

Size Ratio Correlates With Intracranial Aneurysm Rupture Status

A Prospective Study

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Background and Purpose—The prediction of intracranial aneurysm (IA) rupture risk has generated significant controversy. The findings of the International Study of Unruptured Intracranial Aneurysms (ISUIA) that small anterior circulation aneurysms (<7 mm) have a 0% risk of subarachnoid hemorrhage in 5 years is difficult to reconcile with other studies that reported a significant portion of ruptured IAs are small. These discrepancies have led to the search for better aneurysm parameters to predict rupture. We previously reported that size ratio (SR), IA size divided by parent vessel diameter, correlated strongly with IA rupture status (ruptured versus unruptured). These data were all collected retrospectively off 3-dimensional angiographic images. Therefore, we performed a blinded prospective collection and evaluation of SR data from 2-dimensional angiographic images for a consecutive series of patients with ruptured and unruptured IAs.

Methods—We prospectively enrolled 40 consecutive patients presenting to a single institution with either ruptured IA or for first-time evaluation of an incidental IA. Blinded technologists acquired all measurements from 2-dimensional angiographic images. Aneurysm rupture status, location, IA maximum size, and parent vessel diameter were documented. The SR was calculated by dividing the aneurysm size (mm) by the average parent vessel size (mm). A 2-tailed Mann-Whitney test was performed to assess statistical significance between ruptured and unruptured groups. Fisher exact test was used to compare medical comorbidities between the ruptured and unruptured groups. Significant differences between the 2 groups were subsequently tested with logistic regression. SE and probability values are reported.

Results—Forty consecutive patients with 24 unruptured and 16 ruptured aneurysms met the inclusion criteria. No significant differences were found in age, gender, smoking status, or medical comorbidities between ruptured and unruptured groups. The average maximum size of the unruptured IAs (6.18 ± 0.60 mm) was significantly smaller compared with the ruptured IAs (7.91 ± 0.47 mm; $P=0.03$), and the unruptured group had significantly smaller SRs (2.57 ± 0.24 mm) compared with the ruptured group (4.08 ± 0.54 mm; $P<0.01$). Logistic regression was used to evaluate the independent predictive value of those variables that achieved significance in univariate analysis (IA maximum size and SR). Using stepwise selection, only SR remained in the final predictive model (OR, 2.12; 95% CI, 1.09 to 4.13).

Conclusion—SR, the ratio between aneurysm size and parent artery diameter, can be easily calculated from 2-dimensional angiograms and correlates with IA rupture status on presentation in a blinded analysis. SR should be further studied in a large prospective observational cohort to predict true IA risk of rupture. (*Stroke*. 2010;41:916-920.)

Key Words: intracranial aneurysm rupture ■ size ratio ■ subarachnoid hemorrhage

Subarachnoid hemorrhage from ruptured intracranial aneurysms (IAs) is associated with significant morbidity (eg, hydrocephalus, seizures, vasospasm, and stroke) and mortality.¹ As a result, IA treatment is often performed as a prophylactic measure before rupture. However, IA treatments, including both surgical clipping and endovascular coiling, are associated with substantial risks of their own.² Therefore, risk stratification of IAs has become critical to

counseling patients and the treatment decision-making process.

Predicting the rupture risk of IAs has recently generated considerable controversy. The International Study of Unruptured Intracranial Aneurysms (ISUIA) reported low rupture rates for IAs when stratified according to size² with small anterior circulation aneurysms (<7 mm) demonstrating a 0% risk of subarachnoid hemorrhage in 5 years. However, other

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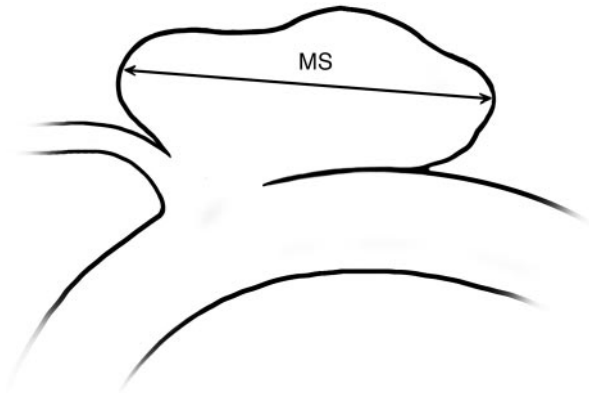


Figure 1. Maximal size (MS) measurement.

