

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 (sIA) 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 univariate analysis, logistic regression was used in multivariate 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 multivariate 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.¹ 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%).^{2,3} Because unruptured sIAs are relatively common (an estimated prevalence of 3%)⁴ and many of them never rupture (only one third in a cohort with lifelong follow-up),⁵ 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.^{11,12} 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.⁶ Larger size increased the risk of rupture also in the Japanese (Unruptured Cerebral Aneurysm Study [UCAS]) and Finnish natural history studies.^{5,7} Observational studies, however, demonstrate that a significant portion of those sIAs that ruptured did so

Received December 11, 2015; final revision received March 4, 2016; accepted March 7, 2016.

From the Department of Neurosurgery, KUH NeuroCenter, Kuopio University Hospital, Kuopio, Finland (A.E.L., T.K., J.B., M.v.u.z.F., K.H., J.E.J., J.F.); Department of Neurosurgery, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland (T.K., M.v.u.z.F., J.E.J., J.F.); and Kuopio Intracranial Aneurysm Database (A.E.L., T.K., M.v.u.z.F., K.H., J.E.J.) and Hemorrhagic Brain Pathology Research Group (A.E.L., J.B., J.F.), KUH NeuroCenter, Kuopio University Hospital, Kuopio, Finland.

The online-only Data Supplement is available with this article at <http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.115.012404/-/DC1>.

Correspondence to Juhana Frösen, MD, PhD, Department of Neurosurgery, KUH NeuroCenter, Kuopio University Hospital, PO Box 100, 70210 Kuopio, Finland. E-mail juhana.frosen@kuh.fi

© 2016 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.115.012404

at a small size, especially if located at the anterior communicating artery.^{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.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.^{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.¹⁶ Irregular shape strongly associates with sIA rupture in large observational series¹⁵ and was an independent predictor of rupture risk in the Japanese natural history study.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 that the predictive value of irregular shape as marker to distinguish rupture-prone sIAs among small sIAs remains undetermined.⁸ 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)¹⁷ and the Unruptured Intracranial Aneurysm Treatment Score (UIATS).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

Study	Population	Selection Criteria	Patients/Aneurysms	Follow-Up, y	Identified Aneurysm-Related Risk Factors
ISUIA ⁶	Multinational	Selected by treating physician for follow-up Aneurysm ≥ 2 mm Rankin ≤ 2 No previous SAH	4060/6221	9 (0–15)	Size Location
UCAS ^{7*}	Japanese	Aneurysm > 3 mm Age > 20 y Rankin ≤ 2 No prior intracranial hemorrhage of unknown cause	5720/6697	1 (0–9)	Size Location Secondary pouch
SUAve ^{8*}	Japanese	Aneurysms < 5 mm Rankin ≤ 2	446/540	3.2 (0–20)	Size > 4 mm Multiple aneurysms
Ishibashi et al ⁹	Japanese	Aneurysm referred to Tokyo Jikei School of Medicine 2003–2006 and not considered for treatment	419/529	2.1 (0–22)	Size Location
Matsumoto et al ¹⁰	Japanese	Aneurysms referred to Osaka Iseikai Hospital 2000–2012 and not considered for treatment (size < 5 mm, age > 75 , medical comorbidities, or refused intervention)	111/136	Median not given, range 0–12 y	Size
Helsinki cohort† ⁵	Finnish	Patients admitted from 1956 to 1978 to Helsinki University Central Hospital 24% multiple aneurysm patients presenting with SAH	118/na	12 (1–51)	Size

Only studies with > 50 patients and with > 3 ruptures during follow-up are included. Follow-up years are given as median (range). ISUIA 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.

*UCAS and SUAve were the only studies that systematically assessed the presence of secondary pouches or irregular shape.

