Original research

Bifurcation geometry remodelling of vessels in de novo and growing intracranial aneurysms: a multicenter study

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ABSTRACT

Background Geometrical parameters, including arterial bifurcation angle, tortuosity, and arterial diameters, have been associated with the pathophysiology of intracranial aneurysm (IA) formation. The aim of this study was to investigate whether these parameters were present before or if they resulted from IA formation and growth.

Methods Patients from nine academic centers were retrospectively identified if they presented with a de novo IA or a significant IA growth on subsequent imaging. For each patient, geometrical parameters were extracted using a semi-automated algorithm and compared between bifurcations with IA formation or growth (aneurysmal group), and their contralateral side without IA (control group). These parameters were compared at two different times using univariable models, multivariable models, and a sensitivity analysis with paired comparison.

Results 46 patients were included with 21 de novo IAs (46%) and 25 significant IA growths (54%). The initial angle was not different between the aneurysmal and control groups (129.7±42.1 vs 119.8±34.3; p=0.264) but was significantly wider at the final stage (140.4±40.9 vs 121.5±34.1; p=0.032), with a more important widening of the aneurysmal angle (10.8±15.8 vs 1.78±7.38; p=0.001). Variations in other parameters were not significant. These results were confirmed by paired comparisons.

Conclusion Our study suggests that wider bifurcation angles that have long been deemed causal factors for IA formation or growth may be secondary to IA formation at pathologic bifurcation sites. This finding has implications for our understanding of IA formation pathophysiology.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Geometrical parameters have been associated in with the pathophysiology of intracranial aneurysms (IA) formation. The aim of this study was to investigate whether these parameters were present before or conversely if they resulted from the IA formation and growth.

WHAT THIS STUDY ADDS

⇒ Our results suggest that wider bifurcation angles, that have long been deemed causal factors for IA formation or growth, may rather be secondary to IA formation at pathologic bifurcation sites.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This finding has implications on for our understanding of IA formation pathophysiology.

INTRODUCTION

The pathophysiology of intracranial aneurysm (IA) development is incompletely understood and many potential pathways are still active areas of investigation, including genetic, transcriptomic, and inflammatory imaging.[1–3] IAs are preferentially located at proximal bifurcations of the circle of Willis, and several studies have provided insight into the geometrical characteristics of arterial bifurcations associated with IA formation and rupture.[4–11] Indeed, the bifurcation angle has been shown to be larger on bifurcations harboring IAs, which constitutes a geometrical pattern that can influence flow and wall shear stress leading to a higher risk of IA formation, growth, and rupture.[6–13]

However, a causal relationship has never been proved regarding the association observed between geometrical parameters and IAs. It could be argued that remodelling of the bifurcation due to the IA itself can also account for the phenomenon observed.[7] In this multicenter retrospective study, and through comparisons of geometrical parameters of bifurcations before and after IA formation or growth, we have investigated the chronology of this pathophysiological mechanism.

PATIENTS AND METHODS

Study design and participants

The analyses used data from a multicenter, retrospective, core lab adjudicated, cohort study of patients with de novo bifurcation IAs or bifurcation

IAs that grew significantly during follow-up. These cohort results were from the collaborative work of a trainee led research network (Jeunes en Neuroradiologie Interventionnelle; JENI-RC[12]). Patients were included from databases from nine university hospital centers (Angers, Basel, Bordeaux, Limoges, Nantes, Pitié-Salpétrière, Rouen, Sainte-Anne, and Tours). Local JENI-RC members were asked to provide deidentified data and images for patients meeting the following criteria during longitudinal imaging follow-up: de novo IA development or significant growth of an IA over time, defined as an increase of at least 2.5 mm and at least 50% of the initial size during follow-up.

Patients were excluded if they had a known connective tissue disorder (Marfan, Ehlers–Danlos, autosomal dominant polycystic kidney disease, fibromuscular dysplasia, moyamoya disease), a non-saccular IA, a non-bifurcation IA (including trifurcation or multiple trunk IAs), or for which imaging examinations were either unavailable or of insufficient quality for the analysis. Previously treated aneurysms with a neoaneurysm from the same neck were excluded.

For all patients, we collected two examinations, with two similar imaging modalities where possible (MRI, CT angiograms, or three dimensional DSA), the first one before the appearance or the growth of the IA, and a second one at the time of IA discovery or when a significant increase of a known IA was diagnosed. On each examination, we extracted the aneurysmal bifurcation (IA development group) and, when possible, the healthy contralateral one (control group). Imaging studies of potentially eligible patients were transferred after complete anonymization to an expert neuroradiological core lab for post-processing.