studies have shown that a significant portion of ruptured IAs are small.^{3–6} These discrepancies have fueled the search for better aneurysm parameters to predict rupture. These efforts resulted in the discovery that alternative morphometrics and IA hemodynamics correlate strongly with IA rupture.^{7–10}

We previously reported that size ratio (SR), IA size divided by parent vessel diameter, correlated strongly with IA rupture status (ruptured versus unruptured) in a retrospective review of patients presenting with IAs.⁸ We also demonstrated that IA hemodynamics changed significantly with changes in SR, even when holding other IA morphometrics constant.⁹ Specifically, increased SR resulted in more complex IA flow patterns, multiple vortices, and low aneurysmal wall shear stress. Although interesting, these data were all collected retrospectively off 3-dimensional angiographic images. Therefore, we undertook to prospectively collect and evaluate SR data from 2-dimensional angiographic images for a consecutive series of patients presenting to Millard Fillmore Gates Cir Hospital, Buffalo, NY.

Methods

Power analysis based on prior retrospectively collected data⁸ provided a total required sample size of 39 patients to achieve an α of 0.05 and β of 0.8. Therefore, we decided a priori to prospectively enroll 40 consecutive patients with IA presenting to Millard Fillmore Gates Cir Hospital secondary to either a ruptured IA or for first-time evaluation of an incidental IA. Institutional Review Board approval was obtained before prospective data collection.

A clinical data form was provided to the angiography suite technicians who were required to fill in the requested data fields. Each technician underwent educational sessions as to how to measure the aneurysm as well as the parent vessel (see subsequently); however, at no time was the calculation of SR or a discussion/explanation of the study goals explained to them. It was explained that they were expected to remain blinded as to the study purpose.

All patients underwent 2-dimensional digital subtraction angiography and these images were used for study measurements. Aneurysm rupture status, location, IA maximum size, and parent vessel diameter were documented (Figure 1). Parent vessel diameter was measured at the nearest region of definable vessel for all vessels that had direct contact with the aneurysm neck (in the case of a sidewall aneurysm, the region of vessel on the proximal side of the aneurysm was used). With aneurysms whose orifice directly involved more than a single parent vessel, for the purposes of SR calculation, a mean parent vessel diameter was used (generated by averaging each of the involved vessels). Additionally, the patient's age, gender,

Table 1. Patient Characteristics in Unruptured and Ruptured IA Groups

Parameter	Unruptured IAs	Ruptured IAs	P
Age	64.8 ± 13.5 (mean ± SD)	60.6 ± 12.5 (mean ± SD)	0.32
Gender (female/male)	20/4	12/4	0.69
Smoking	11	7	1.0
Hypertension	14	8	0.73

smoking status, and history of medical comorbidities were also collected.

The SR was calculated by dividing the aneurysm size (mm) by the average parent vessel size (mm). This calculation was performed by 2 of the authors (J.S. and M.R.) and was completely formulaic based on the blinded raw measurements.

The mean and SD were calculated for the SR ratio calculations in the ruptured and unruptured groups. A 2-tailed Mann-Whitney test was performed to assess statistical significance between ruptured and unruptured groups. Fisher exact test was used to compare medical comorbidities between the ruptured and unruptured groups. Significant differences between the 2 groups were subsequently tested with logistic regression. Receiver operating characteristics were generated for SR and rupture risk. SE and probability values are reported. Statistical analysis was performed using Microsoft Excel 2003 (Microsoft 2007), InStat3 (Graphpad, Inc), and SPSS (SPSS, Inc).

Results

Forty consecutive patients with 24 unruptured and 16 ruptured aneurysms met the inclusion criteria. According to a priori study design, 3 additional patients were excluded during the study duration secondary to their presenting with symptomatology clearly referable to their aneurysm but unruptured. (No significant differences in outcome were obtained when these aneurysms were included in post hoc analysis [data not shown].) Also, no significant differences were found in age, gender, smoking status, or medical comorbidities between ruptured and unruptured groups (Table 1).

The average maximum size of the unruptured IAs (6.18 ± 0.60 mm) was significantly smaller compared with the ruptured IAs (7.91 ± 0.47 mm; $P=0.03$; Figure 2). The average vessel size did not vary significantly between the 2 groups (2.58 ± 0.19 mm unruptured versus 2.24 ± 0.20 mm ruptured, $P=0.25$). The unruptured group had significantly

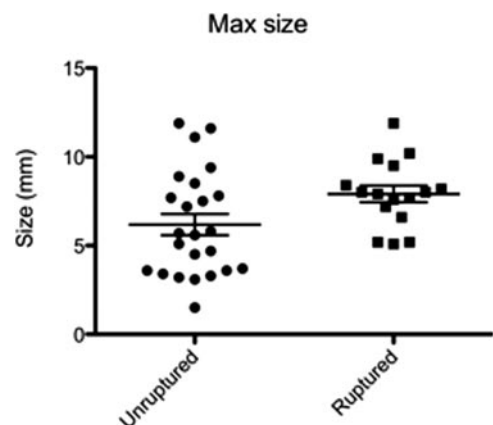


Figure 2. Size parameters in unruptured versus ruptured IAs.