†Helsinki cohort refers to the patient population with untreated unruptured aneurysms followed by Juvela et al⁵ 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 underwent 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 χ^2 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

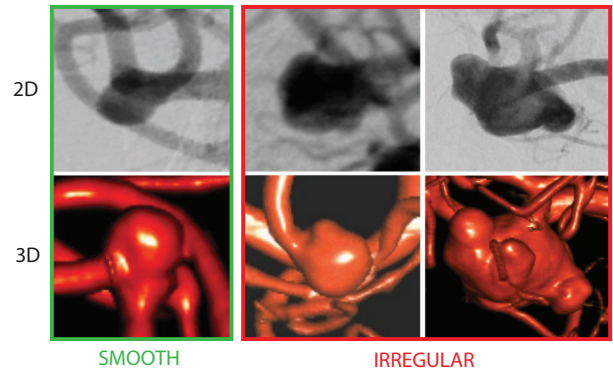


Figure 2. Demonstrative examples of smooth or irregular shape determined from 2D digital subtraction (2-dimensional DS) angiography projections or 3D-DS angiography images. Shape was classified as irregular when small bleb(s) or secondary aneurysm(s) were protruding from the saccular intracranial aneurysm fundus in any angiography image projection, or when the aneurysm fundus was clearly bi- or multilobular.

shape of sIA, smoking, PHASES score,¹⁷ familial background, and hypertension as indicators of ruptured sIA 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).

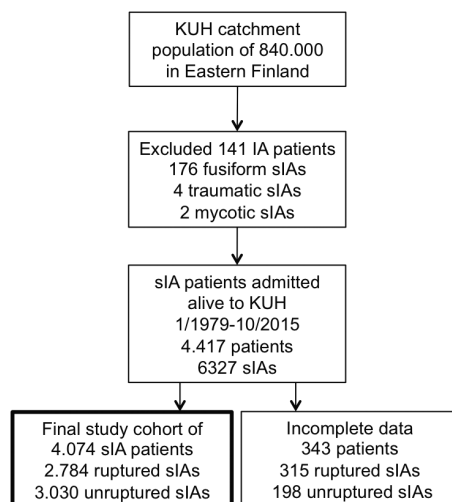


Figure 1. Flowchart description of selection criteria for the studied population. sIAs indicates saccular intracranial aneurysms; and KUH, Kuopio University Hospital.

