# Smoking and Intracranial Aneurysm Morphology

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**BACKGROUND:** Smoking is a well-known independent risk factor for both aneurysm formation and rupture. There is mounting evidence that aneurysm morphology beyond size can have a significant role in aneurysm formation and rupture risk by its effects on aneurysmal hemodynamics.

**OBJECTIVE:** To study the variation in aneurysm morphology between smokers and nonsmokers and delineate how changes in these factors might affect aneurysm formation and rupture.

**METHODS:** We generated 3-dimensional models of aneurysms and their surrounding vasculature by analyzing preoperative computed tomography angiograms with Slicer software. We then examined the association between smoking status and intrinsic, transitional, and extrinsic aspects of aneurysm morphology in both univariate and multivariate statistical analyses.

**RESULTS:** From 2005 to 2013, 199 cerebral aneurysms in never smokers and current smokers were evaluated/treated at a single institution with available computed tomography angiograms (102 in never smokers and 97 in current smokers). Multivariate analysis of current smokers vs never smokers demonstrated that aneurysms in current smokers were significantly associated with multiple aneurysms (odds ratio [OR]: 2.15, $P = .03$), larger daughter vessel diameters (OR: 3.13, $P = .01$), larger size ratio (OR: 1.78, $P = .01$), and location at the basilar apex (OR: 6.26, $P = .02$).

**CONCLUSION:** The differences in aneurysm morphology between smoking and nonsmoking patient populations may elucidate the effects of smoking on aneurysm formation and eventual rupture. We identified several aspects of aneurysm morphology significantly associated with smoking status that may provide the morphological basis for how smoking leads to increased aneurysm rupture.

**KEY WORDS:** Aneurysm, Fluid dynamic, Morphology, Smoking

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The number of incidentally discovered intracranial aneurysms continues to increase with the increased use of cranial imaging,[1] and unruptured aneurysms now occur in nearly 3% of the general population.[2] Smoking has been implicated as an independent risk factor for both intracranial aneurysm formation[3-5] and rupture.[4,6,7] In population-based and cohort studies, nearly 75% of patients with aneurysmal subarachnoid hemorrhage have a history of smoking, and 50% to 60% are current smokers.[8,9] Several prospective cohort studies have shown that smoking was also a predictor of de novo aneurysm formation as well as increased rates of aneurysm growth.[3-5] However, there remains no clear mechanism for aneurysm formation and rupture as a function of smoking status, although there have been several biochemical and biomechanical theories proposed.[10-13]

Smoking has been shown to exacerbate atherosclerotic disease and to damage blood vessels in a predictable fashion, including injury to endothelial cells, occlusion of vasa vasorum, and interruption of elastin and collagen synthesis, that could lead to aneurysm genesis and rupture.[11,12,14] It has also been shown that alterations in wall shear stress play a role in the initiation and rupture of intracranial aneurysms, although contradictory evidence has been offered regarding the direction of correlation of such a relationship.[15-19] Smoking, along with hypertension, the other

**ABBREVIATIONS: ACoA,** anterior communicating artery; **PCoA,** posterior communicating artery; **MCA,** middle cerebral artery

well-known aneurysmal risk factor, leads to increased blood viscosity and concomitant alterations in wall shear stress that may affect aneurysm formation and rupture.[20,21] There is now increasing evidence to suggest that aneurysm morphology beyond the predominant parameter of size used in clinical practice today has a profound effect on aneurysmal hemodynamics such as wall shear stress and a role in the clinical evaluation of aneurysm rupture risk.[22-28] To date, no one has studied the variation in aneurysm morphology between smokers and nonsmokers and how these 2 factors may interact to affect aneurysm rupture. Our study was designed to identify the significant differences in aneurysm morphology between smokers and nonsmokers and delineate how these factors might affect rupture risk in these patients.

