See the Editorial and the Response in this issue, pp 220–221.

J Neurosurg 99:248–253, 2003

Smaller cerebral aneurysms producing more extensive subarachnoid hemorrhage following rupture: a radiological investigation and discussion of theoretical determinants

STEPHEN M. RUSSELL, M.D., KE LIN, B.A., SIGRID A. HAHN, M.D., AND JAFAR J. JAFAR, M.D.

Department of Neurosurgery, New York University School of Medicine, New York, New York

Object. The goal of this study was to determine the relationship between aneurysm size and the volume of subarachnoid hemorrhage (SAH).

Methods. One hundred consecutive patients who presented with acute SAH, which was diagnosed on the basis of a computerized tomography (CT) scan within 24 hours postictus and, subsequently, confirmed to be aneurysmal in origin by catheter angiography, were included in this study. The data were collected prospectively in 32 patients and retrospectively in 68. The volume of SAH on the admission CT scan was scored in a semiquantitative manner from 0 to 30, according to a previously published method.

The mean aneurysm size was 8.3 mm (range 1–25 mm). The mean SAH volume score was 15 (range 0–30). Regression analysis revealed that a smaller aneurysm size correlated with a more extensive SAH ($r^2 = 0.23$, $p < 0.0001$). Other variables including patient sex and age, intraparenchymal or intraventricular hemorrhage, multiple aneurysms, history of hypertension, and aneurysm location were not statistically associated with a larger volume of SAH.

Conclusions. Smaller cerebral aneurysm size is associated with a larger volume of SAH. The pathophysiological basis for this correlation remains speculative.

KEY WORDS • cerebral aneurysm • subarachnoid hemorrhage • aneurysm size

ALTHOUGH it has been reported that smaller aneurysms tend not to bleed,[10,19] clinical experience has indicated otherwise. In fact most aneurysms that rupture are smaller than 1 cm in diameter.[7] Despite the fact that the volume of SAH is a known predictor of vasospasm and delayed ischemic neurological deficits,[1,2,5] to date there have been no reports correlating the volume of SAH with the sizes of ruptured aneurysms. Therefore, we were interested in determining the relationship between aneurysm size and volume of SAH, specifically whether smaller aneurysms produce more extensive SAH.

Clinical Material and Methods

Patient Population

Between October 1999 and April 2002, 100 consecutive patients who presented with an acute SAH were included in this study. The SAH was diagnosed on the basis of findings from a CT scan of the brain or lumbar puncture (when CT findings were nondiagnostic) obtained within 24 hours after ictus and was subsequently confirmed to be aneurysmal in origin by catheter angiography.

Abbreviations used in this paper: ACoA = anterior communicating artery; CT = computerized tomography; ICA = internal carotid artery; ICP = intracranial pressure; INR = international normalized ratio; IPH = intraparenchymal hemorrhage; IVH = intraventricular hemorrhage; MCA = middle cerebral artery; PCoA = posterior communicating artery; SAH = subarachnoid hemorrhage.

For each patient, age, sex, aneurysm size (greatest dimension), aneurysm location, volume of SAH, presence of IPH or IVH, and the incidence of ventriculostomy placement within 24 hours after hospital admission was recorded. These data were collected by reviewing admission CT scans, diagnostic cerebral angiograms, and inpatient records. A history of hypertension, as well as the use of aspirin, warfarin, and cigarettes was recorded. Admission platelet and INR values were checked. A platelet count less than 100,000/μl or an INR greater than 1.3 were considered to be abnormal. Data for the first 68 patients were reviewed retrospectively, whereas data for the final 32 patients were collected prospectively.

All patients underwent CT scanning of the head on arrival at the hospital. The volume of cisternal blood on the admission CT scan was graded from 0 to 30, with a score of 0 indicating no radiographic evidence of SAH (although the results of the lumbar puncture were positive) and a score of 30 indicating a maximal volume of cisternal blood. This semiquantitative grading system has been previously described and confirmed to have high interobserver reliability.[9] In brief, the basal subarachnoid space was divided into 10 separate cisternal segments, each receiving a score ranging from 0 (no blood) to 3 (maximal blood) (Fig. 1). The scores for all subarachnoid compartments were added together, yielding a total score. Positive results of a lumbar puncture were defined as the findings of xanthochromia in the cerebrospinal fluid of a patient presenting with severe, sudden headache. A single physician reviewed the admis-

