetrical inflow on the distribution of atherosclerotic lesions, the circumferential distribution of the plaques has also been plotted differently. For this purpose, the left-to-right difference between both vertebral arteries was taken into account. In 10 of 17 vertebrobasilar junctions, the left vertebral artery was larger than the right, which is in accordance with studies of Hillen and Kamath. If the vertebrobasilar junction had a larger right vertebral artery (in 5 of 17 junctions), the circumferential distribution of atherosclerotic lesions in the basilar artery was mirrored. In this way, the lateral wall of the basilar artery at the side of the vertebral artery with the smallest diameter was always located at 90°. Consequently, the lateral wall of the basilar artery at the side of the vertebral artery with the largest diameter was always located at 270°. The location of the middle of the wall facing the skull base (0°) and the middle of the wall facing the pons (180°) remained unchanged. Statistical analysis was applied with the package StatView 4.5 (Abacus Concepts, Inc.).

Study of Atherosclerotic Plaques at the Apex of Human Vertebrobasilar Junctions

The presence of atherosclerosis at the apex was studied more extensively. For this purpose, 85 vertebrobasilar junctions with 1 cm of the basilar artery were obtained from human cadavers at the dissecting room (fixed under physiological pressure [Pa=120 mm Hg] with a solution with 4% formalin). Two geometric parameters were quantified, each by two independent observations without magnification: the confluence angle (degrees) and the shape of the apex (sharp-edged or blunted). For the assessment of the confluence angle and the shape of the apex, the projection of each junction was used. Care was taken to keep the basilar and vertebral arteries in plane during the measurements. The confluence angle was defined as the angle between the inner walls of both vertebral arteries. The blunting of the apex was defined as the radius of a circular arc. The magnitude of this radius was estimated by overlaying a transparency with a set of concentric circles and fitting the projection of the outline of each apex to a specific circle. If the radius of arc was <1 mm, or the arc length was <3 mm, the apex was considered to be sharp edged.

To examine the junction region at the inside, the lateral walls of the basilar and vertebral arteries were cut longitudinally. The inner lining of the junctions was examined with the aid of a macroscope (Wild Makroskop M420). Apexes with raised atherosclerotic plaques, identified with the macroscope, were labeled as affected in this study. Apexes were labeled as unaffected if no raised plaque could be found in this way. Several types of raised plaques were identified, such as fibrous plaques (multiple collagen layers), fibro-lipid plaques (a lipid core, with a surrounding fibrotic cap), and complicated plaques (defect surface of the plaque with thrombi and fibrotic organization), in accordance with the definitions of Solberg.
and Eggen for atherosclerotic plaques in carotid and vertebral arteries. Control histological sections reveal that in this group, fibrolipid and fibrous plaques form the majority of the atherosclerotic plaques. Using the definition and classification of atherosclerotic lesions of Stary et al, the plaques found in this study were mainly type IV and V lesions.

To determine statistically the relation of confluence angle, apex shape, and asymmetrical inflow to the presence of an atherosclerotic plaque at the apex, two-tailed unpaired \( t \) tests were used (StatView 4.5 statistical package). The mean angle of confluence with and without an atherosclerotic plaque at the apex was compared for the group of 85 vertebrobasilar junctions and separately for the subgroup with sharp-edged apexes and for the subgroup with blunted apexes. In addition, Fisher’s exact test was used to analyze the relationship of the confluence angle and the blunting with the presence of an atherosclerotic plaque at the apex.

The possible effect on atherosclerosis at the apex was also assessed with a logistic regression analysis (NCSS statistical package). This analysis was applied to the effect of the confluence angle and the blunting, and to their effect in combination. Predicted probabilities for atherosclerosis at the apex for junctions with blunted and sharp-edged apexes were computed for a range of confluence angles.

