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Deviation from Optimal Vascular Caliber Control at Middle Cerebral Artery Bifurcations Harboring Aneurysms

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Abstract

Cerebral aneurysms form preferentially at arterial bifurcations. The vascular optimality principle (VOP) decrees that minimal energy loss across bifurcations requires optimal caliber control between radii of parent (r_0) and daughter branches (r_1 and r_2): $r_0^n = r_1^n + r_2^n$, with n approximating three. VOP entails constant wall shear stress (WSS), an endothelial phenotype regulator. We sought to determine if caliber control is maintained in aneurysmal intracranial bifurcations. Three-dimensional rotational angiographic volumes of 159 middle cerebral artery (MCA) bifurcations (62 aneurysmal) were processed using 3D gradient edge-detection filtering, enabling threshold-insensitive radius measurement. Radius ratio (RR) = $r_0^3 / (r_1^3 + r_2^3)$ and estimated junction exponent (n) were compared between aneurysmal and non-aneurysmal bifurcations using Student t-test and Wilcoxon rank-sum analysis. The results show that non-aneurysmal bifurcations display optimal caliber control with mean RR of 1.05 and median n of 2.84. In contrast, aneurysmal bifurcations had significantly lower RR (0.76, $p < .0001$) and higher n (4.28, $p < .0001$). Unexpectedly, 37% of aneurysmal bifurcations revealed a daughter branch larger than its parent vessel, an absolute violation of optimality, not witnessed in non-aneurysmal bifurcations. The aneurysms originated more often off the smaller daughter (52%) vs. larger daughter branch (16%). Aneurysm size was not statistically correlated to RR or n . Aneurysmal males showed higher deviation from VOP. Non-aneurysmal MCA bifurcations contralateral to aneurysmal ones showed optimal caliber control. Aneurysmal bifurcations, in contrast to non-aneurysmal counterparts, disobey the VOP and may exhibit dysregulation in WSS-mediated caliber control. The mechanism of this focal divergence from optimality may underlie aneurysm pathogenesis and requires further study.

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Keywords

Optimal caliber control; intracranial aneurysm; bifurcation morphology; middle cerebral artery

INTRODUCTION

It has been suggested that the cerebral arterial network follows to some extent the optimal design of biological vascular structures (LaBarbera, 1990; Pries et al., 1995), which enforces a minimization of metabolic cost on the expenditure of energy a system requires to build and maintain its infrastructure while performing its physiological tasks (Murray, 1926; Rosen, 1967). In the case of vascular trees, the optimality principle dictates the design of the branching hierarchy needed to maintain continuity of flow while minimizing energy losses at bifurcations, which leads to constant wall shear stress (WSS) across arterial bifurcations. This vascular optimality principle (VOP) (Zamir, 1976) is a parametric optimization model expressed as a balanced relation between the sizes and the angles of parent and daughter vessels. This principle of optimal caliber control states that the radius of the parent vessel (r_0) dictates the radii of its daughter branches ($r_1, r_2, \dots, r_i$) according to the formula $r_0^n = r_1^n + r_2^n + \dots + r_i^n$, in which n is the junction exponent. According to Rosen (1967) and confirmed by Rossitti and Lofgren (1993) and Ingebrigtsen et al. (2004), in human cerebral arterial bifurcations the junction exponent n approximates the theoretical value of 3. Previous studies have shown that arterial bifurcations in animals and humans, including the cerebral arterial tree, follow this golden rule (Rossitti and Lofgren, 1993; Zamir et al., 1983), mediated by an underlying endothelial regulatory mechanotransduction aimed at maintaining WSS constant on the arterial side. This regulatory pathway is thought to be a locally controlled global feedback loop, in which WSS is sensed by endothelium and transduced by the latter to regulate its autocrine and paracrine growth factor production (Malek et al., 1999). The latter then signals to the smooth muscle cells, fibroblasts, and the extracellular matrix to alter vessel wall structure in such a manner as to maintain a constant wall shear, which constitutes a minimum energy expenditure state described by Murray's Law (LaBarbera, 1990; Langille and O'Donnell, 1986; Murray, 1926). The primordial role of the endothelium in this feedback loop has been previously demonstrated by Langille and O'Donnell (1986).