Collected variables

Onsite investigators collected the following data from electronic health records: baseline characteristics, such as age, sex, cardiovascular risk factors (high blood pressure, smoking, alcohol consumption history), personal and familial medical history of IA (ruptured or unruptured), and treatment (statins, non-steroidal anti-inflammatory drugs, and aspirin). The topography of the IA (posterior inferior cerebellar artery, basilar, and posterior communicating artery aneurysms were considered as posterior aneurysms), the circumstances of diagnosis (ruptured or unruptured IA), type of imaging (MRI, CT angiograms or three dimensional DSA), and the date of each imaging were collected to define the follow-up intervals.

Bifurcation characteristics post-processing and measurements

To characterize the arterial bifurcations, we used a dedicated developed inhouse vascular tree characterization software, reported in detail elsewhere.[13] The accuracy of the results obtained had been tested previously and validated in dedicated studies.[14] The vascular compartment was isolated from all imaging studies with the use of dedicated software (Slicer 3D, version 4.11.20210226, revision 29738 built 2021-03-01, Fedorov *et al*).[15] The segmentations were manually performed by neuroradiologists, first with a standardized thresholding method, which was then improved with an object detection method that discarded the small islands independent of the vascular tree (smaller than 700 voxels). The cropped and segmented files were analyzed by an algorithm developed by the RMeS laboratory and the Thorax Institute (UMR Inserm U1229, Université de Nantes, Oniris-Anass Nouri, Florent Autrusseau) in association with l'Unité de Recherche de l'Institut du Thorax UMR1087 UMR6291 (eight quai Moncousu-BP 70721–44007 Nantes Cedex 1– France, Inserm).

In brief, the algorithm detects the centers of the different bifurcations by a graph based approach and reproduces a three dimensional skeleton of the vascular tree, the tracing of which is facilitated upstream by the segmentation. Various mathematical morphology tools are being exploited to obtain accurate measurements of the following anatomical properties: angles formed by the arteries at a given bifurcation, the diameters and cross sections of each artery, and a measurement of arterial tortuosity.

Definitions of geometrical parameters

The initial ($\alpha_{initial}$) and final (α_{final}) bifurcation angle was defined as the angle between the daughter arteries, corresponding to the sum of the angles between the axis of the mother branch and the two daughter arteries on either side. The minimal and maximal diameters of the vessel (Φ_{min}/Φ_{MAX}) are collected from two arteries' orthogonal plane (cross sections) located at the very center of the considered artery, hence halfway between two consecutive bifurcations. Moreover, to minimize measurement error, a second measure is taken three voxels further along the centerline (two planes are extracted three voxels apart from the center).

Tortuosity (τ) of an artery can be defined by its degree of curvature. For each voxel of a target artery, the three dimensional normal vector is first computed. Then, its curvature degree is obtained by assessing the variations between its normal vector and the normal vectors of its neighboring voxels. Once the curvature degree of each voxel is computed, the values obtained are averaged using a weighted Minkowski sum to obtain a scalar between 0 and 1, reflecting the global tortuosity of the artery bifurcation. A scalar of 0 reflects low tortuosity (straight artery) while a scalar near 1 reflects high tortuosity. This method was validated by comparison of its objective results and ground truth tortuosity measurements from human observers.[14] To determine if the geometrical changes during follow-up were not due solely to normal aging of intracranial arteries, we extracted wherever possible the contralateral bifurcation to use the patient as their own control during the same timeline.

Statistical analysis

Statistical analysis was performed using JMP Pro 14 (SAS Institute Inc 2015, JMP Pro 14, Cary, North Carolina, USA) software. Continuous variables were summarized using means (SD) or median (IQR) where appropriate, and discrete variables were summarized using counts (percentages). The χ^2 test, Fisher's exact test, the t test, the Mann–Whitney U test, and the Wilcoxon signed rank test were used as appropriate for the univariable analyses, with a p value <0.05 (two-tailed) as the threshold for statistical significance.

