Differences in simple morphological variables in ruptured and unruptured middle cerebral artery aneurysms

Clinical article

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Object. Management of unruptured intracranial aneurysms remains controversial in neurosurgery. The contribution of morphological parameters has not been included in the treatment paradigm in a systematic manner or for any particular aneurysm location. The authors present a large sample of middle cerebral artery (MCA) aneurysms that were assessed using morphological variables to determine the parameters associated with aneurysm rupture.

Methods. Preoperative CT angiography (CTA) studies were evaluated using Slicer software to generate 3D models of the aneurysms and their surrounding vascular architecture. Morphological parameters examined in each model included 5 variables already defined in the literature (aneurysm size, aspect ratio, aneurysm angle, vessel angle, and size ratio) and 3 novel variables (flow angle, distance to the genu, and parent-daughter angle). Univariate and multivariate statistical analyses were performed to determine statistical significance.

Results. Between 2005 and 2008, 132 MCA aneurysms were treated at a single institution, and CTA studies of 79 aneurysms (40 ruptured and 39 unruptured) were analyzed. Fifty-three aneurysms were excluded because of reoperation (4), associated AVM (2), or lack of preoperative CTA studies (47). Ruptured aneurysms were associated with larger size, greater aspect ratio, larger aneurysm and flow angles, and smaller parent-daughter angle. Multivariate logistic regression revealed that aspect ratio, flow angle, and parent-daughter angle were the strongest factors associated with ruptured aneurysms.

Conclusions. Aspect ratio, flow angle, and parent-daughter angle are more strongly associated with ruptured MCA aneurysms than size. The association of parameters independent of aneurysm morphology with ruptured aneurysms suggests that these parameters may be associated with an increased risk of aneurysm rupture. These factors are readily applied in clinical practice and should be considered in addition to aneurysm size when assessing the risk of aneurysm rupture specific to the MCA location.

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Key Words • aneurysm • subarachnoid hemorrhage • epidemiology • unruptured intracranial aneurysm • morphological parameter • cerebral flow dynamics • vascular disorders

The prevalence of cerebral aneurysms is estimated to be 1%–2%16,17,23 in the general population and could be higher in the elderly.7 The management of an incidentally discovered intracranial aneurysm remains one of the most controversial topics in neurosurgery. Therapeutic options such as microsurgical clipping or endovascular coiling are offered to eradicate the risk of aneurysm rupture, which results in SAH and can lead to devastating morbidity and mortality. As a result of the ISUIA (International Study of Unruptured Intracranial Aneurysms)4,7,10,24 the treatment decision for unruptured intracranial aneurysms is based mainly on the size and location of the aneurysm in the anterior or posterior circulation. The contribution of morphological parameters of an aneurysm and its surrounding vascular architecture has not been included in the treatment paradigm in a systematic manner. Recently, a number of investigators evaluated geometric factors of ruptured and unruptured aneurysms1,3,5,11,14,15 and demonstrated that variables such as aspect ratio, undulation index, and size ratio could be important predictors of aneurysm rupture. However, such studies grouped together all aneurysm types, which may confound characteristics that are specific to the vascular anatomy associated with a specific location. Here, we
present a large sample of MCA aneurysms that were assessed using a diverse array of morphological variables to determine the parameters associated with aneurysm rupture at this specific location.

Methods

Patient Selection

The study population consisted of all patients with a diagnosis of an MCA aneurysm who were treated at the Brigham and Women’s Hospital between 2005 and 2008. Reoperated aneurysms, fusiform aneurysms, or those associated with arteriovenous malformations were excluded from the study. Demographic and clinical information was collected from medical records. In particular, patient data regarding the risk factors commonly associated with aneurysm development or aneurysm rupture were noted, including smoking status, family history, presence of multiple aneurysms, history of hypertension, and history of SAH. The study was approved by the Partners/Brigham and Women’s Hospital Institutional Review Board.