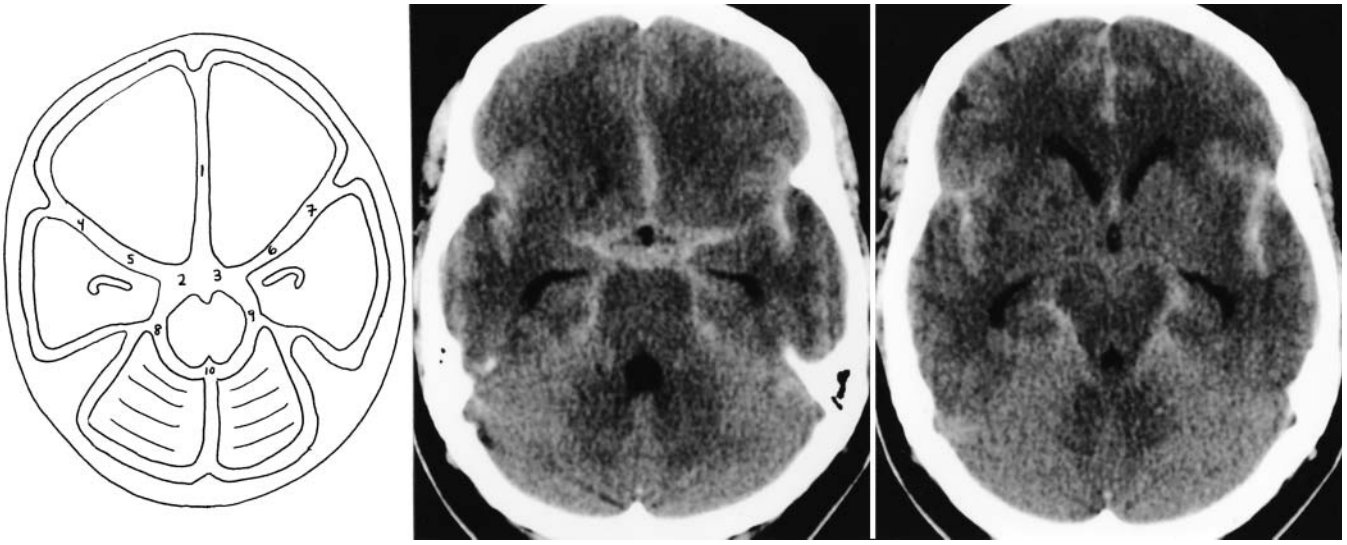

FIG. 1. *Left:* Diagram showing the division of the basal subarachnoid space into 10 cisternal compartments for the quantification of SAH. Each compartment was scored from 0 (no hemorrhage) to 3 (maximal hemorrhage). The total score (0–30) was the sum of all compartments. *Center* and *Right*: Representative axial CT scans obtained in a single patient, revealing acute SAH. The SAH volume score for each cisternal compartment are as follows: Compartment 1, 2; Compartment 2, 3; Compartment 3, 3; Compartment 4, 1; Compartment 5, 1; Compartment 6, 2; Compartment 7, 2; Compartment 8, 1; Compartment 9, 1; Compartment 10, 1; giving a total score of 17 (of a possible 30).

sion CT scans and was blinded to data concerning the size of the aneurysm.

Cerebral angiography was performed within 24 hours after hospital admission. The greatest aneurysm dimension (in millimeters) was measured using either the cavernous ICA (4-mm diameter) or the basilar artery (3-mm diameter) as a reference.[8,11,16] The parent vessel and location of each aneurysm was determined. Twenty-eight patients had multiple aneurysms. In these patients, the aneurysm that ruptured was obvious in all cases, as determined by the focality of hemorrhage on the admission CT scan and on operative findings.

The statistical relationship between aneurysm size and SAH volume was evaluated using regression analysis. The coefficient of determination (r^2), slope coefficient, and their respective significance values were calculated. The data were also divided into groups based on aneurysm size (1–5 mm, 6–10 mm, 11–15 mm, and $>$ 15 mm). The mean volumes of SAH for each group were compared using analysis of variance with a linear contrast statement. The frequencies of IPH, IVH, and ventriculostomy placement for each group were analyzed using the Mantel–Haenszel chi-square test. Statistical computations were performed using commercially available software (JMP Statistical Analysis Program [version 3.0] or the SAS System; SAS Institute, Cary, NC). Findings with a probability value less than 0.05 were considered significant.

