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ORIGINAL RESEARCH

High curvature of the internal carotid artery is associated with the presence of intracranial aneurysms

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ABSTRACT

Objective Aneurysm formation in locations not involving vascular bifurcations has not been thoroughly analyzed. This study evaluated the relationship between the degree of vessel curvature and the presence of intracranial sidewall aneurysms of the internal carotid artery (ICA).

Methods Catheter-based 3D-rotational angiographic volumes and demographic data were available for 130 ICAs. Mean and peak curvatures were evaluated for the intracranial ICA (50 mm caudal from ICA bifurcation) and for its distal segment (from ICA bifurcation to carotid siphon). Four ICA groups, statistically matched for age, were identified: non-aneurysmal women (n=33) and men (n=25), aneurysmal women (n=58) and men (n=14). Univariate and multivariate analyses were employed to evaluate statistical performance.

Results Aneurysmal ICAs had significantly higher mean curvatures than non-aneurysmal ICAs in both the intracranial ($p<0.001$) and the distal ICA ($p<0.001$) for both genders. Peak curvature was significantly higher in aneurysmal versus non-aneurysmal men ($p=0.008$) but not in aneurysmal versus non-aneurysmal women ($p=0.12$). Mean curvature in non-aneurysmal ICAs was lower in men than in women but higher in aneurysmal ICAs in men than in women. In multivariate analysis, curvature was highly correlated with aneurysm presence but was independent of age, hypertension, hypercholesterolemia and smoking status.

Conclusions The presence of a sidewall aneurysm on the ICA is associated with high curvature in both genders. High curvature of the intracranial ICA, as well as of the distal segment, may indicate a higher risk for aneurysm formation. Non-aneurysmal ICAs are less curved in men than in women, which may explain the gender predisposition to aneurysm formation.

INTRODUCTION

Intracranial aneurysms are estimated to occur in 2–6% of the population,[1] with the vast majority of these being asymptomatic. Rupture of these aneurysms, however, can cause subarachnoid hemorrhage leading to a high level of morbidity and mortality. It is therefore important for clinicians to understand the factors that increase the rate of aneurysm formation and rupture. The internal carotid artery (ICA) is a preferred site for aneurysm formation,[1–3] with more than 30% of all aneurysms originating from ICA segments. Almost all ICA aneurysms are considered sidewall aneurysms as they originate either directly from the ICA or from the origin of a branch that is much smaller than the ICA, including the ophthalmic, anterior choroidal and posterior communicating arteries. It has been suggested that, in the absence of underlying disease, aneurysm formation is a mechanically mediated event.[4] Clinical and experimental studies strongly suggest that hemodynamic factors play a role in aneurysm formation, growth and eventual rupture.[5] While aneurysms originating at arterial bifurcations are believed to occur partly because of an increase in wall shear stress (WSS) at the impingement region, it is unclear what role hemodynamic forces play in the formation of sidewall aneurysms.

Vessel morphology is an important determinant of hemodynamic patterns[6–8] and it is often employed as a more practical (less time and resource consuming) means of gaining insight into complex hemodynamic behaviors.[9] In particular, the curvature of a vessel was previously shown to influence hemodynamic patterns in arterial bends.[10 11] Few studies, however, have evaluated the association between vessel morphology, as described by curvature, and aneurysm formation and evolution. Piccinelli *et al*[9] reported that higher curvature at ICA bends harboring aneurysms tend to be associated with rupture status. Similarly, Sangalli *et al*[12] reported that aneurysmal ICAs have a higher curvature than the ICA of patients with aneurysms in locations distal to the bifurcation ICA.

To the best of our knowledge, the role of vessel morphology in the absence of a bifurcation, specifically the role of vessel curvature, has not been thoroughly evaluated in relation to sidewall aneurysm formation. We set out to evaluate the effect of vessel curvature on aneurysm formation in the ICA, especially in aneurysms which pose a risk of subarachnoid hemorrhage by originating from the intradural portion of the ICA. In addition, we examined whether there were any gender differences in ICA curvature. We present the first report to systematically evaluate the association of ICA curvature with sidewall aneurysm formation.

