Irregular Shape of Intracranial Aneurysm Indicates Rupture Risk Irrespective of Size in a Population-Based Cohort

Antti E. Lindgren, MD, PhD; Timo Koivisto, MD, PhD; Joel Björkman, MB; Mikael von und zu Fraunberg, MD, PhD; Katariina Helin, RN; Juha E. Jääskeläinen, MD, PhD; Juhana Frösen, MD, PhD

Background and Purpose—Size and shape of saccular intracranial aneurysms (sIAs) reflect the condition of the sIA wall and were risk factors for rupture in previous follow-up studies. We investigated how well size or shape identify rupture-prone sIAs.

Methods—In a population-based registry, we investigated the characteristics of ruptured sIAs treated in a single neurosurgical center (1980–2014). In addition to univariable analysis, logistic regression was used in multivariable analysis, and sensitivity and specificity of size or shape were calculated using receiver operating characteristic curves.

Results—Ruptured sIAs were on average larger than unruptured sIAs (median, 7 versus 4 mm; P<0.000), but location and patient background affected the size at rupture. Of the ruptured sIAs, 38% were smaller than 7 mm and 18% were smaller than 4 mm. Of those sIAs that had ruptured at a small (<7 mm) size, 87% had an irregular shape. In multivariable analysis, irregular shape had the strongest association with presentation as ruptured sIA (odds ratio, 7.1; 95% confidence interval, 6.0–8.3), with better sensitivity (91%) and specificity (76%), in contrast to smoking (odds ratio, 0.7; 95% confidence interval, 0.6–0.9; sensitivity, 28%; specificity 57%) and Population, Hypertension, Age, Size of sIA, Earlier SAH from another sIA, Site of sIA score (odds ratio, 1.5; 95% confidence interval, 1.4–1.6).

Conclusions—Irregular or multilobular shape is strongly associated with rupture in sIAs of all sizes and independent of location and patient background. Especially sIAs with irregular shape should be considered as high rupture risk lesions, even if small in diameter and in nonsmoking patients with low PHASES scores. (Stroke. 2016;47:1219-1226. DOI: 10.1161/STROKEAHA.115.012404.)

Key Words: aneurysm ■ intracranial aneurysm ■ registries ■ rupture ■ subarachnoid hemorrhage

Rupture of a saccular intracranial aneurysm (sIA) causes a devastating form of stroke, with a 27% mortality at 12 months after acute admission. Therefore, unruptured sIAs, when diagnosed, are often occluded to prevent rupture although current endovascular and microsurgical interventions carry a non-negligible risk of morbidity (5%–7%) and mortality (1%–2%). Because unruptured sIAs are relatively common (an estimated prevalence of 3%) and many of them never rupture (only one third in a cohort with lifelong follow-up), it is paramount to find diagnostic markers that identify rupture-prone sIAs from stable ones with sufficiently high positive and negative predictive value to focus interventions on those sIAs that need them.

Several patient-related and aneurysm-related risk factors of sIA rupture have been identified (Table). Of these, the size and shape of the aneurysm are of particular interest because change in them may reflect changes in the structure of the sIA wall. Structure of the sIA wall varies among sIAs, and degenerative remodeling of the sIA wall has been shown to associate with sIA rupture. Moreover, structure of the sIA wall determines its mechanical strength, which ultimately determines whether the sIA will rupture under the mechanical load imposed on it by blood pressure and flow.

Increase in sIA size has been shown to increase the risk for sIA rupture in the International Study of Unruptured Intracranial Aneurysms that followed a selected cohort of unruptured sIAs in patients of different ethnicity and found a significant risk of rupture in sIAs ≥7 mm but a low risk of rupture in sIAs <7 mm. Larger size increased the risk of rupture also in the Japanese (Unruptured Cerebral Aneurysm Study [UCAS]) and Finnish natural history studies. Observational studies, however, demonstrate that a significant portion of those sIAs that ruptured did so...
at a small size, especially if located at the anterior communicating artery.\textsuperscript{13,14} Also aneurysms at other locations do rupture at a small size (<7 mm), as clearly demonstrated in a single institution series of 1309 consecutive middle cerebral artery (MCA) aneurysms, in which 29% of the 407 ruptured MCA sIAs were <7 mm at the time of rupture.\textsuperscript{15} This controversy between the natural history follow-up studies and observational series suggests that the degenerative remodeling of the sIA wall that ultimately leads to sIA rupture does not necessarily manifest as sIA growth or large sIA size. Follow-up studies in the Japanese and Finnish populations confirm this.\textsuperscript{5,7–10} Additional diagnostic markers for a degenerated rupture-prone sIA wall are therefore needed especially for those small sIAs that are rupture prone despite their small size.

Irregular shape of the sIA and secondary protrusion in the aneurysm main sac may reflect focal weakening of the sIA wall, as suggested by 4-dimensional (4D) computed tomographic angiography studies that demonstrate protrusion of secondary aneurysms from the main sIA sac during peak mechanical stress at systole.\textsuperscript{16} Irregular shape strongly associates with sIA rupture in large observational series\textsuperscript{15} and was an independent predictor of rupture risk in the Japanese natural history study.\textsuperscript{7} In the Japanese follow-up study that focused on the natural history of small (<7 mm) unruptured sIAs, those sIAs that developed secondary protrusions were treated, so the predictive value of irregular shape as marker to distinguish rupture-prone sIAs among small sIAs remains undetermined.\textsuperscript{4} Risk scores combining multiple risk factors to predict the rupture of unruptured sIAs have been developed, such as Population, Hypertension, Age, Size of sIA, Earlier SAH From Another sIA, Site of sIA (PHASES)\textsuperscript{17} and the Unruptured Intracranial Aneurysm Treatment Score (UIATS).\textsuperscript{18}

To determine the usefulness of size and irregular sIA shape as markers of an unstable rupture-prone sIA wall at different locations and in different patient subpopulations, we studied an unselected consecutive series of ruptured and unruptured saccular nonmycotic aneurysms diagnosed and treated 1980 to 2014 in the Kuopio University Hospital (KUH). We focused especially on those sIAs that eventually ruptured, and on how well size or shape would have identified those sIAs as rupture prone and thus necessitating treatment. Our results demonstrate that size-dependent rupture risk significantly varies in different anatomic locations, but irregular shape associates with rupture independent of size, location, or patient.

Materials and Methods

Kuopio Intracranial Aneurysm Database

During the study period from 1980 to 2007, Neurosurgery of KUH served as the only neurosurgical reference center for Eastern Finland. All cases of subarachnoid hemorrhage (SAH) diagnosed by computed tomography or spinal tap have been acutely admitted to KUH for angiography and treatment if not moribund or very aged. Cases with unruptured IA(s) and no SAH have also had neurosurgical consultation for elective occlusion. The findings were confirmed by 4-vessel catheter angiography, magnetic resonance angiography, or computed tomography angiography. Kuopio Intracranial Aneurysm Database contains all cases of unruptured and ruptured intracranial aneurysms admitted to the KUH since 1980.

