In Vitro Measurement of Fluid-Induced Wall Shear Stress in Unruptured Cerebral Aneurysms Harboring Blebs

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Background and Purpose—Little attention has been focused on the role of fluid-induced wall shear stress in fully developed cerebral aneurysms. The purpose of this study is to evaluate the alternation and distribution of wall shear stress over 1 cardiac cycle in patients' aneurysms.

Methods—A middle cerebral artery aneurysm and a basilar tip aneurysm with localized outpouching (blebs) in their domes were selected for this study. With the use of a stereo lithography machine, geometrically realistic aneurysm models were created on the basis of 3-dimensional CT angiograms. In vitro shearing velocity measurement was conducted with the use of laser-Doppler velocimetry at multiple points on the aneurysmal wall to calculate the value of wall shear stress. The wall shear stress was documented at multiple points in the aneurysm inflow zone, dome, and outflow zone.

Results—Distribution of wall shear stress was not uniform in the aneurysm walls, and particular regions were exposed to relatively high wall shear stress. The wall shear stress changed dynamically throughout 1 cardiac cycle at the point where a high value of wall shear stress was noted. The blebs of both aneurysms were exposed to high wall shear stress. Unlike previous reports in which an ideal spherical aneurysm model was used, the aneurysm inflow zone was not exposed to high shear stress.

Conclusions—In vitro aneurysm models based on the patients’ angiograms allowed us to conduct a more realistic evaluation of wall shear stress in the aneurysms harboring blebs. These results provide us with further indications of the correlation of wall shear stress with the natural history of cerebral aneurysms. (Stroke. 2003;34:187-192.)

Key Words: bleb cerebral aneurysm hemodynamics shear stress

Blood vessels are exposed to many forces induced by pulsatile blood flow, such as hydrostatic pressure, dynamic pressure, and fluid-induced wall shear stress. Although all of these intravascular forces are thought to be responsible for various vascular diseases, recent studies have focused on the significance of fluid-induced wall shear stress in terms of the pathogenesis of vascular diseases.1,2 Fluid-induced wall shear stress is unique in that it elicits a strong biological impact on the vascular wall influencing endothelial cell functions, whereas intravascular pressure primarily elicits a mechanical impact on the vessel wall.3-7 Current evidence supports the concept that the pathogenesis of intracranial aneurysm has a multifactorial origin.8 However, there is no doubt that blood flow dynamics play an important role in the genesis, growth, and possible rupture of cerebral aneurysms.9-11 Recent reports in the literature show that wall shear stress contributes to the genesis of cerebral aneurysms.10,11 Focal high wall shear stress appears to be a predisposing factor for aneurysm formation in healthy arteries.10 However, little attention has been given to the role of wall shear stress in fully developed cerebral aneurysms. Therefore, whether wall shear stress has some influence not only on the genesis of cerebral aneurysms but also on their growth and rupture is an unanswered question.

In this study we present an in vitro flow dynamics study to evaluate the distribution and alternation of wall shear stress over 1 cardiac cycle in 2 aneurysms with different locations in the circle of Willis. Geometrically realistic aneurysm models were manufactured from 3-dimensional CT angiography (3-D CTA), and data on aneurysm wall shear stress were collected. The wall shear stress value was estimated from flow velocity sampled near the aneurysmal wall (shearing velocity). Particular attention was paid to the wall shear stress in aneurysmal blebs, the point at which cerebral aneurysms commonly rupture.

Subjects and Methods

In Vitro Aneurysm Models

Two unruptured aneurysms harboring localized small outpouching of the wall (early bleb lesion) were selected from the 3-D CTA library of patients’ aneurysms. One patient had a right middle
cerebral artery (MCA) aneurysm, and another patient had a basilar tip aneurysm. The CTA data set was obtained with the use of a helical CT scanner (GE CTi; General Electric). A total of 175 mL of nonionic contrast material (iohexol; Nycomed, Amersham) was injected at a rate of 3 mL/s with scan delay of 24 seconds after the contrast injection. Slice collimation was 1.0 mm with a 0.5-mm reconstruction interval. Field of view was 180 mm, with a matrix size of 512×512. Spatial resolution was 0.35×0.35 mm. Image reconstruction employed 180-degree linear interpolation.

The 3-D CTA data set of the MCA aneurysm consisted of the following: supraclinoid internal carotid artery; origin of anterior cerebral artery; prebifurcation segment of MCA; both anterior and posterior divisions of postbifurcation MCA branches; and the MCA aneurysm itself (Figure 1A). The greatest diameters of the MCA aneurysm, prebifurcation segment of MCA, anterior division, and posterior division were 6.3, 3.7, 2.4, and 2.1 mm, respectively. The 3-D CTA data set of the basilar tip aneurysm included the following: basilar artery; both posterior cerebral arteries; both superior cerebellar arteries; and the aneurysm itself (Figure 1B). The greatest diameters of the basilar tip aneurysm, basilar artery, posterior cerebral arteries, and superior cerebellar arteries were 11.5, 3.5, 3.1, and 1.4 mm, respectively.