METHODS

Patient selection and demographics

Consecutive high-resolution 3D angiographic data of patients with intracranial aneurysms located on the ICA were obtained from a prospectively maintained database over a period of 5 years. Fusiform and mycotic aneurysms were excluded from the current analysis. A total of 130 ICA datasets from

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93 patients (age 51.6±14.7 years; 57 women) were available for analysis. The dataset included 72 aneurysmal ICAs (age 53.1 ±14.9 years), five of which were labeled as ruptured by the treating physician at the time of presentation. The ICAs were evaluated under four groups: non-aneurysmal control women (n=33; age 49.1±12.6), non-aneurysmal control men (n=25; age 48.3±16.2), aneurysmal women (n=58; age 54.3±16.5) and aneurysmal men (n=14; age 54.1±11.3).

Regarding the location of the 72 aneurysms, 18 were located in the carotid siphon, 39 were located on the ophthalmic segment and 15 were located on the communicating segment of the ICA.

Clinical information regarding hypertension, high cholesterol and smoking status was extracted from a prospectively maintained aneurysm database.

Cerebral angiography and morphological feature extraction

All patients underwent catheter-based cerebral angiograms by one interventional neurosurgeon and included 3D-rotational angiography (3DRA) imaging performed on the Siemens Axiom-Artis system. 3DRA was performed using 3 mL/s contrast medium for 5 s with a 1.5 s pre-injection delay). All raw 3D acquisition data were reconstructed using the Leonardo/Syngo workstation software (Siemens AG, Munich, Germany). Vessel segmentation was performed using in-house software based on level-set functions available as open source (Insight Segmentation and Registration Toolkit V.3.20; Kitware, Clifton Park, New York, USA).

The centerline of the vasculature was determined using the algorithm proposed by Bouix *et al.*[13] The ICA branch was isolated from the centerline and curvature along the ICA was automatically computed[14] from the discrete curve representing the ICA (figure 1). The curvature of a curve at a point is defined geometrically as the inverse of the radius of the osculating circle at that point (figure 2). Here this value is estimated analytically by employing discrete derivatives. In order to compensate for variability in the reconstruction window position across patients, a fixed portion of the ICA was considered for this analysis and 5 cm were measured starting from the internal carotid bifurcation, along the principal axis of the ICA in the proximal direction (figure 1). For the purposes of this study, the resulting ICA segment is referred to as the 'intracranial ICA'. Because all aneurysms evaluated here are located at or distal to the carotid siphon, we also evaluated the curvature of the distal ICA located between the site of peak curvature of the carotid siphon and the ICA bifurcation. The proximal starting point of the distal ICA is marked in figures 1 and 3 by black arrows. Figure 3 shows curvature computation for three aneurysmal ICAs with aneurysms located in the carotid siphon, on the ophthalmic segment and on the communicating segment.

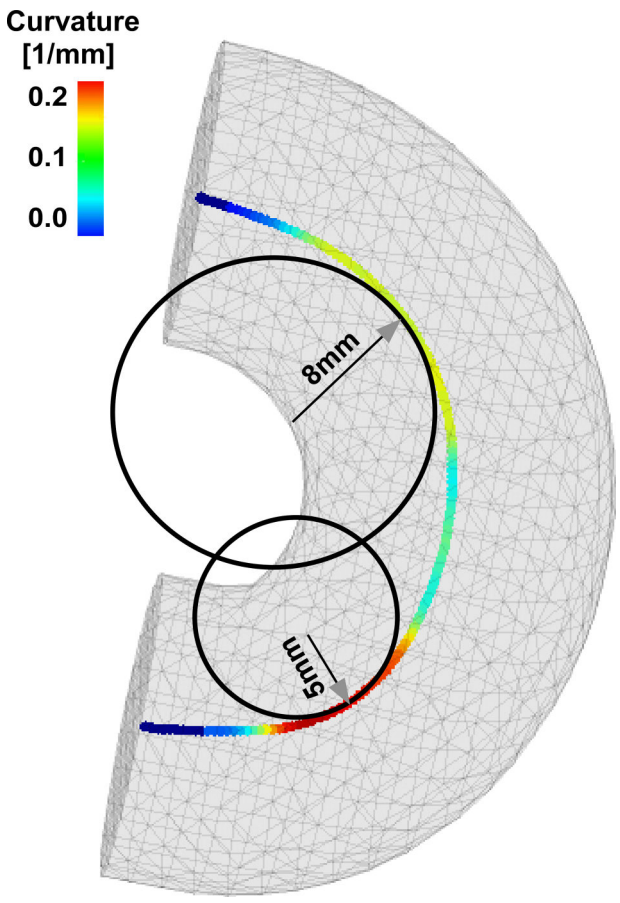


Figure 2 Curvature of the centerline at each point is defined geometrically as the inverse of the radius of the osculating circle at that point.