Some concerns have been raised regarding the application of VOP to bifurcations within the circle of Willis (Ingebrigtsen et al., 2004), and indeed research indicates that the hemodynamics within the circle of Willis do not follow VOP, likely because of the confluence of flow from the anterior and posterior communicating arteries (Alnaes et al., 2007; Ingebrigtsen et al., 2004). However, bifurcations of cerebral arteries outside the circle of Willis, such as anterior cerebral artery branches, have been shown to follow VOP (Ingebrigtsen et al., 2004; Rossitti and Lofgren, 1993).

The middle cerebral artery (MCA) bifurcation is one of the most common sites for aneurysm development (Juvela et al., 2000). With the advent of improved noninvasive vascular imaging methods, MCA aneurysms are often discovered incidentally. The prevalence of MCA aneurysms and consequent angiographic availability, coupled with the relatively

larger size of MCA parent and daughter vessels, makes MCA bifurcations excellent candidates for evaluating the relationship of bifurcation size ratios and aneurysmal involvement. While other studies have investigated the anatomical differences between control and aneurysmal MCA bifurcations (Sadatomo et al., 2013), in this study we evaluate MCA bifurcations in the context of optimal caliber control as stated by VOP. More specifically, the objective of this study was to (1) confirm whether non-aneurysmal MCA bifurcations follow the golden rule of VOP and (2) test the hypothesis that the radii of aneurysm-bearing MCA bifurcations deviate from optimality due to local abnormal flow-mediated vascular caliber control.

METHODS

Patient Selection

All patients treated for intracranial aneurysms over an eight years period were eligible for inclusion if high-resolution 3D catheter-based angiographic datasets were available. All MCA bifurcations harboring aneurysms, excluding mycotic and fusiform aneurysms, were consecutively included. Additionally non-aneurysmal MCA bifurcations from patients with aneurysms at other locations, as well as control patients (patients without aneurysms who had undergone cerebral angiography for different indications, excluding patients with familial history of intracranial aneurysms) were also included (Figure 1). All angiograms were performed on unruptured aneurysms or in the acute setting of rupture (within 24-36 hours), before the possibility of vasospasm onset. Data on patient age, gender, and aneurysm rupture status was collected from a prospectively maintained database. The study was approved by Tufts Health Sciences Campus Institutional Review Board.

Data Acquisition

3D cerebral angiograms were obtained from either Philips Integris (Bothell, WA) or Siemens Artis (Malvern, PA) biplane systems and reconstructed using their respective clinical software package, to yield a 3D volumetric dataset. The dataset was then imported into and processed in the Amira visualization software platform version 5.4 (FEI Visualization Sciences Group, Burlington, MA).

Morphological Feature Extraction

Similar to Bescos et al. (2005), 3D gradient edge-detection filtering was employed in order to avoid the operator bias involved in manual thresholding and level choice of the aneurysm surface, which often limits quantitation in 3D imaging. In contrast to Bescos et al. (2005), the Sobel filter was preferred to the Canny edge-detection, because it is efficient and does not require input parameters (Figure 2A-B). To guide the measurement process, an isosurface of the vasculature was also created using a threshold value and refined by so that the final surface sits within the Sobel edges (Figure 2C). It has been found that, using the Sobel filter in guiding the segmentation process, results in a very narrow range of acceptable threshold values (Figure 2D).

The measuring cutting planes were placed approximately two vessel diameters from the aneurysm neck or bifurcation point for each vessel comprising the bifurcation (Figure 3). If

measurement at two or three diameters was not possible, because of the bifurcation morphology, the measurement was made just sufficiently distal downstream on the branch of interest to enable measurement. The vessels were then sectioned in 3D space. Every vessel cross-section was treated as an ellipse with major and minor axes, which enabled calculation of mean vessel radii by averaging 4 measured diameters for each vessel taken at 45°. Mean parent vessel radius was termed r_0 , mean daughter branch radii were termed, by convention, r_1 and r_2 , with r_1 being the larger of the two (Figure 3B). For bifurcations harboring aneurysms the origin of the aneurysm neck was evaluated to determine if it emanated off of the apex of the bifurcation or off of one or the other of the daughter branches. Parent to daughter vessel radius ratio (RR) was calculated using the formula: $r_0^3/(r_1^3 + r_2^3)$. Daughter branch ratio was calculated using the formula r_1 / r_2 . MATLAB software ((MathWorks, Natick MA) was used to solve $r_0^n = r_1^n + r_2^n$ for n by bisection with inverse quadratic interpolation(Ingebrigtsen et al., 2004).