Table. Summary of Previous Prospective Follow-Up Studies of Unruptured Saccular Intracranial Aneurysms

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Selection Criteria</th>
<th>Patients/ Aneurysms</th>
<th>Follow-Up, y</th>
<th>Identified Aneurysm-Related Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISJ\textsuperscript{a}</td>
<td>Multinational</td>
<td>Selected by treating physician for follow-up Aneurysm &gt;2 mm Rankin ≤ 2</td>
<td>4060/6221</td>
<td>9 (0–15)</td>
<td>Size Location</td>
</tr>
<tr>
<td>UCAS\textsuperscript{a}</td>
<td>Japanese</td>
<td>Aneurysm &gt;3 mm Age &gt;20 y Rankin ≤ 2 No prior intracranial hemorrhage of unknown cause</td>
<td>5720/6697</td>
<td>1 (0–9)</td>
<td>Size Location Secondary pouch</td>
</tr>
<tr>
<td>SUAVe\textsuperscript{a}</td>
<td>Japanese</td>
<td>Aneurysms &lt;5 mm Rankin ≤ 2</td>
<td>446/540</td>
<td>3.2 (0–20)</td>
<td>Size &gt;4 mm Multiple aneurysms</td>
</tr>
<tr>
<td>Ishibashi et al\textsuperscript{a}</td>
<td>Japanese</td>
<td>Aneurysm referred to Tokyo Jikei School of Medicine 2003–2006 and not considered for treatment</td>
<td>419/529</td>
<td>2.1 (0–22)</td>
<td>Size Location</td>
</tr>
<tr>
<td>Matsumoto et al\textsuperscript{a}</td>
<td>Japanese</td>
<td>Aneurysms referred to Osaka Iseikai Hospital 2000–2012 and not considered for treatment (size &lt;5 mm, age &gt;75, medical comorbidities, or refused intervention)</td>
<td>111/136</td>
<td>Median not given, range 0–12 y</td>
<td>Size</td>
</tr>
<tr>
<td>Helsinki cohort\textsuperscript{a}</td>
<td>Finnish</td>
<td>Patients admitted from 1956 to 1978 to Helsinki University Central Hospital 24% multiple aneurysm patients presenting with SAH</td>
<td>118/na</td>
<td>12 (1–51)</td>
<td>Size</td>
</tr>
</tbody>
</table>

Only studies with >50 patients and with >3 ruptures during follow-up are included. Follow-up years are given as median (range). ISJ\textsuperscript{a} indicates International Study of Unruptured Intracranial Aneurysms; na, not applicable; SAH, subarachnoid hemorrhage; SUAVe, Small Unruptured Aneurysm Verification Study; and UCAS, Unruptured Cerebral Aneurysm Study.

\textsuperscript{a}UCAS and SUAVe were the only studies that systematically assessed the presence of secondary pouches or irregular shape.

\textsuperscript{a}Helsinki cohort refers to the patient population with untreated unruptured aneurysms followed by Juvela et al\textsuperscript{a} and reported in several publications.
Study Population
The cohort consisted of 4074 sIA patients, fulfilling the following criteria:

1. A citizen of Finland and resident of the KUH catchment area at first diagnosis of sIA disease between January 1, 1980, and December 31, 2014.
2. Admission alive to KUH.
3. Verification of sIA(s) by angiography.
4. sIAs with incomplete data on the size or shape excluded (513 sIAs).

The patient characteristics are shown in Tables I and II in the online-only Data Supplement. Fusiform aneurysms and aneurysms with either traumatic or infectious etiology were excluded (Figure 1).

Size, Shape, and Location of sIAs
The sIA size was measured by the attending neuroradiologist at the time of diagnosis, defined as the largest diameter of the aneurysm fundus, and measured on a 1-mm scale. The sIA shape was classified as

5. regular when the sIA surface was smooth and regular in angiography in all projections, or
6. irregular when small bleb(s) or secondary aneurysm(s) were protruding from the sIA fundus in any angiography image projection, or when the aneurysm fundus was clearly bi- or multilobular. Demonstrative examples are given in Figure 2.

Inter- and intraobserver variability for the shape classification was calculated from a subset of 198 aneurysms that had undergone at least two 3-dimensional (3D) digital subtraction angiographies without any growth. The overall Cohen κ value was 0.818 for interobserver variability. The Cohen κ value for intraobserver variability for the neuroradiologist with most assessments (98/198; 49% of all cases including 22 cases with repeated assessment by the same observer) reached 0.831.

Statistical Analysis
Univariate analyses were performed using the Mann–Whitney U test, Fisher exact test, or the χ² test. Multivariate analyses were performed using linear regression and binomial logistic regression. P<0.05 was considered significant. The specificity and sensitivity of the size and shape of sIA, smoking, PHASES score, familial background, and hypertension as indicators of ruptured sIAs were investigated by plotting receiver operating characteristic curves.

Results
Characteristics of Ruptured and Unruptured sIAs Treated in Eastern Finland During a 35-Year Follow-Up
Altogether 6327 nontraumatic and noninfectious sIAs were found in 4417 patients. Of these, 5814 sIAs in 4074 patients were included in the study (2784 ruptured, 48% and 3030 unruptured, 52%; Figure 1). IAs from patients with multiple sIAs represented 43% (n=2488) of the studied aneurysms, and 24% (n=987) of the studied patients had multiple sIAs. Of the unruptured sIAs, 52% (n=1561) were true incidental findings without any history of prior SAH or other neurological symptoms related to the sIA. Most sIAs ruptured in the fifth or sixth decade (median age, 52 years) of life. The size at which sIAs ruptured did not change with age, whereas the size of unruptured sIAs had a slight tendency to increase with age. Patient demographics and the frequency of known SAH risk factors are given in Table I in the online-only Data Supplement. The frequency of ruptured and unruptured sIAs in different cerebral arteries, in different size classes and of different shape, is given in Table II in the online-only Data Supplement.

Location of Unruptured and Ruptured sIAs
Whether the sIA presented with rupture or was found unruptured was clearly influenced by anatomic location. Although MCA bifurcation and anterior communicating artery were the most frequent locations for ruptured sIAs, 70% and 62% of anterior communicating artery or posterior communicating artery sIAs presented with rupture compared with only 46% in MCA bifurcation. Anterior communicating artery and posterior communicating artery sIAs represented 31% and 13% of ruptured sIAs but only 13% and 8% of unruptured sIAs (Table II in the online-only Data Supplement).
Size-Dependent Risk of Rupture at Different Anatomic Locations and Patient Populations

Ruptured sIAs were on average larger (median, 8 versus 4 mm; Mann–Whitney U test, \(P < 0.000\)), but the distributions were largely overlapping, with 39% of all ruptured sIAs being <7 mm (Figures 3 and 4). Of small sIAs (≤7 mm in diameter), 24% presented with rupture.