First, bifurcation features were compared between IA bifurcations and control bifurcations. A multivariable logistic regression model was used to determine factors that were independently associated with IA formation or growth. Hence we examined putative risk factors for IA formation or growth, including all variables with a significant association in the univariate analyses (predefined $p<0.1$). Furthermore, the initial bifurcation angle was also included in the analysis as a risk factor, as debated as a predictor for IA formation or growth in previous reports.[7–10] Backward elimination was then used to remove non-significant variables ($p>0.05$). The adjusted OR (aOR) and 95% CI of developing aneurysm were reported.

A sensitivity analysis with a paired comparison was performed to assess changes in the results when including only bifurcations with available control bifurcations, using the Wilcoxon signed

rank test (to consider the hypothesis where aneurysmal bifurcation and control bifurcation are a matched sample). Then, a multiple linear regression model was used to determine the variables associated with the kinetics of the bifurcation angle change (Δ ((α_{final}–$\alpha_{initial}$)/time of follow-up)). Likewise, we examined putative risk factors for this continuous endpoint, including all variables with a significant association in the univariate analyses (predefined $p<0.1$) and backward elimination was used to remove non-significant variables ($p>0.05$). The aORs and 95% CIs were reported. Finally, the relationship between the variation in bifurcation angle and aneurysm size was tested by a linear regression analysis (with adjusted R square parameter).

RESULTS

A total of 66 patients were identified by onsite investigators and screened for inclusion. Twenty patients were excluded: 11 were non-bifurcation IAs; six did not have a suitable examination before or after the birth or growth of the IA, usually angiography examinations without three dimensional reformatable images; two had at least one of the two examinations with too low quality to be reliably analyzed by the algorithm; and one presented with a non-significant growth of the IA during follow-up after core lab assessment.

Forty-six patients were included in the final statistical analysis, including 21 with de novo IAs (46%) and 25 with significant IA growth (54%). Of these 46 patients, only 30 were included in the control group due to asymmetric bifurcations (eg, basilar IA or anatomical variation) or unavailable healthy contralateral side. It should be noted that of the 46 patients included, 28 had the same imaging modality for the initial and final analyses. Follow-up ranged from 4 to 228 months, with an average follow-up of 84.8 months (7.07±3.77 years).

Clinical and demographic characteristics are shown in online supplemental table l. Overall mean age was 52.7±15.3 years. There was a significant difference in age between the de novo IA group (44.8±13.8) and the IA growth one (59.4±13.4), but no difference for the other characteristics.

Aneurysm development and geometrical parameters of the arterial bifurcation

Stepwise logistic regression approach on the entire bifurcation cohort

The geometrical features of the bifurcations are summarized in table 1. The initial bifurcation angle appeared to be wider in the aneurysmal group, but this difference was not significant (129.7±42.1 vs 119.8±34.3; p=0.264). The final bifurcation angle was significantly wider in the aneurysmal group (140.4±40.9 vs 121.5±34.1 p=0.032). The angle variation Δ (α_{final}–$\alpha_{initial}$) was significantly larger by 10.76±15.8 for the aneurysmal bifurcation angle versus 1.78±7.38 for the control bifurcations (p=0.001). Focusing on each bifurcation type, only the sylvian bifurcation angle variation was significant, with a trend for the others (online supplemental table III). Moreover, these results were significant in the sensitivity analyses, comparing only de novo or growing aneurysms and available contralateral bifurcations (online supplemental table IV).

Two additional initial morphological parameters differed significantly between the groups. The maximal diameter of the smallest daughter branch ($\Phi_{MAX\text{-}initial}$ DA_2) was bigger in the aneurysmal group (2.44±0.62 mm vs 2.15±0.34 mm; p=0.012) and the minimal diameter of the parent vessel ($_{\Phi min\text{-}initial}$ PA) was smaller in the aneurysm group (2.33±0.71 mm vs 2.61±0.52 mm; p=0.049). Both parameters were no longer significantly different at the final stage. All of the other initial and final morphological features did not differ significantly between the groups.