Reconstruction of 3D Models

The 3D Slicer (referred to as “Slicer” henceforth) is an open source, multiplatform visualization and image analysis software developed by the Surgical Planning Laboratory at the Brigham and Women’s Hospital. Preoperative CTA images were used to generate composite 3D models of the aneurysm and surrounding vasculature. All CTA studies were performed using a SOMATOM Definition scanner (Siemens) with a slice thickness of 0.75 mm and an increment of 0.5 mm. The vascular compartment was separated by thresholding, and aneurysm contours were delineated using a triangle reduction and smoothing algorithm. The resultant 3D surface model of the aneurysm and surrounding vessels could be tumbled freely in the Slicer environment (Fig. 1). Fiducial-based tractography was then created to measure the length and angle in 3D space. All measurements were obtained independently by 2 observers, and the average value was used for subsequent statistical analyses.

Definition of Morphological Parameters

Morphological parameters examined in 3D aneurysm models included 5 variables already defined in the literature (aneurysm size, aspect ratio, aneurysm angle, vessel angle, and size ratio) and 3 novel variables (flow angle, distance to genu, and parent-daughter angle). These parameters are described below (Fig. 2).

Size. The definition of size indices was adapted from Raghavan et al. The maximum diameter was used in univariate and multivariate analyses as an estimate for aneurysm size, which was defined as the largest cross-sectional diameter from the reconstructed 3D model. The maximum perpendicular height was measured from the neck of the aneurysm to the dome of the aneurysm and was used to calculate the aspect ratio.

Aspect Ratio. As defined by Ujiie et al. and Dhar et al., the aspect ratio is the ratio of the maximum perpendicular height of the aneurysm to the average neck diameter of the aneurysm.

Aneurysm Angle. The aneurysm angle, as defined by Dhar et al., is the angle formed between the neck of the aneurysm and the maximum height of the aneurysm. The maximum height is determined by the distance between the center of the aneurysm neck and the greatest distance to the dome of the aneurysm. This parameter captures the angle of inclination of the aneurysm and its neck plane. The viewing plane used for the measurement of this angle was determined by the velocity vectors of the flow upstream of the aneurysm, and, as such, the plane captures the direction of incoming flow entering the aneurysm.

Vessel Angle. The vessel angle is the angle between the parent vessel feeding into the aneurysm and the plane of the aneurysm neck. The centerline of the parent vessel was determined by connecting the center points of the 2 cross-sections used to measure parent vessel diameter (see Size Ratio). This inlet angle of the parent vessel into the aneurysm has been shown to influence flow within the aneurysm.

Size Ratio. This parameter was first defined by Dhar et al. and is the ratio between the maximum aneurysm height and the mean vessel diameter of all branches associated with the aneurysm. Specifically, the vessel diameter of a particular branch is determined by averaging the diameter of the cross-section of this vessel directly proximal to the neck of the aneurysm (D1) and the diameter of the cross section at 1.5 × D1 from the neck of the aneurysm. Then, the average diameter for each vessel feeding into and flowing out of the aneurysm was calculated to generate the composite mean vessel diameter used to evaluate the size ratio.

Distance to the Genu. This parameter is new and has not previously been investigated. The distance to the genu is defined as the distance between the center point of the neck of the aneurysm and the genu of the MCA.

Flow Angle. The flow angle is a variation of the aneurysm angle and vessel angle. Instead of calculating the angle with respect to the plane of the aneurysm neck, we measure the angle between the vector of the maximum height of the aneurysm and the vector of centerline of the parent vessel as determined by connecting the center points of the 2 cross-sections used to measure parent vessel diameter for the size ratio. This measurement captures the angle at which the aneurysm is tilted with respect to the vector of flow through the parent vessel.

Parent-Daughter Angle. The parent vessel–daughter vessel angle (referred to as “parent-daughter angle” henceforth) is defined as the angle formed between the vector of flow through the parent vessel and the vector of flow through the daughter vessel(s). If more than 1 daughter vessel is present, the angle associated with each daughter vessel is averaged to calculate a composite parent-daughter angle value. Of note, the parent-daughter angle is independent of the aneurysm itself and captures the context of the surrounding vasculature within which the aneurysm arises. This parameter measures the degree
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to which the blood flow through the parent vessel must deviate to emerge into the daughter vessel(s).

**Statistical Analysis**

Differences in demographic and clinical characteristics by rupture status were examined using the chi-square test and 2-tailed t-test for binary and continuous variables, respectively. Univariate analysis was performed to compare the value of each morphological parameter between the ruptured and unruptured groups. Multivariate logistic regression was used to calculate the odds ratios and 95% confidence intervals for the likelihood of aneurysm rupture after adjusting for age, sex, smoking status, family history, presence of multiple aneurysms, hypertension, and prior history of SAH. Statistical significance was defined as the probability for a Type I error being < 0.05. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc.) and Excel 2007 (Microsoft Corp.).

