Widening and High Inclination of the Middle Cerebral Artery Bifurcation Are Associated With Presence of Aneurysms

Merih I. Baharoglu, MD; Alexandra Lauric, PhD; Mina G. Safain, MD; James Hippelheuser, BS; Chengyuan Wu, MD; Adel M. Malek, MD, PhD

Background and Purpose—The middle cerebral artery (MCA) bifurcation is a preferred site for aneurysm formation. Wider bifurcation angles have been correlated with increased risk of aneurysm formation. We hypothesized a link between the presence of MCA aneurysms and the angle morphology of the bifurcation.

Methods—Three-dimensional rotational angiography volumes of 146 MCA bifurcations (62 aneurysmal) were evaluated for angle morphology: parent–daughter angles (larger daughter $\Phi_1$, smaller daughter $\Phi_2$), bifurcation angle ($\Phi_3$), and inclination angle ($\gamma$) between the parent vessel axis and the plane determined by daughter vessel axes. Statistics were evaluated using Wilcoxon rank-sum analysis and area under the receiver operator characteristic curve.

Results—Aneurysmal bifurcations had wider inclination angle $\gamma$ (median 57.8° versus 15.4°; $P<0.0001$). Seventy-five percent of aneurysmal MCAs had $\gamma > 10^\circ$, compared with 25% nonaneurysmal. $\Phi_1$ and $\Phi_2$, but especially $\Phi_3$, were significantly larger in aneurysmal bifurcations (median 171.3° versus 98.1°; $P<0.0001$). Sixty-seven percent of aneurysmal bifurcations had $\Phi_1 + \Phi_2 > 161^\circ$, compared with 0% nonaneurysmal MCAs. An optimal threshold of 140° was established for $\Phi_1 + \Phi_2$ (area under the curve, 0.98). Sixty-eight percent of aneurysms originated off the daughter branches. Seventy-six percent of them originated off the branch with the largest branching angle, specifically if this was the smaller daughter branch. Wider $\Phi_1 + \Phi_2$ correlated with aneurysm neck width, but not dome size.

Conclusions—MCA bifurcations harboring aneurysms have significantly larger branching angles and more often originate off the branch with the largest angle. Wider inclination angle is strongly correlated with aneurysm presence, a novel finding. The results point to altered wall shear stress regulation as a possible factor in aneurysm development and progression. (Stroke. 2014;45:2649-2655.)

Key Word: intracranial aneurysm

Intracranial aneurysms are not present at birth, but are rather pathological conditions acquired during life, usually during adulthood. Recent research has evaluated the basic mechanisms of aneurysm initiation and formation, with a focus on hemodynamic patterns, which has been suggested to play an essential role in aneurysm formation.1,2 The apex of bifurcations, where the vessel wall is exposed to the highest wall shear stress (WSS) and spatial wall shear stress gradient (WSSG), is a location where saccular cerebral aneurysms arise with high frequency. The hemodynamic environment at the bifurcation apex is highly dependent on the bifurcation geometry,4 and WSS is minimized in cases where the bifurcation follows the optimality principles of minimum work.5–7 The principle of minimum work provides an optimization model for the growth and adaptation of biological systems.5,6 Previous studies have shown arterial bifurcations in animals and humans, including the cerebral arterial tree, to follow this principle,4,11 which decrees the optimal relationship between the bifurcation angle and the relative size of daughter vessels. Changes in bifurcation morphology were previously linked to changes in hemodynamic forces at the bifurcation apex. Specifically, wider bifurcation angles have been associated not only with aneurysmal presence but also with particular hemodynamic characteristics previously associated with an increased risk of aneurysm formation.12

The middle cerebral artery (MCA) bifurcation is a preferred site for aneurysm formation. Studies have estimated that MCA aneurysms represent between 18% and 36% of all intracranial aneurysms.13 MCA aneurysms account for ≈30% of the aneurysms presenting with acute subarachnoid hemorrhage and for 16% of all giant aneurysms.14 Because of the high prevalence of MCA aneurysms, detection of local morphological patterns more prone to aneurysm formation could help assist in risk assessment of aneurysm initiation.

