Difference in Aneurysm Characteristics Between Ruptured and Unruptured Aneurysms in Patients With Multiple Intracranial Aneurysms

Daan Backes, MD; Mervyn D.I. Vergouwen, MD, PhD; Birgitta K. Velthuis, MD, PhD; Irene C. van der Schaaf, MD, PhD; A. Stijntje E. Bor, MD; Ale Algra, MD, PhD; Gabriel J.E. Rinkel, MD, FRCPE

Background and Purpose—Prediction of the risk of rupture of unruptured intracranial aneurysms is mainly based on aneurysm size and location. Previous studies identified features of aneurysm shape and flow angles as additional risk factors for aneurysm rupture, but these studies were at risk for confounding by patient-specific risk factors such as hypertension and age. In this study, we avoided this risk by comparing characteristics of ruptured and unruptured aneurysms in patients with both aneurysmal subarachnoid hemorrhage and multiple intracranial aneurysms.

Methods—We included patients with aneurysmal subarachnoid hemorrhage and multiple aneurysms who presented to our hospital between 2003 and 2013. We identified the ruptured aneurysm based on bleeding pattern on head computed tomography or surgical findings. Aneurysm characteristics (size, location, shape, aspect ratio [neck-to-dome length / neck-width], flow angles, sidewall or bifurcation type, and contact with bone) were evaluated on computed tomographic angiograms. We calculated odds ratios with 95% confidence intervals with conditional univariable logistic regression analysis. Analyses were repeated after adjustment for aneurysm size and location.

Results—The largest aneurysm had not ruptured in 36 (29%) of the 124 included patients with 302 aneurysms. Odds ratios for aspect ratio ≥1.3 was 3.3 (95% confidence intervals [1.3–8.4]) and odds ratios for irregular shape was 3.0 (95% confidence intervals [1.0–8.8]), both after adjustment for aneurysm size and location.

Conclusions—Aspect ratio ≥1.3 and irregular shape are associated with aneurysm rupture independent of aneurysm size and location, and independent of patient characteristics. Additional studies need to assess to what extent these factors increase the risks of rupture of small aneurysms in absolute terms. (Stroke. 2014;45:00-00.)

Key Words: anatomy and histology • intracranial aneurysm • multidetector computed tomography • subarachnoid hemorrhage

About 3% of the population has an unruptured intracranial aneurysm, and increasing numbers are detected because of the wider availability of imaging techniques.14 When an unruptured aneurysm is detected, the risk of rupture has to be balanced against the risks of preventive treatment. However, assessment of rupture risk is inaccurate. In a recent pooled analysis of individual patient data from 6 prospective cohort studies, predictors of rupture were geographical region, hypertension, age, history of subarachnoid hemorrhage (SAH) from another aneurysm, aneurysm size and location, with aneurysms >7 mm and aneurysms in the vertebrabasilar, anterior communicating, and posterior communicating arteries carrying the highest risk of rupture.3 Most aneurysms are small, with inherent low risk of rupture, and are left untreated because in general the risk of complications of preventive treatment does not outweigh this small risk of rupture.4,6 Still, in absolute numbers, many small aneurysms do rupture.7,8 Identification of small aneurysms with a high risk of rupture is pivotal to improve management of these aneurysms. Thus, additional risk factors for aneurysm rupture are needed to improve risk assessment and patient selection for treatment of unruptured aneurysms.

Previous studies identified additional risk factors for aneurysm rupture such as aneurysm shape,3–14 various size and shape ratios,10,12,15–24 flow angles,11,18,25 and contact between the aneurysm wall and surrounding anatomic structures.14,26–28 However, studies on these morphological and geometric characteristics had conflicting results. This can be explained by variation in imaging techniques and the use of a case–control design where patients with ruptured aneurysms are compared with patients with unruptured aneurysms, which may lead to confounding by patient-specific characteristics such as hypertension, age, and history of SAH from another aneurysm. Confounding by specific patient characteristics can be avoided by comparing the aneurysm characteristics of ruptured and unruptured aneurysms.
Methods

