Wall Shear Stress Distribution of Small Aneurysms Prone to Rupture
A Case–Control Study

Vitor Mendes Pereira, MD, MSc; Olivier Brina, TRM; Philippe Bijlenga, MD; Pierre Bouillot, PhD; Ana Paula Narata, MD; Karl Schaller, MD, PhD; Karl-Olof Lovblad, MD; Rafik Ouared, PhD

Background and Purpose—Subarachnoid hemorrhage after intracranial aneurysm rupture remains a serious condition. We performed a case–control study to evaluate the use of computed hemodynamics to detect cerebral aneurysms prone to rupture.

Methods—Four patients with incidental aneurysms that ultimately ruptured (cases) were studied after initially being included in a prospective database including their 3-dimensional imaging before rupture. Ruptures were located in different arterial segments: M1 segment of the middle cerebral artery; basilar tip; posterior inferior cerebellar artery; and anterior communicating artery. For each case, 5 controls matched by location and size were randomly selected. An empirical cumulative distribution function of aneurysm wall shear stress percentiles was evaluated for every case and used to define a critical prone-to-rupture range. Univariate logistic regression analysis was then used to assess the individual risk of rupture.

Results—A cumulative wall shear stress distribution characterizing a hemodynamic prone-to-rupture range for small-sized aneurysms was identified and fitted independent of the location. Sensitivity and specificity of the preliminary tests were 90% and 93%, respectively.

Conclusions—The wall shear stress cumulative probability function may be a potential predictor of small-sized aneurysm rupture.

Key Words: aneurysm ■ computer simulation ■ hemodynamics ■ rupture

Intracranial aneurysms are prevalent in 2% to 5% of the population and the frequency of bleeding varies with aneurysm location, size, and specific populations. Attempts to study the correlations between aneurysm rupture and patient-specific hemodynamic factors have been performed simultaneously during past decades. Unfortunately, computational fluid dynamics have not sufficiently evolved to be used in daily clinical routine, possibly because studies were based on postrupture aneurysm shapes. Out of the all studies based on prerupture geometries, few were analyzing the hemodynamic features. Alternatively, there are few clinical studies collecting unruptured cases prospectively, particularly small aneurysms, which were imaged before rupture. The present study analyzes the hemodynamic features of unexpected small ruptured aneurysms based on prerupture imaged shapes.

Methods

We designed a computational fluid dynamics case–control study to evaluate the rupture odds of such small aneurysms using prerupture geometries and explored a novel predictor related to wall shear stress (WSS) percentile function. Cases were 4 patients with small saccular intracranial aneurysms that were not initially designated for treatment and who presented with subarachnoid hemorrhage during follow-up. Ruptures were located in different arterial segments: M1 segment of the middle cerebral artery; basilar tip; posterior inferior cerebellar artery; and anterior communicating artery. Controls included patients with unruptured saccular intracranial aneurysms matched by location and size from the same database (Figure 1). Data collected included patient age, sex, aneurysm dimensions, aneurysm neck size, location, rupture status, and medical history. The primary end point of this study was to determine whether some of the significant geometry and hemodynamic predictors were applicable to our small-sized aneurysm sample. We evaluated these factors in the rupture state for cases and controls. We collected the following geometric parameters: aspect ratio (aneurysm apex/neck size) and both aneurysm and neck sizes, size ratio and inflow angle: inclination of aneurysm with regard to the direction of flow in the parent artery. We evaluated the hemodynamic parameters related to WSS averaged over a cycle (mean, maximum, minimum) and other relevant calculated parameters. In addition to scalar hemodynamic factors, we evaluated a novel empirical hemodynamic function, that is, the WSS cumulative distribution function (WSScdf), with values between 0 and 1 characterizing the aneurysm WSS percentiles (Methods in the online-only Data Supplement).
Results
The changes in the likelihood of rupture between cases and controls in univariate conditional logistic regression analysis were not statistically significant (P>0.05) for all geometry and hemodynamic variables (Table I in the online-only Data Supplement). However, the WSS percentile distribution specific to prone-to-rupture, small-sized aneurysms is characterized by the following WSS percentile figure (Figure 2A).

Figure 2 shows the WSScdf for the 4 cases and 20 controls. Figure 3A shows the average WSScdf for the control groups.

