Hemodynamic Differences Between Unruptured and Ruptured Intracranial Aneurysms During Observation

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Background and Purpose—We evaluated several hemodynamic parameters for the prediction of rupture in a data set of initially unruptured aneurysms, including aneurysms that ruptured during follow-up observation.

Methods—Aneurysm geometry was extracted from CT angiographic images and analyzed using a mathematical formula for fluid flow under pulsatile blood flow conditions. Fifty side-wall internal carotid posterior communicating artery aneurysms and 50 middle cerebral artery bifurcation aneurysms of medium size were investigated for energy loss, pressure loss coefficient, wall shear stress, and oscillatory shear index. During follow-up observation, 6 internal carotid posterior communicating artery and 7 middle cerebral artery aneurysms ruptured (44 and 43 remained unruptured, respectively, with the same location and a similar size as the ruptured cases).

Results—A significant difference in the minimum wall shear stress between aneurysms that ruptured and those that remained unruptured was noted only in internal carotid artery aneurysms (P<0.001). Energy loss showed a higher tendency in ruptured aneurysms but statistically not significant. For pressure loss coefficient, a significant difference was noted in both internal carotid artery (P=0.0046) and middle cerebral artery (P<0.001) aneurysms.

Conclusions—Pressure loss coefficient may be a potential parameter to predict future rupture of unruptured aneurysms. (Stroke. 2012;43:1436-1439.)

Key Words: aneurysms ▪ computational fluid dynamics ▪ hemodynamics ▪ rupture

Prediction of rupture is desirable for the management of incidentally found unruptured aneurysms (UAs).1 Recently, studies reported the use of computational fluid dynamic techniques to investigate cerebral aneurysm rupture mechanism.2–9 Contributions of several hemodynamic factors such as wall shear stress (WSS) or oscillatory shear index (OSI) have been reported,2,3,6,8,9 but results are still controversial. We investigated the rupture mechanism through several computational fluid dynamic-derived hemodynamic parameters on a data set of 100 patients with initially UAs, including 13 aneurysms that ruptured during the course of follow-up observation.

Methods

Clinical Cases
Of the patients with UAs waiting for scheduled surgery or who refused surgery and underwent only observation, rupture occurred in 13 cases (internal carotid artery [ICA] 7, middle cerebral artery [MCA] 6). We defined those aneurysms as “ruptured aneurysms (RAs)” in this analysis. All RA sizes ranged from 5 to 10 mm (average, ICA 6.23 mm, MCA 6.21 mm).

Matching 44 ICA-UA (average, 6.0 mm) and 43 MCA-UA, 5 to 10 mm were selected from our observation database (average, ICA 6.0 mm, MCA 6.0 mm).

Computational Fluid Dynamic Modeling
Starting from head CT angiographic images, the geometry of blood vessels was extracted using manual cropping, image thresholding, and converted into a triangulated surface through “Real Intage” (Cybernet Systems, Tokyo, Japan). An unstructured computational volumetric mesh was constructed from the triangulated surface. The mesh was mainly comprised of tetrahedrons with several layers of prism elements used near the wall surface to increase the analytic precision of the boundary layer. Under the assumptions of pulsatile laminar flow, zero pressure at the blood vessel outlet, Newtonian fluid, and rigid blood vessel walls with nonslip condition, the Naver-Stokes equations were used to simulate blood flow on the computational mesh. Commercial software (ANSYS ICEM CFD 12.1) was used for both mesh generation and fluid simulation. Additional computational fluid dynamic modeling details are provided in Figure 1.

For RA, the latest CT angiographic image available before rupture was used. For UA, the latest CT angiographic image acquired during follow-up was used. Rupture occurred on average175±328 days after the last CT angiogram. In addition to WSS2,6,8 and OSI9 we investigated 2 additional hemodynamic parameters, energy loss...
(EL), and pressure loss coefficient (PLc), which are associated with the expenditure of flow energy in the aneurysm region.