Study Population and Data Extraction

This study was performed at the University Medical Center Utrecht, the Netherlands. Approval was obtained from the Institutional Research Ethics Board. Patient data were extracted from a prospective institutional database, which includes consecutive patients with confirmed SAH. The diagnosis of SAH from a ruptured aneurysm was confirmed by a pattern of hemorrhage on head computed tomography (CT) compatible with a ruptured aneurysm and the presence of an aneurysm on CTA, MR- or conventional angiography. We included all patients presenting between January 1, 2003, and January 1, 2013, with the diagnosis of aneurysmal SAH and more than one intracranial aneurysm on CT angiography (CTA). Exclusion criteria were (1) insufficient CTA quality to evaluate aneurysm geometry and morphology; (2) inability to identify the location of the ruptured aneurysm based on the pattern of hemorrhage on CT or neurosurgical findings; (3) the presence of fusiform, mycotic, or partially thrombosed aneurysms.

Imaging

In our center, all patients with a clinical suspicion of SAH undergo noncontrast head CT using a 16-, 64-, or 256-multidetector CT scanner (Philips Healthcare). Patients with confirmed SAH immediately undergo CTA to investigate the presence of an intracranial aneurysm as a cause of SAH. The CTA scans are performed with a field of view of 160 mm and a slice thickness of 1 mm reconstructed at 0.5 mm, resulting in a voxel size of 0.3×0.3×0.5 mm. Subsequently, digital subtraction angiography is performed if the CTA does not reveal an aneurysm or if more information is needed for the decision whether an aneurysm should be clipped or coiled.

For the purpose of this study, the location of the ruptured aneurysm within each patient was identified systematically and blinded for aneurysm geometry and morphology. First, 2 authors (G.J.E. Rinkel or M.D.I. Vergouwen) assessed the most likely location of the ruptured aneurysm on the basis of the pattern of hemorrhage on conventional head CT. A third author (D. Backes) checked if a single aneurysm had been found at this predicted location on CT- or conventional angiography. Second, for the patients with an inconclusive focus of hemorrhage, the conventional CT scans were reviewed by one author (G.J.E. Rinkel) after he was given information regarding the location of all identified aneurysms only, to assess the site of the ruptured aneurysm. In case it was not possible to identify the ruptured aneurysm on the basis of the pattern of hemorrhage on CT (ie, extensive SAH symmetrically confined to all fissures or 2 aneurysms in close vicinity) and ≥ 2 aneurysms were treated by endovascular coiling, the patient was excluded. In case it was not possible to identify the ruptured aneurysm on the basis of the pattern of hemorrhage and ≥ 2 aneurysms were treated neurosurgically, the patient was excluded if the neurosurgeon could not point out which aneurysm had bled on the basis of surgical findings.

The CTA source image data were transferred to an offline workstation (IntelliSpace Portal v4.0.0.40259, Philips Healthcare) for interactive viewing and postprocessing. All aneurysms were reviewed on geometric and morphological aneurysm characteristics on CTA images by the same observer (D. Backes), who was blinded for clinical data, conventional head CT images, and aneurysm rupture status. In case of any doubt or complexity, the aneurysm was reviewed in a consensus meeting with 2 experienced neuroradiologists (I.C.v.d. Schaaf and B.K. Velthuis). Maximum intensity projection images with 1.0-mm slice thickness and a standardized window setting (window level and window width equal to the Hounsfield units within the aneurysm) were used to perform all measurements (Figure). The aneurysm wall was evaluated for contact with bone using maximum intensity projection images in standard brain setting, with additional volume rendering if needed. The maximum intensity projection images could be rotated in 3 dimensions for assessment of all aneurysm characteristics.

Aneurysm Location and Parent Artery Configuration

The location of ruptured and unruptured aneurysms was categorized into anterior cerebral artery and branches (including the anterior communicating artery). The A1 segment of the anterior cerebral artery; ICA, internal carotid artery; and PCOM, posterior communicating artery.
communicating artery, callosomarginal artery, and pericallosal artery), internal carotid artery other than posterior communicating artery, posterior communicating artery, middle cerebral artery, and posterior circulation arteries (including the vertebrobasilar system and posterior cerebral arteries). Aneurysms located at parent artery bifurcations in the Circle of Willis were defined as bifurcation type aneurysms. If the aneurysm originated from only one parent vessel visible on CTA, the aneurysm was defined as sidewall aneurysm.