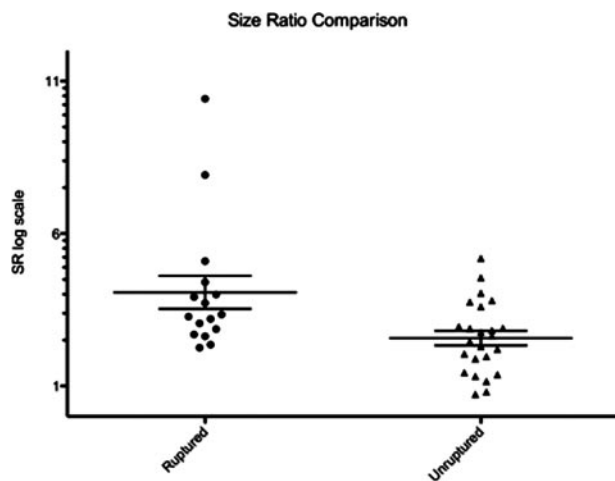


Figure 3. SR based on maximum aneurysm size.

smaller SRs (2.57 ± 0.24 mm) compared with the ruptured group (4.08 ± 0.54 ; $P < 0.01$; Figure 3).

Logistic regression was used to evaluate the independent predictive value of those variables that were significantly different between the 2 groups (IA maximum size and SR). Using stepwise selection, only SR remained in the final predictive model (OR, 2.12; 95% CI, 1.09 to 4.13; Figure 4). Correlation between SR and size demonstrated a Pearson correlation coefficient of 0.50.

Sixty-nine percent of the ruptured aneurysms had a SR > 3 compared with only 25% of the unruptured aneurysms. A receiver operating characteristic curve was generated for SR to determine the ideal threshold for rupture status. An SR threshold of > 3 was associated with IA rupture with a sensitivity of 69% and specificity of 75% (Figure 5).

Discussion

Subarachnoid hemorrhage from a ruptured IA is associated with tremendous morbidity and mortality.^{11,12} However, the enthusiasm to treat unruptured IAs to prevent rupture has been tempered by significant risks associated with IA treatment.² Specifically, in the ISUIA study, the overall morbidity and mortality for patients who underwent either surgical clipping or coiling for their unruptured IA was approximately 10% at 1 year.² Because treatment is not without risks, much effort has been expended on determining those IAs that may be at a higher risk of rupturing, thereby improving the risk benefit profile of treatment. The ISUIA study was 1 of the

Size and SR:

Rupture status = $-2.97 + 0.63(\text{SR}) + 0.80(\text{size})$

p value SR = 0.13

p value size = 0.66

SR only:

Rupture status = $-2.76 + 0.75(\text{SR})$

p value = 0.03

Figure 4. Logistic regression using SR and IA size to predict rupture risk. Size and SR: rupture status = $-2.97 + 0.63(\text{SR}) + 0.80(\text{size})$. Probability value SR = 0.13. Probability value size = 0.66. SR only: rupture status = $-2.76 + 0.75(\text{SR})$. Probability value = 0.03.

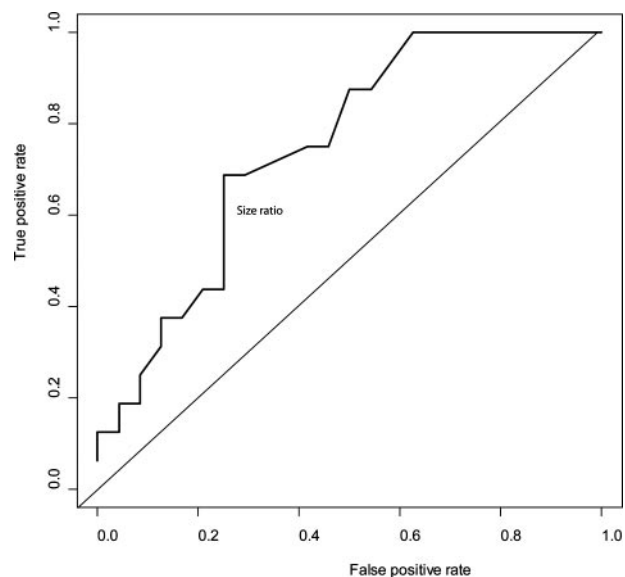


Figure 5. Receiver operating characteristic curve of SR and rupture status.