Results

The mean age of the patients was 49.6 years (range 23–81 years); 58% of the patients were women and 42% were men. In six patients the CT scans lacked evidence of SAH and, subsequently, these patients underwent lumbar punctures, the samples from which proved positive for xanthochromia. The mean aneurysm size was 8.3 mm (range 1–25 mm) and the mean SAH volume score was 15 (range 0–30). The aneurysm locations were as follows: 31 lesions on the ACoA complex (31%); 27 on the PCoA (27%); 16 on the MCA (16%); nine in the paraclinoid region (ophthalmic or superior hypophysial artery) (9%); 10 at the basilar bifurcation or superior cerebellar artery (10%); five in the pericallosal region (5%); and two aneurysms at the ICA bifurcation (2%). A review of the clinical records and admission CT scans of the brain showed that 25 patients had an IPH (25%), 30 had some IVH (30%), and 44 required placement of a ventriculostomy (44%). Thirty patients smoked cigarettes (30%), 22 had a history of hypertension (22%), and three ingested aspirin on a daily basis (3%). No patient received anticoagulant medications or had evidence of abnormal coagulation profiles. Table 1 summarizes the clinical and radiographic data.

Patient age and sex, aneurysm location, cigarette use, history of hypertension, presence of multiple aneurysms, and the side on which the aneurysm was located had no statistically significant relationship to the volume of SAH (Table 2). Regression analysis revealed that smaller aneurysm size correlated with more extensive SAH (Table 3). This relationship can be seen in the scatterplot and best-fit line shown in Fig. 2 *upper*. When ACoA or PCoA aneurysms were analyzed separately, a similar inverse relationship between the size of the aneurysm and the volume of SAH was found (Table 3). The scatterplot and best-fit line for PCoA aneurysms can be seen in Fig. 2 *lower*. Excluding patients with IVH and/or IPH did not significantly change the degree of correlation between aneurysm size and volume of SAH (Table 3). When the data were divided into groups based on aneurysm size (1–5 mm, 6–10 mm, 11–15 mm, and $>$ 15 mm), the analysis revealed a significant associa-

TABLE 1

*Clinical and radiographic characteristics of 100 patients**

Characteristic	No. of Patients
age (yrs)	
range	23–81
mean	49.6
median	48
sex	
male	42
female	58
side of aneurysm†	
lt	30
rt	36
midline	34
size of aneurysm (mm)	
range	1–25
mean	8.3
median	8
SEM	0.49
volume of SAH (score)	
range	0–30
mean	15
median	15
SEM	0.89
abnormal coagulation study‡	0
hypertension	22
location	
ACoA	31
PCoA	27
MCA	16
basilar	10
paraclinoid	9
pericallosal	5
ICA bifurcation	2
multiple aneurysms	28
IPH	25
IVH	30
ventriculostomy	44
aspirin use	3
cigarette use	30
warfarin use	0

* Basilar = basilar tip and superior cerebellar artery; paraclinoid = ophthalmic and superior hypophysial arteries; SEM = standard error of the mean.

† Midline aneurysms include those located on the ACoA complex and the basilar tip.

‡ Abnormal coagulation was considered to be either a platelet count lower than 100,000/μl or an INR greater than 1.3.

TABLE 2

*Volume of SAH by variable analyzed**

Variable	Mean SAH Vol Score
age (yrs)	
<median	14.1
>median	16.2
sex	
male	13.6
female	16.1
side of aneurysm	
lt	14.9
rt	14.1
midline	16.1
cigarette use	
yes	15.7
no	14.7
multiple aneurysms	
yes	16.6
no	14.4
location of aneurysm	
ACoA	15.9
PCoA	14.9
MCA	13.2
basilar	14.1
paraclinoid	18.4
pericallosal	12.6
ICA bifurcation	13.5
hypertension	
yes	15.3
no	14.7

* No variables listed achieved statistical significance ($p < 0.05$) with regard to volume of SAH.

tion between smaller aneurysm size and a higher incidence of ventriculostomy placement ($p = 0.0007$) (Table 4). There was also a higher incidence of IPH occurring with smaller aneurysms ($p = 0.02$) (Table 4). When analysis of variance was applied to data grouped by size, the correlation between smaller aneurysm size and more extensive SAH was again found to be statistically significant ($p < 0.0001$) (Table 5). These results are presented in Fig. 3.