## METHODS

### Patient Selection

The study population consisted of patients with intracranial aneurysms evaluated and/or treated at the Brigham and Women's Hospital during an 8-year period between 2005 and 2013 who were never smokers or current smokers. Patients with aneurysms that underwent reoperation, aneurysms that were associated with arteriovenous malformations, and aneurysms that lacked preoperative computed tomography (CT) angiograms were not included in the study. The anterior communicating artery (ACoA), posterior communicating artery (PCoA), and middle cerebral artery (MCA) aneurysm cohorts were consecutively treated patients, whereas the basilar apex aneurysm cohort was composed of consecutive patients who were evaluated and/or treated. Medical records for these patients were queried for the relevant demographic and clinical information. Smoking history was defined as current smoker vs never. To avoid the heterogeneity present in the group of former smokers, only current smokers and never smokers were evaluated. In addition to smoking history, we also collected information on other risk factors commonly associated with aneurysm development and rupture including family history, presence of multiple aneurysms, history of hypertension, and history of aneurysm rupture. The study was approved by our institutional review board.

### Reconstruction of 3-Dimensional Models

To conduct the morphological analysis of the aneurysms in our study, we deployed 3-dimensional (3-D) Slicer software (referred to as Slicer in the following text),[29,30] an open-source, multiplatform visualization and image analysis software, as described previously.[22] We created composite 3-D models of the aneurysms and their surrounding vasculature using preoperative CT angiography images. All CT angiograms were obtained using a SOMATOM Definition scanner (Siemens Medical Solutions USA, Malvern, Pennsylvania) with a slice thickness of 0.75 mm and increments of 0.5 mm. We were able to isolate the vascular compartment via thresholding. A triangle reduction and smoothing algorithm reconstructed the aneurysm borders and contours and generated a 3-D surface model of the aneurysm and surrounding vasculature that could be freely manipulated in the Slicer environment (Figures 1 and 2). Fiducial-based tractography enabled manual measurement of the volumes, lengths, and angles of the aneurysm and associated vessels.

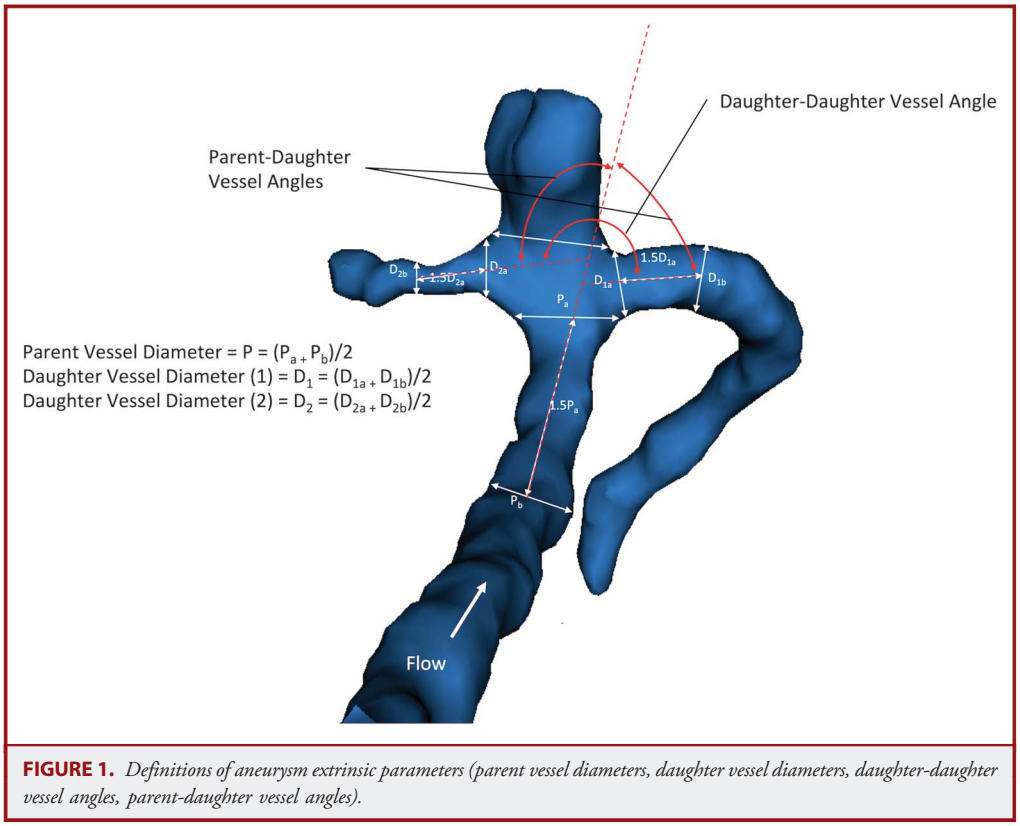


**FIGURE 1.** *Definitions of aneurysm extrinsic parameters (parent vessel diameters, daughter vessel diameters, daughter-daughter vessel angles, parent-daughter vessel angles).*