largest and best designed attempts at answering this question with prospective observational follow-up on patients with unruptured IAs to determine incidence of IA rupture.^{2,11} The ISUIA study confirmed that increasing IA size is associated with an increased rupture risk. However, their results caused concern because the reported rupture risk was lower than previous and subsequent reports.^{3–6} For example, small anterior circulation aneurysms (< 7 mm) were found to have a 0% risk of subarachnoid hemorrhage in 5 years. These values were difficult to reconcile with the findings of Weir et al that 70% of ruptured aneurysms were < 10 mm in size in a study of 945 patients.⁶

Interestingly, Weir et al also noted that 40.3% of the ruptured IAs originated from the anterior cerebral artery or anterior communicating artery compared with only 13% of the unruptured aneurysms.⁶ The role of aneurysm location was partially addressed in the ISUIA studies with a gross system of localization that entailed separating anterior circulation aneurysms from posterior circulation aneurysms. However, interestingly, the ISUIA authors chose to group posterior communicating aneurysms with the posterior circulation group rather than the anterior group, a decision that was counter to established anatomic convention. Based on this dichotomous analysis, the ISUIA investigators did demonstrate that a clear difference in rupture risk existed between their posterior versus anterior groups. However, to date, no more detailed analysis of aneurysm location and rupture risk has been published from the ISUIA data. This idea that location, in addition to size, conferred different rupture risks was furthered by a study in 2006 demonstrating that ruptured IAs originating from distal blood vessels were smaller compared with ruptured IAs originating from proximal, larger blood vessels¹³ (Figure 6). These results were in contrast to unruptured aneurysms that did not have significant differences in size based on location.

In an effort to develop a single, simple morphometric to account for both aneurysm size and location, as reflected in

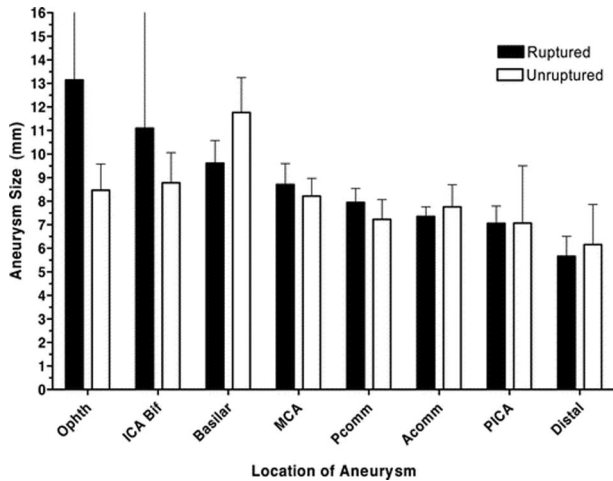


Figure 6. Location of IA based on rupture status from Carter et al.¹

parent vessel size, we developed a measure of the relationship of aneurysm size to parent artery diameter, SR. In a retrospective study of 3-dimensional angiographic images in 45 patients, SR and undulation index had the strongest independent correlation with ruptured IAs in a logistic regression analysis of multiple aneurysm parameters.⁸ Although undulation index involves a somewhat complicated analysis, SR may provide an easily applicable, and yet improved, metric. To further improve the applicability of SR and to make it more easily applied to 2-dimensional angiography as well as to evaluate its use in a manner more typical to standard aneurysm measurement practice (and the same method of size measurement used in ISUIA), for the current study, we used the maximal size of a given aneurysm rather than the maximal height, as was used in our prior 3-dimensional studies (Figure 7). For completeness, SR was also calculated using maximum height with similar results between the 2 groups (Table 2). In the previous study, the optimal SR for distinguishing between ruptured and unruptured groups was found to be 2.⁸ Seventy-seven percent of ruptured IAs had an SR >2 and 83% of unruptured IAs had a SR of ≤2. Our current results appears to favor a higher SR threshold to best distinguish between ruptured and unruptured groups with 69% of ruptured IAs compared with only 25% of ruptured IAs having a SR >3. Certainly larger, truly observational

