Size Ratio Can Highly Predict Rupture Risk in Intracranial Small (<5 mm) Aneurysms

Daina Kashiwazaki, MD; Satoshi Kuroda, MD, PhD; on behalf of the Sapporo SAH Study Group

Background and Purpose—Management strategies for unruptured intracranial aneurysms (UIAs) are controversial. This study aimed to identify surrogate parameters that highly predict the rupture risk of small (<5 mm) UIAs.

Methods—Radiological data were collected from 854 patients with aneurysmal subarachnoid hemorrhages who were enrolled in the Sapporo SAH Study. They had a total of 854 ruptured intracranial aneurysms and 180 UIAs. The size, aneurysm-to-vessel size ratio, and distribution were precisely compared between ruptured intracranial aneurysms and UIAs.

Results—For all aneurysms, the size was significantly larger in ruptured intracranial aneurysms (7.0±1.3 mm) than in the UIAs (3.7±1.2 mm; P<0.001). Size ratio was also significantly higher in ruptured intracranial aneurysms (4.3±1.9) than in the UIAs (2.2±1.6; P<0.001). Multivariate logistic analysis showed that size and size ratio were correlated with aneurysm rupture. However, in small aneurysms, multivariate logistic regression revealed that only size ratio was associated with ruptured aneurysms (P=0.008; odds ratio, 9.1). There were no significant differences in size or aneurysm location. A receiver operating characteristic analysis was performed for size ratio in small aneurysms, and the threshold separating ruptured and unruptured groups was 3.12 and the area under the curve was 0.801.

Conclusions—This study revealed that the size ratio, and not the absolute size, may highly predict the risk of rupture in small UIAs. Size ratio measurements are very simple and provide useful information for determining treatment and follow-up strategies for patients with small UIAs. (Stroke. 2013;44:2169-2173.)

Key Words: aneurysm  ■  digital subtraction angiography  ■  intracranial  ■  morphology

The decision-making process for treating unruptured intracranial aneurysms (UIAs) is still controversial. The results of the largest registries available, including the International Study on Unruptured Intracranial Aneurysms (ISUIA), have suggested that surgical or endovascular treatments are rarely justified. The rupture risk is known to increase with the increasing size of an aneurysm. However, it is quite important that a large number of patients have subarachnoid hemorrhages (SAH) as a result of the rupture of aneurysms with diameters <5 mm. For example, the incidence of anterior communicating artery (AcomA) aneurysms is significantly lower in patients with UIAs than in those with aneurysmal SAH. Very recently, the natural course of unruptured cerebral aneurysms in a Japanese cohort (UCAS Japan) has been precisely studied. Patients with a total of 6697 aneurysms were enrolled in that study. The results showed that the annual rate of rupture was 0.95%. Compared with middle cerebral artery (MCA) aneurysms, those in the anterior and posterior communicating arteries were more likely to rupture. Especially, AcomA aneurysms have been shown to rupture at a relatively high rate, even when they are <7 mm in diameter. In a majority of previous studies, however, only the absolute values of the aneurysm diameters have been used as a clinical variable when testing the risk of their rupture, suggesting the possibility that other factors have been overlooked. Thus, aneurysm size alone may not be enough to predict their rupture risk accurately. It would, therefore, be quite valuable to establish a logical stratification to better define rupture risk for clinicians. Based on these observations, this study aimed to identify the morphological parameters that more accurately discriminate the rupture of UIAs.

Patients and Methods

This study was based on the database from a prospective cohort study, the Sapporo SAH Study (SSS), which was conducted between 2003 and 2011 in Sapporo City, Japan (Appendix). The population of Sapporo City is ≈2 million. The epidemiological, demographic, and therapeutic features of aneurysmal SAH in Sapporo City have been reported before.

In this study, the clinical and radiological information of patients with aneurysmal SAH was precisely collected. Patient age and sex and the location of aneurysm were recorded. Patients with nonaneurysmal SAH were excluded. Patients with aneurysms that were related to cerebral arteriovenous malformation, arteriovenous fistula, moyamoya disease, dissection, or infection were excluded. The patients were also excluded when they had significant vaso spasms on initial cerebral angiography or when cerebral angiography was not performed...
because of the patients’ severe neurological conditions. When the patients had multiple aneurysms, ruptured intracranial aneurysms (RIAs) were identified by direct observation during surgery. All RIAs and UIAs were included in this study.