Recent studies have shown a significant difference in branching angles between MCA bifurcations that harbor aneurysms...
compared with bifurcations without aneurysmal involvement.\textsuperscript{15–17} These findings suggest that the geometry of branching angles might play a role in aneurysm formation. However, most studies were limited by the small sample of aneurysmal MCA bifurcations.\textsuperscript{15,16} To the best of our knowledge, the morphological differences between aneurysmal and nonaneurysmal MCA bifurcations have not been thoroughly investigated. The objective of this study was to evaluate the morphology of MCA bifurcations with and without aneurysm involvement and to determine a possible link between aneurysm presence and bifurcation angles.

**Methods**

**Patient Selection**

Three-dimensional volumetric data sets of patients presenting with intracranial aneurysms within a period of 8 years were included. Mycotic and fusiform aneurysms were excluded. MCA bifurcations without aneurysmal involvement were gathered from patients with aneurysms at other locations and separately from a group of healthy individuals who had undergone cerebral angiography for different purposes (excluding patients with familial history of intracranial aneurysms). Data on patient age, sex, smoking status, hypertension, hyperlipidemia, and aneurysm rupture status were collected from a prospectively maintained database. The study was approved by Tufts Health Sciences Campus Institutional Review Board.

**Data Acquisition**

Three-dimensional cerebral angiograms were obtained from either Philips Integris (Bothell, WA) or Siemens Artis (Malvern, PA) biplane systems and reconstructed using the manufacturers’ clinical software package. Three-dimensional volumetric data sets were analyzed using Amira visualization software platform version 5.4 (FEI Visualization Sciences Group, Burlington, MA). Gradient edge-detection filtering was used to enable threshold-independent measurements.\textsuperscript{18}

**Morphological Feature Extraction**

The branching angles were measured on longitudinal 2-dimensional cut-planes placed through the center of both the parent and daughter branches. This approach is similar to the one used by other similar studies\textsuperscript{15–17} and has the advantage that the angle measurement is easily obtainable during the 3-dimensional rotational angiography, making it practical for clinical applications. By convention, the angle between parent vessel and the larger daughter vessel was termed $\Phi_1$, whereas the angle between parent vessel and the smaller vessel was termed $\Phi_2$ (Figure 1). Additionally, the angle between the parent vessel and both daughter branches was measured to obtain the angle between 2 planes ($\gamma$ angle). The location of origin was noted for every aneurysm as either originating purely off the larger or smaller daughter branch or off the apex of the bifurcation.

**Statistical Analysis**

JMP version 10.0 (SAS Institute, Cary, NC) was used for statistical analysis, with significance assumed for $P<0.05$. Bifurcations were

![Figure 1.](http://stroke.ahajournals.org/)

A. Measurement of branching angles in a control middle cerebral artery (MCA) bifurcation (patient with no aneurysms), a nonaneurysmal MCA bifurcation (patient with aneurysms at other locations), and an aneurysmal MCA bifurcation. B. Schematic drawing of a bifurcation showing measurement of branching angles: $\Phi_1$ between parent vessel main axis and largest daughter vessel (branch 1) axis and $\Phi_2$ with the axis of the smallest branch (branch 2). C. Schematic drawing of a bifurcation (lateral view) that shows measurement of the inclination angle ($\gamma$) between the parent vessel plane and the daughter branches plane.
divided into 3 categories for analysis: control bifurcations from patients without aneurysms, nonaneurysmal bifurcations from patients with aneurysms at other locations (no MCA), and aneurysmal bifurcations harboring aneurysms. All variables were tested independently using ANOVA and post hoc Student t test for normal distributed data and Wilcoxon rank-sum test for non-normal distributed data. Statistics for non-normal distributed data are reported as median and interquartile range (IQR). The relative correlation between parameters (branch angles, age, and aneurysm morphology) was evaluated by multivariate analysis using least square linear regression. Whenever data were available on both aneurysmal and nonaneurysmal contralateral MCA bifurcation within the same patient, a separate pair-matched analysis was performed to compare the corresponding angles. Receiver operator characteristics analysis was performed to determine the area under the curve (AUC) index as well as optimal cut-off values for $\Phi_1$, $\Phi_2$, $\Phi_1+$ $\Phi_2$, and $\gamma$. Finally, the data were again analyzed after exclusion of ruptured aneurysms to address possible vasospasm distorting the findings.