Statistical Analysis

JMP version 10.0 (SAS Institute, Carey, NC) was used, with significance assumed for $p < 0.05$. MCA bifurcations were divided into 3 categories for analysis: *control* bifurcations from patients without aneurysms, *non-aneurysmal* bifurcations from patients with aneurysms at other locations (non MCA), and *aneurysmal* bifurcations harboring aneurysms. RR and n were tested independently using ANOVA and post-hoc Student's t-test for normal distributed data, and Wilcoxon rank-sum test for non-normal distributed data. Whenever data was available on both aneurysmal MCA bifurcation and also for its non-aneurysmal contralateral within the same patient, the two MCA bifurcations were compared separately in matched pair analysis in order to observe whether any possible deviation from optimality affected the entire patient or was a local phenomenon. The daughter branch ratio (r_1 / r_2) was compared for the different locations from which the neck of the aneurysms originated off, using Kruskal Wallis and post-hoc Wilcoxon rank-sum test. Receiver operator characteristics (ROC) analysis was performed to determine the area under the curve (AUC) index, as well as optimal cutoff values, for RR, n , and r_1 / r_2 . Finally all analyses were repeated after exclusion of ruptured aneurysm to address the possibility of vasospasm distorting the measurements.

RESULTS

Patient Demographics

A total of 353 aneurysms in 282 consecutive patients were identified. After exclusion of mycotic and fusiform aneurysms, 62 MCA bifurcation aneurysms were available of which 13 had ruptured (20.3 %). A total of 97 bifurcations with no aneurysmal involvement were analyzed (74 from patients with aneurysms in other locations and 23 from control patients with no aneurysms). In a subset of 16 patients with MCA bifurcation aneurysms, data from the contralateral non-aneurysmal MCA bifurcations were also available. In total, 113 patients and 159 bifurcations were included in the study. Mean age of the entire patient group was 58.2 (range 23 – 92 years old) and 78 patients were female (69 %). Mean ages for the three bifurcation groups were: (1) the *aneurysmal* group 57.6 (range 29 – 92 years), (2) *non-aneurysmal* MCA in patients with aneurysms in other locations 52.9 (range 23 – 85

years), and (3) *control* MCA in patients with no aneurysms 55.7 (range 24 – 85 years). There was no statistical difference between the mean ages of the three bifurcation groups.

Bifurcation Morphology

Mean RR was close to the ideal value of 1 in non-aneurysmal bifurcations (1.05, 95% CI 1.01 – 1.09), but significantly lower for aneurysmal bifurcations (0.76, 95% CI 0.71 – 0.80; $p < 0.0001$) suggesting relatively larger daughter radii. A cutoff value of $RR = 0.89$ yielded the highest diagnostic accuracy (AUC = 0.89) with sensitivity of 81% and specificity 88%. There was no statistical significance within the non-aneurysmal MCA bifurcations when RR was compared between controls (no aneurysm anywhere) and non-aneurysmal bifurcations in patients with aneurysms in other locations ($p=0.65$) (Figure 4). Importantly, in 23 (37 %) bifurcations with aneurysms, the daughter vessel was patently larger than its parent ($r_1 > r_0$) vessel (Figure 5), a novel finding. This was observed in only one non-aneurysmal bifurcation (Table 1).

Median junction exponent n was close to the ideal value of 3 for all non-aneurysmal MCA bifurcations (2.84, IQR 2.51 – 3.25), but significantly higher for aneurysmal bifurcations (4.28, IQR 3.26 – 5.85; $p < 0.0001$) for which n could be computed. A cutoff value of $n = 3.25$ yielded the highest diagnostic accuracy (AUC = 0.83) with sensitivity of 81% and specificity of 76%. The junction exponent n could not be computed in 24 bifurcations because r_0 was smaller or equal to r_1 . There was no statistical significance within the non-aneurysmal bifurcations when n was compared between control (no aneurysm) and non-aneurysmal bifurcations in patients with aneurysms in other locations ($p=0.30$) (Figure 4).

Analysis of patients with data on both aneurysmal and contralateral MCA bifurcations showed that, in contrast to their aneurysmal counterparts, the contralateral MCA follows VOP. Mean RR for contralateral bifurcations was 1.02 (95% CI 0.95 – 1.09 vs. 0.69 (95% CI 0.63 – 0.76) for aneurysmal bifurcations ($p = 0.02$); median n for contralateral bifurcations with interquartile range 3.02 (IQR 2.18 – 3.87) vs. 5.99 (IQR 4.87 – 7.12) for aneurysmal bifurcations ($p = 0.03$). The results did not change after exclusion of patients with ruptured aneurysms (data not shown). RR and n were not statistically different between contralateral MCA bifurcations and control bifurcations from patients with no aneurysms, suggesting a local rather than a global vascular radius regulation phenomenon.