**Measurements of Geometric and Morphological Aneurysm Characteristics**

Measurements of maximal neck-width, neck to dome length (length from the neck center to the dome of the aneurysm), and aneurysm width (measured perpendicular to the neck to dome length) were performed on a 0.1-mm scale. The maximum measurement of aneurysm width or aneurysm neck-to-dome length was defined as the aneurysm size (Figure). Aneurysm size was dichotomized into ≥7.0 and <7.0 mm for further analysis. The aspect ratio describes the relationship between the aneurysm length and the aneurysm neck, and it was calculated on a 0.1 point scale by dividing aneurysm neck-to-dome length by aneurysm neck-width.

Aneurysm shape was categorized into spherical (defined as aneurysm width is 80% to 100% of its length), nonspherical, and irregularly shaped. An aneurysm was defined as being irregularly shaped when blebs, aneurysm wall protrusions, or multiple lobes were present.

Intracranial aneurysms can have contact with anatomic structures that bound the subarachnoid space, such as bone, brain tissue, dura, cranial nerves, and vessels. Contact with incompressible structures such as bone can alter aneurysm hemodynamics and wall shear stress, and thereby influence aneurysm shape and the risk of rupture. We evaluated the presence of contact between the aneurysm wall and bone.

We measured the angles of the parent artery for all sidewall aneurysms and the angle between the parent artery and the 2 daughter branches for all bifurcation aneurysms (Figure). All angles were measured on a 1° scale and were divided into tertiles for additional analysis. Flow into the aneurysm was considered as straight flow when the inflow angle was larger than the main branching angle. Flow into the aneurysm was considered as curved flow when the inflow angle was smaller than the main branching angle. In case the inflow angle and the main branching angle showed <5° difference, flow was considered equivalent.

**Statistical Analysis**

Aneurysm rupture status was categorized as ruptured and unruptured. The median aspect ratio of all included aneurysms was used as cutoff value for further analysis. Discrete variables are presented as number with percentage (%) and continuous variables as a mean with SD, or as a median with range where appropriate. We calculated odds ratios (OR) with 95% confidence intervals (CI) to investigate which geometric and morphological aneurysm characteristics were associated with aneurysm rupture, using conditional univariable logistic regression analysis. In a second analysis, adjusted odds ratios (aOR) were calculated adjusting for aneurysm size as a continuous variable and aneurysm location as a categorical variable because these are established and strong predictors of aneurysm rupture.

**Results**

**Study Population**

During the study period, a total of 192 patients with aneurysmal SAH and multiple intracranial aneurysms were admitted to our hospital. Sixty-eight patients were excluded, mainly because the location of the ruptured aneurysm could not be determined based on the pattern of hemorrhage or neurosurgical findings (n=50), or because of insufficient quality of CTA (n=12). Six patients were excluded because of the presence of fusiform, mycotic, or partially thrombosed aneurysms. We included 124 patients with a total of 302 aneurysms. The median number of aneurysms per patient was 2 (range 2–6).

**Geometric and Morphological Characteristics Associated With Aneurysm Rupture**

The median size of ruptured aneurysms was 6.8 mm (range 2.2–31.5 mm) and of unruptured aneurysms 3.8 mm (range 1.5–16.9 mm). In 36 patients (29%), the ruptured aneurysm was not the largest aneurysm and, in 34 of these patients, the ruptured aneurysm was <7 mm. The geometric and morphological characteristics of ruptured and unruptured aneurysms are given in the Table. Aneurysm size ≥7 mm showed the strongest association with rupture (OR 10.7; 95% CI 4.8–23.8). After adjustment for aneurysm size and location, aspect ratio ≥1.3 (aOR 3.3; 95% CI 1.3–8.4) and irregular shape (aOR 3.0; 95% CI 1.0–8.8) were significantly associated with aneurysm rupture, but not flow angles, parent artery configuration, and contact between the aneurysm wall and bone.