When the patient's age was dichotomized at the median (48 years), no statistical difference in the volume of SAH ($p = 0.2$) or the mean aneurysm size ($p = 0.76$) was found between the two groups. Also, no statistical correlation between patient age and volume of SAH was found when regression analysis was performed ($p = 0.08$). These subanalysis results indicated that cortical atrophy, which is related to old age, did not have a significant relationship with the volume of SAH recorded and, therefore, did not confound our results.

Discussion

It has been our general impression that smaller cerebral aneurysms produce more extensive SAH. On a review of the literature, however, we could not find any report confirming this supposition. Indirect evidence of this was provided by Roos, et al.,[15] who in their investigation of the relationship between aneurysm size and overall clinical outcome following SAH, reported that patients with larger aneurysms tended to present with smaller amounts of SAH; however, their data were not quantified. Our radiographic study confirms an inverse relationship between aneurysm size and volume of SAH. As expected, the low coefficient of determination ($r^2 = 0.23$) of the regression analysis indicates that the volume of SAH is only partially determined by aneurysm size. Other factors likely affect the volume of SAH, and may include transmural pressure (arterial pressure), wall strength (affected by cigarette smoking, alcohol use, aneurysm age), neck/dome ratio, and aneurysm shape.[14] As discussed later, the role that aneurysm size plays in determining the extent of SAH may shed light on the pathophysiology of cerebral aneurysm rupture.

The Laplace law (wall tension = transmural pressure × the radius) may be applied to cerebral aneurysms. To achieve the same critical aneurysm wall tension leading to rupture, smaller aneurysms must be subjected to a higher arterial pressure than larger lesions. This higher pressure may yield a more extensive hemorrhage following rupture. Unfortunately, a history of hypertension and mean arterial pressure on admission are both unreliable predictors of arterial pressure at the moment of rupture and, therefore, are