The size at which the aneurysm had ruptured was much influenced by the anatomic location (Figures 4 and 5) and the characteristics of the patient, as was also the size of unruptured sIAs (Figures 4 and 5; Table II in the online-only Data Supplement). When stratified into subgroups according to anatomic location and multiplicity of the sIAs, MCA bifurcation was the only location where ruptured sIAs were significantly larger than unruptured ones in all patient groups. However, even in MCA bifurcation sIAs, the difference in size of ruptured and unruptured sIAs was age related (Figure 5) and different in solitary and multiple sIAs.

Size and Shape as Diagnostic Markers for Rupture-Prone (Ruptured) Aneurysms

Irregular shape was clearly associated with rupture in univariate analysis (22% in unruptured and 92% in ruptured sIAs; Fisher exact test, \(P = 0.000\)). To determine the relative importance of size, shape, and patient-related risk factors as markers of rupture-prone sIAs, we performed backward stepwise logistic regression in each anatomic location separately. Interestingly, irregular shape was the only factor consistently associated with high odds ratio for rupture in every location. The positive predictive value of irregular shape for presentation as ruptured sIA was high (>80% in sIAs <20 mm and >76% in large and giant sIAs) and the false discovery rate was low (<20% in sIAs <20 mm and <23% in large and giant sIAs) in sIAs of all sizes, including small sIAs (≤7 mm). For comparison, positive predictive value for <7-mm size was 61% (54%–71%), and false discovery rate was 31% (9%–45%) in sIAs <20 mm.

Receiver operating characteristic curves demonstrate that the sensitivity and specificity of irregular shape as a marker for sIA rupture are far better than those of size or largest diameter/neck width ratio, or those of patient-related risk factors (including PHASES score; Figure I in the online-only Data Supplement). To control for the potential error in the measurement of size in ruptured sIAs (possibly introduced by luminal thrombosis after rupture), receiver operating characteristic curves were recalculated adding 1 and 2 mm to the size of the ruptured sIAs. The respective areas under the curve for those receiver operating characteristic curves were 0.796 and 0.841 when compared with 0.838 of irregular shape.

Does Size or Shape Change After Rupture?

Of the 6327 sIAs in Kuopio sIA database, we identified 13 unruptured sIAs that presented as unruptured but ruptured...
Angiographies were available for 8 after the rupture. Of these, 2 were giant sIAs (>25 mm) and did not change in size or shape after rupture. Of the 6 nongiant sIAs, size was reduced in 1 sIA by 1 mm after rupture, increased before or after rupture in 5 cases and remained unchanged in 1. Change in shape was observed in 2 of them.

**Discussion**
In a population-based, minimally biased large clinical data set, we demonstrate that irregular shape associates with sIA rupture independently of other risk factors, including sIA size. As such, irregular shape could be considered as a marker of sIAs that can have a significant risk of rupture despite their small size.

**Why Large, Population-Based Consecutive Series Are Needed to Complement Follow-Up Cohorts**
Natural history studies of medical conditions that have high morbidity if left untreated are prone to have selection bias. This is also true for all natural history studies of unruptured sIAs (Table), which all had strict inclusion criteria and some unruptured sIAs treated during follow-up because they were considered to have been at a high risk of rupture. This selection bias may lead to underestimation of the risk of rupture because many of the sIAs that are considered rupture prone are excluded. Population-based consecutive and unselected series such as KUH Aneurysm registry have the advantage of reflecting the patient cohort seen in daily practice more than selected...
follow-up cohorts of natural history studies. This type of setting can be used to determine how well risk factors for sIA rupture can distinguish sIAs that did eventually rupture and thus would have necessitated treatment before the rupture.

**Why Size and Shape Are of Particular Interest as Markers of Rupture-Prone sIA Wall**

Of the aneurysm-related parameters, size and shape do not remain constant and may reflect unstable sIA wall and subsequent risk of progression to a more rupture-prone type. Large size is a marker of a rupture-prone sIA, but also some small sIAs are rupture prone and need to be treated.

Previous large multicenter follow-up studies have demonstrated that large size (>7 mm) indicates significant rupture risk even during short-term follow-up (5 years). The rupture risk of smaller aneurysms, however, remains controversial. Although short-term (5 years) rupture risk for <7 mm sIAs was small in a large multinational follow-up study, observational data demonstrate that a significant percentage of sIAs ruptured at a small size, especially if located in anterior communicating artery. A Japanese sIA follow-up study demonstrated that sIAs at anterior or posterior communicating artery location indeed have increased risk of rupture despite <7 mm size, and a later Japanese follow-up study that focused...
only on small (<5 mm) sIAs reported that the presence of multiple sIAs almost triples the risk of rupture of a small sIA.\(^8\)

The findings of these natural history studies suggest that some small sIAs are rupture prone despite their small size although the average risk of rupture for small sIAs is low.\(^5\)–\(^10\)

In the only lifelong follow-up cohort of unruptured sIAs, 25% of sIAs that were small (<7 mm) at initial diagnosis eventually ruptured.\(^3\) This suggests that small sIAs should not be excluded from treatment just based on their small size and the apparent low average risk of rupture. This approach is strongly supported by previous observational data indicating that many sIAs that did rupture did so at a small size.\(^11\),\(^15\) In our series, 39% of ruptured sIAs were <7 mm and 10% were ≤4 mm.

**Location Matters—Different Natural History and Rupture Risk for Aneurysms at Different Locations?**

Overall in our series, sIAs tended to increase in size with increasing age, suggesting that they tend to grow. Interestingly, this association of size and patient age was not found in all sIA locations and varied significantly between the different sIA locations (Figure 5) and populations (solitary or multiple sIAs). This suggests that unruptured sIAs grow differently in different locations and patient populations, and thus seem to have different natural history.

The size at which sIAs had ruptured, did not increase with age in most locations although the overall diameter of unruptured sIAs did (Figure 5). At first glance, this might seem to suggest that there is a threshold size at which the sIA ruptures. It is, however, important to note that the size at which sIAs had ruptured was much influenced by anatomic location and patient background (Figures 4 and 5). This in turn implies that the increase in risk of rupture resulting from sIA growth is dependent on location and patient background, and no universal size threshold to indicate need for treatment can be determined. Extrapolating from our observational data, the rigid use of a 7-mm size threshold to indicate treatment of an unruptured sIA would have left untreated approximately two fifths of those sIAs that required treatment (those that eventually did rupture).