**Results**

**Study of Atherosclerotic Plaques in Human Basilar Arteries**

Of the 17 human vertebrobasilar junctions and basilar arteries under study, 6 were completely free of atherosclerosis. Of the remaining 11 specimens, 2 had only a limited amount of small plaques (1 of these 2 had only a plaque at the apex). The other 9 were more or less severely affected; 8 of 9 had also a plaque at the apex. The longitudinal distribution of the plaques, as defined in the previous section, is shown in Fig 3. Although the degree of atherosclerotic involvement varies, a significant negative correlation is found (\( r=.75, P=.0001 \)). Fig 4 shows the circumferential distribution of the plaques. The error bars indicate the standard deviation for the measurements. As can be seen, the summed plaque thickness is large at around 90° and 270°, ie, at both lateral walls. The summed plaque thickness at both lateral walls differs significantly (two-tailed paired \( t \) test, \( P=.03 \)) from that at the walls facing the pons (180°) and the skull base (0°/360°). A left-to-right difference is visible and a larger summed plaque thickness is found at the wall facing the skull base in comparison with the wall facing the pons. However, these differences are both insignificant (two-tailed paired \( t \) test, \( P=.56 \) and \( P=.10 \) respectively). The results of these tests are summarized in Table 1.

The variation of the circumferential distribution of the plaques in the basilar artery, in which this distribution was mirrored for vertebrobasilar junctions with a larger right vertebral artery, is shown in Fig 5. A striking and significant (two-tailed paired \( t \) test, \( P=.05 \)) left-to-right difference is demonstrated in this diagram: the summed plaque thickness is two times larger at 270°, ie, at the lateral wall at the side of the vertebral artery with the largest diameter, in comparison with 90°.

**TABLE 1. Parameters of \( t \) Test on the Thickness of Atherosclerotic Plaques at Different Locations Around the Circumference**

<table>
<thead>
<tr>
<th></th>
<th>Pons/Skull Base</th>
<th>Lateral Walls</th>
<th>Right Lateral Wall</th>
<th>Left Lateral Wall</th>
<th>Pons</th>
<th>Skull Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean summed plaque thickness</td>
<td>5.61</td>
<td>12.32</td>
<td>5.51</td>
<td>6.81</td>
<td>2.17</td>
<td>3.44</td>
</tr>
<tr>
<td>SD</td>
<td>4.49</td>
<td>10.29</td>
<td>4.97</td>
<td>7.19</td>
<td>1.39</td>
<td>3.30</td>
</tr>
<tr>
<td>( P )</td>
<td>.03</td>
<td>.56</td>
<td>.17</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( n=17 \) at all locations.
Study of Atherosclerotic Plaques at the Apex of Human Vertebrobasilar Junctions

In 43 of 85 vertebrobasilar junctions, a plaque was found at the apex. The subgroups of junctions with sharp-edged apexes and of junctions with blunted apexes differed significantly (Fisher’s exact \( P < .0001 \), \( \phi = 0.56 \)) with respect to the frequency of the presence of an atherosclerotic plaque at the apex. Table 2 shows the frequencies of the presence of an atherosclerotic plaque at the apex, together with the results of the measurements of the confluence angle and the shape of the apex. In three groups of junctions (viz all 85 junctions, junctions with sharp-edged apexes and junctions with blunted apexes), the mean angle of confluence of affected and unaffected junctions was compared using a two-tailed \( t \) test, corrected for unequal variances. In two groups, the mean angle of confluence of junctions with an atherosclerotic plaque at the apex (“affected”) differed significantly from the mean angle of confluence of unaffected junctions. However, in the subgroup with the blunted apexes, the probability value of this difference was too high, probably due to the fact that only a few apexes in this subgroup were unaffected. The results of these tests are summarized in Table 3. The difference between the mean confluence angle for affected and unaffected junctions is most marked in the subgroup with the sharp-edged apexes. In this subgroup, the confluence angle of affected junctions is larger in comparison with the angle of unaffected junctions. Noticeably, in the subgroup with blunted apexes, the confluence angle for affected junctions is smaller in comparison with the angle of unaffected junctions.