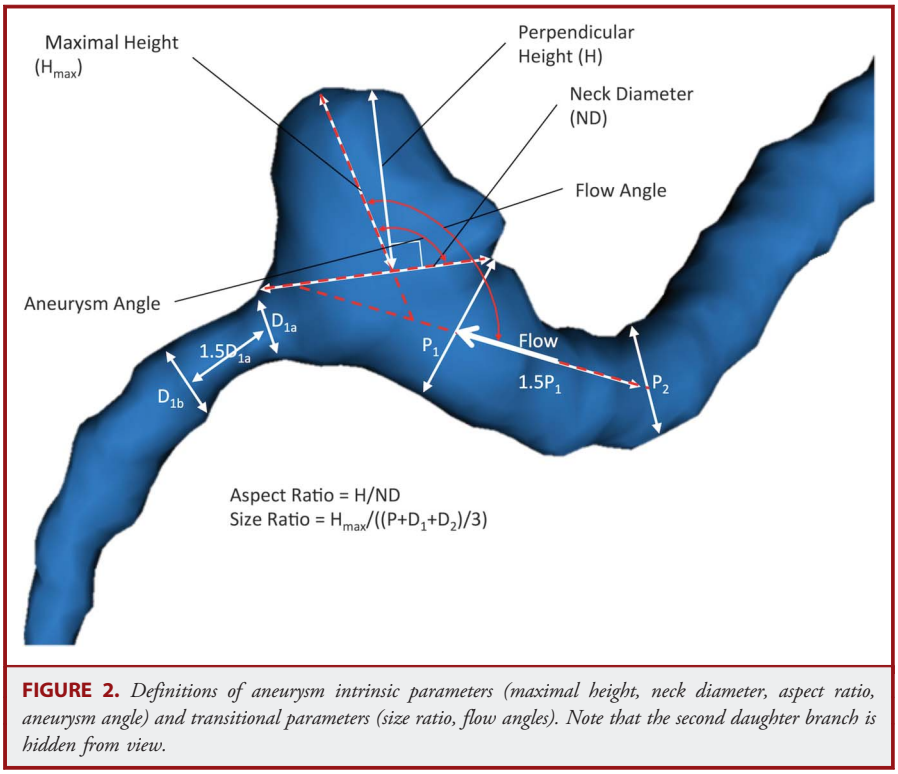


**FIGURE 2.** *Definitions of aneurysm intrinsic parameters (maximal height, neck diameter, aspect ratio, aneurysm angle) and transitional parameters (size ratio, flow angles). Note that the second daughter branch is hidden from view.*

## Definition of Morphological Parameters

Aneurysm intrinsic, transitional, and extrinsic morphological parameters have been studied at length to assess their effects on rupture risk.[14-18,23-27] Aneurysm intrinsic parameters are those that are intrinsic to the aneurysm morphology and include aneurysm size, volume, aspect ratio, and aneurysm angle.[22-26,31-34] Transitional parameters are those that characterize the relationship between the aneurysm and its surrounding vasculature. Finally, aneurysm extrinsic parameters are those that are independent of the aneurysm and involve the surrounding vasculature as defined in our previous studies, such as parent-daughter vessel angle and daughter-daughter vessel angle.[22,25,26]

## Intrinsic Aneurysm Parameters

1. Aneurysm maximal height is the largest cross-sectional diameter of the aneurysm measured from the base of the aneurysm.[31,35,36]
2. Aspect ratio is the ratio of the maximal perpendicular height of the aneurysm to the average neck diameter of the aneurysm.[32,33,37]
3. Volume is the calculated volume of the 3-D aneurysm models.
4. Aneurysm angle is the angle formed between the plane of the neck of the aneurysm and the vector of the maximal height of the aneurysm. The aneurysm angle captures the angle of inclination of the aneurysm from the base of the neck.[32]

## Transitional Aneurysm Parameters

Transitional and extrinsic aneurysm parameters that incorporated the morphology of the surrounding vasculature were also included in our study. The parent vessels were defined as the source of blood flow into the aneurysm, and daughter vessels were those that carry blood flow away from the aneurysm. Parent vessel data did not include ACoA aneurysms because many had 2 parent vessels. Similarly, daughter vessel analysis excluded some PCoA aneurysms because the PCoA is frequently not visualized on a CT angiogram.