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

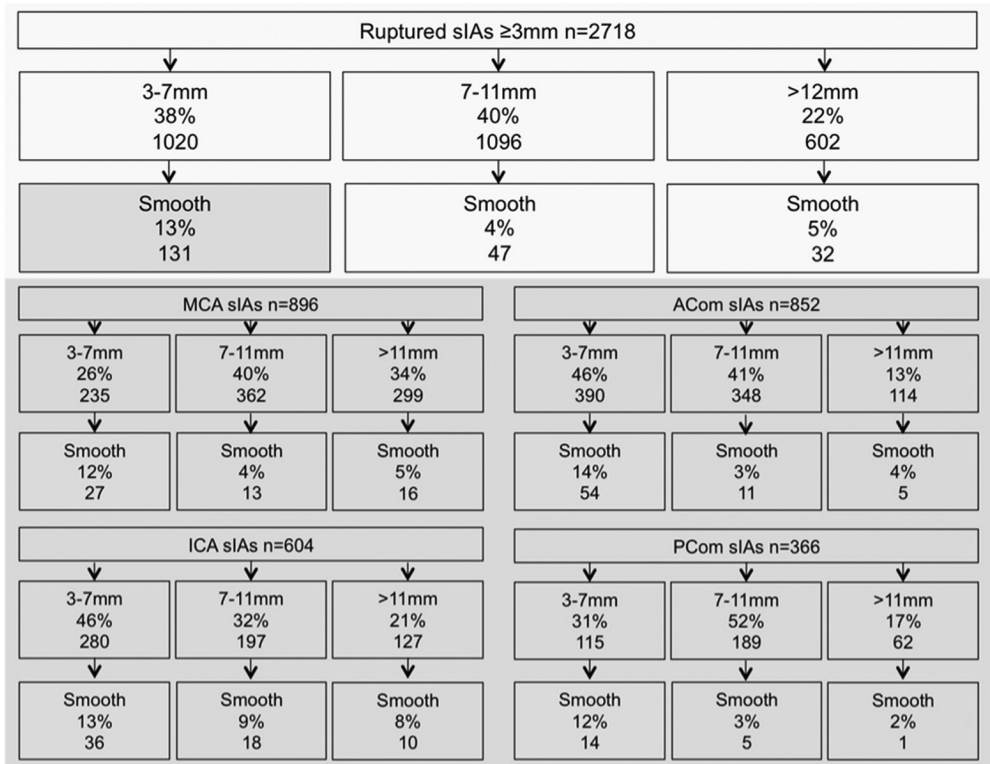


Figure 3. Distribution of ruptured aneurysms according to size and shape. The first 3 rows of the flowchart represents all studied ruptured saccular intracranial aneurysms (sIAs), of which 38% had ruptured at a size of 3 to 7 mm. Of these, 87% were irregular in shape. If irregular shape would be considered as a treatment criteria, only 13% of small (3–7 mm) sIAs would have been left untreated. Irregular shape was common (96%–95%) also in larger ruptured sIAs. The bottom 6 rows of the flowcharts demonstrate how location affects the size at which sIAs rupture (46% 3–7 mm in anterior communicating artery [ACom] vs 26% 3–7 mm in middle cerebral artery [MCA]). Irregular shape is, however, prevalent among ruptured sIAs in all locations. ICA indicates internal carotid artery; and PCom, posterior communicating artery.