**Irregular Shape Is a Sign of a Rupture-Prone sIA—Regardless of sIA Size or Location**

Irregular shape of the sIA wall in angiogram may reflect either focal weakening with subsequent distention of the sIA wall or could be explained by thrombosis on the luminal surface of the sIA wall because angiogram is just a cast of the sIA lumen rather than an image of the actual sIA wall. Both focal wall degeneration and luminal thrombosis associate with sIA wall degeneration and rupture.\(^11\),\(^12\)

UCAS, the large Japanese follow-up study, indeed demonstrated that irregular shape indicates increased risk of rupture.\(^7\) In our unselected population-based registry study, irregular sIA wall shape was the only factor consistently associated with high odds ratio for presentation as ruptured sIA at diagnosis in every location independently of patient background or sIA size. Moreover, although increase in size clearly associated with the increase in rupture rate, irregular shape had significantly stronger association with presentation with rupture than any other of the known risk factors for rupture (Figure I in the online-only Data Supplement).

**Limitations**

Definition of irregular shape varies a lot between studies, radiologists interpreting the angiograms, and to some extent even between the assessments of the same radiologist at different times.\(^19\) In our study, everything else than a smooth sIA surface on the angiogram in any projection was defined as being irregular, as well as a clearly bi- or multilobular shape, which is a robust and simple definition. The angiograms in our institution are and have been interpreted by a small group of dedicated angiologists and vascular neurosurgeons during the whole study period, reducing variability, as demonstrated by excellent Cohen \(k\) values for inter- and intraobserver variability (>0.80). Since 2000, 3D digital subtraction angiography has been available and used at KUH. Before that, shape and size were assessed from 2-dimensional (2D) projections taken from directions that the radiologist performing the angiography saw most appropriate. Computerized shape analysis such as presented by Raghavan et al\(^20\) could have been even more accurate to detect irregular shape than our visual scoring. In addition, assessment of shape from 2D projections may have led to some of the irregularly shaped aneurysms being misclassified as smooth-surfaced aneurysms and may have caused more intra- and interobserver variability than demonstrated by our analysis of 3D digital subtraction angiography era data. However, the possibility of having these false-negatives does not critically undermine the association of irregular shape with rupture (22% versus 92%).

Because of the comparative setting and observational nature of this study, the strong association of irregular shape and rupture should be interpreted cautiously. We cannot exclude the possibility that in some cases, the irregular shape or the so-called secondary pouch would have resulted from rupture, and thus would have biased the results of the regression analysis. Nevertheless, irregular shape was also found in 22% of unruptured sIAs, showing that the formation of the so-called secondary pouches is not just a reaction to rupture. Whether preceding rupture or caused by rupture, irregular shape or a secondary pouch seems to be a strong marker for a past rupture or one that will occur—and as such is an indicator of a sIA that should be treated.

The observation that many of ruptured sIAs are small and the apparent controversy of this finding, and the low rupture risk of small sIAs in natural history studies has been explained by speculated reduction in size that would occur immediately after rupture. There are few reports of such postrupture shrinkage happening in real life, and in fact published data suggest mostly the opposite,\(^21\) which is consistent with our findings from the 6 patients of whom we had several perirupture angiograms available.

In our cohort, the presence of established risk factors for aneurysmal SAH, such as smoking, hypertension, or family background has influenced the decisions to treat unruptured sIAs. Because some rupture-prone sIAs were treated before rupture and classified as unruptured sIAs, the apparent effect of some established risk factors such as...
smoking and hypertension may be very biased in our series. Nevertheless, despite the same bias, irregular shape had a much stronger association with rupture in our cohort than any other factor.

Conclusions
Instead of considering small unruptured sIAs as safe lesions with low rupture risk, other markers of increased rupture risk should be considered, such as sIA shape, location, and patient history. Irregular shape is strongly associated with rupture in sIAs of all sizes and independent of location and patient background. Especially sIAs with irregular shape should be considered as high rupture risk lesions, even if small in diameter or in patients with otherwise low risk factor profile.

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Disclosures
None.

References
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SUPPLEMENTAL MATERIAL

“Irregular shape of intracranial aneurysm indicates rupture irrespective of size in a population based cohort”

Table I. Patient demographics and prevalence of known risk factors for sIA rupture in patients with ruptured and unruptured sIAs. Multiple disease was defined as patient having more than one angiographically diagnosed aneurysm. Familial disease was defined as having at least two first degree relatives with diagnosed saccular intracranial aneurysm in the same family

<table>
<thead>
<tr>
<th>Patient demographics and prevalence of known risk factors for sIA rupture in 4074 sIA patients 1979-2015</th>
<th>Unruptured n=1296</th>
<th>Ruptured n=2777</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at presentation (range)</td>
<td>57 (10-85)</td>
<td>52 (11-86)</td>
</tr>
<tr>
<td>Female gender</td>
<td>740</td>
<td>1514</td>
</tr>
<tr>
<td>Multiple disease</td>
<td>354</td>
<td>633</td>
</tr>
<tr>
<td>Familial disease</td>
<td>250</td>
<td>303</td>
</tr>
<tr>
<td>Hypertension</td>
<td>530</td>
<td>852</td>
</tr>
<tr>
<td>Positive smoking history</td>
<td>541</td>
<td>806</td>
</tr>
<tr>
<td>APCKD</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>PHASES*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-7</td>
<td>382</td>
<td>349</td>
</tr>
<tr>
<td>8-9</td>
<td>295</td>
<td>573</td>
</tr>
<tr>
<td>10-11</td>
<td>262</td>
<td>526</td>
</tr>
<tr>
<td>≥12</td>
<td>357</td>
<td>1323</td>
</tr>
</tbody>
</table>

* for patients with multiple aneurysms, the highest PHASES score is shown
Table II. Characteristics of solitary and multiple aneurysms in Kuopio Aneurysm Registry (1980-2014). Locations with a significant number of cases (>25) are displayed.

