Intracranial Aneurysm Enlargement on Serial Magnetic Resonance Angiography
Frequency and Risk Factors

Joseph D. Burns, MD; John Huston, III, MD; Kennith F. Layton, MD; David G. Piepgras, MD; Robert D. Brown, Jr, MD

Background and Purpose—Size of an unruptured intracranial aneurysm (UIA) may be an important risk factor for rupture. Accordingly, serial noninvasive imaging is commonly used to assess untreated UIA for enlargement. Few data exist regarding the frequency and predictors of enlargement. We obtained this information from a group of patients followed with serial MR angiography (MRA).

Methods—We retrospectively identified 165 patients with 191 UIA followed with serial MRA. Fusiform aneurysms, UIA <2 mm, and UIA that were surgically or endovascularly treated before the first MRA were excluded. MRA was performed using 1.5-T and 3-T MRI. Maximal diameter was determined on MRA source images. Multivariate regression analysis was used to determine independent risk factors for growth.

Results—Twenty aneurysms (10%) grew over a median follow-up period of 47 months. Frequency of enlargement was 6.9%, 25%, and 83% for aneurysms <8 mm, 8 to 12 mm, and ≥13 mm, respectively (P <0.001 for trend). Of the variables we evaluated, original aneurysm diameter (OR, 1.28 per mm; 95% CI, 1.07 to 1.58) was the only independent predictor of enlargement. Aneurysms ≥8 mm in diameter were at highest risk for enlargement (OR, 7.25; 95% CI, 1.96 to 27.1). There was a trend toward increased risk of enlargement in patients with multiple aneurysms (OR, 2.50; 95% CI 0.86 to 7.53).

Conclusions—Over a median follow-up period of 47 months, 10% of UIA enlarged. Larger aneurysms had a significantly increased risk of enlargement. The likelihood of enlargement was highest in aneurysms with diameters ≥8 mm. However, a clinically significant proportion of small aneurysms grow, and this growth can be detected by serial MRA. (Stroke. 2009;40:406-411.)

Key Words: enlargement ■ magnetic resonance angiography ■ risk factors ■ unruptured intracranial aneurysm

Intracranial aneurysms are common, with autopsy and imaging studies reporting frequencies of aneurysm detection of 1% to 9%1,2 and 0.5% to 2%,3,4 respectively. In a population-based study, the prevalence of intracranial aneurysms was 83.4 per 100 000 persons.5 On the basis of these data, it can be estimated that at least 3 to 6 million people in the United States have an intracranial aneurysm.

Because a subset of these aneurysms cause approximately 80% of subarachnoid hemorrhage cases,6 selected unruptured intracranial aneurysms (UIAs) are often treated using surgical and endovascular techniques. These treatments, however, are associated with a significant degree of morbidity and mortality.7 Ideally then, only aneurysms with a high risk of rupture that outweighs the risk of treatment would undergo a corrective procedure. For those patients selected for conservative management, questions arise regarding the need for repeat imaging during follow-up. The decision to repeat imaging is typically driven by concern that the aneurysm might enlarge or otherwise change in appearance, thus potentially portending an increased risk of future rupture. This strategy raises important questions regarding aneurysm enlargement. What is the frequency of enlargement for UIA? What characteristics of patient and aneurysm affect this frequency?

Relatively few data are available to answer these questions, leaving clinicians with little guidance in determining the optimal surveillance strategy in patients with UIA. Four existing studies have used noninvasive imaging techniques to address these questions.8–11 Of these, only 2,9,10 including an earlier study from our institution, have exclusively used MR angiography (MRA), and only one has used multivariate analysis in the identification of risk factors for enlargement.9 We sought to provide further information about the frequency and predictors of enlargement of conservatively managed
aneurysms by retrospectively analyzing serial MRA and clinical data in 165 patients with UIA.

Methods
We retrospectively identified 165 patients with 191 unruptured intracranial saccular aneurysms who were followed with serial MRA between 1987 and 2006. Fifty-seven of these patients (62 aneurysms) were included in the earlier study of similar design.10 Fusiform, mycotic, and traumatic aneurysms and UIA that were surgically or endovascularly treated before the first MRA were excluded. UIA measured at 5 mm or more on a follow-up MRA.

Clinical Data
Clinical data were obtained by a review of medical records performed by one of the authors (J.D.B.). Collected data included demographic information such as date of birth, gender, and race. We also recorded putative risk factors for subarachnoid hemorrhage and aneurysm formation: personal history of subarachnoid hemorrhage, history of subarachnoid hemorrhage in a first-degree relative, total number of known intracranial aneurysms at the time of the first MRA and were therefore also excluded. All included patients had at least 2 MRA examinations separated by at least 12 months. The study was approved by the Mayo Foundation Institutional Review Board.