**Results**

**Patient Demographics**

A total of 353 aneurysms in 282 patients were identified. After exclusion of mycotic and fusiform aneurysms, a total of 62 MCA bifurcation aneurysms were available, of which 13 had previously ruptured. Nonaneurysmal MCA bifurcations were evaluated in 84 patients (57 from patients with aneurysms at other locations and 27 from healthy control patients). In a subset of 16 patients, data on both aneurysmal and normal contralateral MCA bifurcation could be obtained. Mean age of the entire population was 56.6 (range, 30–92) years with 97 bifurcations from female patients (67%). Mean ages for the 3 bifurcation groups were: the aneurysmal group, 57.6 (range, 30–92) years; nonaneurysmal MCA in patients with no aneurysms, 58.8 (range 30–85) years; and control MCA in patients with no aneurysms, 53.5 (range, 31–85) years; and control MCA in patients without aneurysms, 57.8 (range 30–92) years. Because the angle of healthy cerebral bifurcations has been previously shown to increase with age, only control MCA bifurcation aneurysms were available, of which 13 had a total bifurcation angle of $<121^\circ$. Exclusion of ruptured aneurysms did not affect the results (data not shown).

As shown in Table 1, within the nonaneurysmal group, $\Phi_1$ was significantly wider in patients with aneurysms at other locations (median 50.2°) compared with control patients (median 32.3°; P<0.001; Figure 2). $\Phi_1+$ $\Phi_2$ was also significantly wider in nonaneurysmal MCA from patients with aneurysms in other locations (median 103.6°) compared with control MCA (median 92.1°; P=0.009). However, there was no difference in $\Phi_2$ (median 54.3° in patients with aneurysms in other locations versus 56.6° in controls).

The inclination angle $\gamma$, formed between the parent vessel axis and the plane containing the axes of the 2 daughter vessels, was significantly wider in aneurysmal bifurcations (median [IQR], 57.8° [16.5–82.3°] versus 15.4° [0.5–36.2°]; P<0.001). There was no statistical significance within the nonaneurysmal bifurcations when $\gamma$ was compared between control (no aneurysm) and nonaneurysmal...
MCA bifurcations in patients with aneurysms in other locations \((P=0.73)\).

In pair-matched analysis, aneurysmal MCA bifurcations had significantly wider bifurcation angles compared with their nonaneurysmal contralateral counterparts (Table 2). This was true for \(\Phi_1\) (median 75.34° aneurysmal versus 51.2° contralateral), for \(\Phi_2\) (median 105.5° aneurysmal versus 53.5° contralateral), but also for angle \(\gamma\) (median 69.2° aneurysmal versus 30.5° contralateral). When compared with other nonaneurysmal MCA bifurcations, MCA contralateral to an aneurysmal bifurcation had significantly wider \(\Phi_2\) compared with controls (median 51.2° versus 32.3°; \(P=0.004\)). Contralateral \(\Phi_1\) was similar to that of nonaneurysmal MCA bifurcations from patients with aneurysms in other locations (\(P=0.92\)). \(\Phi_2\) and \(\gamma\) were not different between the contralateral MCA and other nonaneurysmal bifurcations.