Table 1 Bifurcations features: univariate analysis

	Aneurysmal bifurcations (n=46)	Control bifurcations (n=30)	P value
Initial features			
Diameters (mm)			
$\Phi_{min\text{-}initial}$ PA	2.35±0.71	2.61±0.52	0.049
$\Phi_{MAX\text{-}initial}$ PA	3.22±0.64	3.18±0.49	0.742
$\Phi_{min\text{-}initial}$ DA_1	2.04±0.61	2.22±0.52	0.181
$\Phi_{MAX\text{-}initial}$ DA_1	2.88±0.58	2.8±0.49	0.533
$\Phi_{min\text{-}initial}$ DA_2	1.57±0.49	1.64±0.33	0.432
$\Phi_{MAX\text{-}initial}$ DA_2	2.44±0.62	2.15±0.34	0.012
Tortuosity $\tau_{initial}$ PA	0.88±0.02	0.87±0.03	0.504
Bifurcation angle α_{intial} (°)	129.7±42.1	119.8±34.3	0.264
Final features			
Diameters (mm)			
$\Phi_{min\text{-}final}$ PA	2.51±0.64	2.43±0.63	0.573
$\Phi_{MAX\text{-}final}$ PA	3.07±0.53	3.07±0.49	0.959
$\Phi_{min\text{-}final}$ DA_1	2.09±0.76	2.17±0.6	0.643
$\Phi_{MAX\text{-}final}$ DA_1	2.6±0.65	2.65±0.6	0.72
$\Phi_{min\text{-}final}$ DA_2	1.68±0.46	1.65±0.37	0.817
$\Phi_{MAX\text{-}final}$ DA_2	2.19±0.48	2.08±0.37	0.235
Tortuosity τ_{final} PA	0.88±0.03	0.88±0.03	0.545
Bifurcation angle α_{final} (°)	140.4±40.9	121.5±34.1	0.032
Δ Angle = α_{final}-$\alpha_{initial}$	10.76±15.8	1.78±7.38	0.001

Continuous values are expressed as means±SD.
DA1, daughter artery, by convention the largest one; DA2, daughter artery, by convention the smallest one; MAX-initial/final, initial/final maximal diameter; min-initial/final, initial/final minimal diameter; PA, parent artery.

After multivariable adjustment, only Δ angle (α_{final}–$\alpha_{initial}$) remained significantly wider in the aneurysmal group versus the control group (aOR 1.08, 95% CI 1.02 to 1.15, p=0.003). The initial bifurcation angle, $\Phi_{MAX\text{-}initial}$ DA_2, and $\Phi_{min\text{-}initial}$ PA did not differ significantly between the groups (all $p>0.05$) (see online supplemental table II for detailed aOR values).

Sensitivity analysis and paired comparison of bifurcations with available control

In this analysis, a paired comparison of aneurysmal and contralateral bifurcations (n=30 vs 30) was performed using the Wilcoxon signed rank test. The variation (final measure–initial measure) of each morphological feature was tested (table 2). In this subset, morphological features which differed significantly between the groups were: Δ angle (5.8±14.6 in the aneurysm group vs 2.0±9.3 in the control group; p=0.002), Δ Φ_{min} PA (2.33±0.71 mm in the aneurysm group vs 2.61±0.52 mm in the control group; p=0.022), and the variation in the maximal diameter of the largest daughter branch (Δ Φ_{MAX} DA_1) (−0.395±0.95 in the aneurysm group vs −0.11±0.59 in the control group; p=0.049). Variations in other parameters did not differ significantly between the groups.

Variables that influence the kinetic of bifurcation angle modification

In the univariate analysis, the kinetics of angle change decreased significantly with increasing age (beta coefficient −0.07 (-0.12 to

Table 2 Bifurcations features: Wilcoxon sign-rank test

	Aneurysmal bifurcations (n=30)	Control bifurcations (n=30)	P value
Δ Diameters = Φ_{final}-$\Phi_{initial}$ (mm)			
Φ_{min} PA	0.11±1.25	−0.03±0.94	0.022
Φ_{MAX} PA	−0.41±0.79	−0.16±0.65	0.381
Φ_{min} DA_1	−0.04±0.65	0.12±0.99	0.859
Φ_{MAX} DA_1	−0.395±0.95	−0.11±0.59	0.049
Φ_{min} DA_2	0.06±0.58	0.01±0.34	0.684
Φ_{MAX} DA_2	−0.21±0.61	−0.10±0.49	0.233
ΔTortuosity PA = τ_{final}-$\tau_{initial}$	0.002±0.029	−0.002±0.050	0.670
Δ Angle = α_{final}-$\alpha_{initial}$	5.8±14.6	2.0±9.3	0.002

Continuous values are expressed as median ±IQR.
DA1, daughter artery, by convention the largest one; DA2, daughter artery, by convention the smallest one; MAX-initial/final, initial/final maximal diameter; min-initial/final, initial/final minimal diameter; PA, parent artery.