1. Size ratio is the ratio between the maximal aneurysm height and mean vessel diameters of all vessel branches associated with the aneurysm. The mean vessel diameter of a particular vessel is determined by averaging the diameter of the cross section of the vessel at the neck of the aneurysm (D1) with the diameter of the cross section at 1.5 × D1 distance from the neck of the aneurysm. This mean vessel diameter was calculated for all vessels involved with the aneurysm and then averaged to generate the composite mean vessel diameter used to calculate the size ratio.[32,38] Finally, the 2 center points of the vessel cross sections created in the size ratio measurement were connected to represent vessel vectors of flow in vessel angle measurements.
2. Flow angle is the angle formed between the vector of the maximal height of the aneurysm and the vector of flow through the parent artery. This angle captures the angle at which the aneurysm deviates in its formation from the vector of flow through the parent vessel.[39,40]

## Extrinsic Aneurysm Parameters

1. Vessel diameter is the diameter of the respective vessel most proximal to the aneurysm neck. Given that vessel and vessel diameters varied significantly between aneurysms in different locations, these measured vessel diameters were also normalized by the mean for each location subtype of aneurysm to adjust for any differences between absolute vessel sizes based on location. Both absolute and normalized values were included in our analysis.

2. Parent-daughter vessel angle is a composite mean of angles formed between the vector of flow of the parent artery and the vector of flow for each daughter artery.
3. Daughter-daughter vessel angle is the angle formed between each pair of daughter vessels.

### Statistical Analysis

Demographic and clinical characteristics were analyzed for differences by smoking status using the $\chi^2$ and 2-tailed $t$ tests for binary and continuous variables, respectively. Univariate analysis was performed to compare the value of each morphological parameter between the smoking and nonsmoking groups. Multivariate logistic regression was also used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for association with smoking status. Missing data were not removed from analysis. All statistical analyses were performed using JMP Pro 10, SAS version 9.2 (SAS Institute Inc, Cary, North Carolina) and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

From 2005 to 2013, 199 cerebral aneurysms in never smokers and current smokers were evaluated/treated at a single institution at which CT angiograms were available (102 never smokers, 97 current smokers). Demographic and clinical data are provided in Table 1. The rate of aneurysm rupture was 56% in never smokers vs 61% in current smokers. However, this relationship was not statistically significant ($P$ = .26). The mean ± SD age was 53.8 ± 12.4 years. There was no significant difference in age between never smokers and current smokers (mean of 54.73 years never smokers vs 52.78 years current smokers, $P$ = .27). There were 67 MCA aneurysms (34%), 56 ACoA aneurysms (28%), 49 PCoA aneurysms (25%), and 27 basilar tip aneurysms (14%). There were 154 women in the cohort, representing 77% of the total sample. There was no significant difference in the sex distribution between never smokers and current smokers with aneurysms. Among our cohort of patients with aneurysms, current smokers were more likely to have multiple aneurysms (39%) than never smokers (25%, $P$ = .04). There was no significant difference in the proportion of patients with hypertension or a family history of aneurysms between current smokers and never smokers.

Univariate statistical analysis of aneurysm intrinsic, transitional, and extrinsic morphological parameters is also provided in Table 2. There was no significant difference in aneurysm size as determined by the maximal diameter between never smokers (6.3 mm) and current smokers (6.6 mm, $P$ = .63). Aneurysms in smokers were correlated with smaller volumes (299 $mm^3$ in never smokers vs 246 $mm^3$ in current smokers). However, this relationship was not statistically significant ($P$ = .65). Smaller adjusted parent vessel diameters were also found in smokers (1.02 in never smokers vs 0.96 in current smokers, $P$ = .03). There were no other significant differences in other metrics or vessel angles between nonsmoking and smoking patients using univariate analysis.