Aneurysm Measurement Technique
MRA was used to determine aneurysm number, location, and size. All MRA interpretations were performed by 2 neuroradiologists (J.H., K.F.L.). The location of an aneurysm was defined as extradural or intradural on the basis of its relationship to the ophthalmic artery. The name used to describe the aneurysm was based on the junction or intradural on the basis of its relationship to the ophthalmic artery. The aneurysms were independently measured on a workstation (Advantage Windows; General Electric Medical Systems) to the nearest 0.1 mm and the average between the 2 readers used for analysis. Aneurysm size was determined in the transverse plane on the axial source images to be the largest diagonal measurement, including any appendages. The superior–inferior dimension was determined by the number of axial source images that included the aneurysm multiplied by 0.7 mm (the reconstructed axial slice thickness). Final aneurysm size was defined as the larger of the transverse or superior–inferior measurements. Results that differed by 1 mm or more were adjudicated by consensus. The investigators who performed the interpretations were blinded to previous measurements of the lesion, clinical history of the patient, and any available conventional angiography findings. Aneurysms <5 mm in diameter were considered to have enlarged if the maximum transverse measurement had increased by ≥1 mm on a follow-up MRA. Aneurysms ≥5 mm were considered to have enlarged if the maximum transverse measurement had increased by ≥2 mm on a follow-up MRA.

MR Angiography Technique
Time of flight MRA was performed on 1.5- and 3.0-T MR imagers (General Electric Medical Systems). The sequences included 3 axial slabs of 32 sections per slab with 1.4-mm thick sections yielding an imaging volume extending from the posterior inferior cerebellar arteries to the bifurcation of the pericallosal and callosal marginal arteries. Imaging parameters for 1.5 T included: TE 6.9 ms, TR 38 ms, flip angle 25°, matrix 256 x 224, and field of view 18 cm. Imaging parameters for 3.0 T included: TE 38 ms, TR 3.4 ms, flip angle 25°, matrix 288 x 224, and field of view 18 cm. For both the 1.5- and 3.0-T acquisitions, a ramped radiofrequency pulse and 3-directional zero-filling were used.

Statistical Analysis
Clinical and MRA variables were described statistically as appropriate for the data. Mean diameters of cavernous and intradural aneurysms were compared using the Wilcoxon rank sum test. Univariate logistic regression analysis was performed to investigate potential associations between these variables and UIA enlargement. Those parameters that yielded a probability value <0.2 in the univariate analysis were combined with duration of follow-up in a multivariate logistic regression analysis. All analyses were carried out using individual aneurysms as the unit of observation. Although this could lead to confounded results in the logistic regression analyses by oversampling data from patients with multiple aneurysms, we chose this method because our central question concerned the likelihood of growth of individual aneurysms. A 2-sided probability value of <0.05 was considered statistically significant. All analyses were performed using JMP version 6.0 (SAS Institute Inc, Cary, NC).

Results
Patient and aneurysm characteristics are summarized in Tables 1 and 2, respectively.

Table 1. Summary of Patient-Specific Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With Aneurysm Enlargement (n=17)</th>
<th>Patients Without Aneurysm Enlargement (n=148)</th>
<th>All Patients (n=165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean±SD</td>
<td>69±8.9</td>
<td>63±13</td>
<td>64±13</td>
</tr>
<tr>
<td>Female gender</td>
<td>14 (82%)</td>
<td>106 (72%)</td>
<td>120 (73%)</td>
</tr>
<tr>
<td>Smoking, past or current*</td>
<td>8/16 (50%)</td>
<td>83/144 (58%)</td>
<td>91/160 (57%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (71%)</td>
<td>104 (70%)</td>
<td>116 (70%)</td>
</tr>
<tr>
<td>History of aneurysm rupture</td>
<td>1 (5.9%)</td>
<td>11 (7.4%)</td>
<td>12 (7.3%)</td>
</tr>
<tr>
<td>Family history of SAH*</td>
<td>4/16 (25%)</td>
<td>16/147 (11%)</td>
<td>20/163 (12%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3 (18%)</td>
<td>19 (13%)</td>
<td>22 (13%)</td>
</tr>
<tr>
<td>ADPKD</td>
<td>1 (5.9%)</td>
<td>16 (11%)</td>
<td>17 (10%)</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>0</td>
<td>8 (5.4%)</td>
<td>8 (4.8%)</td>
</tr>
<tr>
<td>Multiple aneurysms</td>
<td>10 (59%)</td>
<td>36 (24%)</td>
<td>46 (28%)</td>
</tr>
</tbody>
</table>