The images that were obtained with 3-dimensional angiography were used to evaluate the morphology of intracranial aneurysms accurately. Rotational digital subtraction angiographic images were acquired and transferred to a reconstructed unit. Spatial resolution was measured to evaluate the accuracy of the reconstructed images. The absolute diameters of the aneurysms and their parent vessels were independently determined by 2 experienced neurosurgeons (D.K. and S.K.). Then, the size ratio was calculated for each aneurysm. The aneurysm-to-vessel size ratio was calculated according to the method described by Dhar et al. Thus, the value was defined as the ratio of the maximum aneurysm diameter to the average vessel diameter. The average vessel diameter was obtained by measuring 2 representative vessel cross sections upstream of the aneurysm (D1a at the proximal neck and D1b at 1.5×D1a upstream). The local diameters were calculated in the same way as the neck diameters, and their average values were determined (Figure 1). The degree of agreement in the measurements of size ratios between the 2 observers was quantified with the \( \kappa \) test. In cases where the observers disagreed, the size ratio was recalculated by both observers, and a consensus was reached.

The continuous data were expressed as means±SDs. The data were compared between the 2 groups with Mann–Whitney U tests and \( \chi^2 \) tests as appropriate. To identify the independent parameters that had significant correlations with the rupture, multivariate logistic regression analyses were separately performed for all of the aneurysms and for the small (<5 mm) aneurysms. Furthermore, a receiver operating characteristic analysis was performed on the size ratios to determine the optimal thresholds that separated the ruptured and unruptured groups by calculating the area under the receiver operating characteristic curve (area under the curve).

Results

Locations and Morphologies of All Aneurysms

A total of 1153 patients with aneurysmal SAH were enrolled in the SSS between 2003 and 2011. Of these, 299 patients were excluded because of the aforementioned reasons. Finally, a total of 854 patients were included in this study. Their mean age was 58.2±10.2 years, with a range of 20 to 92 years. There were 179 men and 675 women. Of the 854 patients, 146 (17.1%) had ≥2, or multiple, aneurysms. Thus, this study included a total of 854 RIAs and 180 UIAs. The overall data for the aneurysms are shown in Table 1. The locations of the aneurysms significantly differed between RIAs and UIAs (\( \chi^2 \) test, \( P<0.001 \)). As shown in Table 1, the most frequent site for RIAs was the AcomA (n=267; 31.3%), which was followed by the MCA (n=206; 24.1%) and the internal carotid artery (ICA; n=195; 22.8%). In contrast, UIAs were most frequently found at the MCA (n=60; 33.3%), which was followed by the ICA (n=39; 21.7%), the AcomA (n=12; 6.7%), and the distal anterior cerebral artery (n=9; 5.0%).

The maximum diameter of the RIAs was significantly larger than that of the UIAs (7.0±1.3 and 3.7±1.2 mm, respectively; \( P<0.001 \)). For the next step, the size ratios were compared between the RIAs and UIAs. As a result, the size ratio was significantly higher in the RIAs than in the UIAs (4.3±1.9 and 2.2±1.6, respectively; \( P<0.001 \)). Table 1 shows the distributions of the sizes of RIAs and UIAs. There was a significant difference in the size distribution between the 2 groups (\( \chi^2 \) test, \( P<0.001 \)). However, 236 (27.6%) of the 854 RIAs were <5 mm.

The interobserver reliability of the measures of the size ratios based on the \( \kappa \) statistic for paired observers was 0.827 (95% confidence interval, 0.809–0.947). A multivariate logistic analysis showed that both the size and size ratio could predict the aneurysm (Table 1).

Size Ratio Predicts the Rupture of Small (<5 mm) Aneurysms

The radiological data were precisely analyzed for small (<5 mm) aneurysms to extract predictors of their rupture because more than one fourth of the RIAs were <5 mm in diameter. The data are summarized in Table 2. First, their size was compared between the RIAs and UIAs. There was no significant difference in the sizes between the 2 groups (3.3±1.9 and 3.2±1.7 mm, respectively; \( P=0.51 \)). Second, the size ratios were quantified for each aneurysm. As a result, the size ratio was significantly higher for the RIAs than for the UIAs (3.2±1.2 and...
The locations were compared between RIAs and UIAs. The small (<5 mm) RIAs were most frequently located in the AcomA (n=115; 48.7%), which was followed by the MCA (n=27; 11.4%), the distal anterior cerebral artery (n=25; 10.6%), and the ICA (n=15; 6.4%). In contrast, the small (<5 mm) UIAs were most frequently located in the MCA (n=61; 44.2%), which was followed by the ICA (n=19; 13.8%), the AcomA (n=6; 4.3%), and the distal anterior cerebral artery (n=2; 1.4%). There was a distinct difference in location between the small (<5 mm) RIAs and UIAs (P<0.01).

A multivariate logistic regression analysis showed that size ratio was the only significant predictor of aneurysm rupture (P=0.008; odds ratio, 9.1). A receiver operating characteristic analysis was performed on the size ratios of the small aneurysms. As a result, the threshold separating the ruptured and unruptured groups was 3.12, and the area under the curve was 0.801. The receiver operating characteristic curve is shown in Figure 3.