### Optimal Discriminating Angle Thresholds

Optimal angle threshold values distinguishing between MCA bifurcations with and without aneurysms were determined by using receiver operating characteristic analysis (Figure 3A). The total bifurcation angle \(\Phi_1+\Phi_2\) was the best performer in discriminating between aneurysmal and nonaneurysmal MCA. The resulting optimal \(\Phi_1+\Phi_2\) threshold was 140° (AUC, 0.98), with 93% sensitivity and 93% specificity. The optimal \(\Phi_1\) threshold was 69° (AUC, 0.84), resulting in a sensitivity of 63% and specificity of 96%. The optimal \(\Phi_2\) threshold was 83° (AUC, 0.91), resulting in a sensitivity of 78% and specificity of 91%. The optimal \(\gamma\) threshold was 56° (AUC, 0.71), resulting in a sensitivity of 53% and specificity of 91%.

### Aneurysm Location and Size

The aneurysm location was as follows: 10 (16%) originated off the larger daughter branch, 32 (52%) off the smaller branch, and 20 (32%) off the apex of the bifurcation. Pair-matched analysis comparing \(\Phi_1\) and \(\Phi_2\) based on aneurysm location showed that the aneurysm consistently originated off the vessel corresponding to the larger angle (Table 3). When the aneurysm originated off the larger daughter, \(\Phi_1\) was significantly wider than \(\Phi_2\) (median 92.6° versus 72.1°; \(P=0.04\); Figure 3B). When the aneurysm originated off the smaller daughter, \(\Phi_2\) was significantly wider than \(\Phi_1\) (median 112.3° versus 53°; \(P<0.001\); Figure 3C). However, when the aneurysm originated at the apex, there was no statistical difference between \(\Phi_1\) and \(\Phi_2\) (median 86.1° versus 94.3°; \(P=0.19\)). Although not statistically significant, the inclination angle \(\gamma\) was larger in aneurysms originating at the bifurcation apex compared with aneurysms originating off one of the daughter vessels (\(P=0.08\)).

Mean aneurysm size was 6.43±2.63 mm with a neck size of 4.46±1.33 mm. \(\Phi_1\) and \(\Phi_2\) were not correlated to the aneurysm size. However, \(\Phi_1\) was positively correlated to the aneurysm neck (\(P=0.02\)). In addition, \(\Phi_1+\Phi_2\) was highly correlated to the aneurysm neck (\(P=0.006\)). The inclination angle \(\gamma\) was not statistically correlated to aneurysm morphology.

### Age and Sex

\(\Phi_1\) was positively correlated with age in aneurysmal MCA (\(P=0.001\)) and in nonaneurysmal MCA from patients with aneurysms in other locations (\(P=0.02\)), but not in controls (\(P=0.65\)). In contrast, \(\Phi_2\) was not correlated with age in any of the groups. Similarly, \(\gamma\) showed no age dependency in any of the groups. Similar to \(\Phi_1\), the total bifurcation angle, \(\Phi_1+\Phi_2\), was positively correlated with age in aneurysmal MCA (\(P=0.02\)) and in nonaneurysmal MCA from patients with aneurysms in other locations (\(P=0.04\)), but not in controls (\(P=0.21\)).

Regarding sex differences, there were no statistical differences between men and women in any of the 3 groups analyzed.

### Smoking, Hypertension, and Hyperlipidemia

Overall 21% of the bifurcation samples were from patients currently smoking (45% had a smoking history). In the aneurysmal MCA group, 30% samples were from current smokers (65% had smoking history). In contrast, in the nonaneurysmal group, only 14% of the samples were from current smokers (30% had a smoking history). The difference in smoking status between aneurysmal and nonaneurysmal samples was statistically significant both for current smokers (\(P=0.02\)) and for smoking history (\(P<0.001\)). Both in the smoking and nonsmoking groups, angles \(\Phi_1\), \(\Phi_2\), \(\Phi_1+\Phi_2\), and \(\gamma\) were