*Data concerning these variables were unavailable for some patients.
SAH indicates subarachnoid hemorrhage; ADPKD, autosomal-dominant polycystic kidney disease; IQR, interquartile range.
Interobserver agreement for the determination of growth was excellent (κ = 0.942). The occurrence of aneurysm enlargement for all aneurysms was 10% (20 of 191). When cavernous carotid aneurysms were excluded, thus restricting the analysis to only intradural aneurysms, the occurrence of enlargement over the study period was 8% (14 of 172). There was a trend toward larger original diameters for cavernous carotid aneurysms compared with aneurysms in all other locations (mean ± SD, 7.1 ± 4.6 mm versus 4.9 ± 2.0 mm; P = 0.07).

The likelihood of enlargement increased with larger original diameter: enlargement was noted in 6.9% (12 of 173; 95% CI, 4.0% to 12%) of aneurysms with original diameter <8 mm, 25% (3 of 12; 95% CI, 8.9% to 53%) in the 8- to 12-mm group, and 83% (5 of 6; 95% CI, 44% to 97%) for aneurysms ≥13 mm in diameter. This trend was statistically significant (P < 0.001). In addition, although 17% (12 of 69; 95% CI, 10% to 28%) of aneurysms in patients with a history of multiple aneurysms, increased original diameter, and location on the cavernous carotid artery; aneurysms in the intradural anterior circulation were significantly less likely to grow. We also performed an analysis of patient-specific risk factors using individual patients as the unit of observation to determine if oversampling from patients with multiple aneurysms in the by-aneurysm analysis led to false associations between these variables and enlargement. Age was statistically insignificant in this analysis. Otherwise, results for all other variables were similar to those obtained in the by-aneurysm analysis.

Ten aneurysms in 8 patients were treated by surgical or endovascular methods after the second MRA examination. Of these, 8 had demonstrated enlargement before treatment. The median size of these aneurysms was 7.7 mm.

### Table 2. Summary of Aneurysm-Specific Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aneurysms With Enlargement (n = 20)</th>
<th>Aneurysms Without Enlargement (n = 171)</th>
<th>All Aneurysms (n = 191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time, months</td>
<td>Median, IQR 56.0, 39.3–88.5</td>
<td>47, 25–73</td>
<td>47, 25–74</td>
</tr>
<tr>
<td></td>
<td>Range 14–126</td>
<td>12–171</td>
<td>12–171</td>
</tr>
<tr>
<td>Aneurysm diameter, mm</td>
<td>Median, IQR 5.5, 3.9–12.2</td>
<td>4.8, 3.2–6.0</td>
<td>4.9, 3.4–6.0</td>
</tr>
<tr>
<td></td>
<td>Range 2.75–18.4</td>
<td>2–13.5</td>
<td>2.0–18.4</td>
</tr>
<tr>
<td>Original diameter &lt;8 mm</td>
<td>12 (60%)</td>
<td>161 (94%)</td>
<td>173 (91%)</td>
</tr>
<tr>
<td>Original diameter 8–12 mm</td>
<td>3 (15%)</td>
<td>9 (5.2%)</td>
<td>12 (6.3%)</td>
</tr>
<tr>
<td>Original diameter ≥13 mm</td>
<td>5 (25%)</td>
<td>1 (0.6%)</td>
<td>6 (3.1%)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavernous carotid artery</td>
<td>6 (30%)</td>
<td>13 (7.6%)</td>
<td>19 (9.9%)</td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>10 (50%)</td>
<td>139 (81%)</td>
<td>149 (78%)</td>
</tr>
<tr>
<td>ACA</td>
<td>0</td>
<td>6 (3.5%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>ICA</td>
<td>1 (5%)</td>
<td>47 (27%)</td>
<td>48 (25%)</td>
</tr>
<tr>
<td>MCA</td>
<td>7 (35%)</td>
<td>49 (29%)</td>
<td>56 (29%)</td>
</tr>
<tr>
<td>ACom</td>
<td>1 (5%)</td>
<td>23 (13%)</td>
<td>24 (13%)</td>
</tr>
<tr>
<td>PCom</td>
<td>1 (5%)</td>
<td>14 (8.1%)</td>
<td>15 (7.9%)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>4 (20%)</td>
<td>19 (11%)</td>
<td>23 (12%)</td>
</tr>
<tr>
<td>PCA</td>
<td>1 (5%)</td>
<td>5 (2.9%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>BA</td>
<td>3 (15%)</td>
<td>9 (5%)</td>
<td>12 (6.3%)</td>
</tr>
<tr>
<td>SCA</td>
<td>0</td>
<td>3 (1.8%)</td>
<td>3 (1.6%)</td>
</tr>
<tr>
<td>PICA</td>
<td>0</td>
<td>2 (1.2%)</td>
<td>2 (1.0%)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; ACom, anterior communicating artery; PCom, posterior communicating artery; PCA, posterior cerebral artery; BA, basilar artery; PICA, posterior inferior cerebellar artery.