Figure 3B shows the univariate logistic regression fit based on variable Np (the fraction of the WSScdf curve intersecting with the prone-to-rupture range) for which the log odds ratio was found equal to b0=-8.13±1.95 and b1=0.62±0.16 (mean±SD), respectively; statistical significance of likelihood of rupture was P=0.047. Because the outcome of rupture is boolean (rupture versus no rupture issues), every variation below the median risk would be zero. The Np threshold suggests that rupture becomes certain if ≈70% of the entire WSScdf curve intersects with the prone-to-rupture range. The

Figure 1. Qualitative representation of wall shear stress (WSS) averaged over a cycle for cases and controls. The 4 aneurysm locations from top to bottom are row 1: middle cerebral artery (MCA) aneurysm; row 2: basilar artery (BAT) aneurysm; row 3: posterior inferior cerebellar artery (PICA) aneurysm; row 4: anterior communicating artery (AcomA) aneurysm. The mean WSS magnitude averaged over a cycle between 1.0 and 10 Pa is represented by a logarithmic color scale: blue, for WSS <1.0 Pa, and red for WSS >10 Pa. Columns show a comparison of overall cases with controls: cases present similar mean WSS magnitudes independent of the location, but with different spatial distributions; controls have wider WSS distributions and different magnitudes. Rows: controls have similar WSS levels at each location, but these differ from their respective case that ruptured. Moreover, WSS in MCA and AcomA aneurysms have both higher WSS compared with BAT and PICA aneurysms. BAT is the only location where controls and cases have a similar mean WSS magnitude.

Figure 2. Wall shear stress cumulative distribution function (WSScdf) of cases (A) and for controls (B). The red crosses superimposed in B represent cases. AcomA indicates anterior communicating artery; BAT, basilar artery; CI, confidence interval; MCA, middle cerebral artery; and PICA, posterior inferior cerebellar artery.
A contingency table associated with the threshold (Np=13.9) indicated that cases and 1 control tested positive, whereas the remaining controls tested negative. Using Yates correction, the performance of the prone-to-rupture range method associated with our small case–control sample was characterized by sensitivity=0.90 (63.7%, 100%); specificity=0.93 (81.8%, 100%).

**Discussion**

This study was based on the prerupture imaging of 4 small aneurysms (cases) in different locations that were compared with 20 unruptured controls selected from a prospective database and matched by location and size. We observed the existence of a narrow WSScdf hemodynamic prone-to-rupture range common to all cases, independent of their location. Because most controls were not included in this range, we proposed a novel rupture risk assessment method based on a new potential predictor. The definition of the predictor was simplified by counting the number of WSS cutoff values (out of 18) included in the prone-to-rupture range for each individual aneurysm. The case–control odds ratio corresponding to the threshold (Np=13.9) was then significantly estimated to be 24. The results demonstrated that a small-sized aneurysm is likely to rupture if ≈70% of its associated WSScdf curve is contained in the risk zone (positive predictive value, 75%), and would not otherwise (negative predictive value, 97%).

It is also interesting to note that on average, the WSScdf of basilar tip aneurysm controls largely intersects with the prone-to-rupture zone. This basilar tip location trend most likely corresponds to epidemiological observations (ie, the rupture odds of the associated aneurysms are larger than in other locations).9

Because it is generally admitted that WSS is involved in both the fatigue preceding aneurysm tear and remodeling of wall tissue, extensive studies of its magnitude, direction, and distribution have been performed by several authors with divergent opinions on the correlation of low and high WSS with rupture.11 It seems rather that a more balanced WSS percentile distribution (50%; <0.4 Pa) was required to trigger the biological response specific to rupture, which could lead to faster endothelial cell turnover compared with other regions of the vessel, hence modifying the morphological remodeling.4

It is foreseeable that the challenge for computational fluid dynamics in the coming years would be to detect an increasing number of potentially dangerous small-size lesions that may rupture despite being presumably of low risk according to epidemiological studies.1,5,12–14 Indeed, large aneurysms are rarely followed conservatively because their estimated rupture risk is not questionable, and the therapeutic decision can be taken without any ambiguity.7,15

**Conclusions**

WSScdf prone-to-rupture ranges exist and may potentially highlight small-sized aneurysm tears with high positive and negative predictive values.

**Acknowledgments**

We thank Rosemary Sudan for the English review.

**Sources of Funding**

This study was supported by Swiss National Science Foundation grant (SNF 32003B_141192).

**Disclosures**

None.

**References**

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Stroke. 2014;45:261-264; originally published online November 19, 2013; doi: 10.1161/STROKEAHA.113.003247

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Supplemental Methods

Case-control Study design

This was a case-control study including patients referred to a reference center accredited by the Swiss government for the evaluation of all intracranial vascular diseases reported in this region (catchment area, 2 million inhabitants). Cases and controls were collected from a local prospective database including all patients with intracranial aneurysms who had been evaluated and followed up or treated at our institution since 2006. Patients provided written consent to be included in the database. Aneurysms were located at the M1 segment of the middle cerebral artery (MCA), at the basilar tip (BAT), on the posterior inferior cerebellar artery (PICA), and on the anterior communicating artery (AcomA) (Figure 1) and were all smaller than 5 mm (4.5 mm, 2.9 mm, 3.3 mm and 4.2 mm for cases, respectively). For each case, we selected randomly a set of 5 control patients harboring unruptured IAs matched for location and size and monitored for at least 1 year to avoid any interference with other regression covariates. In addition, since the contralateral first segment of the anterior cerebral artery (A1) was hypoplastic for case AcomA, homologous controls were also matched on this anatomy criterion.