<table>
<thead>
<tr>
<th>Location</th>
<th>Rupture ratio</th>
<th>Size in mm</th>
<th>Irregular shape</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unruptured P-value</td>
<td>Unruptured</td>
<td>Ruptured P-value</td>
</tr>
<tr>
<td>Solitary aneurysms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA-oft</td>
<td>29% (31/106)</td>
<td>5 (1-32)</td>
<td>7 (2-50)</td>
</tr>
<tr>
<td>ICA-PCom</td>
<td>76% (285/377)</td>
<td>5 (1-20)</td>
<td>8 (2-25)</td>
</tr>
<tr>
<td>ICA bifurcation</td>
<td>60% (75/125)</td>
<td>5.0 (1.5-24)</td>
<td>7 (2-60)</td>
</tr>
<tr>
<td>ACom</td>
<td>80% (721/899)</td>
<td>5 (2-48)</td>
<td>7 (1-30)</td>
</tr>
<tr>
<td>Distal ACA</td>
<td>70% (105/151)</td>
<td>4 (2-19)</td>
<td>6 (2-40)</td>
</tr>
<tr>
<td>M1 segment</td>
<td>45% (58/129)</td>
<td>4 (2-9)</td>
<td>6 (2-48)</td>
</tr>
<tr>
<td>MCA bifurcation</td>
<td>57% (588/1029)</td>
<td>5 (1-65)</td>
<td>9 (1-80)</td>
</tr>
<tr>
<td>Distal MCA</td>
<td>59% (16/27)</td>
<td>3.5 (2-15)</td>
<td>5.0 (3-25)</td>
</tr>
<tr>
<td>BA bifurcation</td>
<td>60% (88/146)</td>
<td>8 (1-50)</td>
<td>10 (2-26)</td>
</tr>
<tr>
<td>PICA origin</td>
<td>85% (39/46)</td>
<td>6 (4-22)</td>
<td>4.0 (2-15)</td>
</tr>
<tr>
<td>Structure</td>
<td>Frequency (%)</td>
<td>Median Length (mm)</td>
<td>Minimum Length (mm)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------</td>
<td>-------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>ICA-oft</td>
<td>14% (13/92)</td>
<td>4 (1-36)</td>
<td>8 (2-28)</td>
</tr>
<tr>
<td>ICA-PCom</td>
<td>38% (84/221)</td>
<td>4 (1-26)</td>
<td>8 (2-25)</td>
</tr>
<tr>
<td>ICA bifurcation</td>
<td>28% (23/81)</td>
<td>4 (1-40)</td>
<td>7 (2-22)</td>
</tr>
<tr>
<td>ACom</td>
<td>42% (146/352)</td>
<td>4 (1-20)</td>
<td>7 (2-55)</td>
</tr>
<tr>
<td>Distal ACA</td>
<td>28% (43/153)</td>
<td>3 (1-13)</td>
<td>6 (2-14)</td>
</tr>
<tr>
<td>M1 segment</td>
<td>11% (25/231)</td>
<td>3 (1-35)</td>
<td>8 (3-33)</td>
</tr>
<tr>
<td>MCA bifurcation</td>
<td>25% (215/848)</td>
<td>4 (1-40)</td>
<td>9 (3-45)</td>
</tr>
<tr>
<td>Distal MCA</td>
<td>9% (9/97)</td>
<td>3 (1-12)</td>
<td>8 (2-16)</td>
</tr>
<tr>
<td>BA bifurcation</td>
<td>35% (32/92)</td>
<td>5 (1-23)</td>
<td>10 (3-30)</td>
</tr>
<tr>
<td>PICA origin</td>
<td>36% (8/22)</td>
<td>3.5 (1-22)</td>
<td>9 (3-22)</td>
</tr>
</tbody>
</table>
Supplementary Figure I.

Association of irregular shape with presentation as a ruptured aneurysm is further illustrated by ROC-curve that shows high sensitivity (90%) and specificity (76%). Because size is not as clearly associated with rupture, ROC-curve for size is poorer: Even with the most optimal threshold values, the sensitivity and specificity of size in the estimation of rupture-risk would be around 80% and 50%. This means that 4 out of 5 sIAs that presented with rupture would be identified but the estimate would be wrong in 50% of cases. Patient-related known risk factors such as smoking history, hypertension, and family history had even worse sensitivity and specificity demonstrating that many patients develop sIAs without these risk factors. It should be noted that the fact that some of the rupture-prone sIAs were treated as unruptured ones before rupture introduces bias to the results, and at least partly explain the poor sensitivity and specificity for smoking and hypertension as diagnostic marker of rupture-risk.
Irregular Shape of Intracranial Aneurysm Indicates Rupture Risk Irrespective of Size in a Population-Based Cohort

Antti E. Lindgren, MD, PhD; Timo Koivisto, MD, PhD; Joel Björkman, MB; Mikael von und zu Fraunberg, MD, PhD; Katiarina Helin, RN; Juha E. Jääskeläinen, MD, PhD; Juhana Frösen, MD, PhD


Background and目的:既往随访研究提示囊状颅内动脉瘤(saccular intracranial aneurysms, sIA)的大小和形状反映了瘤壁的状况，同时也是动脉瘤破裂的风险因素。我们旨在研究怎样的大小或形状能识别有破裂倾向的 sIA。

Methods:我们从一个神经外科学单中心取得人群登记数据并对在该中心治疗的破裂 sIA 特征进行研究。统计学上除了采用单变量分析，还在多元分析中运用逻辑回归的方法，同时采用受试者工作特征曲线对动脉瘤的大小或形状的敏感性和特异性进行分析。

Results:破裂的 sIA 普遍比未破裂的(中位数，7 vs 4 mm; P < 0.000)，但动脉瘤破裂时瘤的位置及患者背景会影响瘤的大小。在破裂的 sIA 中，38% 的动脉瘤小于 7 mm，18% 的动脉瘤小于 4 mm，87% 小于 7 mm 且已破裂的 sIA 具有不规则外形。多元分析显示不规则外形与破裂 sIA 的临床表现联系最紧密(比值比，7.1; 95% 可信区间 [confidence interval, CI], 6.0-8.3)，且其敏感性和特异性(分别为 91%、76%)较吸烟(比值比，0.7; 95% CI, 0.6-0.9; 敏感性 28%; 特异性 28%; 特异性 67%)更高，同时亦均高于人口、高血压、年龄、sIA 的部位、其他 sIA 导致的早期蛛网膜下腔出血及 sIA 部位评分这一系列因素(比值比，1.5; 95% CI, 1.4-1.6)。

Conclusion:无论 sIA 的大小、部位及患者背景如何，sIA 的不规则或多个外形与其破裂明显相关。即使有时 sIA 直径小，患者不吸烟且 PHASES 评分低，一旦 sIA 具有不规则外形，仍应考虑该类 sIA 是具有高破裂风险的病灶。

Keywords:动脉瘤;颅内动脉瘤;登记;破裂;蛛网膜下腔出血

Cerebral Aneurysm Study, UCAS)及芬兰疾病自然史研究亦提示越大的动脉瘤破裂风险越高。但是一些观察性研究却表明有较多小 sIA 尤其是位于前交通动脉处的动脉瘤，其体型小但仍破裂。此外，一项纳入了 1309 例大脑中动脉动脉瘤的单中心系列研究明确指出其他部位的小动脉瘤(< 7 mm)也存在一定比例的破裂，该研究显示 407 例破裂的大脑中动脉 sIA 中有 29% 的 sIA < 7 mm。上述疾病自然史随访研究和观察性研究的结论相悖，两者间的争议说明最终引发 sIA 破裂的壁结构重塑变形不一定与 sIA 的发展或大小必然相关。日本和芬兰的人群随访研究证实了这一点。因此，需要找到能帮助诊断瘤壁变形且有破裂倾向 sIA 的诊断性标志，该诊断性标志对于那些有破裂倾向的小 sIA 尤为重要。