In a multivariate logistic regression analysis (Table 4), the only independent predictor of aneurysm enlargement was original diameter (OR, 1.27 per mm; 95% CI, 1.05 to 1.57; P = 0.01). By substituting diameter as a dichotomous variable in place of diameter as a continuous variable into this model and sequentially increasing the cutoff size by 1 mm, we found that a diameter of ≥8 mm was a strong independent predictor of growth (OR, 6.13; 95% CI, 1.63 to 23.0; P = 0.003). This substitution did not significantly change the results for the remainder of the variables in the model. In the multivariate model, there was a trend toward an increased risk of enlargement in patients with multiple aneurysms (OR, 2.50; 95% CI, 0.86 to 7.53; P = 0.09).

Ten aneurysms in 8 patients were treated by surgical or endovascular methods after the second MRA examination. Of these, 8 had demonstrated enlargement before treatment. The median size of these aneurysms was 7.7 mm. One aneurysm
from the cohort ruptured. It was located on the posterior communicating artery and had enlarged from 6 mm to 9.4 mm over 100 months. Before rupture, this patient developed an ipsilateral posterior cerebral artery aneurysm that grew from 4.9 mm to 5.6 mm over 62 months. Our follow-up information regarding aneurysm rupture is, however, incomplete. Many of the patients included in this study were referred from geographically distant locations. Because our clinical data were obtained by reviewing medical records at only our institution, it is possible that other aneurysms ruptured and were either treated locally or led to the patient’s death.

Discussion

We report on the frequency of and risk factors for enlargement as measured by serial MRA in the largest collection of aneurysms evaluated for this purpose to date in the English language literature. Strengths of our study include the large number of patients and aneurysms, rigorous measurement techniques applied by neuroradiologists, strictly and clearly defined criteria for enlargement, and the use of multivariate logistic regression models. We found that aneurysm enlargement occurred in one in 10 aneurysms and that larger size, particularly a diameter ≥8 mm, was predictive of future enlargement. We also showed that even small aneurysms...
carry a clinically relevant risk of enlargement. As well, there was a statistically nonsignificant trend toward increased risk of enlargement in patients with multiple aneurysms. These data suggest that serial MRA monitoring of aneurysms should be considered for all patients with conservatively managed UIA and that those with larger and perhaps multiple aneurysms should be imaged more frequently.

In our cohort, the proportion of aneurysms that enlarged over a median follow-up period of 47 months was one in 10. This is almost identical to the 10.8% frequency of enlargement over a mean of 29.3 months reported by Miyazawa et al.9 Wermer et al found a lower frequency of enlargement of 3.2%, but their study included only aneurysms with diameters <5 mm and had a shorter medial follow-up time of only 1.3 years.11 In a study that used serial CT angiography to assess aneurysm growth, Matsubara et al described a frequency of enlargement of 6.4% over a mean of 17.7 months.8 Bleb formation was included in their definition of enlargement, making comparison of these results to those of the present study problematic.

The most striking finding from the current study is the independent effect of size on an aneurysm’s risk for future enlargement (OR, 1.27 per mm; 95% CI, 1.05 to 1.57). Aneurysms ≥8 mm in diameter were particularly likely to enlarge with an OR of 6.13 (95% CI, 1.63 to 23.0). Aneurysm diameters of ≥5 mm and ≥10 mm have been shown to be predictive of enlargement in 2 studies from other centers that have examined this relationship.