From the previous tests, the effect of confluence angle and the effect of apex shape on the presence of atherosclerosis seemed to be interdependent. Therefore, a logistic regression analysis was applied. In this way, the probability to find an atherosclerotic plaque at the apex can be computed for each vertebrobasilar junction. Two parameters are taken into account: confluence angle and apex shape (blunted or sharp-edged). Based on the distribution of atherosclerotic plaques at the apex of the group of 85 human vertebrobasilar junctions, the separate effect of both parameters on the probability of an atherosclerotic plaque at the apex and their effect in combination can be determined (Table 4).

Fig 6 shows the predicted probability of an atherosclerotic plaque at the apex for each specimen of the 85 human vertebrobasilar junctions. Although the predicted probability is based on the distribution of atherosclerotic plaques in this group, it is certainly not identical with it. For example, in the group of 85 junctions, 6 junctions with a confluence angle smaller than 63° (the mean value) and a sharp-edged apex had a plaque, whereas 2 junctions with a confluence angle smaller than 63° and a blunted apex were unaffected. Fig 6 and Table 4 show that in general, the predicted probability for atherosclerosis is significantly higher for blunted apexes in comparison with sharp-edged ones. For confluence angles larger than 90° the predicted probability is larger than 0.5 for junctions with either sharp-edged or blunted apexes. Furthermore, for sharp-edged apexes, the predicted probability of an atherosclerotic plaque increases with increasing confluence angles. In contrast, for blunted apexes, this probability gradually decreases with increasing confluence angles.

### TABLE 2. Geometric Parameters and Frequencies (n) of the Presence of an Atherosclerotic Plaque at the Apex of 85 Human Vertebrobasilar Junctions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Degrees</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confluence Angle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>6</td>
<td>...</td>
</tr>
<tr>
<td>Maximum</td>
<td>158</td>
<td>...</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>63.0 (29.9)</td>
<td>...</td>
</tr>
<tr>
<td>Apex Shape*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blunted</td>
<td>...</td>
<td>36</td>
</tr>
<tr>
<td>Sharp-edged</td>
<td>...</td>
<td>49</td>
</tr>
<tr>
<td>Atherosclerosis at Apex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected Axes</td>
<td>...</td>
<td>43</td>
</tr>
<tr>
<td>Blunted</td>
<td>...</td>
<td>30</td>
</tr>
<tr>
<td>Sharp-edged</td>
<td>...</td>
<td>13</td>
</tr>
<tr>
<td>Unaffected Axes</td>
<td>...</td>
<td>42</td>
</tr>
<tr>
<td>Blunted</td>
<td>...</td>
<td>6</td>
</tr>
<tr>
<td>Sharp-edged</td>
<td>...</td>
<td>36</td>
</tr>
</tbody>
</table>

The confluence angle is the inner angle of the vertebral arteries.

*Blunted indicates radius >1 mm, arc length >3 mm.

Discussion

In the present study, 50% of all basilar arteries had a plaque at the apex. A detailed analysis revealed further preferential locations of atherosclerosis in the basilar artery. From the investigation of atherosclerotic plaques in 17 human basilar arteries it can be concluded that atherosclerotic plaques are not distributed at random but have a distinct longitudinal and circumferential distribution pattern. The amount of plaques gradually decreases downstream, and plaques are more often found at the lateral walls in comparison with the posterior and anterior walls.

By contrast, bifurcations show a quite different distribution pattern of atherosclerotic plaques. In general, the outer...
walls of the daughter vessels appear to be most prone to atherosclerosis and, unlike the vertebrobasilar junction, the apex (flow divider) and the lateral walls of the mother vessel are often spared. From numerical and experimental studies of the flow in models of bifurcations, it was concluded that along the outer walls of the daughter vessels, the flow pattern was complex, including recirculation areas and low wall shear stress. Along the flow divider and the inner walls and along the walls of the mother vessel, the flow was more unidirectional (axially aligned) and moderate to high wall shear stresses occurred. In several studies, a statistical relationship between intimal thickening and mean wall shear stress was found. A majority of these authors studied the carotid bifurcation. One daughter vessel of that particular bifurcation, ie, the internal carotid artery, has the geometric complication of a carotid bulb, which results in a diameter increase followed by a decrease. In comparison with a bifurcation without a bulb, eg, the aortic bifurcation, the difference between the wall shear stress at the outer and inner wall is more marked in the internal carotid artery. The most likely explanation is the presence of a large recirculation area at the outer wall of the bulb.