### Table 1. Summary of Statistic Data in Ruptured and Unruptured Intracranial Aneurysms

<table>
<thead>
<tr>
<th></th>
<th>RIA</th>
<th>UIA</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.2±10.2</td>
<td>59.6±9.2</td>
<td>P=0.341</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>179</td>
<td>41</td>
<td>P=0.588</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>675</td>
<td>139</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of aneurysms</td>
<td>854</td>
<td>180</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location of aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA (%)</td>
<td>195 (22.8)</td>
<td>39 (21.7)</td>
<td>P&lt;0.001</td>
<td>P=0.089</td>
<td></td>
</tr>
<tr>
<td>MCA (%)</td>
<td>206 (24.1)</td>
<td>60 (33.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AcomA (%)</td>
<td>267 (31.3)</td>
<td>12 (6.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal ACA (%)</td>
<td>38 (4.4)</td>
<td>9 (5.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others (%)</td>
<td>148 (17.3)</td>
<td>60 (33.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm size, mm (mean±SD)</td>
<td>7.0±1.3</td>
<td>3.7±1.2</td>
<td>P&lt;0.001</td>
<td>P=0.018</td>
<td>3.2 (2.3–14.1)</td>
</tr>
<tr>
<td>SR (mean±SD)</td>
<td>4.3±1.9</td>
<td>2.2±1.6</td>
<td>P&lt;0.001</td>
<td>P=0.014</td>
<td>5.1 (2.1–19.1)</td>
</tr>
</tbody>
</table>

Distribution of aneurysm size

- 2–5 mm (%) : 236 (27.6) 138 (76.7)
- 5–10 mm (%) : 492 (57.6) 33 (18.3)
- 10–15 mm (%) : 77 (9.0) 5 (2.8)
- 15–24 mm (%) : 44 (5.1) 4 (2.2)
- 25 mm (%) : 5 (0.6) 0 (0.0)

ACA indicates anterior cerebral artery; AcomA, anterior communicating artery; CI, confidence interval; ICA, internal carotid artery; MCA, middle cerebral artery; OR, odds ratio; RIA, ruptured intracranial aneurysm; SR, size ratio; and UIA, unruptured intracranial aneurysm.

### Table 2. Summary of Statistic Data in Ruptured and Unruptured Small (<5 mm) Aneurysms

<table>
<thead>
<tr>
<th></th>
<th>RIA</th>
<th>UIA</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.2±11.9</td>
<td>60.6±12.1</td>
<td>P=0.289</td>
<td></td>
<td></td>
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<tr>
<td>Sex</td>
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</tr>
<tr>
<td>Male</td>
<td>47</td>
<td>29</td>
<td>P=0.799</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>189</td>
<td>109</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of aneurysms</td>
<td>236</td>
<td>138</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm size, mm (mean±SD)</td>
<td>3.3±1.9</td>
<td>3.2±1.7</td>
<td>P=0.510</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR (mean±SD)</td>
<td>3.2±1.2</td>
<td>2.2±1.2</td>
<td>P&lt;0.01</td>
<td>P=0.008</td>
<td>9.1 (3.1–15)</td>
</tr>
</tbody>
</table>

Location of aneurysm

- ICA (%) : 15 (6.4) 19 (13.8) P<0.001 P=0.109
- MCA (%) : 27 (11.4) 61 (44.2)
- AcomA (%) : 115 (48.7) 6 (4.4)
- Distal ACA (%) : 25 (10.6) 2 (1.4)
- Other (%) : 54 (22.9) 50 (36.2)

ACA indicates anterior cerebral artery; AcomA, anterior communicating artery; CI, confidence interval; ICA, internal carotid artery; MCA, middle cerebral artery; OR, odds ratio; RIA, ruptured intracranial aneurysm; and UIA, unruptured intracranial aneurysm.
Finally, the size ratios were compared between the unruptured and ruptured aneurysms in each location. As a result, the values were significantly different between the 2 groups in all locations (Table 3).

**Discussion**

In this study, radiological findings were compared between the RIAs and UIAs in patients with aneurysmal SAH. The results of this study revealed that the RIAs were significantly larger than the UIAs. Their location also differed between them. More than 30% of the RIAs were located in the AcomA, whereas only 6.7% of the UIAs were found in the AcomA. These findings correlated very well with those of previous multicenter studies, including the ISUIA and UCAS Japan. Thus, the risk of aneurysm rupture is closely related to aneurysm site, size, morphology, blood flow hemodynamics, and history. Of these, aneurysm size and morphology are quite important parameters for predicting rupture. The ISUIA has concluded that the annual rupture risk of UIAs that are ≤6 mm in diameter is very low (0.069%) when the subjects do not have a history of aneurysmal SAH. However, the risk increases to 2.6% when the aneurysm size is >7 mm. Thus, compared with UIAs that are 3 to 4 mm in diameter, the risk of rupture significantly increases for all aneurysms that are ≥7 mm. Similar results have been reported before. In addition, information on the sizes of the UIAs is enough to discuss the risk of their rupture when their diameter is >5 mm.