In a previous study of this topic from our institution that included 57 of the patients (62 aneurysms) included in the present study, we reported a frequency of enlargement of 7% over a median duration of follow-up of 47 months and that diameter ≥9 mm was a significant risk factor for growth.10 These findings are similar to those of the present study. However, whereas no aneurysm <9 mm enlarged in the earlier study, we found in the present group that 6.9% of aneurysms <8 mm enlarged. This difference possibly stems from a combination of the inclusion of more patients in the present study as well as improvement in MRA technology since the first study, which might have better allowed for detection of enlargement. Other studies have also shown that an important proportion of small aneurysms grow.8,11 This suggests that even small aneurysms should be carefully followed with serial noninvasive imaging.

Miyazawa et al found that the presence of multiple aneurysms was a strong independent risk factor for aneurysm enlargement,9 whereas Wermer et al found a significant association between these factors on univariate analysis.11 There was a trend toward statistical significance for the presence of multiple aneurysms at the time of first MRA as an independent predictor for future enlargement in the current study (P=0.09). Interestingly, when our definition of multiple aneurysms is changed to include all aneurysms noted at any time during the study period, this variable becomes strongly and independently associated with enlargement (OR, 4.24; 95% CI, 1.42 to 14.5; P=0.01) without otherwise affecting the multivariate model. Another study, however, did not find a history of multiple aneurysms to be predictive of enlargement.8 Accordingly, the usefulness of a history of multiple aneurysms in predicting aneurysm enlargement is uncertain and deserves further study.

In contrast to some earlier studies, we did not find aneurysm location to be an important predictor of enlargement. Location at the tip of the basilar artery was predictive of enlargement in the study by Matsubara et al.8 However, because multivariate analysis was not performed, it is not clear if this effect is independent of other variables, most notably size. Miyazawa et al reported location on the middle cerebral artery to be a risk factor for growth.9 Although we found that location on the cavernous carotid artery and in the anterior circulation were correlated positively and negatively, respectively, with enlargement in the univariate analysis, location was not a significant predictor in the multivariate analysis. This might be because size and location are confounded variables in this selected group of conservatively managed patients.

We found that traditional risk factors for aneurysm formation and rupture such as female gender, smoking, and hypertension were not associated with enlargement.13,14 These findings are in agreement with other studies that have investigated the topic8,9,11 and suggest, as pointed out by Matsubara,8 that aneurysm growth might be a separate process from formation and rupture.

Although conventional angiography remains the gold standard for aneurysm detection, the risks associated with it make it undesirable for use in serial observation.19 Thus, noninvasive techniques are often used to follow UIA. The present study shows that MRA is an effective tool for this purpose. The sensitivity of 1.5-T MRA in the detection of intracranial aneurysms has been demonstrated to be between 79% and 97%.16–18 Its sensitivity is equivalent to that of CT angiography and is dependent on aneurysm size with one study suggesting a minimum size of 5 mm for a clinically useful degree of sensitivity for both techniques.18 Three-Tesla MRA is becoming more widely available and has been shown to be superior to 1.5 T in depiction of intracranial aneurysms.19 This might increase the sensitivity of detection of small aneurysms as well as the accuracy of the determination of size and enlargement.

Several potential limitations of the present study should be noted. This is a retrospective analysis, which could have caused biased selection of patients who underwent follow-up MRA. Specifically, in this group of patients with small aneurysms that went largely untreated, we might have underestimated the risk of enlargement in all patients with aneurysms. However, this group is probably representative of the population of patients to whom this study’s findings are most applicable. A second limitation is the inclusion of patient-specific data in analyses that used aneurysms as the unit of observation. This could confound the univariate and multivariate analyses by oversampling patient-specific data from patients with multiple aneurysms. As demonstrated by the similar results in the by-aneurysm and by-patient univariate analyses, however, this effect is likely minimal. Our study is also limited by variable duration of follow-up. However, this measurement was not significantly associated with enlargement in either the univariate or multivariate analysis. Finally, the small number of aneurysms with enlargement included in
In conclusion, we have shown that 10% of UIA followed by serial MRA will enlarge over a period of approximately 4 years and that original aneurysm diameter as measured from MRA source images is an independent predictor for enlargement. Our data also suggest that even small aneurysms can enlarge during follow-up and that aneurysms in patients with multiple aneurysms might be at increased risk of enlargement. Although it is not presently known if aneurysm enlargement is predictive of a heightened risk of future rupture, because of the concern that the walls of growing aneurysms have not reached a steady state, enlarging aneurysms are more likely to be aggressively treated. Taking this into consideration, this study suggests that when a UIA is managed without surgical or endovascular treatment, intermittent imaging using MRA should be considered for all patients with more frequent imaging in patients with aneurysms ≥8 mm.

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Disclosures
None.

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12. Deleted in proof.
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