Our multivariate analysis included several known risk factors for aneurysm formation and rupture along with the aforementioned morphological parameters (Table 3). This allows us to find differences in parameters between never smokers and current smokers that were independent of known risk factors. For the variables included in the multivariate analysis, there were missing data for the following variables: volume (n = 8), hypertension (n = 1), and family history (n = 9). Current smokers were twice as likely to have multiple aneurysms as never smokers in a relationship that was statistically significant (OR: 2.15, $P$ = .03). Current smokers were also more likely to have larger daughter vessel diameters (OR: 3.31, $P$ = .01) and size ratios (OR: 1.78, $P$ = .01). Finally, smokers were significantly more likely to have basilar apex aneurysms than nonsmokers (OR: 6.26, $P$ = .02). When normalized parameters were used for the parent vessel diameter, daughter vessel diameter, flow angle, and parent-daughter angle, larger daughter vessel diameters (OR: 18.60, $P$ = .004) and larger size ratios (OR: 1.74, $P$ = .010) remained significant, whereas basilar apex location (OR: 3.02, $P$ = .07) and

**TABLE 1. Baseline Characteristics and Clinical Risk Factors of Patients With Intracranial Aneurysms[a]**

| | Never Smokers (n = 102) | Current Smokers (n = 97) | *P* Value |
|---|---|---|---|
| Aneurysm rupture, no. (%) | 56 (54.90) | 61 (62.89) | .26 |
| Age, y, mean (SD) | 54.73 (12.97) | 52.78 (11.79) | .27 |
| Female, no. (%) | 79 (77.45) | 75 (77.32) | .98 |
| Hypertension, no. (%) | 58 (56.86) | 42 (43.75) | .07 |
| Multiple aneurysms, no. (%) | 26 (25.49) | 38 (39.18) | .04[b] |
| Family history, no. (%) | 13 (13.00) | 15 (16.30) | .52 |
| Type, no. (%) | | | |
| MCA | 38 (37.25) | 29 (29.90) | .27 |
| ACoA | 33 (32.35) | 23 (23.71) | .18 |
| PCoA | 21 (20.59) | 28 (28.87) | .18 |
| BA | 10 (9.80) | 17 (17.53) | .12 |

[a]MCA, middle cerebral artery; ACoA, anterior communicating artery; PCoA, posterior communicating artery; BA, basilar apex.
[b]MCA, ACoA, PCoA, and BA.

**TABLE 2. Univariate Analyses of Differences in the Morphological Parameters Between Smokers and Nonsmokers With Aneurysms**[a]

| Metrics | Never Smokers, Mean (SD) | Current Smokers, Mean (SD) | *P* Value |
|---|---|---|---|
| Maximal diameter, mm | 6.3 (4.9) | 6.6 (3.2) | .635 |
| Aneurysm volume, $mm^3$ | 299 (1024) | 246 (531) | .65 |
| Neck diameter, mm | 5.2 (2.8) | 4.8 (2.1) | .18 |
| Aspect ratio | 1.10 (0.79) | 1.35 (1.52) | .14 |
| Aneurysm angle | 93.8 (22.5) | 92.1 (25.7) | .95 |
| Parent vessel diameters, mm | 2.9 (0.8) | 2.9 (0.7) | .92 |
| Parent vessel diameters adjusted, mm | 1.02 (0.21) | 0.96 (0.17) | .03[a] |
| Daughter diameters, mm | 2.4 (0.7) | 2.6 (0.8) | .26 |
| Daughter diameters adjusted, mm | 1.00 (0.19) | 0.99 (0.26) | .80 |
| Size ratio | 2.5 (2.2) | 2.9 (4.1) | .39 |
| Angles | | | |
| Flow angles | 112.7 (34.9) | 107.5 (36.4) | .30 |
| Daughter-daughter angles | 117.1 (55.2) | 111.8 (53.4) | .64 |
| Parent-daughter angles | 75.5 (27.1) | 74.8 (26.6) | .86 |

[a]SD, standard deviation.

smaller parent vessel diameter (OR: 0.15, $P = .06$) were nearly significant. Maximal aneurysm diameter was not included in our multivariate model because it is not completely independent of aspect ratio, size ratio, or volume. Daughter vessel angle was not included in the model because our data did not include daughter vessel angle measurements for ACoA aneurysms. Aneurysm subtype ORs were compared with ACoA aneurysms.