---

**Table 1. Univariate Statistical Analysis Using Wilcoxon Rank-Sum Test**

<table>
<thead>
<tr>
<th></th>
<th>Control MCA (No Aneurysms; n=27)</th>
<th>Nonaneurysmal MCA (Non-MCA Aneurysms; n=57)</th>
<th>Aneurysmal MCA (n=62)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\Phi_1)</td>
<td>32.3° (26–42.4°)</td>
<td>50.2° (34.5–61°)</td>
<td>77.5° (62.9–96°)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(\Phi_2)</td>
<td>56.6° (47.7–66.3°)</td>
<td>54.3° (44.5–73.1°)</td>
<td>101.7° (84.5–115.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(\Phi_1+\Phi_2)</td>
<td>92.1° (76.2–97.7°)</td>
<td>103.6° (91.85–124.4°)</td>
<td>171.5° (150.8–191.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(\gamma)</td>
<td>15.4° (5.2–33.7°)</td>
<td>16.1° (0–38.9°)</td>
<td>57.8° (16.5–82.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Shown are median and interquartile range. MCA indicates middle cerebral artery.

---

**Table 2. Matched-Pair Analysis for Aneurysmal and Nonaneurysmal Contralateral MCA Bifurcations Within Same Patients (n=16)**

<table>
<thead>
<tr>
<th></th>
<th>Contralateral MCA</th>
<th>Aneurysmal MCA</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\Phi_1)</td>
<td>51.2° (37.1–57.7°)</td>
<td>75.4° (42.5–83.575°)</td>
<td>0.02</td>
</tr>
<tr>
<td>(\Phi_2)</td>
<td>53.5° (42.5–64.9°)</td>
<td>105.5° (85.2–123.4°)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(\Phi_1+\Phi_2)</td>
<td>104.5° (92.2–121.8°)</td>
<td>172.1° (150.2–197.3°)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(\gamma)</td>
<td>30.5° (0–51.4°)</td>
<td>69.2° (19.4–84.9°)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Shown are median with interquartile range. MCA indicates middle cerebral artery.
Importantly, within the aneurysmal group, nonsmokers had significantly wider angles compared with control patients ($P<0.02$). Within the aneurysmal group, nonsmokers had significantly wider $\Phi_1$, $\Phi_2$, $\Phi_1+\Phi_2$, and $\gamma$ angles compared with nonaneurysmal bifurcations ($P<0.01$).

Overall, 54% of the bifurcation samples were from patients with hypertension. Seventy percent of the aneurysmal MCA bifurcations were from patients with hypertension compared with 42% in the nonaneurysmal group ($P<0.001$). Regardless of hypertension status, angles $\Phi_1$, $\Phi_2$, $\Phi_1+\Phi_2$, and $\gamma$ were significantly wider in aneurysmal MCA compared with nonaneurysmal bifurcations. Moreover, there was no angle difference between patients with hypertension compared with patients with no hypertension.

Overall, 22% of the bifurcation samples were from patients with hyperlipidemia. Twenty-three percent of the aneurysmal MCA bifurcations were from patients with hyperlipidemia compared with 20% in the nonaneurysmal group ($P=0.66$). Regardless of hyperlipidemia status, angles $\Phi_1$, $\Phi_2$, $\Phi_1+\Phi_2$, and $\gamma$ were significantly wider in aneurysmal MCA compared with nonaneurysmal bifurcations. Moreover, there was no angle difference between patients with hyperlipidemia compared with patients with no hyperlipidemia.

Multivariate Statistical Analysis
Multivariate analysis using least square linear regression was used to determine the relative dependency of the variables. The analysis showed $\Phi_1$ to be independently predicted by aneurysm presence ($P<0.001$), age ($P=0.005$), and current smoking status ($P=0.007$), but not by sex, hypertension, hyperlipidemia, or the width of the aneurysm. Similarly, $\Phi_1+\Phi_2$ was independently predicted by aneurysm presence ($P<0.001$), age ($P=0.01$), and current smoking status ($P=0.02$), but not by sex, hypertension, hyperlipidemia, or the width of the aneurysm neck. In contrast, $\Phi_2$ and $\gamma$ were independently predicted solely by aneurysm presence ($P<0.001$).