**Discussion**

Our study shows that in one third of the patients with aneurysmal SAH and multiple intracranial aneurysms, the ruptured aneurysm was not the largest aneurysm. Aspect ratio and irregular shape were associated with aneurysm rupture after adjustment for aneurysm size and location.

Japanese observational data showed that unruptured aneurysms with a daughter sac have higher rupture rates than aneurysms with a regular shape. Case–control studies found that ruptured aneurysms more often had an irregular shape, but these results were not adjusted for aneurysm size. Other studies showed that contact between the aneurysmal wall and surrounding anatomic structures that bound the subarachnoid space is associated with aneurysm deformation and rupture. However, because large aneurysms are more likely to have contact with other structures and no adjustments were made for aneurysm size, it remained unclear whether the high rupture risk was a result of the presence of contact with other structures or the result of aneurysm size. Previous studies on aneurysm flow angles showed conflicting results, with insignificant or marginally significant odds ratios for aneurysm rupture after adjustment for aneurysm size. Regarding aspect ratio, most but not all previous studies showed that mean aspect ratios were higher in ruptured aneurysms than in unruptured aneurysms. The conflicting results in case–control studies comparing geometric and morphological aneurysm characteristics between patients with ruptured aneurysms and patients with unruptured aneurysms can be explained by the lack of adjustment for patient specific risk factors for aneurysm rupture and by the use of different imaging techniques and measurement methodology. Similar to our study, 2 previous studies aimed to minimize the risk of confounding by patient-specific characteristics by studying patients with aneurysmal SAH and multiple intracranial aneurysms, and demonstrated that a high aspect ratio was associated with aneurysm rupture. However, these studies did not adjust for aneurysm size in the multivariable analysis. One of these studies performed all measurements on 2-dimensional
digital subtraction angiography,16 and in the other study only 30 patients were analyzed.22 With our design, using high quality 3-dimensional CTA images according to a strict protocol, we think we have established aspect ratio and irregular shape as robust risk factors for aneurysmal rupture.

The strength of this study is that we made adjustments for aneurysm size and location. In this way, we were able to evaluate geometric and morphological aneurysm characteristics as a risk factor for aneurysm rupture independent of these well-established risk factors. This is important because the identification of independent risk factors for aneurysm rupture is pivotal to improve risk assessment and patient selection for treatment of small unruptured aneurysms. Moreover, the comparison of ruptured and unruptured aneurysms within the same patient allowed us to study geometric and morphological aneurysm characteristics without the risk of confounding by patient specific characteristics. Also, the systematic workup in which we identified the ruptured aneurysm allowed us to analyze all geometric and morphological characteristics blinded for clinical information, conventional CT images, and

Table. Geometric and Morphological Characteristics of Ruptured and Unruptured Intracranial Aneurysms

<table>
<thead>
<tr>
<th>Aneurysm location</th>
<th>Ruptured N=124</th>
<th>Unruptured N=178</th>
<th>OR (95% CI)</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cerebral artery and branches*</td>
<td>40 32</td>
<td>34 19</td>
<td>2.14 (1.21–3.78)</td>
<td>...</td>
</tr>
<tr>
<td>Internal carotid artery other than posterior communicating artery</td>
<td>4 3</td>
<td>25 14</td>
<td>0.42 (0.11–1.53)</td>
<td>...</td>
</tr>
<tr>
<td>Posterior communicating artery</td>
<td>30 24</td>
<td>12 7</td>
<td>6.50 (2.48–17.05)</td>
<td>...</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>41 33</td>
<td>90 51</td>
<td>Reference</td>
<td>...</td>
</tr>
<tr>
<td>Posterior circulation arteries</td>
<td>9 7</td>
<td>17 10</td>
<td>1.09 (0.41–2.96)</td>
<td>...</td>
</tr>
</tbody>
</table>

Aneurysm size

| Aneurysm size ≥ 7.0 mm | Ruptured 59 48 | Unruptured 16 9 | 10.70 (4.80–23.83) | ... |