四维的计算机体层摄影数字减影血管造影发现在心脏收缩产生最大的物理应力期间，从动脉瘤主囊形成向外凸出的继发性动脉瘤，由此推测动脉瘤主囊的不规则外形及继发前凸也许能反映 sIA 瘤壁存在局灶性的薄弱点。许多大型观察性系列研究指出 sIA 的不规则外形与其破裂明显相关，且日本的疾病自然史研究表示不规则外形是破裂风险的独立预测因子。日本针对未破裂小 sIA(< 7 mm) 进行随访研究，对那些形成继发前凸的 sIA 采取了治疗干预，因此无法确定在 sIA 群体不规则外形是否作为区分破裂倾向动脉瘤的预测性标志。目前针对未破裂 sIA 已经建立了多个结合危险因素进行破裂风险预测的评分...
标准，比如说人口、高血压、年龄、sIA 大小、继发于其他 sIA 的早期蛛网膜下腔出血（subarachnoid hemorrhage, SAH）及 sIA 部位（Population, Hypertension, Age, Size of sIA, Earlier SAH From Another sIA, Site of sIA, PHASES17）评分和未破裂颅内动脉瘤治疗评分（Unruptured Intracranial Aneurysm Treatment Score, UIATS）。

为测定大小及不规则外形作为标志诊断不同部位、不同人群亚组 sIA 壁结构不稳定的有效性，我们从库奥皮奥大学医院（KUH）非选择性地连续纳入 1980-2014 年诊断治疗的破裂及未破裂的囊性非霉菌性动脉瘤进行研究。我们重点关注那些最终破裂的 sIA 以及怎样的大小或外形提示 sIA 的破裂倾向。本研究结果显示 sIA 大小与破裂风险的相关性因 sIA 所在部位而有所不同，不规则外形却是独立于大小、部位或患者之外的危险因素。

### 材料及方法

#### 库奥皮奥颅内动脉瘤数据库

KUH 神经外科是 1980-2007 年在研期间芬兰东部唯一一家参研中心。除了垂死或极高龄以外的所有 SAH 病例均经计算机断层扫描（computed tomography, CT）或腰椎穿刺诊断，且均急诊入住 KUH 进行血管造影及治疗。动脉瘤尚未破裂且无 SAH 的病例也经神经外科会诊讨论选择性栓塞。研究所见由导管造影、磁共振血管成像、CT 血管成像证实。库奥皮奥颅内动脉瘤数据库包含自 1980 年以来收入 KUH 的所有破裂或未破裂颅内动脉瘤病例。

#### 研究人群

队列研究由满足下列纳入标准的 4074 名 sIA 患者组成:
1. 1980 年 1 月 1 日至 2014 年 12 月 31 日期间首次诊断 sIA 的芬兰人及 KUH 区的居民。
2. 收入 KUH 时存活。
3. 经血管造影证实存在 sIA。
4. 大小或外形数据不完全的 sIA 予以排除（513 例）。

患者的特征信息仅收录于在线版数据补充表 1 及表 II。外伤性或感染引发的梭状动脉瘤及微动脉瘤被排除在外（图 1）。

#### sIA 的大小、外形及部位

sIA 的大小由诊断时的主治神经放射学家测定，定义为动脉瘤基底的最大直径，采用 1 mm 比例尺测量。sIA 的外形通过以下说明进行区分:

- **规则外形**：sIA 的表面在血管造影的任意角度投影成像中均光滑且规整。
- **不规则外形**：在任一角度血管造影的投影成像上看到从 sIA 基底部突出小泡或继发动脉瘤，或者动脉瘤基底部呈现清晰的二级或多级分叶。示例见图 2。

不规则外形在任一角度血管造影的投影成像上看到从 sIA 基底部突出小泡或继发动脉瘤，或者动脉瘤基底部呈现清晰的二级或多级分叶。示例见图 2。

### 数据分析

单变量分析采用 Mann-Whitney U 检验、Fisher 精确检验或 χ² 检验。多元分析采用线性回归及二项逻辑回归。P < 0.05 被认为有统计学意义。sIA 的大小及外形、吸烟、PHASES 评分、家族背景及高血压作为 sIA 破裂预测值的敏感性及特异性通过绘制受试者工作曲线进行分析。

### 研究种群

<table>
<thead>
<tr>
<th>种群</th>
<th>选择标准</th>
<th>病例数 / 动脉瘤数</th>
<th>随访, 年</th>
<th>经鉴定动脉瘤相关危险因素</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISUIA</td>
<td>多国, 由经治医师选择随访, 动脉瘤 ≥ 2 mm, Rankin ≤ 2, 无既往 SAH</td>
<td>4060/6221</td>
<td>9 (0-15)</td>
<td>大小, 部位</td>
</tr>
<tr>
<td>UCAS</td>
<td>日本, 动脉瘤 ≥ 3 mm, 年龄 &gt; 20 y, Rankin ≤ 2, 无既往不明原因的颅内出血</td>
<td>5720/6697</td>
<td>1 (0-9)</td>
<td>大小, 部位, 家族病史</td>
</tr>
<tr>
<td>SUAVe</td>
<td>日本, 动脉瘤 &lt; 5 mm, Rankin ≤ 2</td>
<td>4465/40</td>
<td>3.2 (0-20)</td>
<td>&gt; 4 mm 多发性动脉瘤</td>
</tr>
<tr>
<td>Ishibashi 等</td>
<td>日本, 2003-2005 年间就诊于东京 Jikei 医科大学但不考虑治疗的动脉瘤</td>
<td>419/529</td>
<td>2.1 (0-22)</td>
<td>大小, 部位</td>
</tr>
<tr>
<td>Matsumoto 等</td>
<td>日本, 2000-2012 年间就诊于大阪 Isseiki 医院但不考虑治疗的动脉瘤&lt;br&gt;(&lt; 5 mm, 年龄 &gt; 75 岁, 存在医疗合并症, 或拒绝介入治疗)</td>
<td>111/136</td>
<td>未给出中位数, 范围 0-12 年</td>
<td>大小</td>
</tr>
<tr>
<td>Helsinki cohort</td>
<td>芬兰, 1956-1978 年间赫尔辛基大学中心医院收治的患者, 多发性动脉瘤的患者中有 24% 的病例以 SAH 为表现</td>
<td>118/na</td>
<td>12 (1-51)</td>
<td>大小</td>
</tr>
</tbody>
</table>