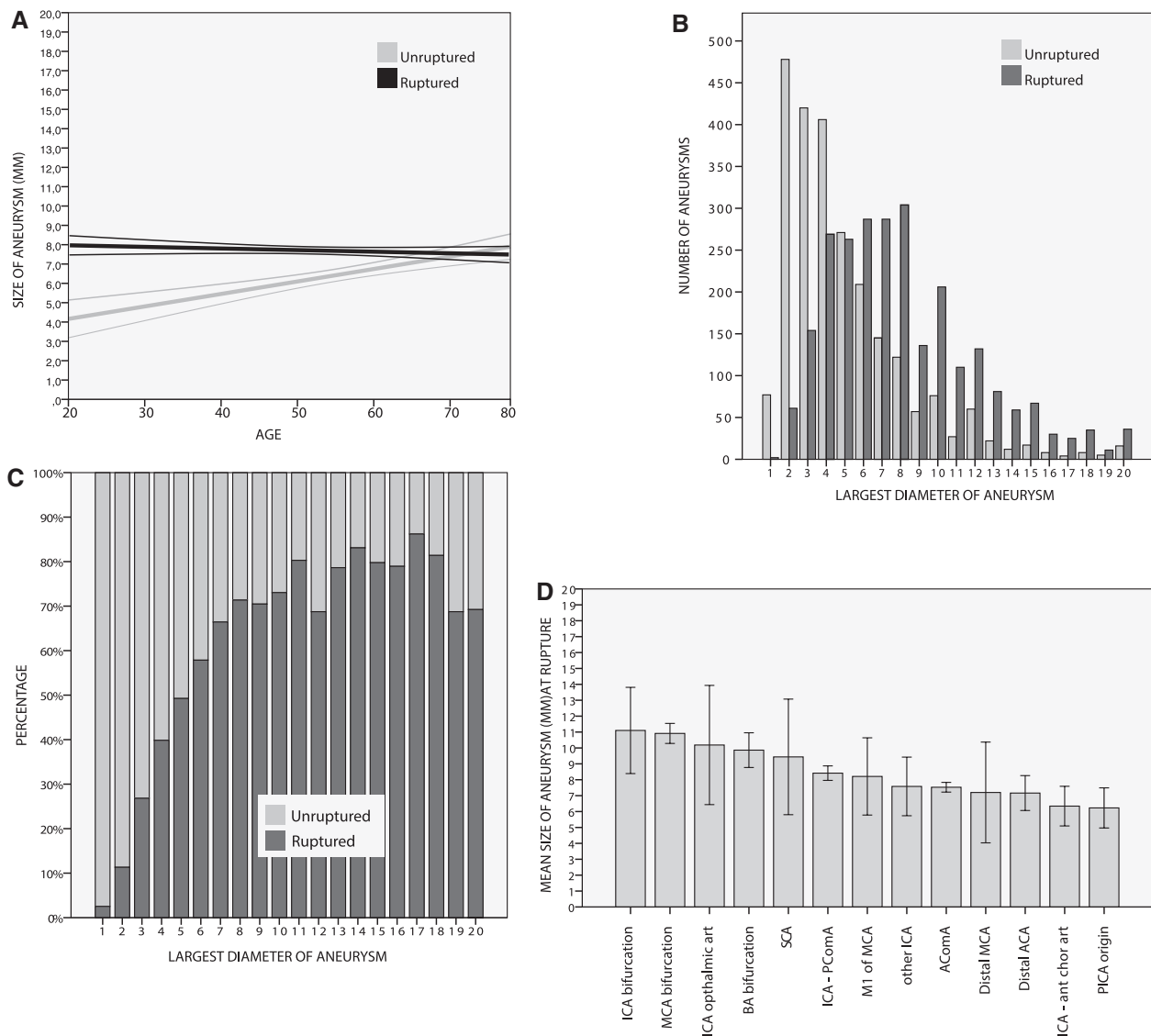


Figure 4. We plotted aneurysm size against patient age at the time of aneurysm detection and found that although the size of unruptured aneurysms seem to grow with increasing age, the size at which the aneurysms rupture does not change with age (**A**). Although this seems to suggest a size threshold critical for rupture, closer analysis reveals that aneurysms of all size had ruptured (**B**) although tendency to rupture clearly increased with size (**C**). Location clearly affected the size at which saccular intracranial aneurysms ruptured (**D**). Graphs display median (straight line) and 95% confidence intervals (curves). ACA indicates anterior cerebral artery; AComA, anterior communicating artery; BA, basilar artery; ICA, internal carotid artery; M1, proximal segment of MCA; MCA, middle cerebral artery; PComA, posterior communicating artery; PICA, posterior inferior cerebellar artery; and SCA, superior cerebellar artery.

during follow-up or before intervention. 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 sIAs 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