Age and Gender

No statistical correlation was found between age and RR, and between age and n . This was true for the whole bifurcation dataset, but also separately for aneurysmal bifurcations and for non-aneurysmal bifurcations.

There was statistical difference ($p=0.02$) between the gender distribution of patients with aneurysmal bifurcation (49 females, 13 males) and that of patients with non-aneurysmal MCA bifurcation (60 females, 37 males). Gender dependent analysis showed that in both males and females RR was closed to the ideal VOP value of 1 in the case of non-aneurysmal bifurcations, statistically different compared to aneurysmal bifurcations (mean females 1.06, 95% CI 1.02 – 1.10 vs. 0.79, 95% CI 0.74 – 0.84; mean males 1.03, 95% CI 0.98 – 1.09 vs.

0.63, 95% CI 0.52 – 0.73; $p < 0.0001$). Interestingly, aneurysmal males have significantly lower RR compared to aneurysmal females (mean male 0.63, 95% CI 0.52 – 0.73 vs. mean female 0.79, 95% CI 0.74 – 0.84; $p = 0.002$). Similarly, n was close to the ideal value of 3 in non-aneurysmal male and female bifurcations, compared to aneurysmal bifurcations (median females 2.82, IOR 2.50 – 3.78 vs. 4.18, IOR 3.25 – 5.84; median males 2.93, IOR 2.51 – 4.03 vs. 4.75, IOR 3.80 – 7.30; $p = 0.0001$).

Aneurysm Location and Size

The aneurysm location was as follows: 10 (16 %) originated off the larger daughter branch (r_1), 32 (52 %) off the smaller branch (r_2) and 20 (32 %) off the apex of the bifurcation.

The mean size of the aneurysms in this dataset was 6.38 mm (95% CI 5.67 – 7.10 mm). There was no statistical difference between the size of ruptured (mean size 6.47, 95% CI 4.63 – 8.31 mm) compared to unruptured aneurysms (mean size 6.36, 95% CI 5.57 – 7.15 mm). There were 23 aneurysmal bifurcations for which r_0 values were smaller compared to r_1 . Again, no difference was found between the size of these 23 aneurysms (mean size 6.55, 95% CI 5.39 – 7.71 mm) and the size of the 38 aneurysms for which $r_0 > r_1$ (mean size 6.34, 95% CI 5.34 – 7.34 mm). There was no statistical correlation between RR and the aneurysm size ($p = 0.72$) nor between junction exponent n and the aneurysm size ($p = 0.06$).

RR and n were no statistically different between each of the aneurysm origination sites (bifurcation apex, off the smaller daughter, off the larger daughter). Comparison of daughter branch ratio (r_1 / r_2) for each aneurysm origin location showed that (r_1 / r_2) was significantly higher in aneurysmal bifurcations in which the aneurysm neck originated off of the smaller daughter branch (r_2), compared to aneurysms that originated off of the apex or the larger branch (median 1.39, IQR 1.27 – 1.70 vs. 1.17, IQR 1.07 – 1.27; $p = 0.008$, AUC = 0.76).

Imaging Acquisition Analysis

Out of 159 MCA bifurcations, 93 bifurcations (27 aneurysmal) have been evaluated on 3D cerebral angiograms obtained from Philips Integris imaging system, and 66 bifurcations (35 aneurysmal) have been evaluated on angiograms obtained from Siemens Artis. In order to determine the impact of acquisition system on statistical findings, the statistical analysis was repeated within the two subgroups. Regardless of the acquisition origin, RR and n were closer to the ideal VOP values of 1 and 3 respectively for non-aneurysmal bifurcations. In contrast, RR was significantly lower in aneurysmal bifurcations (mean 0.71 ± 0.03 for Philips Integris, and 0.79 ± 0.03 for Siemens Artis), whereas n was significantly higher (median 5.22 for Philips Integris, and 3.95 for Siemens Artis). When only non-aneurysmal bifurcations were compared, there was no statistical difference between angiograms acquired from Philips Integris, compared to those acquired from Siemens Artis. This was true for RR (mean 1.04 ± 0.03 vs. 1.07 ± 0.02 ; $p = 0.37$) and n (median 2.94 vs. 2.75; $p = 0.29$).