*UCAS 及 SUAVe 是仅有的对继发小囊或不规则外形进行系统性评估的研究。

† 赫尔辛基队列研究涉及的是未治疗的未破裂动脉瘤人群, 由 Juvela 等†* 研究并在多处报道。
芬兰东部收治的破裂及未破裂 sIA 随访 35 年的特点

4417 例患者中总共发现 6327 个非外伤性、非感染性 sIA。其中 4074 例患者的 5814 个 sIA 被纳入该研究（2784 个破裂，占 48%；3030 个未破裂，占 52%；见图 1）。43%（n=2488）纳入研究的动脉瘤来自多发性动脉瘤患者，且纳入的患者中有 24%（n=987）患有多发性动脉瘤。在未破裂的 sIA 中，52%（n=1561）的动脉瘤是偶然发现的，既无 SAH 病史也无动脉瘤相关的神经病学症状。大多数 sIA 在五六十岁破裂（平均年龄 52 岁）。

未破裂及破裂 sIA 所在的部位

sIA 的解剖学部位显然会对其是否破裂有所影响。尽管大脑中动脉分叉处及前交通动脉是破裂 sIA 最好发的部位，与大脑中动脉分叉处破裂 sIA 发生率为 46% 相比，前交通动脉及后交通动脉的破裂 sIA 发生率分别为 70% 和 62%。前交通动脉及后交通动脉的破裂 sIA 分别占总破裂 sIA 的 31% 和 13%，但其未破裂 sIA 却仅占 13% 和 8%（见在线数据补充表 II）。

不同解剖部位及人群的大小相关破裂风险

破裂的 sIA 平均都较大（中位数，8 vs 4 mm；Mann-Whitney U 检验，P < 0.000），但其分布存在大量重叠，39% 的破裂 sIA < 7 mm（图 3 及图 4）。直径≤ 7 mm 的小动脉瘤中有 24% 破裂。动脉瘤破裂时的大小相当受解剖部位（图 4 及图 5）、患者特点及未破裂动脉瘤的大小（图 4 及图 5；在线版数据补充表 II）的影响。当根据解剖部位及 sIA 复杂性对研究群体进行亚组分析后，大脑中动脉分叉处是所有亚组中唯一处破裂 sIA 显著大于未破裂 sIA 的解剖部位。然而，即使 sIA 位于大脑中动脉分叉处，破裂及未破裂 sIA 之间的大小差异是与年龄相关的，且单个及多发性动脉瘤之间又有所不同。

图 1 研究人群入组的标准流程图。注：sIA：囊状颅内动脉瘤；KUH：库奥皮奥大学医院。

动脉瘤破裂后大小或外形变化吗？

在 Kuopio sIA 数据库的 6327 例 sIA 中，我们发现有 13 例动脉瘤起初未破裂但在随访期间或治疗性干预前发生破裂。发生破裂后我们对其中的 8 例 sIA 进行了血管造影术。其中有 2 例是巨大动脉瘤（> 25 mm），且破裂后其大小或外形未发生改变。剩下的 6 例非巨大动脉瘤里，有 1 例动脉破裂后大小减少了 1 mm，5 例在破裂前后变大且 1 例保持不变。其中 2 例可以观察到外形的变化。

讨论

基于以人群为基础、偏倚最小化的大型临床数据体系，我们证实了不规则外形与 sIA 破裂相关，且独立于包括大小在内的其他危险因素。依据该理论，尽管有些动脉瘤虽小，但不规则外形应被认为是明显破裂风险的一个标志。

大小及外形为有破裂倾向动脉瘤的诊断性标志

多元分析显示不规则外形与破裂明显相关（22% 未破裂 sIA 及 92% 破裂 sIA；Fishers 精确检验，P=0.000）。为了验证大小、外形及患者相关危险因素作为破裂倾向的 sIA 标志的重要性，我们分别在不规则外形及不同解剖部位进行后续逐步逻辑回归分析。有趣的是，在每个解剖部位不规则外形是唯一一个始终与破裂相关并具有高比值比的因素。

受试者工作特征曲线显示不规则外形作为 sIA 破裂标志的敏感性和特异性远远优于其他因素如大小、最大直径与颈宽的比值、患者相关危险因素（包括 PHASES 评分；在线数据补充图 1）等。为了控制在测量破裂 sIA 大小时可能存在的潜在性错误（可能由破裂后管腔内血栓形成影响），在测得的破裂 sIA 大小基础上分别加了 1 mm 和 2 mm 的基础上再次绘制受试者工作特征曲线。不规则外形在受试者工作特征曲线的曲线下面积为 0.838，其他因素的曲线下面积为 0.796 及 0.841。

为何完成补充随访队列研究需要以人群为基础的大型连续性系列数据？

不加以治疗干预的疾病自然史研究患病率高并存在选择性偏倚。现有的关于未破裂 sIA 开展的自然史研究也存在同样的问题（表），即所有研究都有严格的纳入标准，且在随访过程中对它们认为破裂风险高的未破裂 sIA 采取治疗措施。由于许多有破裂倾向的 sIA 被排除在外，上述选择性偏倚可能会造成破裂风险被低估。与疾病自然史研究中选择性随访队列相比，KUH 动脉瘤登记中心具有在日常实践中真实反映人群为基础的连续性及非选择性队列数据的优势。该类型的数据库可以用于明确何等危险因素可区分哪些最终会破裂的动脉瘤，并最终能在动脉瘤破裂前给予有必要的治疗。

大小及外形为何成为有破裂倾向 sIA 瘤壁重要的标志性因素？

在所有动脉瘤相关参数中，大小及外形并不是保持不变的，两者可能都存在不稳定的动脉瘤瘤壁及其随后续发展为破裂倾向更大的类型的可能。体型大是有破裂倾向动脉瘤的一个标志，也存在一些小动脉瘤是具有破裂倾向且需要治疗的。统计一些大型动脉瘤随访研究已证实即使随访期较短（5 年），动脉瘤的最大直径（> 7 mm）与破裂风险明显相关。3。尽管一项大型动脉瘤随访研究指出 < 7 mm 的动脉瘤
短期（5年）内破裂风险小，其他观察性研究却指出一些动脉瘤虽小但有相当一部分发生破裂，尤其是该类小动脉瘤位于前交通动脉时。

一个日本的sIA随访研究发现尽管动脉瘤小于7mm，当其位于前交通或后交通动脉时相应的破裂风险确实增大；随后的另一个日本随访研究则仅将研究重心放在小于5mm的sIA上，它报道指出存在多发性sIA的破裂风险几乎是单个小动脉瘤的破裂风险的三倍。