-0.02); p=0.012 for each 10 years), and statin treatment was also associated with a lower kinetic of angle change (0.04±0.09 with vs 0.19±0.3 without treatment; p=0.027). Other demographic and geometrical parameters did not significantly influence the kinetics of bifurcation change. After adjustment in a multiple linear regression analysis, only older age remained significantly associated with a lower kinetic of angle change (aOR 0.94, 95% CI 0.89 to 1; p=0.046 for each 10 years).

Relationship between aneurysm size and bifurcation angle variations

In our sample, the relationship between variation in aneurysm size and variation in bifurcation angle was non-linear (R^2=0.01; p=0.581; online supplemental figure 1).

DISCUSSION

In this multicenter retrospective study and through comparison of geometrical parameters of bifurcations before and after IA formation or growth, we found that IA development led to enlargement of the bifurcation angle. This finding challenges the classical notion that considers bifurcation remodeling to be responsible for aneurysm development.

Two previous works analyzed in vivo arteries with de novo IAs. The first included three patients, of whom two probably had an unidentified systemic vascular pathology.[16] The second study included 26 patients with 17 newly visualized IAs, but six IAs smaller than 2.0 mm.[8] This latter study showed that the bifurcations with hypoplastic branches, and with sharper angles between the parent and daughter vessels, were at higher risk of developing an aneurysm. However, the authors did not analyze longitudinally the modification of the geometrical features precluding a formal comparison with our study.

Of note, the age related changes in the bifurcation angle, which in healthy individuals is of a small magnitude according to the baseline study by Żyłkowski *et al* (2.0224–2.303° per decade), cannot account solely for our findings.[17] Indeed, we provided a paired comparison analysis that showed significantly more important variation on the pathological side compared with the healthy contralateral angle in our sample, the latter showing a mean variation in angle close to the one expected in Żyłkowski *et al*'s study. We also found that older age was associated with lower longitudinal angle variations. This association could be explained by stiffening of the arteries[18] that may have tended to attenuate the angle variation over time.

Widening of the bifurcation angle could easily be explained in the situation of a bulky IA which directly pushes the anatomical structures around by its mass effect. But this situation is rare, especially in our study where the mean aneurysmal diameter was about 6 mm and cannot explain how smaller aneurysms may have significantly affected the local geometry (figure 1).

Moreover, our results showed a non-linear relationship between the size of the aneurysm over time and the variation in bifurcation angle, suggesting that it is not only the size of the aneurysm that influences the bifurcation geometry. To account for this finding, we hypothesize that, among other possible mechanisms, not only the IA (a well known site of inflammatory changes)[19–21] but also the peri-aneurysmal environment could be the site of inflammatory phenomena which may promote remodeling of the wall which may in turn be responsible for the modifications of local geometrical parameters.