Institution Aneurysm Management

Patients with ruptured aneurysms were treated as soon as they presented at the emergency department and those with unruptured aneurysms were evaluated by a multidisciplinary consultation following two main paradigms. Patients with either a large aneurysm or a personal or family history of SAH were usually treated with the technique most adapted to their lesions, while patients with aneurysms less than 7 mm in the anterior circulation or less than 5 mm in either the posterior circulation or
AcomA aneurysms were managed conservatively. Risk factors were controlled at 6 months, 1 year, 2 years, and every 5 years thereafter, together with regular clinical and imaging follow-up. Conservative management was halted when the lesion was observed to have changed morphologically.

**Geometry and Hemodynamic Modeling**

The triangulated surfaces of the patient-specific vessels were reconstructed from the 3D rotational angiography images (Allura FD20, Philips Healthcare, Best, The Netherlands) through the segmentation steps documented and provided in the Aneufuse toolkit. A commercial software (ICEM CFD 12.1, ANSYS Inc, Canonsburg, PA) was then used to produce a high-resolution, computational, unstructured mesh composed of tetrahedrons in the bulk flow and prism elements delineating three boundary layers near the wall to increase the precision of WSS measurement. The mesh element number ranged between 3.3 and 5.6 million, with mesh density larger than 2000 elements/mm$^3$. The ANSYS CFX commercial Navier-Stokes equation solver was used to simulate blood flow as a Newtonian fluid on the computational mesh. We used generic boundary conditions measured on healthy subjects to impose inlet pulsatile flow and outlets’ pressure curves together with rigid wall boundary conditions according to Reymond et al. and Pereira et al. The mean volumetric flow rates applied to inlets were 4.19 cc/s for internal carotid artery (MCA, AcomA), 2.43 cc/s for basilar artery (BAT) and 1.19 cc/s for vertebral artery (PICA), respectively. The modeling parameters were the following: a) density: 1066 kg/m$^3$; b) viscosity: 0.0035 Pa.s; c) Reynolds number: 350-520; d) Womersley number: 1.8-2.6; e) cycle: 0.8s; f) number of cycles: 2. Analysis of results was performed using ANSYS CFX and Matlab (Mathworks, Natick, MA) customized scripts.
**Geometric Parameters**

In addition to the aspect ratio (aneurysm apex/neck size) and both aneurysm and neck sizes, we routinely evaluated additional geometry parameters reported by some authors as being potentially related to rupture: a) size ratio: defined for sidewall aneurysms as aneurysm apex/diameter of inlet vessel, and for bifurcation aneurysms as aneurysm apex/average diameter of all the feeding and branching vessels; and b) inflow angle: inclination of aneurysm with regard to the direction of flow in the parent artery. These parameters were used to check the homogeneity of the different locations and their potential impact on the rupture.

**Hemodynamic Parameters**

We evaluated the parameters related to WSS averaged over a cycle (mean [MWSS], maximum [MAXWSS], minimum [MINWSS]) and those identified by several authors for their potential correlation with rupture: a) power loss (mW) measuring power dissipation in the region of interest centered around the aneurysm; b) pressure loss coefficient (PLC) defined as the relative total pressure difference in the region of interest, normalized to incoming dynamic pressure; and c) viscous dissipation ratio (VDR), and inflow concentration index (ICI). All hemodynamic factors were registered at every time step together with their average over the entire cycle.

**Wall Shear Stress Cumulative Distribution Function**

In addition to scalar hemodynamic factors, we evaluated a novel empirical hemodynamic function, i.e., the WSS cumulative distribution function (WSScdf), with values between 0 and 1 characterizing the aneurysm WSS percentiles. WSScdf
evaluates the fraction of the aneurysm surface undergoing mean WSS (averaged over a cycle) up to the local maximum value. We defined a set of 18 cut-off values in this WSS range to reliably describe the fast growing edge of WSScdf for low-WSS regime cases, 10 points between 0 and 2 Pa, and 8 equally-spaced points above 2 Pa. Mathematically, WSScdf is a well-ordered set of ordinal WSS percentiles expressed as:

\[
WSScdf = \left\{ S_{W_i}, i = 1, 18 \right\}
\]

where \( W_i \) represents each of the 18 WSS cut-offs defined above and taken in ascending order, and \( S_{W_i} \) represents the WSS percentile up to \( W_i \).