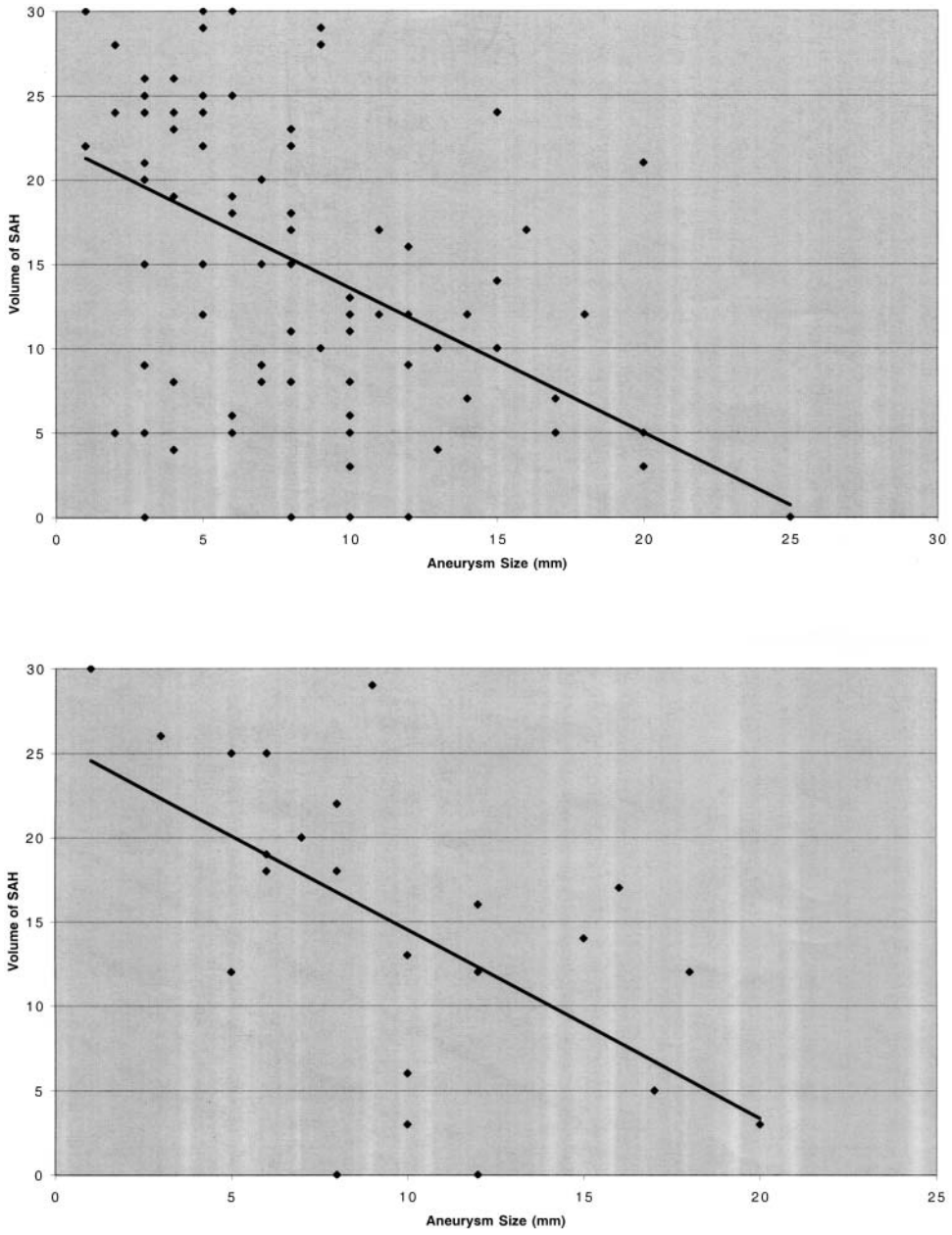

FIG. 2. Scatterplots, best-fit lines, and results of regression analysis displaying the relationship between aneurysm size and volume of SAH for all 100 aneurysms ($r^2 = 0.23$, $p < 0.0001$ *[upper]*), and for 27 PCoA aneurysms ($r^2 = 0.36$, $p = 0.0009$ *[lower]*).

poor historical variables. In our statistical analysis, a history of hypertension was not associated with a larger volume of SAH.

Another possible explanation for our results is the relationship between aneurysm walls and their surrounding environment. Specifically, the walls of larger aneurysms are more likely to be in direct contact with arachnoid membranes and glial limitans of the cortical gray matter, both of which have the highest concentrations of tissue factor found intracranially.[3,4,6,17] Tissue factor, a protein that promotes hemostasis through the extrinsic coagulation pathway, may help limit bleeding from wall defects in larger aneurysms.

Using transcranial Doppler ultrasonography, Wardlaw, et

TABLE 3

Results of a regression analysis comparing aneurysm size and volume of SAH

Type of Aneurysm	No. of Aneurysms	r^2	p Value
all aneurysms*	100	0.23	<0.0001
aneurysms w/o associated IPH or IVH	55	0.19	0.0008
ACoA aneurysms	31	0.36	0.0004
PCoA aneurysms	27	0.36	0.0009

* The slope coefficient for all aneurysms compared with the volume of SAH is −0.857 (95% confidence interval −0.50 to −1.22; $p < 0.0001$).

TABLE 4

Results of a variable analysis with aneurysms grouped by size

Variable	Aneurysm Size (%)				p Value*
	1–5 mm	6–10 mm	11–15 mm	>15 mm	
no. of aneurysms	35	39	18	8	
IPH	13 (37)	9 (23)	3 (17)	0 (0)	0.02
IVH	12 (34)	13 (33)	3 (17)	2 (25)	0.27
ventriculostomy placement	23 (66)	15 (38)	5 (28)	1 (12)	0.0007

* Obtained using the Mantel–Haenszel chi-square test.

al.,[18] discovered that ICP has a dynamic influence on aneurysm size: at a low ICP, aneurysms are maximally distended and minimally pulsatile, whereas, at a high ICP, aneurysms are smaller and markedly pulsatile. We believe that the ICP did not confound the measurements of aneurysm size significantly because all patients with signs of increased ICP (lethargy or evidence of hydrocephalus on the admission CT scan) received an emergency ventriculostomy, which maintained the ICP within normal limits during diagnostic angiography.