**Results**

Between 2005 and 2008, 132 consecutive MCA aneurysms were treated at a single institution. Six aneurysms were excluded because of reoperation (4) or associated arteriovenous malformation (2). Preoperative CTA studies were not available (originally obtained at outside hospital
and not imported to the Brigham and Women’s Hospital picture archiving and communications system) or were of poor quality in 47 aneurysms, leaving 79 aneurysms (40 ruptured and 39 unruptured) available for analysis. Demographic and clinical information of the study population is listed in Table 1. The mean patient age was 52.4 ± 12.1 years, and 58 aneurysms were harbored by women (73.4%). Patients with unruptured aneurysms were significantly more likely to have a positive family history or have experienced prior SAH (Table 1). There were also more aneurysms in women in the unruptured group than in the ruptured group (82.1% vs 65.0%), although the difference was not statistically significant.

We examined the predefined morphological parameters individually and compared their values between the ruptured and unruptured groups (Table 2). Ruptured aneurysms were associated with a greater aspect ratio (1.75 vs 1.01, p = 0.05), larger aneurysm angle (100.1° vs 86.6°, p = 0.01), larger flow angle (132.1° vs 114.3°, p = 0.002), smaller parent-daughter angle (64.4° vs 78.9°, p = 0.03), and greater size ratio (3.28 vs 2.16, p = 0.04). Aneurysm size, as estimated by the maximum cross-sectional diameter, did not significantly differ between the ruptured and unruptured groups (7.90 mm vs 5.71 mm, respectively; p = 0.09). In a multivariate logistic regression model adjusted for morphological and clinical risk factors, aspect ratio, aneurysm angle, flow angle, size ratio, and parent-daughter angle were evaluated as independent variables. The analysis showed that greater aspect ratio (p = 0.05), larger flow angle (p = 0.003), and smaller parent-daughter angle (p = 0.004) were associated with aneurysm rupture, whereas aneurysm angle (p = 0.61) and size ratio (p = 0.51) were no longer statistically significant parameters (Table 3).

We further analyzed the interactions among the morphological parameters that were different between the ruptured and unruptured aneurysms. The 2D scatterplots shown in Figs. 3 and 4 demonstrated that the size ratio could be related to the aspect ratio in a linear fashion, and a simple regression analysis yielded an R² value of 0.88 for the ruptured group and 0.82 for the unruptured group (Fig. 3A). A similar relationship also existed between the aneurysm angle and flow angle, with the R² value of 0.81 and 0.67 for the ruptured and unruptured groups, respectively (Fig. 4A). No apparent dependency was observed between other morphological variables.

Of note, 4 patients in the study population harbored bilateral MCA aneurysms. Three patients suffered SAH from 1 of the MCA aneurysms, and the remaining patient had a ruptured internal carotid artery terminus aneurysm with bilateral unruptured MCA aneurysms. Values of the morphological parameters in this subgroup of aneurysms followed a similar trend: the 3 ruptured aneurysms had a greater aspect ratio, larger flow angle, larger aneurysm angle, and smaller parent-daughter angle compared with the 5 unruptured aneurysms, although the difference was not statistically significant.

### Table 1: Demographic information and clinical risk factors for patients with MCA aneurysms

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unruptured (39 aneurysms)</th>
<th>Ruptured (40 aneurysms)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (yrs)</td>
<td>0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>53.6 ± 10.9</td>
<td>51.2 ± 13.1</td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>53.0</td>
<td>51.0</td>
<td></td>
</tr>
<tr>
<td>no. of aneurysms in women (%)</td>
<td>32 (82.1)</td>
<td>26 (65)</td>
<td>0.08</td>
</tr>
<tr>
<td>location</td>
<td>0.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lt</td>
<td>17</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>rt</td>
<td>22</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>hypertension</td>
<td>19 (48.7)</td>
<td>23 (57.5)</td>
<td>0.43</td>
</tr>
<tr>
<td>smoking</td>
<td>20 (51.3)</td>
<td>23 (57.5)</td>
<td>0.58</td>
</tr>
<tr>
<td>multiple aneurysms</td>
<td>16 (41.0)</td>
<td>10 (25.0)</td>
<td>0.13</td>
</tr>
<tr>
<td>family history</td>
<td>7 (17.9)</td>
<td>4 (10.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>prior SAH</td>
<td>12 (30.8)</td>
<td>3 (7.5)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