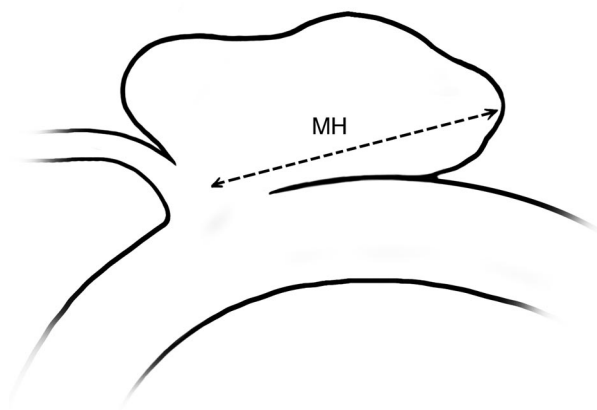


Figure 7. Maximum aneurysm height.

Table 2. Mann-Whitney Test Comparing SR in Unruptured Versus Ruptured IAs

	SR MH	SR MS
Unruptured	2.11	2.57
Ruptured	3.68	4.07
P	0.0012*	0.0091*

MH indicates maximum height; MS, maximum size.

*Statistically significant.

studies are necessary before certainty can be applied to any potential threshold.

This investigation further develops our prior observations made with retrospective data with 40 prospectively identified and recruited patients presenting with incidental or ruptured IAs. Additionally, we demonstrate the ease of use and practical use of SR in a real-world situation with blinded technologists performing SR evaluation off 2-dimensional angiographic images at the time of initial presentation. The ruptured cohort demonstrated statistically significantly larger SRs compared with the unruptured cohort, suggesting that SR may provide a valuable real-world tool in the assessment of IA rupture risk.¹⁴

IA size continues to be an efficient and widely used measure for IA rupture risk assessment. Multiple previous studies, as well as our data, demonstrate that ruptured IAs are larger than unruptured IAs.^{2,11} Although easy to measure and very useful, size alone does not take into account additional characteristics or hemodynamics that may increase rupture risk. Specifically, IA size may miss smaller aneurysms that have a higher rupture risk based on location or relationship with the parent blood vessel.¹³ SR is a stepwise improvement in the use of size for risk assessment of IAs. It is also encouraging that these data reflect blinded technologists' measurements off of 2-dimensional angiographic images obtained at the time of presentation suggesting that there is an ease of real-world applicability with SR, which has been a criticism of other more complicated morphometrics.¹⁵

It should be noted that various patient factors such as age and comorbidities have been shown to confer rupture risk. These factors were not found to be significantly different between the unruptured and ruptured groups in our study. This is in contrast to a retrospective analysis by Nahed et al, which found that in patients with IAs ≤7 mm in size, hypertension, young age, and posterior circulation location were significant risk factors for rupture.⁴ It is possible that this study was insufficiently powered to assess the contributions of these factors. In any case, these nonmorphological parameters are certainly important for IA rupture risk stratification but do not obviate the need for a robust morphometric variable such as SR.

Given the study design, any change in SR as a result of IA rupture could not be determined. Whether IA size changes with rupture is a hotly contested issue. Prospective studies in the 1980s found that unruptured IAs that ruptured during observation had a larger mean size compared with IAs that presented with rupture at the same institution.^{16,17} As a result, the authors hypothesized that IAs may shrink with rupture. However, a histological analysis study of ruptured IAs and

another study documenting IA size before and after rupture found no evidence for IA shrinkage after rupture.^{18,19} Whether or not SR changes with IA rupture would require a prospective observational study of unruptured IAs until they rupture. Unfortunately, such an investigation is beyond the logistical and economic resources of this study, but we hope that such an analysis might be performed on already existing prospective observational natural history study data sets.

A significant limitation of this study is the fact that IA measurement occurred after IA rupture. It must be stressed that the current study does not, in any way, correlate SR with future risk of rupture, but rather with the likelihood of a given aneurysm, on presentation, being ruptured or not. This is a very important distinction that can only be reconciled with the performance of a true observational prospective natural history study or the application of this metric to an existing prospective observational data set (such as the ISUIA data).

Conclusion

Predicting risk of rupture of IAs continues to be a topic of much debate. It appears likely that morphological risk stratification of IAs must at some point involve greater predictive power than that available with aneurysm size alone. SR, the ratio between aneurysm size and parent artery diameter, can be relatively easily calculated from 2-dimensional angiograms and correlates with IA rupture status on presentation in a blinded analysis. To reconcile these findings with a prospective risk of rupture, SR should be further studied in a large prospective observational cohort.

Disclosures

None.

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