Imaging Acquisition Analysis
Out of 146 MCA bifurcations, 86 bifurcations (34 aneurysmal) have been evaluated on 3-dimensional cerebral angiograms obtained from Philips Integris imaging system, and 60 bifurcations (28 aneurysmal) have been evaluated on angiograms obtained from Siemens Artis. To determine the impact of acquisition system on statistical findings, the statistical analysis was repeated within the 2 subgroups. Regardless of the acquisition origin, all angles evaluated here were significantly wider for aneurysmal compared with nonaneurysmal MCA bifurcations with identical statistical performance.

When only aneurysmal bifurcations were compared, there was no statistical difference between angiograms acquired from Siemens Artis compared with those acquired from Philips Integris. This was true for $\Phi_1$ (median 77° versus 76.4°; $P=0.40$), $\Phi_2$ (median 103.3° versus 95.2°; $P=0.41$), and $\Phi_1+\Phi_2$ (median 171.2° versus 167.2°; $P=0.78$). Similarly, when only nonaneurysmal bifurcations were compared, there

![Figure 3. A. Receiver operator characteristics (ROC) plot showing the performance of all bifurcation angles in discriminating between aneurysmal and nonaneurysmal middle cerebral artery (MCA) bifurcations. AUC indicates area under the ROC curve. B. Graph showing significantly larger $\Phi_1$ for bifurcations in which the aneurysm originated off the larger branch compared with bifurcations where the aneurysm originated off the smaller branch. C. Graph showing significantly larger $\Phi_2$ for bifurcations in which the aneurysm originated off the smaller branch compared with bifurcations where the aneurysm originated off the larger branch or the middle of the bifurcation. *$P<0.05$, **$P<0.001$.](image-url)

significantly wider in aneurysmal MCA compared with nonaneurysmal MCA bifurcations. Moreover, in the nonsmoking group, $\Phi_1$ was significantly wider in patients with aneurysms at other locations compared with control patients ($P<0.02$).

Importantly, within the aneurysmal group, nonsmokers had significantly wider $\Phi_1$ (median [IQR], 84.7° [61.3–115.2°] versus 58.5° [42.2–79.1°]; $P=0.002$) and $\Phi_1+\Phi_2$ (median [IQR], 182.3° [159.8–216.5°] versus 155.2° [143.5–171.6°]; $P=0.001$) compared with smokers. This was not observed in the nonaneurysmal group where there was no statistical difference in any of the angles between smokers and nonsmokers. It should be noted that even when aneurysmal nonsmokers were excluded, the aneurysmal bifurcations still had significantly wider $\Phi_1$, $\Phi_2$, $\Phi_1+\Phi_2$, and $\gamma$ angles compared with nonaneurysmal bifurcations ($P<0.01$).

The analysis showed $\Phi_1$ to be independently predicted by aneurysm presence ($P<0.001$), age ($P=0.005$), and current smoking status ($P=0.007$), but not by sex, hypertension, hyperlipidemia, or the width of the aneurysm. Similarly, $\Phi_1+\Phi_2$ was independently predicted by aneurysm presence ($P<0.001$), age ($P=0.01$), and current smoking status ($P=0.02$), but not by sex, hypertension, hyperlipidemia, or the width of the aneurysm neck. In contrast, $\Phi_2$ and $\gamma$ were independently predicted solely by aneurysm presence ($P<0.001$).
was no statistical difference between angiograms acquired with the 2 systems for $\Phi_1$ (median 50.4° versus 48°; $P=0.87$), $\Phi_2$ (median 57.2° versus 49°; $P=0.30$), and $\Phi_1+\Phi_2$ (median 106.1° versus 97°; $P=0.46$).