The following curvature features were evaluated for all ICA data: average curvature of the intracranial ICA (C_{intra_mean}), maximum curvature of the intracranial ICA (C_{intra_max}), average curvature of the distal ICA (C_{distal_mean}) and maximum curvature of the distal ICA (C_{distal_max}). In addition, the difference between the minimum and maximum curvature values was evaluated as a

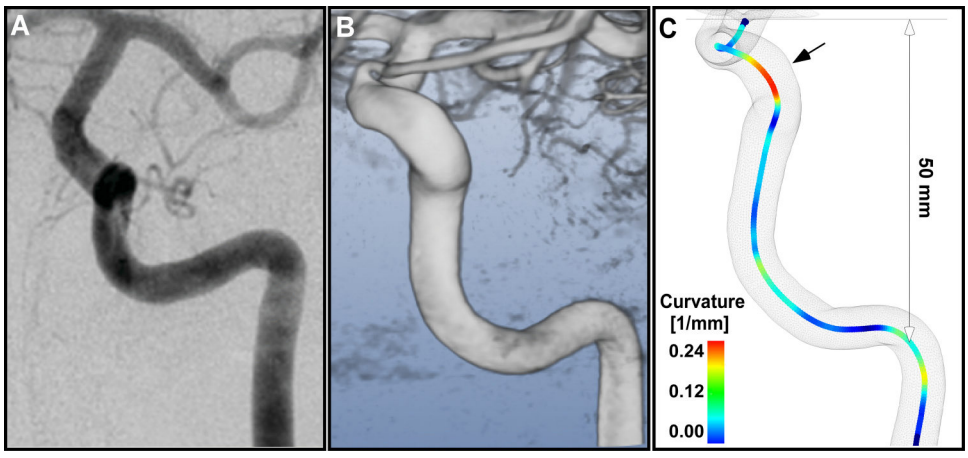


Figure 1 Centerline curvature computation on a non-aneurysmal internal carotid artery (ICA). (A) Anteroposterior (AP) projection of the left ICA during a cerebral angiogram. (B) 3D volumetric representation of the left ICA. (C) Corresponding curvature values. Intracranial ICA is considered 50 mm caudal from the site of ICA bifurcation. The distal ICA is considered from the site of maximal curvature of the carotid siphon (black arrow) to the ICA bifurcation.