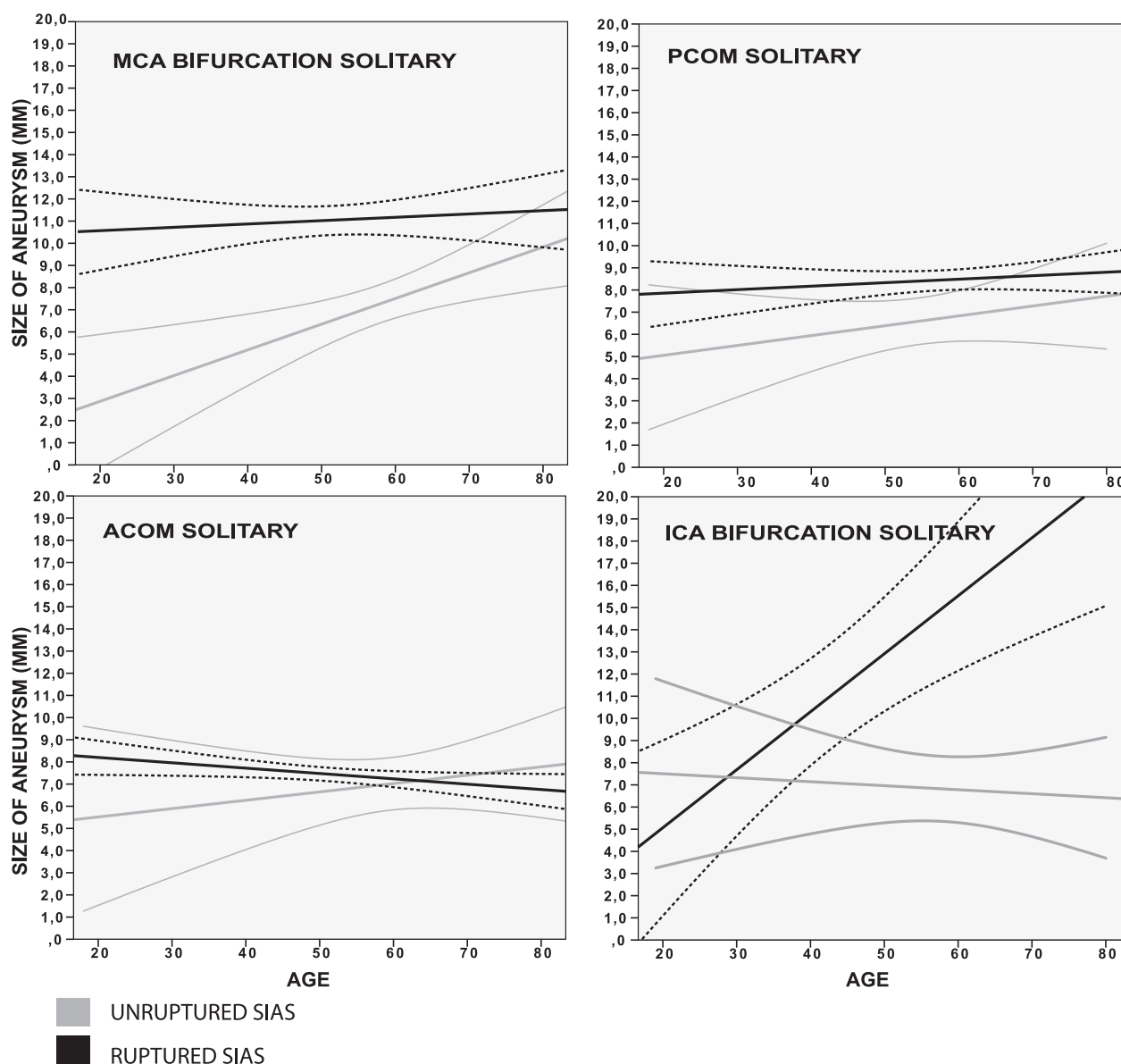


Figure 5. Because location seems to affect the risk of rupture, we plotted aneurysm size against patient age at the time of aneurysm detection in different locations. In some locations (middle cerebral artery [MCA], posterior communicating artery [PCoM], and anterior communicating artery [ACoM]) unruptured aneurysms were larger in older patients, suggesting aneurysm growth with time. In other locations (internal carotid artery [ICA]), however, such tendency to grow was not observed. How age affected the size at which aneurysms ruptured was also clearly different depending on the location. These observations suggest that growth and subsequent size-associated risk of rupture, and therefore the whole natural history of unruptured aneurysms differ in different locations. Graphs display median (straight line) and 95% confidence intervals (curves). sIAs indicates saccular intracranial aneurysms.

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).^{6,7} 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.^{13–15} 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,⁷ 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.^{6–10} In the only lifelong follow-up cohort of unruptured sIAs, 25% of sIAs that were small (<7 mm) at initial diagnosis eventually ruptured.⁵ 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.^{13,15} 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 sIAs 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 κ 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 al²⁰ 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.

Sources of Funding

This study was funded with research funds from The Finnish Medical Foundation, The Petri Honkanen Foundation, The Päivikki and Sakari Sohlberg Foundation, The Maire Taponen Foundation, The Emill Aaltonen Foundation, The North Savo Regional Fund Of Finnish Cultural Foundation, The Academy of Finland, and The Kuopio University Hospital.

Disclosures

None.