The construction method of an in vitro aneurysm model has been reported previously. In brief, stereo lithography (SLA-250 RP&M System; 3D Systems) was used to create geometrically realistic aneurysm models based on the 3-D surface data obtained from CTA images. To conduct reliable shear stress measurements in such a small lesion, the size of the resin aneurysm models was scaled to be 3.0 times the original size. Clear acrylic female casts of both aneurysms were then constructed for the test section by using the geometrically realistic aneurysm models as molds (Figure 2).

**Fluid Flow Conditions**

According to the concept of dimensional analysis and the law of similarity, not all parameters, such as kinematic viscosity, fluid velocity, and duration of 1 cardiac cycle, must be matched between in vitro and in vivo states for accurate flow velocity simulation as long as dimensionless similarity parameters and the waveform shape in the parent artery are matched between them. In this study dimensionless similarity parameters such as the in vitro Reynolds number and the Womersley parameter were arranged to match those values depicted in vivo to achieve a similar flow velocity condition in the scale-up models. Both the Reynolds number and the Womersley parameter in acrylic aneurysm models are summarized in Table 1.

Saturated aqueous solution of sodium iodide was used as a working fluid because its refraction index is exactly the same as that of water.
of acrylic resin. Therefore, the optical distortion at the interface between the working fluid and the acrylic resin could be eliminated. Titanium dioxide particles that ranged in size from 0.63 to 0.80 µm were added to the working fluid for the shearing velocity measurement with the use of laser-Doppler velocimetry (LDV). The kinematic viscosity of the working fluid at an operating temperature of 24°C was 1.64×10⁻² cm²/s.

Pulsatile flow was generated in the experimental circuit by using a velocity-controlled servomotor (VLBS-A11012; Toei Electric). A steady mean flow was generated by the hydraulic pressure of an elevated reservoir tank and was superimposed on the pulsatile flow. The velocity waveform at the parent artery of each model successfully simulated the waveform obtained from Doppler ultrasonography. In our scale-up models with the sodium iodide solution, the in vitro Womersley parameter with that in vivo. The flow rates of each arterial branch were set in accordance with the cross-sectional area of each branch.

Wall Shear Stress Measurement

The fluid-induced wall shear stress (τ) along the aneurysm wall was calculated from the following equation: 

\[ \tau = \frac{dv}{dx} \]

where \( \tau \) is the kinematic viscosity of the working fluid, \( dv \) is the shearing-velocity, and \( dx \) is the distance between the aneurysmal wall and the point where shearing velocity was sampled. The alternation of the shearing velocity (\( dv \)) over 1 cardiac cycle could be quantitatively sampled with the use of the LDV (Ar-ion Laser 500 mW, TSI). The LDV could measure the point velocity by detecting the reflected laser beam from the seeding particles added in the working fluid, with the actual measurement dimension of 180×34.2 µm. The optical distortion of laser beams near the wall of the acrylic aneurysm models could be eliminated by using the sodium iodide solution that had the same refraction index as acrylic resin. The LDV measurements were conducted at the distance of 0.70 mm (\( dx \)) from the aneurysmal wall sampling the point velocity (\( dv \)) tangential to the contour of the aneurysmal wall. An averaged waveform of shearing velocity corresponding to 1 cardiac cycle at each point was produced by ensemble averaging of waveforms taken from 50 consecutive cardiac cycles. With the use of the LDV, intra-aneurysmal flow pattern was also obtained to detect the inflow and outflow zones in the aneurysm neck. The inflow zone is the area of the neck where the blood flow enters into the aneurysm, and the outflow zone is the area of the neck where the blood flow exits from the aneurysm. The time-related mean value and alternation of wall shear stress over 1 cardiac cycle were also evaluated in the inflow zone, dome, and outflow zone of the aneurysms.