Many authors came to the conclusion that hemodynamic factors related to the localization of atherosclerotic plaques are (1) complex flow patterns and (2) low wall shear stress. From our previous numerical and experimental work in models of the vertebrobasilar junction, it appeared that complex flow patterns and/or low wall shear stress can be found at the apex of the junction and along the lateral walls of the outlet tube representing the basilar artery. In the present anatomical study, the apex and the lateral walls of the basilar artery appeared to be preferential locations for atherosclerosis and amis. In summary, regions of complex flow patterns and low wall shear stress are distributed differently in junctions and bifurcations. In both vessel geometries, the preferential locations of atherosclerosis correspond to these specific regions. The findings at the apex are the most meaningful in this respect.

Another strong argument for the (causal) relationship between hemodynamics and atherosclerosis can be found if variations of the geometry result in changes of the location of the atherotic lesions, which correspond to the changes of the flow force distribution. In the present study, the effect of asymmetrical inflow on the distribution of plaques in the basilar artery, as well as the effect on the presence of a plaque at the apex, was studied. The former effect is shown in Fig 5. The amount of plaque is much larger at the lateral wall at the side of the vertebral artery with the larger diameter in comparison with the opposite side. With asymmetrical inflow in our numerical models, fluid with the highest velocities crosses the junction, changing the specific distribution of the wall shear stress in the junction and outlet tube. Fig 7a and 7b illustrate the effect of asymmetrical inflow on the distribution of the wall shear stress. Three-dimensional finite-element computations of steady flow in a rigid vertebrobasilar junction model with a diameter difference between the inlet tubes and with a Reynolds number ($Re$) of 400 ($Re=\frac{uD}{\nu}$, where $u$ is the mean velocity in the artery, $D$ is the diameter, and $\nu$ is the kinematic viscosity) simulate an asymmetrical inflow with a flow ratio 2 in an average vertebrobasilar junction geometry under physiological flow conditions.

TABLE 3. Parameters of f test on the Confluence Angle for Apexes With and Without an Atherosclerotic Plaque

<table>
<thead>
<tr>
<th>Variable</th>
<th>All 85 Junctions</th>
<th>Sharp-Edged Apexes*</th>
<th>Blunt Apexes†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Affected</td>
<td>Unaffected</td>
<td>Affected</td>
</tr>
<tr>
<td>n</td>
<td>43</td>
<td>42</td>
<td>13</td>
</tr>
<tr>
<td>Mean confluence angle</td>
<td>69°</td>
<td>57°</td>
<td>79°</td>
</tr>
<tr>
<td>SD</td>
<td>33</td>
<td>25</td>
<td>32</td>
</tr>
<tr>
<td>$P$</td>
<td>.05</td>
<td>.003</td>
<td>.07</td>
</tr>
</tbody>
</table>

*Subgroup of 49 vertebrobasilar junctions with sharp-edged apexes.
†Subgroup of 36 vertebrobasilar junctions with blunted apexes.


<table>
<thead>
<tr>
<th>Variable</th>
<th>$r$</th>
<th>SE</th>
<th>$\chi^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confluence angle*</td>
<td>-0.025</td>
<td>0.015</td>
<td>2.85</td>
<td>.09</td>
</tr>
<tr>
<td>Bluntingb</td>
<td>-2.980</td>
<td>0.688</td>
<td>18.76</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>Combinationc</td>
<td>0.065</td>
<td>0.022</td>
<td>9.01</td>
<td>.0027</td>
</tr>
<tr>
<td>Intercept</td>
<td>2.017</td>
<td>0.588</td>
<td>11.77</td>
<td>.0006</td>
</tr>
</tbody>
</table>

In(p/1 − p) = −0.025a − 2.98b + 0.065c + 2.017.
*Confluence angle=angle − 63° (mean value).
*bSharp (=1) with regard to blunting (=2).
*cCombination=a×b.
particularly in junctions with sharp-edged apexes. In junctions with blunted apexes, however, the incidence decreases with increasing confluence angles. Significantly more plaques can be found at blunted apexes than at sharp-edged apexes, and it can be concluded that up to a confluence angle of 90°, blunting has a stronger contributing effect on the occurrence of an atherosclerotic plaque at the apex than a large confluence angle.