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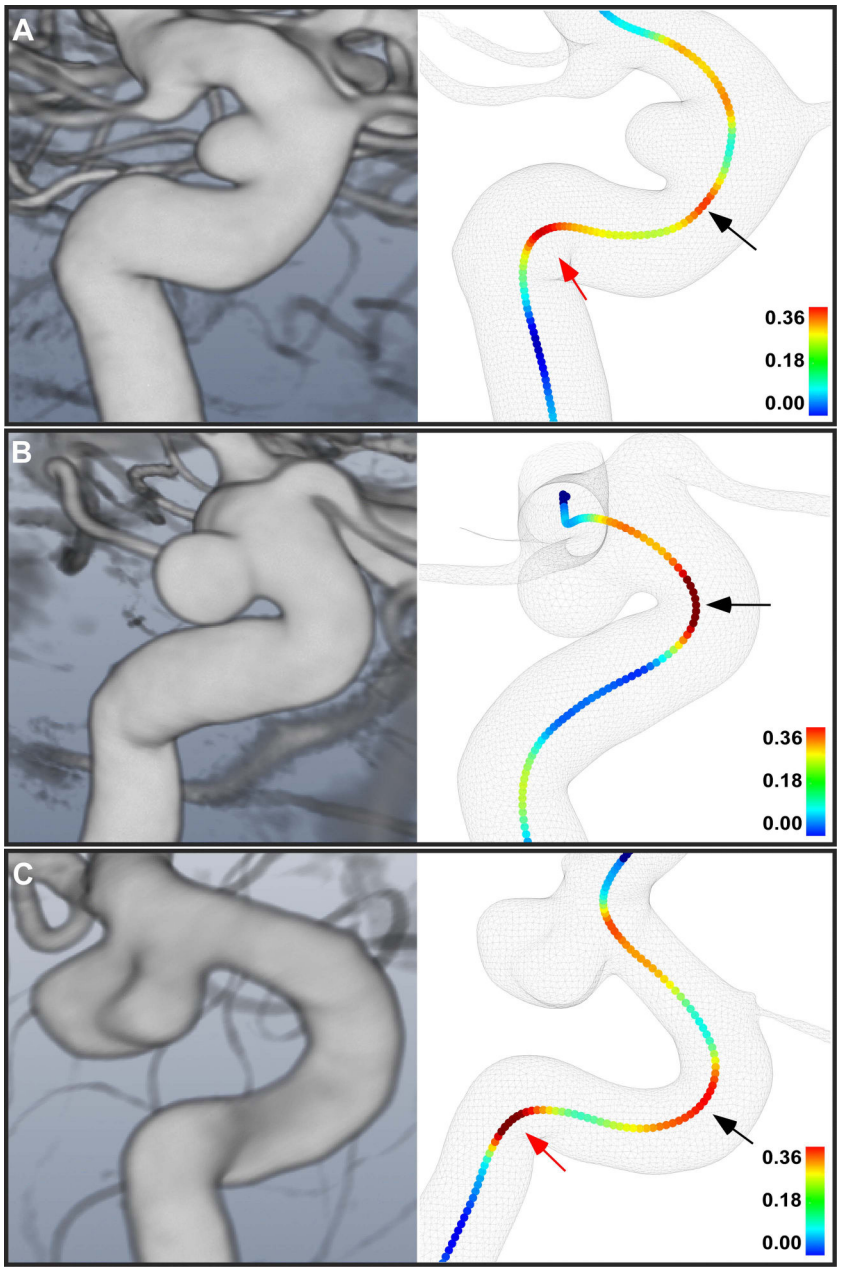


Figure 3 Centerline curvature computation on an aneurysmal internal carotid artery (ICA). All three patients are women (age between 29 and 51 years). (A) ICA harboring an aneurysm within the carotid siphon. (B) ICA harboring an aneurysm arising from the ophthalmic segment. (C) ICA harboring an aneurysm arising from the communicating segment. The black arrows point to the position of the peak curvature of the distal ICA and represent the proximal endpoint of the distal segment as defined here. The red arrows point to the position of the peak curvature of the intracranial ICA.

measure of curvature variability along the vessels, resulting in features C_{intra_range} and C_{distal_range}.

Statistical analysis

JMP V.10.0 (SAS Institute, Cary, North Carolina, USA) was used to analyze the data. All variables were tested independently using the Student t test and statistical significance was assumed for $p<0.05$. First, the analysis was performed on the whole dataset between control and aneurysmal ICAs. Second, the four ICA groups (aneurysmal women and men, control women and men) were evaluated using Student t test pairwise analysis. Whole model multivariate statistics were used to determine the relative dependence of curvature on other clinical features.

RESULTS

Patient selection and demographics

There was no statistical difference between the mean ages of the four groups. Smoking status (ever smoked vs non-smokers) was statistically correlated with the presence of an aneurysm in women ($p<0.001$) but not in men. In contrast, hypertension was statistically correlated with the presence of an aneurysm in men ($p=0.02$) but not in women. No statistical correlation was found between high cholesterol and the presence of an aneurysm.

Curvature of the internal carotid artery

Aneurysmal ICAs had significantly higher curvatures than non-aneurysmal ICAs (table 1). This was true for all curvature features evaluated: mean curvature of the intracranial ICA (C_{intra_mean}, $p<0.001$), peak curvature of the intracranial ICA (C_{intra_max}, $p=0.002$), variability of intracranial ICA curvature (C_{intra_range}, $p=0.002$) and also the curvature of the distal portion of the ICA (C_{distal_mean}, $p<0.001$; C_{distal_max}, $p<0.001$; C_{distal_range}, $p<0.001$). Gender analysis revealed that curvature measures discriminated between controls and aneurysmal ICAs in both men and women, with aneurysmal ICAs being significantly more curved (table 2).