**Energy Loss**

EL is the EL per unit volume, and it comprehensively represents energy expenditure due to viscous friction and whirlpool formation. EL is expressed as:

$$EL = \frac{\rho V_m \left( \frac{1}{2} \rho \nu_\text{in}^2 + P_\text{in} \right) - \frac{1}{2} \rho \nu_\text{out}^2 + P_\text{out} \right)}{V_m}$$

where $\rho$ is the fluid density, $V_m$ represents the volume of the measurement section, and $A_{\text{in}}$ is the area of the test plane at the inlet of the measurement region (Figure 1). $v_\text{in}$ and $P_\text{in}$ represent the mean flow velocity and static pressure of the test plane at the inlet side, respectively, and $v_\text{out}$ and $P_\text{out}$ represent those at the outlet side, respectively.

**Pressure Loss Coefficient**

PLc is a dimensionless quantity representing pressure loss associated with the shape of pipes and obstacles to flow. PLc is calculated by:

$$PLc = \frac{\Delta P}{\rho \nu_\text{in}^2}$$

where $\rho \nu_\text{in}^2$ is the dynamic pressure and $\Delta P$ is the pressure loss, which is given by

$$\Delta P = \frac{1}{2} \rho \nu_\text{in}^2 + P_\text{in} - \frac{1}{2} \rho \nu_\text{out}^2 + P_\text{out}.$$ 

Pressure loss is due to viscous friction and whirlpool formation in the measurement region and therefore, is also related to energy expenditure. Compared with EL, PLc characterizes both energy expenditure and the geometric shape of vessels.

**Data Analysis**

WSS varies in time (at different points in the heart cycle) and space (over the blood vessel wall). A spatial minimum, maximum, and average of WSS were computed over the vessel wall in the measurement section followed by time averages along the simulation time course (2 heart cycles). Because OSI is calculated based on time-integral values of WSS, OSI time-course characteristics were not evaluated, and only maximum and average were computed. By definition, EL and PLc do not change in space. The time-course maximum of these parameters was calculated. Therefore, a total of 7 hemodynamic parameters was analyzed. We performed normality tests on all parameters through the Kolmogorov-Smirnov test. For those parameters that the normality assumption could not be rejected at the 0.05 significance level, we used the $t$ test. For parameters for which the normality could not be established, we used the Wilcoxon rank-sum test. We adopted an overall significance level of $P=0.05$. The Bonferroni method was used to correct for multiple statistical tests yielding an individual significance level of $0.00714 (=0.05/7)$ for each test.

### Results

Streamlines, WSS, and OSI for representative aneurysms are shown in Figure 2. Means, SDs, and statistical test results for hemodynamic parameters are presented in the Table. The only WSS parameter with significant differences between RA and UA was the time-averaged WSS minimum, but these differences were observed for ICA aneurysms only ($P<0.001$). No statistically significant differences were noted in OSI between RA and UA in both ICA and MCA cases ($P>0.303$). Although EL tended to be greater in ruptured cases, these differences were not significant ($P>0.189$). Conversely, PLc was significantly lower for RA in both ICA and MCA aneurysms ($P<0.0074$). Chi-squared tests did not reveal an association between rupture and age, sex, hypertension, hyperlipidemia, diabetes, or family history of subarachnoid hemorrhage. Receiver operator characteristics analysis of PLc revealed an area under the curve of 0.845 for ICA and 0.792 for MCA. PLc threshold values of 1.105 and 1.15 were established, we used the Wilcoxon rank-sum test. We adopted an overall significance level of $P=0.05$. The Bonferroni method was used to
correct for multiple statistical tests yielding an individual significance level of $0.00714 (=0.05/7)$ for each test.

**Figure 1.** CFD model: (A) inlet mass flow rate; (B) physical variable extraction site; (C) modeling parameter values. CFD indicates computational fluid dynamic.
Discussion

Our results demonstrated that a low WSS may be associated with aneurysm rupture, but statistical significance was noted only in ICA cases.

In contrast, significant differences were noted in PLc in both ICA and MCA, and its values were lower in RA. PLc is influenced by the shape of vessel, and it does not vary with the input flow boundary conditions, unlike WSS and OSI. PLc decreases if the shape of the vessel and aneurysm facilitates the easy flow of blood. Therefore, it can be concluded that aneurysms likely to rupture have a shape in which blood flows easily, and the hemodynamics are stable. This stability may induce a decrease in the natural vessel wall resistance to hemodynamic changes such as rapid blood flow.