The specific effect of branching angles in bifurcations has been studied by several other investigators. Most studies indicate that large branching angles cause large secondary velocities and consequently complex flow fields. The effect of branching angles on the distribution of atherosclerotic plaques was not conclusive in these studies. In part, this may be due to the different techniques and (definitions of) parameters that were used. For instance, Friedman et al. studied the relationship between branch angle and atherosclerotic involvement of the left anterior descending coronary artery. The relative proximal involvement, ie, a normalized index of atherosclerotic severity, correlated negatively with branch angle, whereas the results of a subsequent histomorphometric study indicate that large angles are strongly associated with intimal thickening.

From a previous model study, it appeared that the angle of confluence has a strong effect on the flow in the junction and far downstream. Near the apex, a region with low velocities is present. With larger confluence angles, the size of this region increases and recirculation may even occur. Fig 7c and 7d illustrate the effect of a large confluence angle on the distribution of the wall shear stress in vertebrobasilar-junction models. Three-dimensional finite-element computations of steady flow with \( Re = 400 \) represent the flow in two vertebrobasilar-junction geometries with confluence angles of 60° and 120°, respectively. The wall shear stress has been nondimensionalized by the standard wall shear stress at the entrance of the inlet tubes. The size of the low wall shear region at the apex is much larger in the model with the confluence angle of 120° than in the model with the confluence angle of 60°. In models with blunted apexes, large recirculation areas and hence large regions of low wall shear stress were found near the apex. The size of these recirculation areas increases with decreasing confluence angles.

Summarizing, not only are the regions with low wall shear stress and/or recirculation in the junction models consistent with the preferential locations of atherosclerosis in human vertebrobasilar junctions but also the effect of several parameter changes on the flow in the models matches the effect on atherosclerosis in the vessels. Again, this is a strong indication that hemodynamic forces are important determinants of the localization of atherosclerotic plaques. In view of the fact that local hemodynamics is affected by vascular geometry and certain geometric parameters may predispose to atherosclerosis, we propose that a blunted apex and a large confluence angle are geometric risk factors for atherosclerosis, the latter particularly in the case of sharp-edged apexes.

**General Conclusions**

Two general conclusions may be drawn from the results of this study. First, junctions and bifurcations each show a specific distribution of regions with complex flow patterns and low wall shear stress. In both geometries, the preferential locations of atherosclerosis correspond to these specific regions. This connection is found in spite of the mutual differences in the distribution of the wall shear stress and in the location of atherosclerotic plaques, with the apex as a prominent example. Second, the effect of certain parameter changes on the flow in the junction models agrees very well with the effect on the distribution of atherosclerotic lesions observed in the human vertebrobasilar junction and basilar artery. Both results are new findings leading to a better understanding of the role of hemodynamics in atherosclerosis.
Figure 7. Distribution of the wall shear stress for vertebrobasilar junction models. A and B, Asymmetrical inflow (diameter ratio 1.26; flow ratio 2), confluence angle 60°, left and right lateral view. C, Symmetrical model, equal inflow, confluence angle 60°. D, Symmetrical model, equal inflow, confluence angle 120°.
understanding of and a more solid foundation for the causal relationship between hemodynamics and atherosclerosis.

References
Localizing Role of Hemodynamics in Atherosclerosis in Several Human Vertebrobasilar Junction Geometries
J. Ravensbergen, J. W. Ravensbergen, J. K. B. Krijger, B. Hillen and H. W. Hoogstraten

doi: 10.1161/01.ATV.18.5.708

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/18/5/708

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/