### Table 2: Univariate analyses for the morphological parameters measured for MCA aneurysms

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unruptured (39 aneurysms)</th>
<th>Ruptured (40 aneurysms)</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>max diameter (mm)</td>
<td>5.71 ± 2.24</td>
<td>7.90 ± 5.64</td>
<td>1.11 (0.98–1.25)</td>
<td>0.09</td>
</tr>
<tr>
<td>aspect ratio</td>
<td>1.01 ± 0.47</td>
<td>1.75 ± 0.93</td>
<td>1.97 (1.01–3.93)</td>
<td>0.05</td>
</tr>
<tr>
<td>aneurysm angle (°)</td>
<td>86.6 ± 24.1</td>
<td>100.1 ± 21.7</td>
<td>1.03 (1.01–1.05)</td>
<td>0.01</td>
</tr>
<tr>
<td>size ratio</td>
<td>2.16 ± 0.99</td>
<td>3.28 ± 2.26</td>
<td>1.46 (1.02–2.08)</td>
<td>0.04</td>
</tr>
<tr>
<td>distance to genu (mm)</td>
<td>7.1 ± 6.5</td>
<td>9.1 ± 8.8</td>
<td>1.03 (0.97–1.08)</td>
<td>0.35</td>
</tr>
<tr>
<td>vessel angle (°)</td>
<td>32.5 ± 14.4</td>
<td>32.4 ± 16.6</td>
<td>0.99 (0.97–1.03)</td>
<td>0.97</td>
</tr>
<tr>
<td>flow angle (°)</td>
<td>114.3 ± 23.3</td>
<td>132.1 ± 23.2</td>
<td>1.03 (1.01–1.06)</td>
<td>0.002</td>
</tr>
<tr>
<td>parent-daughter angle (°)</td>
<td>78.9 ± 22.9</td>
<td>64.4 ± 21.6</td>
<td>0.98 (0.96–0.99)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

### Table 3: Multivariate analyses after adjustment to clinical and morphological risk factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>aspect ratio</td>
<td>1.85 (1.58–4.54)</td>
<td>0.05</td>
</tr>
<tr>
<td>parent-daughter angle</td>
<td>0.92 (0.82–0.97)</td>
<td>0.004</td>
</tr>
<tr>
<td>flow angle</td>
<td>1.06 (1.02–1.12)</td>
<td>0.003</td>
</tr>
<tr>
<td>aneurysm angle</td>
<td>1.004 (0.95–1.10)</td>
<td>0.61</td>
</tr>
<tr>
<td>size ratio</td>
<td>1.12 (0.79–1.78)</td>
<td>0.51</td>
</tr>
</tbody>
</table>
Discussion

The rupture risk of an intracranial aneurysm depends on a number of demographic and biological factors, in addition to the size and location of the aneurysm. The natural history of an unruptured intracranial aneurysm in a specific patient should be assessed with a clear understanding of his or her medical conditions. The relationship between morphological parameters of an aneurysm and its rupture risk has only recently been systematically studied. Raghavan et al. evaluated 8 geometric factors in 27 aneurysms (9 ruptured and 18 unruptured) and found that ruptured aneurysms were associated with significantly higher aspect ratio, undulation index, and nonsphericity index. Dhar et al. defined additional parameters while studying a larger group of 45 aneurysms (20 ruptured and 25 unruptured) and reported that size ratio was the most significant predictor of aneurysm rupture. In a subsequent prospective study of 40 aneurysms (24 unruptured and 16 ruptured), Rahman et al. again reported that size ratio was the most significant predictor of aneurysm rupture. In our series of 79 MCA aneurysms (40 ruptured and 39 unruptured), we found that aspect ratio, flow angle, and parent-daughter angle were highly associated with ruptured MCA aneurysms in a multivariate logistic analysis. Ruptured aneurysms also demonstrated a tendency toward larger size and greater aneurysm angles and size ratios. These results were mostly consistent with findings from previous reports. The flow angle in the current study was essentially the summation of aneurysm angle and vessel angle defined by Dhar et al. It should come as no surprise that aneurysms projecting more in line with the direction of blood flow were subjected to more hemodynamic stress and would be more likely to rupture. Size ratio in our study was found to be higher in the ruptured aneurysm group, but it was not a significant factor in the multivariate analysis. This might be explained by the close relationship between size ratio and aspect ratio (Fig. 3A) and by the fact that the diameter of MCA branches pre- and postbifurcation is relatively large compared with other intracranial vessels, thus making the differences between size ratios less prominent. In fact, in a separate analysis, we examined similar morphological parameters in a group of anterior communicating artery aneurysms and found that size ratio was a significant predictor of aneurysm rupture (data not shown) (unpublished data).