### Discussion

Previous studies have investigated the possible correlation between the angles formed by parent and daughter vessels and aneurysm presence at the MCA bifurcation.\textsuperscript{15-17} Ingebrigtsen et al\textsuperscript{16} evaluated the geometry of bifurcations in the circle of Willis and showed that aneurysmal bifurcations had wider bifurcation angles compared with nonaneurysmal geometries, although the analysis was limited to 14 aneurysmal bifurcations including not only middle cerebral but also internal carotid and basilar arteries. Similarly, Bor et al\textsuperscript{15} reported that aneurysmal bifurcations in the circle of Willis (including 10 MCA) had narrower lateral angles compared with nonaneurysmal geometries. Finally, Sadatomo et al\textsuperscript{17} showed that aneurysmal MCA bifurcations had smaller lateral angle and higher lateral angle ratio compared with nonaneurysmal bifurcations.

Unlike earlier reports, this study focused specifically on MCA bifurcations that are end vessel–type without collateral supply from anterior or posterior communicators. The study was also concerned uniquely on the geometry of the bifurcation at the actual point of blood flow impingement. Whereas other studies evaluated lateral bifurcation angles, here we use not only individual angles between parent and daughter vessels ($\Phi_1$ and $\Phi_2$) but also total bifurcation angle to describe the bifurcation. Total bifurcation angle was previously shown to determine the hemodynamic environment of bifurcations after stent-mediated treatment.\textsuperscript{19} In addition, this study introduced the overall inclination angle between the parent vessel axis and the plane formed by the axes of the daughter vessels. Because recent studies suggested that aneurysm initiation reflects not only local but also global characteristics of the vasculature,\textsuperscript{20,21} we hypothesized (1) a link between the presence of MCA aneurysms and the angle morphology of the bifurcation, and (2) a link between aneurysm presence at locations other than MCA bifurcation and the morphology of MCA bifurcation.

All evaluated angles were significantly wider in aneurysmal compared with nonaneurysmal MCA bifurcations. Among nonaneurysmal MCA bifurcations, the angle between the parent vessel and the larger daughter, as well as the total bifurcation angle, were significantly wider in patients with aneurysms at other locations compared with patients without any aneurysms (control patients). No control patient had a total bifurcation angle >116°, and no aneurysmal MCA bifurcation had a total bifurcation angle <121°. Similarly, none of the patients with aneurysms at other locations had a total bifurcation angle >161°. In contrast, 67% of aneurysmal bifurcations were wider than 161°. Interestingly, the bifurcation angles of nonaneurysmal MCA bifurcations contralateral to aneurysmal MCAs were not only significantly smaller compared with the corresponding counterparts but also significantly wider compared with control patients. In fact, the nonaneurysmal contralateral MCA bifurcations had similar morphology to that of the nonaneurysmal MCA bifurcations in patients with aneurysms at other locations. These findings suggest a more global arterial weakening at bifurcation sites throughout the cerebral circulation.

Smoking is a well-documented risk factor for cerebral aneurysm formation,\textsuperscript{22} and this study showed that in smokers, aneurysms formed at narrower bifurcation angles compared with nonsmokers ($P=0.001$). To the best of our knowledge, ours is the first report of this phenomenon. The finding suggests that the added risk of smoking may have resulted in a decrease of the angle threshold for aneurysm formation. Still aneurysmal MCA bifurcations in smokers were significantly wider compared with MCA bifurcations in controls and in patients with aneurysms in other locations.

A novel finding in this study is the increased inclination angle in MCA bifurcations that harbor aneurysms. A small inclination angle means that the daughter branches are in line with the parent vessel. However, when the inclination angle increases, the daughter branches make a sharper turn from the parent vessel and thus deviate from the inflow of blood. We had hypothesized that such an increase in angle could lead to aneurysm formation, because it would cause a deviation of the blood flow and of its location of impact on the vessel wall and cause changes in WSS and WSSG. We indeed found a significant increase in the inclination angle between aneurysmal and nonaneurysmal MCA bifurcations.