Table. Univariate Analysis Results for Parameters Examined in RA and UA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ICA Average</th>
<th>SD</th>
<th>P Value</th>
<th>MCA Average</th>
<th>SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EL, W/m³</td>
<td>Ruptured 10417</td>
<td>4954</td>
<td>0.189</td>
<td>Ruptured 11827</td>
<td>9671</td>
<td>0.295</td>
</tr>
<tr>
<td></td>
<td>Unruptured 8743</td>
<td>6881</td>
<td></td>
<td>Unruptured 8515</td>
<td>5570</td>
<td></td>
</tr>
<tr>
<td>PLc</td>
<td>Ruptured 1.035</td>
<td>0.224</td>
<td>0.0046</td>
<td>Ruptured 1.069</td>
<td>0.108</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Unruptured 1.625</td>
<td>0.641</td>
<td></td>
<td>Unruptured 1.359</td>
<td>0.342</td>
<td></td>
</tr>
<tr>
<td>WSSAVE, Pa</td>
<td>Ruptured 5.104</td>
<td>0.96</td>
<td>0.695</td>
<td>Ruptured 6.139</td>
<td>2.055</td>
<td>0.37961</td>
</tr>
<tr>
<td></td>
<td>Unruptured 5.189</td>
<td>1.958</td>
<td></td>
<td>Unruptured 5.349</td>
<td>1.959</td>
<td></td>
</tr>
<tr>
<td>WSSMAX, Pa</td>
<td>Ruptured 30.66</td>
<td>12.70</td>
<td>0.297</td>
<td>Ruptured 41.07</td>
<td>20.35</td>
<td>0.246</td>
</tr>
<tr>
<td></td>
<td>Unruptured 25.96</td>
<td>11.82</td>
<td></td>
<td>Unruptured 32.66</td>
<td>14.42</td>
<td></td>
</tr>
<tr>
<td>WSSMIN, Pa</td>
<td>Ruptured 0.0222</td>
<td>0.0039</td>
<td>&lt;0.001</td>
<td>Ruptured 0.0372</td>
<td>0.0187</td>
<td>0.721</td>
</tr>
<tr>
<td></td>
<td>Unruptured 0.0407</td>
<td>0.0305</td>
<td></td>
<td>Unruptured 0.0350</td>
<td>0.0221</td>
<td></td>
</tr>
<tr>
<td>OSI MAX</td>
<td>Ruptured 0.465</td>
<td>0.022</td>
<td>0.805</td>
<td>Ruptured 0.466</td>
<td>0.021</td>
<td>0.728</td>
</tr>
<tr>
<td></td>
<td>Unruptured 0.461</td>
<td>0.035</td>
<td></td>
<td>Unruptured 0.463</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>OSI AVE</td>
<td>Ruptured 0.00976</td>
<td>0.0047</td>
<td>0.989</td>
<td>Ruptured 0.0102</td>
<td>0.0051</td>
<td>0.303</td>
</tr>
<tr>
<td></td>
<td>Unruptured 0.0128</td>
<td>0.0151</td>
<td></td>
<td>Unruptured 0.0128</td>
<td>0.0090</td>
<td></td>
</tr>
</tbody>
</table>

RA indicates ruptured aneurysm; UA, unruptured aneurysm; ICA, internal carotid artery; MCA, middle cerebral artery; EL, energy loss; PLc, pressure loss coefficient; WSS, wall shear stress; AVE, average; MAX, maximum; MIN, minimum; OSI, oscillatory shear index.
pressure elevation, thereby increasing the risk of rupture. We assume that a region with high PLc changes its shape during aneurysm growth to avoid interfering with blood flow, a “remodeling process” eventually reaching a stable hemodynamic condition and thereafter transitioning from low to high risk of rupture.

As a limitation of this study, the number of RAs was smaller than that of UAs. The boundary conditions were uniform across all cases, whereas in reality, we can expect these to vary from one case to another. Boundary conditions should be established by using MRI and echo if available. Additionally, vessel walls were also assumed rigid, whereas in reality, they may deform during the cardiac cycle. We also assumed no change in the aneurysm shape from the last CT angiogram until rupture.

Conclusions
Our results suggest that PLc may be 1 out of possibly other useful parameters to predict cerebral aneurysm rupture.

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Disclosures
A.M. is full-time employee of Siemens Japan K.K.

References
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