Results

The values of wall shear stress in the MCA aneurysm and in the basilar tip aneurysm are given as a percentage of the maximum wall shear stress measured in the parent arteries because the aneurysm models were scaled up 3-fold. The wall shear stress of the MCA aneurysm was obtained at 10 points in the middle plane of the aneurysmal sac where the aneurysm arises from the anterior and posterior divisions of MCA branches: 3 points in the inflow zone, 4 points in the dome, and 3 points in the outflow zone (Figure 3A). This plane clearly depicted both inward and outward flow areas of the aneurysm. The inflow zone was situated in the distal neck and the outflow zone in the proximal neck. The bleb was situated near the tip of the MCA aneurysm and particularly in the inflow side of the aneurysm. The wall shear stress of the basilar tip aneurysm was also calculated at 10 different points in the coronal section where both posterior cerebral arteries arise from the aneurysm neck: 3 points in the inflow zone, 4 points in the dome, and 3 points in the outflow zone (Figure 4A). The inflow zone of the basilar tip aneurysm was identified at the right side of the aneurysm and the outflow zone at the left side. The aneurysm bleb was located at the left side of the aneurysmal dome.

The time-related mean value of wall shear stress is detailed in Table 2. The value of the wall shear stress was not uniform in the aneurysmal wall, and particular regions were exposed to relatively high shear stress. In both MCA and basilar tip aneurysm models, the mean value of wall shear stress was higher in the outflow zone than in the inflow zone. In the aneurysm dome, the bleb was exposed to higher wall shear stress throughout 1 cardiac cycle than other parts of the dome.
Furthermore, the highest time-related mean value was noted in the blebs on the MCA and basilar tip aneurysms. The alternations of the wall shear stress over a cardiac cycle are presented in Figures 3 and 4. The wall shear stress changed during a cardiac cycle in accordance with the blood flow in the parent arteries. The direction of the wall shear stress was the same as the intra-aneurysmal flow.

In the MCA aneurysm, there was significant change in the value of the wall shear stress during 1 cardiac cycle at the outflow zone (points O1 to O3) and the aneurysm bleb (points D1 and D2). In these points, the wall shear stress was the highest at the early diastolic phase. The maximum instantaneous value of the wall shear stress was 93.0%, which was noted at the aneurysm bleb (point D2). In contrast, the value of the wall shear stress was relatively constant at the inflow zone of the MCA aneurysm.

In the basilar tip aneurysm model, the direction of the shearing velocity oscillated in the inflow zone. There was no significant alternation of wall shear stress during a cardiac cycle in the inflow and outflow zones. On the other hand, the value of wall shear stress changed remarkably over a cardiac cycle in the aneurysm dome. Unlike the MCA aneurysm, a high instantaneous value of wall shear stress was noted at the late systolic phase. The highest instantaneous value was 54.4%, which was again observed at the aneurysm bleb (point D3).

**Discussion**

**Shear-Induced Vasodilatation**

Fluid-induced wall shear stress is a dynamic frictional force induced by a viscous fluid moving across a surface of solid material. Previous studies have demonstrated that wall shear stress has a strong biological influence on vessels by impinging on various endothelial functions rather than a direct mechanical influence.4,5,7,16–19 Wall shear stress appears to be closely related to the development of various vascular diseases, such as atherosclerosis and cerebral aneurysms.2,10,11,20–22 High wall shear stress is related to the formation of cerebral aneurysms. Conversely, low and/or oscillating wall shear stress is regarded as a risk factor in the development of atherosclerotic lesions in healthy arteries.

The endothelial cell is sensitive to alternations of wall shear stress. As wall shear stress increases, more endothelium-derived nitric oxide (a strong vasodilator) is produced.3–6 Therefore, increased wall shear stress on the arterial wall caused by increased flow velocity stimulates vasodilatation and results in decline of flow velocity to the normal range.1,3,23,24 This seems to be the primary manner in which the vessel adapts its diameter appropriately in accordance with the sustained change of blood flow volume.

**Table 2. Time-Related Mean Value of Wall Shear Stress at 10 Points in Acrylic Aneurysm Models**

<table>
<thead>
<tr>
<th></th>
<th>MCAAn</th>
<th>BTAn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck/inflow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I1</td>
<td>0.1356</td>
<td>0.0906</td>
</tr>
<tr>
<td>I2</td>
<td>0.0968</td>
<td>0.0735</td>
</tr>
<tr>
<td>I3</td>
<td>0.2361</td>
<td>0.0761</td>
</tr>
<tr>
<td>Dome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1</td>
<td>0.1869</td>
<td>0.2058</td>
</tr>
<tr>
<td>D2</td>
<td>0.3171</td>
<td>0.1418</td>
</tr>
<tr>
<td>D3</td>
<td>0.0632</td>
<td>0.2576</td>
</tr>
<tr>
<td>D4</td>
<td>0.1096</td>
<td>0.2187</td>
</tr>
<tr>
<td>Neck/outflow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1</td>
<td>0.2191</td>
<td>0.1931</td>
</tr>
<tr>
<td>O2</td>
<td>0.3106</td>
<td>0.1442</td>
</tr>
<tr>
<td>O3</td>
<td>0.1657</td>
<td>0.1945</td>
</tr>
</tbody>
</table>

MCAAn indicates middle cerebral artery aneurysm; BTAn, basilar tip aneurysm.