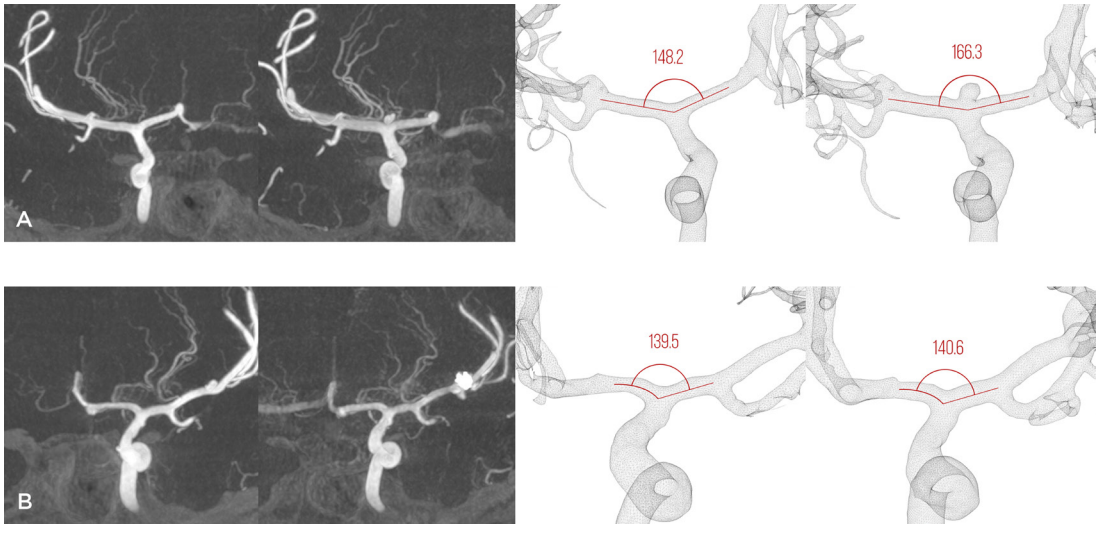

Figure 1 Angle modification over time. Interval time 96 months. (A) Widening angle with a small de novo unruptured intracranial aneurysm of the right carotid terminus, from 148.2° to 166.3°. (B) Contralateral bifurcation from the same patient, from 139.5° to 140.6°. On both lines: DSA with 10 mm maximum Intensity projection (left) and volume rendering (right).

In contrast with previous works, we found no difference in the initial angle between the aneurysm carrying (or doomed to be carrying) bifurcations and control bifurcations.[6–10 22–28] Possibly because of our smaller sample size and different measurement tools, we were unable to replicate this finding. It should however be noted that in these latter studies, the measures deemed to predispose to aneurysm formation were widely distributed around a predicted value, making it difficult to identify a true predisposing value. Although these studies showed an association between bifurcation angles and the presence of an aneurysm, such as in the middle cerebral artery,[8 9] no causal relationship can be conclusively determined as it is still possible that aneurysm formation is an epiphenomenon of larger bifurcations rather than a direct consequence of higher risk bifurcation morphology, as suggested by Baharoglu and colleagues.[7] The geometrical features we chose to focus on have already been linked to the flow parameters at bifurcation sites.[22–24] Hence modifications of these flow parameters are expected to change the local geometry, and vice versa; a changing geometry should have an important impact on flow fields.

Several authors showed that the diameters of parent and daughter arteries are involved in aneurysm pathology as a contributing factor.[5 8–11] In our study, we did not highlight any geometric differences at the initial stage between the aneurysmal and control groups, and no modifications of these parameters during follow-up. However, due to the retrospective nature of the inclusions, we were unable to systematically provide the same imaging modalities during follow-up, which constitutes a severe limitation to reliably compare the diameters of the arteries at the initial and final stages, especially with time-of-flight studies that usually underestimate the calibers compared with contrast enhanced vessel studies. It should be noted that this limitation was of no concern to tortuosity and angles which were only linked to the skeleton of the vascular tree. Regarding tortuosity, we also did not find any difference between the groups, or any significant change in this parameter over time. Considering that this parameter evolves with age, we can assume that the mean follow-up time in our study was too short to unravel differences.[17]

Beyond its novelty, the strength of our study includes the use of an automated algorithm for the assessments of the parameters that reduces the variability of manual measurements and removes some of the subjectivity that might otherwise have made it more difficult to reliably detect changes between the initial and final vasculatures. Here, we bring new insights and the basis for further studies evaluating modifications of the geometrical features of the circle of Willis in follow-up studies with automatized tools. Hence, depending on the geometrical modifications of a given bifurcation harboring or not harboring an IA, future studies can explore the probability of IA formation, growth, or rupture. More realistically, quantitative variables extracted from bifurcations would have to be included in composite scores along with clinical and biological parameters.[29]

Due to the paucity of recorded events (de novo formation or aneurysm growth), we acknowledge a relatively small sample size even if we were able to reach statistical significance in part of our analysis. Furthermore, the retrospective design brings inherent selection bias, such as the exclusion of patients with poor imaging quality. Lastly, variability among machines that acquired the imaging studies can also affect, at least in part, the results of measurements.

CONCLUSION

Our study suggests that wider bifurcation angles, that have long been deemed causal factors for aneurysm development or growth, may be secondary to aneurysm development at pathologic bifurcation sites. This finding has implications for our understanding of aneurysmal development pathophysiology.

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Contributors JBo: collected the data, performed the computational analysis, wrote the manuscript and acted as guarantor. BK: collected the data, performed the statistical analysis, and critically reviewed the manuscript. GT, RB, CR, PBS, HG, ES, FG, GM, JBu, HI, GB, GF, AR, and HD: collected the data and critically reviewed the manuscript. AN and FA: developed the algorithm and critically reviewed the manuscript. GL: critically reviewed the manuscript. VL: had the concept of the study, collected the data, and wrote and critically reviewed the manuscript.

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of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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