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Table 1 Univariate analysis of curvature features of healthy versus aneurysmal ICAs in the whole population

Group	Feature	Aneurysmal	Non-aneurysmal	p Value
Aneurysmal (n=72) vs healthy (n=58) ICAs	C_{intra_mean}	0.15±0.016	0.14±0.015	<0.001*
	C_{intra_max}	0.40±0.053	0.37±0.057	0.002*
	C_{intra_range}	0.38±0.057	0.35±0.056	0.002*
	C_{distal_mean}	0.18±0.031	0.16±0.027	<0.001*
	C_{distal_max}	0.34±0.068	0.28±0.052	<0.001*
	C_{distal_range}	0.26±0.077	0.21±0.063	<0.001*

Values shown are mean±SD.
*Indicates statistical significance (p<0.05).
ICA, internal carotid artery.

Interestingly, control (non-aneurysmal) women had higher mean curvature of the intracranial ICA than control men (p=0.04), whereas women with aneurysms had lower curvature of the distal ICA than men with aneurysms (p=0.03). In general, although not all features were statistically significant, there was a tendency for control (non-aneurysmal) women to have a more curved ICA than control men, and for women with aneurysms to have a less curved ICA than men with aneurysms (figure 4).

In men, the vast majority of ICAs (79.5%) had their peak curvature located in the carotid siphon, with the remaining 20.5% having their peak ICA curvatures located extradural within the cavernous segment. In contrast, in women, only 54.9% of the ICAs had their peak curvature located in the carotid siphon, with the remaining 45.1% having their peak curvature located in the cavernous segment. These percentages were very consistent even when compared between control men and women and between men and women with aneurysms (p=0.04, Pearson correlation).

On the distal ICA, the peak curvature was located in the carotid siphon in both men and women. All aneurysms originated distal to the location of this peak curvature, 31% (22/72) within 5 mm from the site of the distal peak curvature and 67% (48/72) within a distance of 10 mm.

Curvature dependency on age

In the entire dataset, no correlation was found between any of the curvature features and age. Mean curvature of non-aneurysmal intracranial ICAs decreased with age (p=0.007). However, there was no correlation between the mean curvature of the control distal ICA and age (p=0.53), suggesting most of the decrease to be the result of proximal reduction in curvature.

In aneurysmal ICAs, although not statistically significant, a trend was noticed for the mean curvature of the intracranial ICA to increase with age (p=0.07). Figure 5 shows the correlation between the mean intracranial curvature and age for aneurysmal and control subgroups. There was no correlation between the mean curvature of the aneurysmal distal ICA and age (p=0.21). No correlation was found between maximum curvature values and age in any of the groups.

Table 2 Gender-based univariate analysis of curvature features of healthy versus aneurysmal ICAs

Group	Feature	Aneurysmal	Non-aneurysmal	p Value
Aneurysmal (n=58) vs healthy (n=33) ICAs in women	C_{intra_mean}	0.16±0.017	0.15±0.015	0.004*
	C_{intra_max}	0.39±0.049	0.38±0.063	0.12
	C_{intra_range}	0.38±0.054	0.36±0.061	0.14
	C_{distal_mean}	0.18±0.032	0.16±0.029	0.001*
	C_{distal_max}	0.33±0.063	0.29±0.055	<0.001*
	C_{distal_range}	0.25±0.074	0.22±0.067	0.03*
Aneurysmal (n=14) vs healthy (n=25) ICAs in men	C_{intra_mean}	0.15±0.013	0.14±0.015	0.01*
	C_{intra_max}	0.40±0.069	0.35±0.046	0.008*
	C_{intra_range}	0.39±0.072	0.34±0.048	0.002*
	C_{distal_mean}	0.19±0.032	0.15±0.022	<0.001*
	C_{distal_max}	0.37±0.079	0.27±0.046	<0.001*
	C_{distal_range}	0.32±0.073	0.21±0.074	<0.001*

Values shown are mean±SD.
*Indicates statistical significance (p<0.05).
ICA, internal carotid artery.

Curvature dependency on aneurysm size

The 72 aneurysms in the dataset had a mean size of 5.45 ±3.79 mm. No statistical correlation was found between the size of the aneurysms and the curvature features evaluated here. When the aneurysms were grouped according to their size as small (< 5 mm, 36 aneurysms), medium (5–10 mm, 30 aneurysms) and large (>10 mm, 6 aneurysms), a trend was noticed in which larger aneurysms were correlated with lower maximum curvature on the distal ICA (p=0.08) compared with small and medium size aneurysms. No correlation was found between the mean ICA curvature and aneurysm size groups.