The parent-daughter angle is a newly defined variable and has not been investigated previously. Ruptured aneu-

![Fig. 3. Scatter plots depicting the interaction between aspect ratio and other morphological parameters.](image-url)
Aneurysms were associated with smaller parent-daughter angle, which could be understood from the fluid dynamics of flow at a bifurcation. Studies using MRA have shown that wall shear stress is higher at bifurcations with smaller angles, which is consistent with the results of idealized irrotational flow at a stagnation point. Further work is required to understand the exact relationship between the size of parent-daughter angle, the stress profile on the vessel wall, and the molecular mechanism of vascular remodeling.

The 3 significant parameters found in our study (aspect ratio, flow angle, and parent-daughter angle) represent 3 distinct aspects in the hemodynamics of an aneurysm, namely, the morphology of the aneurysm itself, the interaction between the aneurysm and the associated parent and daughter vessels, and the relationship among the surrounding vasculature. Aspect ratio, defined as the maximum perpendicular height divided by the neck, characterizes the morphology of the aneurysm. It is likely that aspect ratio and size ratio are closely related, as was demonstrated by the near-linear relationship between these parameters in our analysis (Fig. 3A) and in the study by Dhar et al.3 (Fig. 4 in their study). Hence, size ratio also belongs to this category. The second kind of morphological relationship is the interaction between the direction of blood flow and the projection of the aneurysm. A variety of parameters, such as aneurysm angle, vessel angle, and flow angle, belong to this category. In contrast, the parent-daughter angle describes the geometric relationship of the surrounding angioarchitecture alone and is independent of the projection and shape of the aneurysm. The combination of all 3 morphological characteristics therefore encompasses the major aspects of the hemodynamics involved in the rupture risk of an aneurysm.

Several limitations need to be considered when interpreting these results. The study was a retrospective review of patients with MCA aneurysms who were treated either surgically or endovascularly. Patients with unruptured aneurysms who were seen in the neurosurgery clinic but were not treated were not included in the study. Therefore, there is an inherent selection bias toward morphologically “dangerous” lesions in the study population. Moreover, comparison of morphological properties between ruptured and unruptured aneurysms assumes that such parameters do not change significantly during aneurysm rupture. While surface morphology (for example, daughter domes and blebs) can be disrupted by the thrust of rupture, factors investigated in our study, such as aspect ratio, flow angle, and parent-daughter angle are less affected. In fact, surface morphology was not considered in the analysis because of the limited resolution of and variable quality of the CTA studies. In addition, 47 aneurysms were excluded because preoperative CTA studies either were not available (studies obtained at outside hospitals that were not imported into the Brigham and Women’s Hospital picture archiving and communications system) or were of poor quality. Nevertheless, the proportion of missing CTA studies was similar in the ruptured and unruptured groups and was not statistically significant (21 ruptured and 26 unruptured, p = 0.32).

Conclusions

We conducted a large study to examine the morphological properties of a specific type of aneurysm and found that aspect ratio, flow angle, and parent-daughter angle were highly associated with MCA aneurysm rupture.
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These simple morphological parameters could be used in conjunction with aneurysm size and location, as well as other demographic and clinical risk factors, to evaluate the rupture risk of MCA aneurysms. These are physically intuitive parameters and can be measured easily. They are superior to aneurysm size alone in assessing the risk of MCA aneurysm rupture, are specific to the MCA location, and can be readily applied in clinical practice.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Du, Lin, Day. Acquisition of data: Lin, Ho, Gross, Frielich. Analysis and interpretation of data: Du, Lin, Ho, Pieper. Drafting the article: Du, Lin. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Du. Study supervision: Du.

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