DISCUSSION

Optimal Vascular Caliber Control

Arterial bifurcations are governed by the optimality principle of work minimization which determines the arrangement of wide and narrow vessels in the branching hierarchy. This optimal vascular design is supposed to maintain continuity of flow at low energy cost, minimize the volume of the system and avoid increased hemodynamic stresses (Rossitti and Lofgren, 1993). VOP has two optimization components, one concerned with the relative calibers of the parent and daughter vessels and one concerned with the bifurcation angles between the parent and daughter vessels. This study is focused on optimal caliber control evaluated from the relationship between the radii of the bifurcations vessels. Previous research showed the branching model to be optimized when the radius of the parent vessel (r_0) dictates the radii of the daughter branches ($r_1 + r_2$): $r_0^n = r_1^n + r_2^n$, where the junction exponent n equals 3 (Ingebrigtsen et al., 2004; Rosen, 1967). This means that radius ratio for a bifurcation that follows these principles should be (close to) 1 (Rossitti and Lofgren, 1993). In this analysis, we have shown that non-aneurysmal MCA bifurcations in both control patients without aneurysms and patients with aneurysms at other locations have a mean RR and a median n close to these ideal values. In contrast, MCA bifurcations harboring aneurysms showed significant deviation from optimal caliber control as they have relatively larger daughter branches compared to the parent vessel, which translated in RR much lower than 1 and n much larger than 3. More importantly, 37% of the aneurysmal bifurcations had a daughter branch larger than its parent, a clear violation of caliber optimality (Figure 5) which, to the best of our knowledge, was not previously described. When aneurysmal MCA bifurcations were compared to their contralateral MCA, the same significant difference between aneurysmal and non-aneurysmal bifurcations were observed. This suggests that deviation from radius VOP may be a local phenomenon at sites harboring aneurysms and may not affect the entire patient cerebrovasculature. This is further supported by the fact that comparison between bifurcations from control individuals without aneurysms and patients harboring aneurysms at other locations showed no difference between these groups for RR or n .

Lindekleiv et al. (2010) reported that males have larger MCA vessel diameters compared to females. In this study, males tended to have larger vessel diameters compared to women, but the differences were not statistically significant. More importantly, both male and female control bifurcations had RR and n closer to the ideal values of 1 and 3, respectively. Interestingly, aneurysmal male bifurcations had significantly lower RR, corresponding to higher deviation from VOP, compared to female counterparts (mean 0.63 vs. 0.79). The junction exponent was also further from the ideal value in aneurysmal male bifurcations compared to aneurysmal females (median 4.75 vs. 4.18). The results suggest that males may have a higher tolerance to deviation from optimal caliber control, which could explain the female gender predisposition to aneurysm formation.

Research shows that hemodynamic forces play a role in aneurysms formation and the amount of shear stress depends on the bifurcation geometry (Alnaes et al., 2007). We have found in this study that most aneurysms originated off the smaller daughter branch. When

this was the case, the bifurcations had a higher r_1/r_2 ratio, as one of the daughter branches was significantly larger than the other. This was previously reported for internal carotid artery (Sakamoto et al., 2006) and for MCA (Sadatomo et al., 2008; Sadatomo et al., 2005) bifurcations. The findings are in accord with Alnaes et al. (2007), which showed WSS increasing and shifting towards the vessel with the smaller radius, especially if the ratio between the larger and smaller daughter branch (r_1/r_2) was higher. Thus, our results support the hypothesis that aneurysm formation might be induced by altered WSS, WSSG at the inflow impact zone on the vessel wall as previously described (Meng et al., 2007). The aneurysm apex, where the vessel wall is exposed to the highest WSS and flow, was shown to be reinforced by a narrow band of densely packed collagen fibers, which covers the bifurcation medial pad and provides strength and stiffness to the region, protecting this high impact area where flow is divided into the separate daughter branches (Finlay et al., 1998; Rowe et al., 2003). Deviation from optimal radius ratio may cause the high WSS and flow impact zone to shift away from the apical tendon towards the vessel with the smallest radius where the vessel wall is unprotected against these forces. This in turn is known to cause endothelial damage and subsequent aneurysm formation (Meng et al., 2007). Our findings, combined with previously reported hemodynamics results showing increased WSS at the origin of the smaller daughter branch (Alnaes et al., 2007), suggest that bifurcations which deviate from VOP may be prone to a shift of WSS and flow impact zone away from the protected apex of the bifurcation, possibly causing endothelial damage and eventual aneurysm formation. Detection of such deviant bifurcations 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 this study, we cannot conclude that deviation from VOP preceded aneurysm formation, because the presence of an aneurysm itself might have altered bifurcation morphology. However, the fact that measurements were collected two to three vessel diameters away from the aneurysm origin, and the small aneurysm sizes here, should have avoided distortion of our measurements by the presence of the aneurysm. Moreover, it is encouraging that the aneurysms size was not related to the magnitude of VOP deviation. Still, it is unknown the degree to which the presence of aneurysms affects the geometry of the parent vessels. This is an issue that can only be conclusively addressed by prospective studies, in which follow-up data is available prior to aneurysm formation. Larger prospective randomized studies will be required to evaluate the potential usefulness of caliber control features for assessment of risk of aneurysm formation.