Multivariate analysis

Whole model analysis of the four curvature features (C_{intra_mean}, C_{intra_max}, C_{distal_mean} and C_{distal_max}) was evaluated in order to determine the relative correlation of curvature with aneurysm presence, age, sex, hypertension, high cholesterol and smoking status. The results confirm the results of univariate analysis and show that all curvature features were highly associated with the presence of an aneurysm (table 3). Age, hypertension, high cholesterol and smoking status were not correlated with curvature. Similar multivariate statistics were reported when the analysis was repeated separately for men and women.

Aneurysm rupture status

Five of the 72 aneurysms (all in women) were labeled as ruptured at the time of presentation. Two of the ruptured aneurysms originated on the ophthalmic segment and the other three originated on the communicating segment. When compared for curvature parameters, age and aneurysm size, no statistical difference was found between ruptured and unruptured aneurysms, probably because of the small sample size.

DISCUSSION

The ICA represents a preferred site for sidewall aneurysm formation. These aneurysms have a low relative risk of rupture, but they tend to grow larger than aneurysms forming at other vascular locations,[15] are often symptomatic and can require surgical or endovascular treatment.[16] In fact, 60% of giant aneurysms (>25 mm) occur on the ICA even though they represent only 5–8% of all aneurysms.[17] While aneurysms are relatively rare in young people, children and young adults who present with aneurysms are more likely to harbor ICA giant aneurysms.[18] Gender difference is also significant: women have a higher risk of aneurysm incidence but men present with aneurysms earlier in life.[19] Preventive care and monitoring is difficult in the absence of reliable tools to predict the risk of aneurysm formation, especially in high-risk populations.

While several morphological and hemodynamic characteristics of aneurysms have been proposed and evaluated for predicting the risk of rupture, there is little research evaluating the risk of aneurysm formation, especially in sidewall aneurysms.

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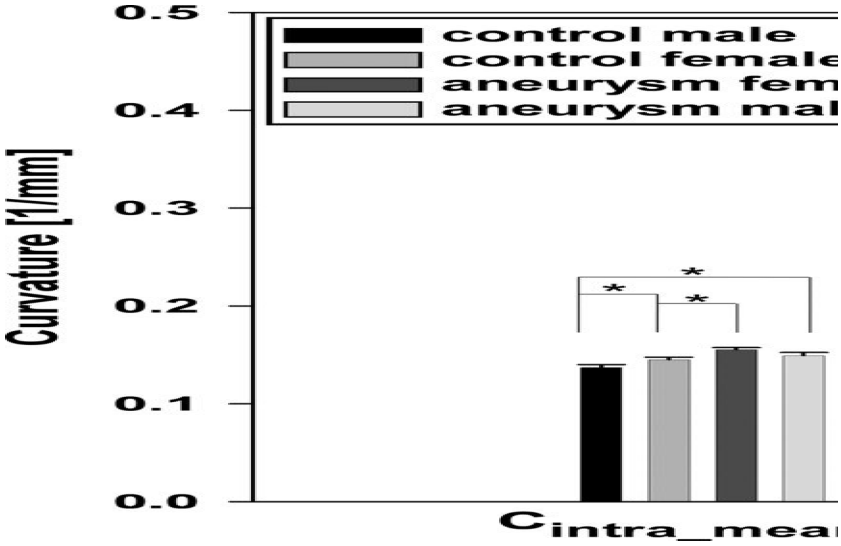


Figure 4 Mean comparison between non-aneurysmal (control) men, non-aneurysmal (control) women, aneurysmal men and aneurysmal women for the four curvature features: mean curvature of the entire internal carotid artery (ICA) (C_{intra_mean}), peak curvature of the intracranial ICA (C_{intra_max}), mean curvature of the distal ICA (C_{distal_mean}) and peak curvature of the distal ICA (C_{distal_max}). *p<0.05; **p<0.001.

Experimental studies on animals with induced cerebral aneurysms have shown that sidewall aneurysms develop near regions of high curvature.[20] On a population of 54 aneurysmal ICAs, local curvature analysis reported by Piccinelli *et al*[9] showed that ICA bends harboring ruptured aneurysms have a higher curvature than ICA bends harboring unruptured aneurysms, suggesting that vessel curvature may be associated with aneurysm evolution. Similarly, on a population of 65 ICAs, Sangalli *et al*[12] reported that aneurysmal ICAs have higher curvatures than the ICA of patients with aneurysms in locations distal to the ICA bifurcation.