However, it should be noted that a certain subgroup of small (<5 mm) UIAs also had a risk of subsequent rupture. In fact, this study clearly demonstrated that ≈30% of RIAs had a small (<5 mm) diameter. Sonobe et al have reported that the annual risk of rupture is 0.54% in 448 small (<5 mm) UIAs. The value is 0.34% for single aneurysms and 0.95% for multiple aneurysms. The value for multiple aneurysms is almost the same as that for all of the UIAs in UCAS Japan. Therefore, it is quite important to identify an alternative marker that more highly predicts the rupture risk of small (<5 mm) UIAs than before. In this study, there was no significant difference in size between the small (<5 mm) UIAs and the RIAs. However, the size ratio was significantly higher in the small (<5 mm) RIAs than in the small (<5 mm) UIAs. These findings strongly suggested that the UIAs that arise from distal or small parent arteries may have a higher risk of rupture than those that arise from proximal or larger parent arteries, even when they have the same diameters. In fact, a majority of previous large studies have used the maximum diameter of aneurysms as a predictor for defining their size. However, several investigators have attempted to find a better geometric index than the absolute maximum size to determine the risk of rupture. For example, Dhar et al have proposed size ratios as a new index for predicting aneurysmal rupture. They precisely analyzed the radiological findings of 25 UIAs and 20 RIAs and found that the aneurysm-to-vessel size ratio and the aneurysm inclination angle were the most reliable factors for predicting their rupture. However, the odds ratio was not very high (1.41; 95% confidence interval, 1.03–1.92), which probably was because they included aneurysms with diameters that were >5 mm. The sample size was also rather small. In addition, they obtained data from 25 patients with UIAs and 20 different patients with RIAs, indicating that other systemic factors may also affect the risk of rupture. Subsequently, they have reported similar results. The present study further...
advanced the clinical significance of the size ratio by applying the index on only small (<5 mm) aneurysms that were thought to have a very low risk of rupture. The hypothesis may be quite natural because 3-mm diameter UIAs that arise from the distal anterior cerebral artery seem to more readily rupture than 3-mm diameter UIAs that arise from the ICA. In fact, the present study revealed that about half of the small (<5 mm) RIAs was located in the AcomA, whereas only 4.3% of small (<5 mm) aneurysms was found in the AcomA. According to the UCAS Japan, the annual rate of rupture is 0.23 in 3- to 4-mm diameter aneurysms that arise from the MCA, but it is 0.90 for same-diameter aneurysms that arise from the AcomA. Therefore, the size ratio should be taken into consideration when we predict the outcome of patients with small (<5 mm) UIAs. This novel information will help to determine treatment and follow-up strategies for patients with small (<5 mm) UIAs.

This study was characterized by a larger sample size (n=1134) than previous studies. In addition, both RIAs and UIAs were collected from patients with only aneurysmal SAH. However, it should be noted that the shape and size of aneurysms may change after their rupture, although the radiological findings for the RIAs were obtained in the acute phase of the SAH. Previous studies have suggested that aneurysms often reduce their size after rupture. It should be noted that the results were retrospective observations that still require validation. Future prospective studies are warranted to validate them.

Conclusions

The present study revealed that the size ratio, and not the absolute size, may highly predict the risk of rupture in small (<5 mm) UIAs. Size ratio measurements are very simple and provide useful information in determining treatment and follow-up strategies for patients with small (<5 mm) UIAs.

Appendix

The clinical data of the Sapporo SAH Study were collected from the following hospitals: Hokkaido University Hospital (Satoshi Kuroda, Duina Kashiwazaki, Takeshi Asano, Naoki Nakayama, Shunsuke Terasaka, Tatsuya Ishikawa, Yoshinobu Iwasaki), Sapporo Asah Neurosurgical Hospital (Hiroshi Yasuda, Hisatoshi Saito), Kashiwaba Neurosurgical Hospital (Tetsuyuki Yoshimoto), Teine Keijinkai Hospital (Yuka Yokoyama, Ken Kazumata, Satoshi Ushikoshi), Koji Ito, Mitsuuru Nunomura), Hokkaido Neurosurgical Memorial Hospital (Takeshi Aoki), Otaru City Hospital (Yoshimasa Niiya, Shoji Mabuchi), Kiiwaki Ebetsu Hospital (Toru Kobayashi, Mikio Nomura), and Chitose City Hospital (Shugo Takigawa).

Disclosures

None.

References

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