We used an established semiquantitative grading system to determine the extent of SAH[9] (Fig. 1). Although a high interobserver agreement for this grading system has been reported,[9] possible flaws in this system include the effect aneurysm location has on the hemorrhage score, specifically the proximity of an aneurysm to the most medial basal cisterns. For example, some MCA aneurysms produced thick clots in the sylvian fissure and large IPHs, yet failed to extend significantly into the contralateral sylvian cistern or into cisterns surrounding the brainstem, thus yielding a low hemorrhage score. An analysis performed using only patients with ACoA complex aneurysms, those with PCoA aneurysms, or patients without IPH or IVH, subgroups that are less susceptible to this potential problem with the grading system, also revealed a correlation between a small aneurysm size and a larger volume of SAH (Table 3 and Fig. 2 *lower*). Furthermore, no one aneurysm location was statistically associated with a larger volume of SAH, a fact that also supports the reliability of the radiographic grading system used (Table 2). Another concern is the consistency of the grading system when applied to patients with cortical atrophy. This was addressed by showing that there was no difference in mean SAH volume, as well as in mean aneurysm size, when data were dichotomized at the median patient age. Moreover, a regression analysis between patient age and volume of SAH did not reveal a significant correlation.

TABLE 5

Mean SAH volume scores for aneurysms grouped by size

Aneurysm Size (mm)	No. of Lesions	Mean SAH Vol Score*	SEM
1–5	35	20.2	1.4
6–10	39	10.7	1.4
11–15	18	5.1	1.4
>15	8	1.6	2.6

* The mean volume of SAH decreases with increasing aneurysm size ($p < 0.0001$).

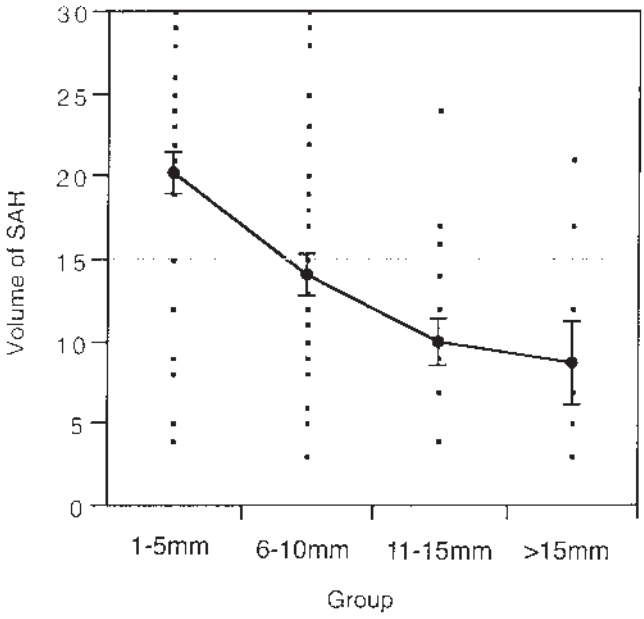

FIG. 3. Graph showing SAH volume scores grouped according to increasing aneurysm size. The means *(dots)* and their standard errors *(bars)* are displayed.

Some authors believe that postrupture, the size of the aneurysm determined by angiography may actually be smaller than the size prior to rupture.[19] If true, this may be caused by compressive forces of the subarachnoid blood itself or be due to an intraaneurysm clot that limits opacification of the aneurysm during angiography. This theory has been used to explain why in some patients with SAH angiograms are nondiagnostic immediately following rupture, whereas the aneurysm appears on angiograms obtained 1 week later. Studies have been performed regarding this issue,[7,12,13,20] with most concluding that this phenomenon does not occur to a significant degree, and that the size of the aneurysm measured angiographically post-SAH is a reliable predictor of the prerupture size.

We infer from our data that small aneurysms are dangerous; they produce a larger volume of SAH. Although we did not report the incidence of vasospasm in our cohort of patients, authors of a previous study, in which the same semiquantitative grading system was used, found that a larger volume of SAH significantly correlated with a higher incidence of vasospasm.[2] The thicker blood clots produced by smaller aneurysms may have contributed to our finding that patients with smaller aneurysms more frequently require urgent placement of a ventriculostomy.

The limitations of our study relate to the accuracy of our data collection. We used the ICA and the basilar artery as references to determine aneurysm size. Although the average dimensions of these vessels and the statistical deviation resulting from normal anatomical variations have been defined in previous anatomical studies, some degree of imprecision cannot be avoided when this method of measurement is used.[8,11,16] Additionally, we used a previously published, semiquantitative method to measure the volume of SAH.[9]

Despite the fact that this method has a high interobserver reliability,[9] its semiquantitative nature precludes it from being a completely objective measure of SAH volume. Nevertheless, these limitations do not change our conclusions, considering the high degree of significance associated with our results.

Conclusions

Smaller cerebral aneurysm size is associated with a larger volume of SAH. The pathophysiological basis for this correlation remains speculative.