To the best of our knowledge, the association of vessel curvature with the presence of aneurysms has not been evaluated. The current report has attempted to assess the effect of vessel curvature on the presence of aneurysms on the intradural ICA. Our results seem to indicate that higher mean and peak curvature may be indicative of a higher risk of aneurysm formation, regardless of gender. Curvature differences between aneurysmal and non-aneurysmal ICAs are shown in figure 6. The aneurysmal ICAs are clearly more tightly curved in both the proximal and distal segments. Aneurysmal ICAs take a very sharp turn as they enter the intradural space and display a narrow anterior genu at the carotid siphon. In contrast, non-aneurysmal ICAs have an almost straight proximal section with a wider anterior genu.

In this study we also aimed to evaluate the gender differences related to vessel curvature. We found that non-aneurysmal ICAs in men tended to have a lower overall curvature than non-aneurysmal ICAs in women, whereas aneurysmal ICAs in men tended to have a higher curvature than aneurysmal ICAs in women. Figure 4 shows increasing higher ICA curvature values for control men, followed by control women, then aneurysmal women and, finally, aneurysmal men. This is especially true for peak curvature values. The results suggest that the curvature threshold for aneurysm initiation may be higher for men, and this may be part of the reason why women are at a higher risk of aneurysm formation.

Moreover, in women (regardless of aneurysm presence), the site of the peak curvature of the intracranial ICA is evenly split between the carotid siphon and the cavernous segment whereas, in men (regardless of aneurysm presence), the location of the peak curvature is predominantly at the carotid siphon. A few studies[21 22] have shown a 'striking preponderance of women' presenting with aneurysms of the proximal ICA. The gender difference in the distribution of the peak curvature sites may also be part of the reason why women are more predisposed to extradural aneurysms.

The geometry of the ICA can affect the blood flow through the artery, with high curvatures causing a complex and non-uniform flow pattern which in turn may alter the function of the arterial endothelium[23] and may trigger pathological degeneration of the arterial wall favorable to aneurysm formation. Hemodynamic simulations on parametric data have shown that a curved bend disturbs the constant flow characteristic of

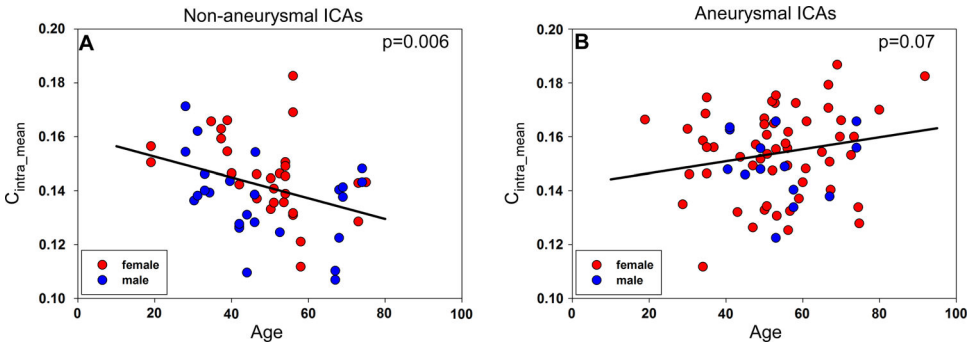


Figure 5 Linear correlation between mean curvature of the intracranial internal carotid artery (ICA) (C_{intra_mean}) and age for (A) non-aneurysmal ICAs and (B) aneurysmal ICAs. Statistical significance was assumed for p<0.05.

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Table 3 Whole model analysis of mean intracranial curvature, evaluating the relative effect of aneurysm presence, age and known risk factors

Predicted value	Whole dataset model		Female model		Male model	
	Effect variable	p Value	Effect variable	p Value	Effect variable	p Value
C_{intra_mean}	Aneurysm?	<0.001*	Aneurysm?	0.01*	Aneurysm?	<0.001*
	Age	0.99	Age	0.67	Age	0.43
	Hypertension	0.61	Hypertension	0.61	Hypertension	0.01*
	High cholesterol	0.72	High cholesterol	0.46	High cholesterol	0.72
	Smoking	0.36	Smoking	0.78	Smoking	0.66

*Indicates statistical significance (p<0.05).
Whole mode statistics were similar for all curvature features.