Aneurysm shape

| Spherical | Ruptured 22 18 | Unruptured 47 26 | Reference | Reference |
| Nonspherical | 43 35 | 107 60 | 1.00 (0.53–1.88) | 1.04 (0.46–2.35) |
| Irregular | 59 48 | 24 13 | 5.78 (2.67–12.52) | 2.99 (1.01–8.79) |

Size ratio

| Aspect ratio ≥ median (1.3)† | Ruptured 86 69 | Unruptured 58 33 | 8.30 (3.93–17.54) | 3.26 (1.26–8.42) |

Contact with anatomic structures

| No contact with bone | Ruptured 99 80 | Unruptured 155 87 | Reference | Reference |
| Contact with bone | 25 20 | 23 13 | 1.89 (0.92–3.89) | 1.32 (0.53–3.33) |

Parent artery configuration

| Sidewall aneurysm | Ruptured 25 20 | Unruptured 51 29 | Reference | Reference |
| Bifurcation aneurysm | 99 80 | 127 71 | 1.44 (0.83–2.52) | 1.43 (0.64–3.16) |

Flow angles

| Mean inflow angle in degrees (SD) | Ruptured 141 23 | Unruptured 133 26 | Reference | Reference |
| 1st tertile (64–124) | 32 26 | 66 37 | Reference | Reference |
| 2nd tertile (124–148) | 42 34 | 59 33 | 1.34 (0.74–2.44) | 1.05 (0.47–2.37) |
| 3rd tertile (148–180) | 50 40 | 53 30 | 1.90 (1.02–3.52) | 1.09 (0.44–2.67) |
| Mean branching angle in degrees (SD) | Ruptured 125 24 | Unruptured 129 24 | Reference | Reference |
| 1st tertile (48–117) | 34 27 | 62 35 | Reference | Reference |
| 2nd tertile (117–140) | 42 34 | 59 33 | 1.29 (0.70–2.35) | 0.97 (0.44–2.15) |
| 3rd tertile (140–180) | 48 39 | 57 32 | 1.46 (0.75–2.84) | 0.58 (0.23–1.47) |
| Curved flow into aneurysm | 37 30 | 83 47 | Reference | Reference |
| Straight flow into aneurysm | 73 59 | 74 42 | 2.46 (1.35–4.48) | 1.32 (0.55–3.16) |
| Equivalent flow into aneurysm | 14 11 | 21 12 | 1.45 (0.61–3.41) | 1.49 (0.46–4.80) |

Data are presented as number (%) unless stated otherwise. aOR indicates odds ratio adjusted for aneurysm size and location; CI, confidence interval; and OR, odds ratio. *Including anterior communicating artery, callosomarginal artery, and pericallosal artery. †N=288 because 14 aneurysms had no definable neck.
aneurysm rupture status. A limitation of this study is that some of the characteristics we studied, such as aneurysm size, and irregular shape, might be the result rather than the cause of aneurysm rupture. In an ideal but unrealistic situation, direct pre- and postreperfusion imaging would be needed. Because irregular shape was also found in a considerable proportion of unruptured aneurysms, it is unlikely that irregularity can entirely be explained by rupture.

Our study has important implications for clinical practice. Although we found that aneurysm size was the strongest risk factor associated with aneurysm rupture, the ruptured aneurysm was not the largest aneurysm in nearly one third of the cases. For the entire group of patients with unruptured aneurysms, future studies need to establish to what extent aspect ratio and irregular shape increase the risk of rupture in patients with unruptured intracranial aneurysms in terms of absolute risks.

Disclosures

Dr Bor has received research support from the Netherlands Heart Foundation (grant no. DHF-2007B106). The other authors report no conflicts.

References

Difference in Aneurysm Characteristics Between Ruptured and Unruptured Aneurysms in Patients With Multiple Intracranial Aneurysms
Daan Backes, Mervyn D.I. Vergouwen, Birgitta K. Vethuis, Irene C. van der Schaaf, A. Stijntje E. Bor, Ale Algra and Gabriel J.E. Rinkel

Stroke. published online March 20, 2014;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2014/03/20/STROKEAHA.113.004421