**TABLE 3. Multivariate Analysis of Morphological Parameters Between Never Smokers and Current Smokers With Aneurysms**[a]

| Variables | OR, Current Smokers vs Never Smokers (95% CI) | *P* Value |
|---|---|---|
| Age | 0.99 (0.96-1.02) | .54 |
| Female | 0.78 (0.36-1.71) | .54 |
| Multiple aneurysms | 2.15 (1.07-4.42) | .03[b] |
| Family history | 1.21 (0.46-3.22) | .70 |
| Hypertension | 0.58 (0.29-1.17) | .13 |
| Volume | 1.00 (1-1) | .12 |
| Neck diameter | 0.85 (0.68-1.04) | .13 |
| Aspect ratio | 0.95 (0.50-1.79) | .87 |
| Parent vessel diameter | 0.54 (0.27-1.08) | .09 |
| Daughter vessel diameter | 3.13 (1.37-7.69) | .01[b] |
| Size ratio | 1.78 (1.16-2.77) | .01[b] |
| Flow angle | 1.00 (0.99-1.01) | .90 |
| Parent-daughter vessel angle | 1.00 (0.99-1.01) | .78 |
| Aneurysm type (relative to ACoA) | | |
| MCA | 1.34 (0.57-3.22) | .51 |
| PCoA | 1.25 (0.33-4.72) | .74 |
| BA | 6.26 (1.46-29.53) | .02[b] |

[a]MCA, middle cerebral artery; ACoA, anterior communicating artery; PCoA, posterior; BA, basilar apex; OR, odds ratio; CI, confidence interval.
[b]MCA, ACoA, PCoA, and BA.

## DISCUSSION

Although the association between smoking and intracranial aneurysm formation and rupture has been well described, the mechanistic underpinnings of this relationship are not well understood. In this study, we examined the specific differences in aneurysm morphology between smokers and nonsmokers that may elucidate the effects of smoking on aneurysm formation and eventual rupture. The differences in morphological characteristics between smokers and nonsmokers suggest that smoking may create an altered environment for aneurysm formation. These differences, in turn, may affect the eventual rupture risk of the aneurysm.

Size ratio was first proposed by Dhar et al[32] as a predictor of rupture risk in intracranial aneurysms, and there have been many studies that have sought to validate this finding in recent years,[32,41-44] including morphological studies of rupture risk in our own cohort of ACoA aneurysms.[25] Intuitively, the association with size ratio implies that larger aneurysms arising from smaller vessels are more likely to rupture than smaller aneurysms arising from larger vessels. In terms of aneurysm genesis, size ratio captures the maximal deformation of the parent vessel achieved by the aneurysm and reflects the degree of aneurysm degradation of the vessel. Aneurysms arising in current smokers in our population were also significantly associated with larger size ratios (OR: 1.78, $P = .01$). Increased size ratio has been shown in a number of hemodynamic studies to lead to more complex intra-aneurysmal[33,42,43,45,46] and aneurysmal[45,47-49] vessel–related flow patterns that could influence the rates of both aneurysm formation and rupture. Our data suggest that smoking may contribute to the same morphological and hemodynamic

conditions for aneurysm formation and may create a more favorable environment for aneurysm rupture.

Our finding that daughter vessel diameters are significantly larger in aneurysm patients who smoke (OR: 3.13, $P = .01$) may initially seem at odds with our size ratio findings because larger size ratios imply smaller vessels. Intuitively, aneurysm formation at a vessel branch point is much more likely to occur with smaller daughter vessel diameters because outflow velocities will be exponentially increased with a smaller radius of outflow through the daughter vessel, and these increased velocities would lead to the hemodynamic changes associated with aneurysm genesis[47-49] and rupture.[46,50,51] However, smoking is also associated with smaller parent vessel diameters, which, although not statistically significant, likely contributes to the larger size ratio. Moreover, the addition of physiological and biochemical changes associated with smoking may be more permissive of and accelerate aneurysm pathophysiology to allow formation to occur despite larger daughter vessel diameters.