上述这些自然史研究提示尽管小动脉瘤的平均破裂风险低，但有些小动脉瘤尽管体型小还是具有破裂倾向的。未破裂sIA的终身随访研究发现25%的初诊<7mm的sIA最终还是破裂了，这说明不能仅于体型小及看似破裂风险低的理由便将小动脉瘤从治疗组剔除。早期的观察性研究记录的体型小的动脉瘤仍破裂的相关数据强烈支持这一观点。本研究则发现39%破裂sIA<7mm，且更是有10%的破裂sIA≤4mm。

位置问题——不同部位动脉瘤的疾病自然史和破裂风险是否不同？

总体来说，本研究发现sIA随着年龄增长而增大，提示sIA有不断增大的趋势。有趣的是，并非在所有部位的sIA上都能发现瘤大小与年龄的相关性，与此同时两者相关性更因不同解剖部位（图5）和人群（单发或多发性动脉瘤）而有所差异。这就提示不同部位和组群的未破裂动脉瘤增大的情况不同，因此似乎也就造成了解不同的疾病自然史。

虽然未破裂sIA的总体直径随年龄增长，大多数部位的sIA破裂时的尺寸并不随年龄变化（图5）。乍一看动脉瘤破裂时的尺寸似乎存在一个临界阈值。但值得指出的是，动脉瘤破裂时的尺寸为解剖部位及患者背景所影响（图4及图5）。换句话说，动脉瘤增大而继发的高破裂风险是由解剖部位及患者背景决定的，无法确定一个通用的动

动脉瘤大小阈值用于提示何时做出治疗决策。从本研究数据延伸出去而言，假如严格采用 7 mm 作为提示未破裂 sIA 需治疗的一个阈值，将会造成近五分之二需要治疗的 sIA 被忽略（且这些 sIA 最终也确实破裂了）。

忽略 sIA 大小及部位：不规则外形是有破裂倾向 sIA 的标志

由于血管造影显示的只是动脉瘤囊腔而不是真实的动脉瘤壁，因此血管造影中 sIA 的不规则外形可能反映的只是瘤壁局部性薄弱继发的膨胀改变，又或者是动脉瘤管腔表面形成的血栓 

日本的大型随访研究 UCAS 指出不规则外形确实提示了破裂风险的增加。在我们的非选择性人群登记研究中，动脉瘤的不规则外形是独立于患者背景或大小之外的唯一与诊断破裂动脉瘤的临床表现始终高度相关的因素。此外，尽管体型增大与破裂风险增加明显相关，统计学上不规则外形与破裂临床表现的相关性比其他任何已知的破裂相关危险因素更明显（在线版数据补充的图 1）。

局限性

不同的研究、解读影像的放射学家对不规则外形的定义差别很大，某种程度上甚至同一放射学家在不同时期对该定义的判读都有所不同。本研究将造影条件下看到动脉瘤光滑表面上的任意凸起、明显的分叶（两叶或多叶）定义为不规则外形，这样的定义简洁明了。为降低差异性，本研究将造影条件下看到动脉瘤光滑表面上的任意凸起、明显的分叶（两叶或多叶）定义为不规则外形，这样的定义简洁明了。为降低差异性，本研究的血管造影影像均由一组有资质的放射学家和血管专业的神经外科医师共同审阅，最终获得良好的组内组间差异性（Cohen k 值 > 0.80），KUH 自 2000 年起开展三维数字减影血管造影。在此之前，动脉瘤的大小及外形由操作造影的放射学家自行观察并成像在二维图片上。Raghavan 等指出对不规则外形的电脑成像进行分析比造影中直接肉眼判断精确。此外，二维影像条件下评估动脉瘤外形可能会导致一些不规则表面的动脉瘤被误分组到表面光滑组，同时较通过三维数字减影血管造影进行分析相比会造成更大的组内及组间差异性。然而，虽然研究过程可能存在上述假阳性的情况，但并不会明显妨碍不规则外型与破裂之间的相关性（22% vs 92%）。
动脉瘤大小（MM）
年龄
未破裂 sIA
破裂 sIA

图 5 由于解剖部位可能影响破裂风险，我们对照不同解剖部位检测到动脉瘤时的患者年龄、动脉瘤大小作图。在某些部位（大脑中动脉、后交通动脉和前交通动脉），未破裂动脉瘤在老年患者表现的更大，这提示动脉瘤随着时间在增大。然而，类似的大趋势在其他部位（颈内动脉）却未观察到。年龄如何影响动脉瘤破裂时的大小显然因所在部位不同而有所差异。上述研究发现提示不同部位的未破裂动脉瘤的增大，随之而来的大小相关破裂风险乃至整个疾病自然史都将不同。线图展示中位数（直线）及 95% 可信区间（曲线），注：sIA，囊状颅内动脉瘤。

由于本研究的观察性病史及比较性设置，应谨慎解读研究得出的不规则外形与破裂之间强烈相关这一结论。我们不排除有些病例的不规则外形或所谓的继发性凸起可能是由破裂本身造成的，因此回归分析的结果可能存在偏倚。然而，有 22% 未破裂 sIA 具有不规则外形，这意味着所谓的继发性凸起的形成不仅仅是破裂造成的一个反应。无论破裂前存在还是由破裂引发，不规则外形（或继发性凸起）似乎是动脉瘤已发生破裂或即将发生破裂的重要标志。如此看来，不规则外形的存在提示该动脉瘤需要治疗。

关于某些研究观察到许多破裂 sIA 体型小这一点本身存在明显争议，且众多自然史研究指出小动脉瘤破裂风险低，上述观点也许可通过下列假想进行解释：动脉瘤破裂后其体积立即缩小。在现实生活中，类似这种动脉瘤破裂后萎缩的情况鲜有报道，且已发表的数据往往提示相反的情况。这些与我们观察到的 6 名患者的大量围破裂期血管造影影像表现相一致。

在我们的队列研究中，一些已被证实的动脉瘤 sAH 危险因素的存在影响了未破裂动脉瘤的治疗决策，这些危险因素包括吸烟、高血压、家族史等。由于某些有破裂倾向的动脉瘤在破裂前采取了治疗措施从未被分析到未破裂 sIA 组，一些已被证实的危险因素如吸烟和高血压将对我们的系列研究造成偏倚。然而，尽管存在同样的偏倚，不规则外形仍较其他任何因素更强烈地与动脉瘤破裂相关。

结论

与其将未破裂的 sIA 当做破裂风险小的安全病灶，不如结合其他增加破裂风险的标志一起综合考虑，这些标志有 sIA 的外形、部位及病史等。不规则外形与任意大小的 sIA 的破裂强烈相关，且这一危险因素独立于动脉瘤部位及患者背景之外。尽管有些 sIA 直径小且其他破裂相关因素风险低下，一旦具有不规则外形，我们仍可认为是高破裂风险的病灶。

参考文献