Acknowledgments

We thank Theresa Perlis, Ph.D., and Eileen Willets, Ph.D., for performing the statistical analysis used in this communication.

References

1. Adams HP Jr, Kassell NF, Torner JC, et al: Predicting cerebral ischemia after aneurysmal subarachnoid hemorrhage: influences of clinical condition, CT results, and antifibrinolytic therapy. A report of the Cooperative Aneurysm Study. **Neurology 37:** 1586–1591, 1987
2. Brouwers PJ, Dippel DW, Vermeulen M, et al: Amount of blood on computed tomography as an independent predictor after aneurysm rupture. **Stroke 24:**809–814, 1993
3. del Zoppo GJ, Yu JQ, Copeland BR, et al: Tissue factor localization in non-human primate cerebral tissue. **Thromb Haemost 68:** 642–647, 1992
4. Eddleston M, de la Torre JC, Oldstone MB, et al: Astrocytes are the primary source of tissue factor in the murine central nervous system. A role for astrocytes in cerebral hemostasis. **J Clin Invest 92:**349–358, 1993
5. Fisher CM, Roberson GH, Ojemann RG: Cerebral vasospasm with ruptured saccular aneurysm—the clinical manifestations. **Neurosurgery 1:**245–248, 1977
6. Fleck RA, Rao LV, Rapaport SI, et al: Localization of human tissue factor antigen by immunostaining with monospecific, polyclonal anti-human tissue factor antibody. **Thromb Res 59:**421–437, 1990
7. Forget TR Jr, Benitez R, Veznedaroglu E, et al: A review of size and location of ruptured intracranial aneurysms. **Neurosurgery 49:**1322–1326, 2001
8. Gabrielsen TO, Greitz T: Normal size of the internal carotid, middle cerebral and anterior cerebral arteries. **Acta Radiol Diagn 10:** 1–10, 1970
9. Hijdra A, Brouwers PJ, Vermeulen M, et al: Grading the amount of blood on computed tomograms after subarachnoid hemorrhage. **Stroke 21:**1156–1161, 1990
10. The International Study of Unruptured Intracranial Aneurysms Investigators: Unruptured intracranial aneurysms—risk of rupture and risks of surgical intervention. **N Engl J Med 339:**1725–1733, 1998
11. Kamath S: Observations on the length and diameter of vessels forming the circle of Willis. **J Anat 133:**419–423, 1981
12. Kassell NF, Torner JC: Size of intracranial aneurysms. **Neurosurgery 12:**291–297, 1983
13. Kataoka K, Taneda M, Asai T, et al: Difference in nature of ruptured and unruptured cerebral aneurysms. **Lancet 355:**203, 2000 (Letter)
14. Kyriacou SK, Humphrey JD: Influence of size, shape and properties on the mechanics of axisymmetric saccular aneurysms. **J Biomech 29:**1015–1022, 1996
15. Roos EJ, Rinkel GJ, Velthuis BK, et al: The relation between aneurysm size and outcome in patients with subarachnoid hemorrhage. **Neurology 54:**2334–2336, 2000
16. Smoker WR, Price MJ, Keyes WD, et al: High-resolution computed tomography of the basilar artery: I. Normal size and position. **AJNR 7:**55–60, 1986
17. Suzuki M, Kudo A, Otawara Y, et al: Extrinsic pathway of blood coagulation and thrombin in the cerebrospinal fluid after subarachnoid hemorrhage. **Neurosurgery 44:**487–494, 1999
18. Wardlaw JM, Cannon J, Statham PF, et al: Does the size of intracranial aneurysms change with intracranial pressure? Observations based on color "power" transcranial Doppler ultrasound. **J Neurosurg 88:**846–850, 1998
19. Wiebers DO, Whisnant JP, Sundt TM Jr, et al: The significance of unruptured intracranial saccular aneurysms. **J Neurosurg 66:** 23–29, 1987
20. Yasui N, Magarisawa S, Suzuki A, et al: Subarachnoid hemorrhage caused by previously diagnosed, previously unruptured intracranial aneurysms: a retrospective analysis of 25 cases. **Neurosurgery 39:**1096–1101, 1996

Manuscript received May 13, 2002.
Accepted in final form March 4, 2003.
Address reprint requests to: Jafar J. Jafar, M.D., Department of Neurosurgery, New York University Medical Center, 530 First Avenue, Suite 8R, New York, New York 10016. email: jafar.jafar@med.nyu.edu.