In addition to absolute vessel diameters and angles, we had also normalized the parameters so that they are relative measures with respect to the average within each aneurysm type. Because each location in the vasculature is associated with different average sizes and angles, the normalization decreases the confounding secondary to location-specific characteristics. In our study, this normalization maintained the significance of both morphological parameters, size ratio and daughter vessel diameter, but increased the relative impact of daughter vessel diameter.

In our study, smokers with aneurysms were significantly more likely to have basilar apex aneurysms than nonsmokers with aneurysms (OR: 6.26). There have only been a few studies of location-specific associations of aneurysm development with clinical risk factors such as smoking. Several studies examine the clinical risk factors associated with posterior circulation aneurysms.[23,26,52,53] Of these, only Lindner et al[52] reported on clinical risk factors in basilar apex aneurysms. They identified a similar relationship in these aneurysms to smoking, in which patients who smoke were significantly more likely to have basilar apex aneurysms compared with nonsmokers with aneurysms, with no significant differences with regard to smoking in any other aneurysm location (OR: 3.3). Basilar apex aneurysms carry with them a higher risk of rupture, morbidity, and mortality.[54-56] They also present significant management considerations in terms of neurosurgical approaches and techniques.[57-59] Thus, the association between smoking and basilar apex aneurysm formation and rupture is significant and warrants further study.

Current smokers with aneurysms in our study were significantly more likely to have multiple aneurysms. Smoking is a well-known risk factor for de novo aneurysm formation,[60,61] and in a recent prospective study of de novo aneurysm formation identified by routine delayed radiographic surveillance studies in patients with at least 1 previous intracranial aneurysm, smoking significantly increased the risk of de novo aneurysm formation (hazard ratio: 2.58, 95% CI: 1.13-5.90).[62] Given that a significant number of de novo aneurysms present with rupture, the effects of smoking on the morphology and hemodynamics of aneurysms presented in this study are likely predictive of both aneurysm formation and rupture.

### Limitations

There are several limitations to this study that should be acknowledged. First, smoking in our study was defined as current smokers. There was no specific determination of the relationship of pack-years with the variables studied; thus, the dynamic effects of increasing degrees of smoking are not well captured in our results. Because of the retrospective case-control design of this study, most patients (except for those with basilar apex aneurysms) were treated either surgically or endovascularly, and the study population is inherently biased toward morphologically "dangerous"-appearing lesions. This may limit the applicability of our data to general aneurysm patients in whom there is less clinical equipoise about treatment. Also, the effect that aneurysm rupture and subsequent hemorrhage may have on aneurysm geometry was not taken in account, although several studies suggested that rupture does not significantly alter aneurysm morphology.[31-33]

## CONCLUSION

Research linking the effects of smoking on aneurysm formation and rupture risk has largely focused on potential biochemical and biomechanical mechanisms. However, in addition to physiological conditions (such as flow rate and blood viscosity), aneurysm hemodynamics are mostly directly influenced by aneurysm and vascular morphology, which we have shown in the present study is significantly more altered in the smoking population of patients with aneurysms. There were several aspects of aneurysm morphology significantly associated with smoking status including larger daughter vessel diameters, larger size ratio, and location at the basilar apex. Future study on how these specific morphological changes may influence aneurysmal hemodynamics may provide the morphological basis for how smoking leads to increased aneurysm formation and rupture. Understanding of these morphological changes may allow clinicians to more accurately determine rupture risk in smokers and counsel/treat accordingly.

### Disclosures

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## COMMENT

The authors present an interesting analysis looking at associations between smoking status and aneurysm location and morphology. The aspects of aneurysm location and morphology that were significantly associated with smoking status—larger daughter vessel diameters, larger size ratio, and location at the basilar apex—are of interest with regard to explaining why smokers may have a higher risk of rupture. As noted by the authors, the relationship between wall shear stress and aneurysm rupture is a complicated one. The ability to quantify aneurysm size and shape and to determine how these geometric features affect aneurysm hemodynamics and biology have become important tools in the attempt to understand how aneurysms develop and grow and to predict the natural history risks for individual patients with intracranial aneurysms.[1-7]

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