![Figure 4](image_url)
The distribution of fluid-induced wall shear stress in a curved tube is not uniform, as it is in a straight tube.\textsuperscript{25,26} Since the endothelium regulates local vascular tone, local increase of wall shear stress may cause local dilatation of arterial walls. Previous investigations using laboratory animals have demonstrated that aneurysms were formed on the arterial wall as a result of locally increased wall shear stress.\textsuperscript{10,11} Fukuda et al\textsuperscript{10} showed, in a rat model, the influence of nitric oxide induced by increased wall shear stress on the development of cerebral aneurysms.

**Wall Shear Stress in Cerebral Aneurysms**

It remains unclear whether the endothelial cells on the aneurysmal wall are sensitive to modifications of wall shear stress. Kataoka et al\textsuperscript{27} used a scanning electron microscope for the histological evaluation of cerebral aneurysms obtained at surgery. They reported that the inner surface of the unruptured aneurysm sac was covered with normally shaped arterial endothelial cells. There is therefore a possibility that endothelial cells in a cerebral aneurysm react to wall shear stress in the same way as those in a normal artery.

In our study the distribution of wall shear stress was not uniform in both aneurysms. There was a specific point where the aneurysmal wall was exposed to higher shear stress. Unlike past wall shear stress measurements obtained with ideal spherical aneurysm models, the wall shear stress value varied at each point in our geometrically realistic aneurysm models.\textsuperscript{28,29} In particular, in this study aneurysmal blebs were exposed to higher shear stress than other measured points on the aneurysmal wall.

Two hypotheses may be proposed from these results. Given the preferential localization of blebs in aneurysmal regions exposed to relatively high shear stress, these results may be consistent with the notion that intra-aneurysmal regions exposed to high wall shear stress are more prone to bleb formation. An increased production of endothelium-derived nitric oxide may be induced by the increased wall shear stress on the wall of an unruptured aneurysm producing localized dilatation of the wall. Another hypothesis is that the bleb induced a higher shearing velocity, which resulted in increased wall shear stress. Nitric oxide is known not only as a potent vasodilator but also as a potential participant in flow-induced arterial remodeling in healthy arteries.\textsuperscript{19,30}–32 A previous report showed that the wall of ruptured aneurysms contained fewer smooth muscle cells and more irregular layers of collagen IV than in the wall of unruptured aneurysms.\textsuperscript{27} Therefore, locally increased shear stress may accelerate the degeneration of the blebs and may increase the risk of aneurysmal rupture. Given the concept of shear stress–induced arterial remodeling in healthy arteries, shear stress in cerebral aneurysms may play a role in the modification of the histological structure of the aneurysm wall.\textsuperscript{1,4,5,33} Thus, histopathological investigations of human cerebral aneurysms combined with wall shear stress and molecular biological evaluations of their walls will add important data to our understanding of the basic phenomena that regulate aneurysm development, growth, and rupture.

**Geometrically Realistic Acrylic Aneurysm Model**

Vascular geometry is an important parameter that determines flow patterns. The development of geometrically realistic acrylic aneurysm models allowed us to evaluate wall shear stress in blebs depicted in aneurysm models from patients. With the application of dimensional analysis and the law of similarity, scale-up aneurysm models could be used for the analysis of wall shear stress in relatively small lesions.\textsuperscript{12–14} One of the major limitations of this experimental system may be the lack of distensibility and compliance in the aneurysm wall. A previous in vitro study demonstrated that there was no remarkable difference in flow characteristics between rigid and elastic aneurysm models.\textsuperscript{34} Given the difficulty of accurate measurement of shearing velocity on a moving wall, reasonable flow simulation can be performed with rigid aneurysm models. This experimental model allows the comparison of the wall shear stress profile with the morphology, geometric disposition, location, and natural history of aneurysms.

**Conclusions**

Geometrically realistic aneurysm models were manufactured from the patients’ 3-D CTA data sets to conduct wall shear stress measurements. Quantitative wall shear stress measurements were successfully taken in patients’ irregularly shaped aneurysms with the use of LDV. This experimental system allowed us to reveal characteristics of wall shear stress in aneurysms harboring blebs, at which point aneurysms frequently rupture. The distribution of wall shear stress was not equal in the patients’ aneurysms. The aneurysmal blebs were exposed to relatively higher shear stress than other measured points on the aneurysmal wall. These results provide us with further indications of the correlation of wall shear stress with the natural history of cerebral aneurysms.

**Acknowledgments**

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**References**


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