We hypothesize that because branching angles are relatively larger in diseased bifurcations, the blood stream has to deviate more profoundly at that point. Finlay et al\textsuperscript{20} described a collagen tendon-like medial pad that is thought to protect the apex of the bifurcation where the flow is divided into daughter branches and the highest WSS and WSSG is supposed to occur. Meng et al\textsuperscript{21} studied canine arteries and described the presence of an intimal pad in the impingement region where the flow jet hits the bifurcation tip. This intimal pad was a healthy reaction of the endothelium for protection of itself against high WSS and WSSG. When branching angles increase, the impingement region shifts away from the bifurcation apex\textsuperscript{12} where the arterial wall is protected from these forces. Higher branching angles lead to dispersal of high WSS and WSSG impact zone on the adjacent arterial wall, away from the protection at the bifurcation apex onto the more vulnerable arterial wall of the daughter vessel. These conditions of high WSS and WSSG have been shown to lead to aneurysm formation.\textsuperscript{2,24} Consequently, detection of bifurcations with

### Table 3. Univariate Statistical Analysis Using Wilcoxon Rank-Sum Test

<table>
<thead>
<tr>
<th>Aneurysm Originates Off Apex (n=20)</th>
<th>Aneurysm Originates Off Smaller Daughter (n=32)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Phi_1$ (median 92.6° versus 86.1° (78–105.8°))</td>
<td>53° (41.5–82.15°)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$\Phi_2$ (median 72.1° versus 94.3° (86.05–108.25°))</td>
<td>112.3° (97.7–128.45°)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Shown are median and interquartile range for aneurysms originating off the larger daughter, off the smaller daughter branch, or off the apex of the bifurcation.
such deviant morphology could potentially enable follow-up for longitudinal risk evaluation of aneurysm initiation. Further testing of this hypothesis requires in-depth computational fluid dynamics studies, which will be the focus of future research. Prospective studies are required to elucidate any causal versus associative relationship.

Study Limitations

Given the retrospective nature of our study, we cannot conclude that wider bifurcation angles preceded aneurysm formation, because aneurysm formation might have altered bifurcation morphology itself. Prospective analysis of a small set of MCA bifurcations seems to suggest that wide branching angles precede aneurysm initiation. However, to the best of our knowledge, no conclusive data have yet been presented to address this issue. Moreover, although this study showed a strong correlation between MCA bifurcation angles and aneurysm presence, no cause-and-effect relation can be conclusively determined. The possibility remains that aneurysm formation is an epiphenomenon to wider bifurcations rather than a direct consequence to higher-risk bifurcation morphology. Further investigations are required to clarify the potential utility and applicability of the MCA bifurcation angle assessment in cerebral aneurysm risk stratification analysis.

Conclusions

MCA bifurcations harboring aneurysms have significantly wider bifurcation and inclination angles compared with nonaneurysmal bifurcations. Moreover, patients with aneurysms at locations other than MCA have significantly wider MCA angle configurations compared with control patients with no cerebral aneurysms. A bifurcation angle of 140° was established as a highly accurate optimal threshold to distinguish between MCA bifurcations with and without aneurysms. Control MCA bifurcations from patients with no cerebral aneurysms have smaller bifurcation angles compared with nonaneurysmal bifurcations from patients with aneurysms in other locations, suggesting a global morphological risk for aneurysm formation. In smokers, MCA bifurcation aneurysms occur at smaller bifurcation angles compared with nonsmokers. Overall, our data suggest that the angle morphology of the MCA bifurcation might play an important role in the formation of MCA aneurysms and may be indicative of aneurysm presence at other locations.

Sources of Funding

This work was supported by a grant from the National Institutes of Health (NIH-R21HL102685).

Disclosures

The senior author (A.M. Malek) has received unrestricted research funding by ev3 Inc, Microvention Inc, Siemens Inc, and Stryker Inc for research unrelated to the submitted work. The other authors report no conflicts.

References

Widening and High Inclination of the Middle Cerebral Artery Bifurcation Are Associated With Presence of Aneurysms
Merih I. Baharoglu, Alexandra Lauric, Mina G. Safain, James Hippelheuser, Chengyuan Wu and Adel M. Malek

Stroke. 2014;45:2649-2655; originally published online August 12, 2014;
doi: 10.1161/STROKEAHA.114.005393
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/45/9/2649

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/