CONCLUSION

Non-aneurysmal MCA bifurcations in the human cerebral arterial tree abide by the vascular optimality principle, whereas MCA bifurcations harboring aneurysms deviate from it, with a number of daughter branches exceeding parent caliber. Our results indicate that aneurysmal bifurcations have relatively larger daughter branches compared to their parent vessel, with

aneurysms tending to originate off the smaller daughter branch, especially if the ratio between the larger and smaller daughter branches was high. While the presence of an aneurysm was statistically correlated with deviation from VOP, the size of the aneurysm was not an indicator of the magnitude of this deviation. This study suggests that the detection of bifurcations which deviate from optimal caliber control could have the potential of being a candidate for evaluating the anatomic propensity for aneurysm formation.

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Figure 1.

Maximum intensity projection of 3D cerebral angiography showing (A) a control MCA bifurcation from a patient with no cerebral aneurysms, (B) a non-aneurysmal MCA bifurcation from a patient harboring an aneurysm on the internal carotid artery, and (C-D) aneurysmal MCA bifurcations.

Figure 2.

Volumetric processing and gradient edge detection (Sobel) measurement of vessel radii. (A) 2D orthogonal slice of the original volume. (B) Corresponding filtered image. (C) Oblique 2D slice through the filtered volume is oriented perpendicular on the MCA at the point of measurement. (D) The difference between unfiltered measurement (left) and Sobel filtered measurement (right) at increasing window threshold settings (top to bottom) showing decreasing radius phenomenon in the unfiltered data (left) and window threshold independence of the center of the edges in the Sobel filtered dataset (right).

Figure 3.

(A) The radius of the vessel cross-section was computed as the average of several diameters measured on the plane cut. (B) Schematic drawing of a bifurcation with radii measurement of parent vessel (r_0) and branching vessels (r_1 and r_2). Each radius is determined by averaging the diameter at two and three vessel diameters away from the bifurcating point.

Figure 4.

(A) Graph showing RR and n statistics for control MCA bifurcations, non-aneurysmal MCA bifurcation from patients with aneurysms at other locations, and aneurysmal MCA bifurcations. (B) Plot of r_0^3 (x-axis) against $r_1^3 + r_2^3$ (y-axis) for control and aneurysmal MCA bifurcations. (C) ROC analysis showing RR and n performance in discriminating between aneurysmal and non-aneurysmal MCA bifurcations.

Figure 5.

Radius ratio (RR) and junction exponent (n) for (A) an aneurysmal MCA bifurcation, (B) an aneurysmal MCA bifurcation in which the daughter is larger than the parent vessel, in violation of the vascular optimality principle (VOP). Because $r_1 > r_0$, n is undefined. (C-D) control bifurcations showing VOP agreement, with RR and n values close to ideal values of 1 and 3, respectively.

Table 1

Univariate analysis comparing MCA bifurcation morphology between (1) control patients without aneurysms, (2) non-aneurysmal bifurcations in patients with aneurysms at other locations, and (3) bifurcations harboring MCA aneurysms; RR=radius ratio; n=junction exponent.

	Control MCA (no aneurysms)	Non-aneurysmal MCA (aneurysms at other locations)	Aneurysmal MCA	p value
RR	1.08 (1.00 – 1.16) [*]	1.04 (1.00 – 1.08) [*]	0.76 (0.71 – 0.80) [*]	<0.001
n	2.69 (2.12 – 3.06) [†]	2.94 (2.52 – 3.29) [†]	4.28 (3.26 – 5.85) [†]	<0.001
r ₁ > r ₀	0	1	23	<0.001

* mean with 95% confidence interval, statistics using ANOVA

† median with interquartile range, statistics using Wilcoxon rank-sum test