References

- Karamanakis PN, von Und Zu Fraunberg M, Bendel S, Huttunen T, Kurki M, Hernesniemi J, et al. Risk factors for three phases of 12-month mortality in 1657 patients from a defined population after acute aneurysmal subarachnoid hemorrhage. *World Neurosurg*. 2012;78:631–639. doi: 10.1016/j.wneu.2011.08.033.
- Kotowski M, Naggara O, Darsaut TE, Nolet S, Gevry G, Kouznetsov E, et al. Safety and occlusion rates of surgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis of the literature from 1990 to 2011. *J Neurol Neurosurg Psychiatry*. 2013;84:42–48. doi: 10.1136/jnnp-2011-302068.
- Naggara O, Darsaut T, Trystram D, Tselikas L, Raymond J. Unruptured intracranial aneurysms: why we must not perpetuate the impasse for another 25 years. *Lancet Neurol*. 2014;13:537–538. doi: 10.1016/S1474-4422(14)70091-2.
- Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol*. 2011;10:626–636. doi: 10.1016/S1474-4422(11)70109-0.
- Korja M, Lehto H, Juvela S. Lifelong rupture risk of intracranial aneurysms depends on risk factors: a prospective Finnish cohort study. *Stroke*. 2014;45:1958–1963. doi: 10.1161/STROKEAHA.114.005318.
- Wiebers DO, Whisnant JP, Huston J III, Meissner I, Brown RD Jr, Piepgras DG, et al; International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet*. 2003;362:103–110.
- Morita A, Kirino T, Hashi K, Aoki N, Fukuhara S, et al; UCAS Japan Investigators. The natural course of unruptured cerebral aneurysms in a Japanese cohort. *N Engl J Med*. 2012;366:2474–2482.
- Sonobe M, Yamazaki T, Yonekura M, Kikuchi H. Small unruptured intracranial aneurysm verification study: SUAVE study, Japan. *Stroke*. 2010;41:1969–1977. doi: 10.1161/STROKEAHA.110.585059.
- Ishibashi T, Murayama Y, Urashima M, Saguchi T, Ebara M, Arakawa H, et al. Unruptured intracranial aneurysms: incidence of rupture and risk factors. *Stroke*. 2009;40:313–316.
- Matsumoto K, Oshino S, Sasaki M, Tsuruzono K, Taketsuna S, Yoshimine T. Incidence of growth and rupture of unruptured intracranial aneurysms followed by serial MRA. *Acta Neurochir (Wien)*. 2013;155:211–216.
- Frösen J. Smooth muscle cells and the formation, degeneration, and rupture of saccular intracranial aneurysm wall—a review of current pathophysiological knowledge. *Transl Stroke Res*. 2014;5:347–356. doi: 10.1007/s12975-014-0340-3.
- Kataoka K, Taneda M, Asai T, Kinoshita A, Ito M, Kuroda R. Structural fragility and inflammatory response of ruptured cerebral aneurysms. A comparative study between ruptured and unruptured cerebral aneurysms. *Stroke*. 1999;30:1396–1401.
- Weir B, Disney L, Karrison T. Sizes of ruptured and unruptured aneurysms in relation to their sites and the ages of patients. *J Neurosurg*. 2002;96:64–70. doi: 10.3171/jns.2002.96.1.0064.
- Bijlenga P, Ebeling C, Jaegersberg M, Summers P, Rogers A, Waterworth A, et al. Risk of rupture of small anterior communicating artery aneurysms is similar to posterior circulation aneurysms. *Stroke*. 2013;44:3018–3026. doi: 10.1161/STROKEAHA.113.001667.
- Elsharkawy A, Lehecka M, Niemela M, Billon-Grand R, Lehto H, Kivisaari R, et al. A new, more accurate classification of middle cerebral artery aneurysms: computed tomography angiographic study of 1,009 consecutive cases with 1,309 middle cerebral artery aneurysms. *Neurosurgery*. 2013;73:94–102, discussion 102.
- Hayakawa M, Katada K, Anno H, Imizu S, Hayashi J, Irie K, et al. CT angiography with electrocardiographically gated reconstruction for visualizing pulsation of intracranial aneurysms: identification of aneurysmal protuberance presumably associated with wall thinning. *AJNR Am J Neuroradiol*. 2005;26:1366–1369.
- Greving JP, Wermer MJ, Brown RD Jr, Morita A, Juvela S, Yonekura M, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol*. 2014;13:59–66. doi: 10.1016/S1474-4422(13)70263-1.
- Etiman N, Brown RD Jr, Beseoglu K, Juvela S, Raymond J, Morita A, et al. The unruptured intracranial aneurysm treatment score: a multidisciplinary consensus. *Neurology*. 2015;85:881–889. doi: 10.1212/WNL.0000000000001891.
- Suh SH, Cloft HJ, Huston J III, Han KH, Kallmes DF. Interobserver variability of aneurysm morphology: discrimination of the daughter sac. *J Neurointerv Surg*. 2016;8:38–41. doi: 10.1136/neurintsurg-2014-011471.
- Raghavan ML, Ma B, Harbaugh RE. Quantified aneurysm shape and rupture risk. *J Neurosurg*. 2005;102:355–362. doi: 10.3171/jns.2005.102.2.0355.
- Rahman M, Ogilvy CS, Zipfel GJ, Derdeyn CP, Siddiqui AH, Bulsara KR, et al. Unruptured cerebral aneurysms do not shrink when they rupture: multicenter collaborative aneurysm study group. *Neurosurgery*. 2011;68:155–160, discussion 160. doi: 10.1227/NEU.0b013e3181ff357c.