**Statistical Analysis**

We generated descriptive statistics from all listed geometry and hemodynamic scalar variables and performed a matched case-control analysis with univariate conditional logistic regression. For each variable, we evaluated the increased likelihood of rupture with statistical significance set at \( P \leq 0.05 \) and the associated odds ratio when the null hypothesis was rejected. In addition, we observed that the WSScdf for cases were all aligned within a narrow range (WSScdf vs WSS) unlike controls where it spanned a wider range. We then determined the “prone-to-rupture” range by fitting the optimal empirical WSScdf for cases with their related 95% confidence interval (CI) using the following power function model:

\[
f(x) = \frac{1}{1 + \exp \left[ -a \left( x^b - c \right) \right]}
\]
where \( x \) represents the WSS variable averaged over a cycle and ranges between 0 and the local maximum value (18 discrete values were selected to represent the function \( f \)), and \( f(x) \) is the optimum WSS percentile function (WSScdf) associated with variable \( x \). The three parameters \( a \), \( b \), and \( c \) are required to take into account the saturation, the raising edge, and the median level of the function, respectively. The non-linear least squares residuals and covariance matrix were estimated using a Matlab (Mathworks v2011a) non-linear regression utility based on the Levenberg-Marquardt algorithm.\(^{10} \) By contrast to controls, cases are expected to have their WSScdf representation curve largely within the prone-to-rupture zone. Since the fraction of the WSScdf curve in the risk zone is directly correlated to rupture odds, a variable \( N_p \) was set to take into account the number of WSScdf cut-off points intersecting with this zone. Case-control rupture odds were evaluated by univariate logistic regression analysis based on variable \( N_p \). The \( N_p \) threshold associated with the median risk of rupture \((r=0.5)\) fixes the level of the rupture odds ratio between case and control groups and allows to evaluate the performance of the test. All analyses were performed with SPSS statistical package (IBM SPSS statistics, v21)

**Supplemental Results and Tables**

Table I shows that the change in the likelihood of rupture between cases and controls in univariate conditional logistic regression analysis was not statistically significant \((P>0.05)\) for all listed geometry and hemodynamic variables. Consequently, no odds ratio related to the listed variables was statistically significant \((P>0.05)\).

**Table I.** Results of univariate conditional logistic regression analysis. Average values (mean) and standard deviations (SD) are summarized for each variable and for cases and controls. \( P \)-values represent a summary of likelihood change of rupture.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (mean±SD)</th>
<th>Controls (mean±SD)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR</td>
<td>1.10±0.40</td>
<td>1.20±0.40</td>
<td>0.767</td>
</tr>
<tr>
<td>Necksize (mm)</td>
<td>3.20±0.80</td>
<td>3.90±1.50</td>
<td>0.255</td>
</tr>
<tr>
<td>Aneurysm size (mm)</td>
<td>3.70±0.70</td>
<td>4.70±1.80</td>
<td>0.275</td>
</tr>
<tr>
<td>IA °</td>
<td>56.1±21.0</td>
<td>38.8±16.9</td>
<td>0.079</td>
</tr>
<tr>
<td>SR</td>
<td>2.20±0.30</td>
<td>1.90±0.40</td>
<td>0.252</td>
</tr>
<tr>
<td>MWSS, Pa</td>
<td>1.20±0.50</td>
<td>2.20±1.00</td>
<td>0.372</td>
</tr>
<tr>
<td>MAXWSS, Pa</td>
<td>12.20±10.10</td>
<td>15.10±13.50</td>
<td>0.627</td>
</tr>
<tr>
<td>MINWSS, Pa</td>
<td>0.030±0.020</td>
<td>0.10±0.20</td>
<td>0.422</td>
</tr>
<tr>
<td>ICI</td>
<td>1.10±0.80</td>
<td>2.00±1.40</td>
<td>0.300</td>
</tr>
<tr>
<td>VDR</td>
<td>0.24±0.14</td>
<td>0.35±0.30</td>
<td>0.483</td>
</tr>
<tr>
<td>PL, mW</td>
<td>0.23±0.42</td>
<td>0.27±0.54</td>
<td>0.892</td>
</tr>
<tr>
<td>PLC</td>
<td>1.17±0.88</td>
<td>3.38±3.56</td>
<td>0.287</td>
</tr>
</tbody>
</table>

AR – aspect ratio; IA – aneurysm inclination angle (degree); SR – aneurysm to vessel size ratio; MWSS – mean WSS; maxWSS – maximum WSS; MINWSS – minimum WSS; ICI - inflow concentration index; VDR - viscous dissipation ratio; PL - power loss; PLC - pressure loss coefficient
Supplemental References