straight vessels, and induces regions of high WSS on the lateral walls of the bend[4] as well as regions of low WSS on the inner wall of the bend.[23] Hoi *et al*[24] found that increased arterial curvature was associated with high pressure, high WSS and high impingement zones in sidewall aneurysms, known predisposing factors to aneurysm formation.[5] Most (67%) of the aneurysms in the population studied here originated distal and within 10 mm from the site of peak curvature. While this study was concerned with the association between global curvature and aneurysm presence, future studies will need to focus on the local effects of high curvature on aneurysms originating in the proximity of curved bends. In particular, similar to the study by Piccinelli *et al*[9] which compared bends harboring ruptured and unruptured aneurysms, the local curvature of bends harboring aneurysms will need to be compared with those of healthy controls.

Although morphological and hemodynamic research concerned with aneurysm formation and evolution is usually focused locally in the vicinity of the lesion, increasing evidence suggests that aneurysm initiation may reflect global characteristics of the vasculature.[25–27] Overall, our data suggest that high curvature of the ICA represents an additional predisposing factor favoring the pathological formation of aneurysms. Future larger studies are required to determine the utility and applicability of vessel curvature in cerebral aneurysm risk stratification analysis.

Study limitations

Although the ICA population described here is double the size of that compared in previous research,[9 12] the sample per subgroup is still relatively small for aneurysmal and non-aneurysmal men. Larger studies are required to confirm the findings

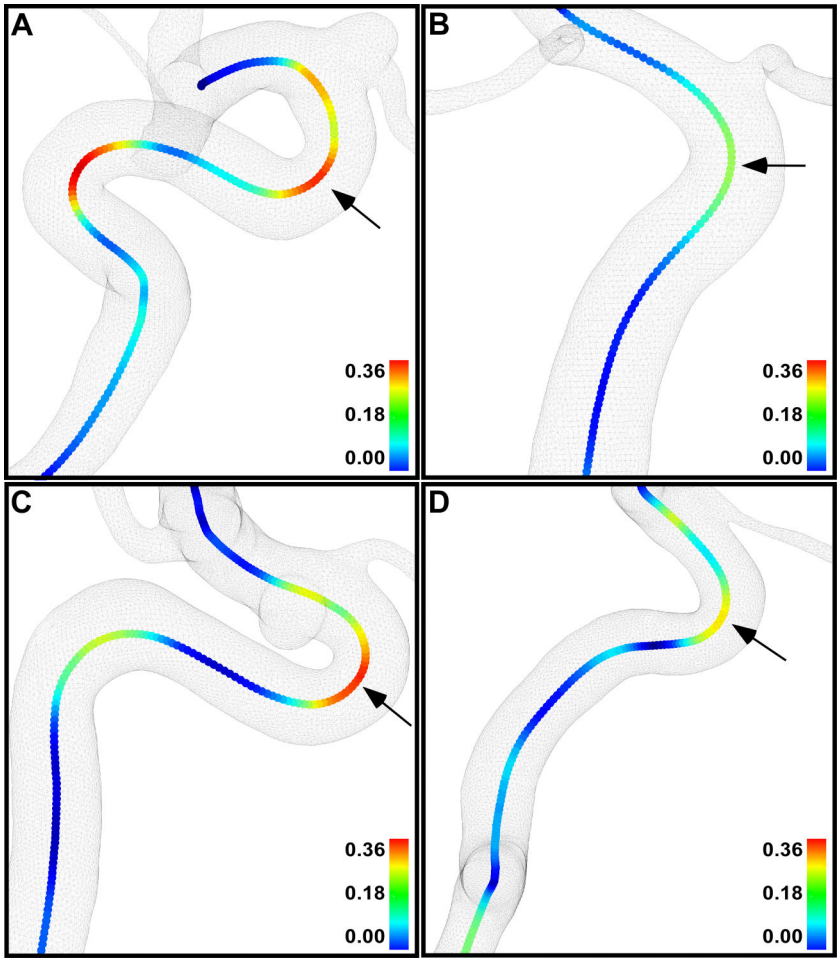


Figure 6 Multiple 3D reconstructions of internal carotid arteries (ICA) comparing non-aneurysmal men and women and aneurysmal men and women (aged between 53 and 68 years). The black arrows point to the position of the peak curvature of the distal ICA. (A) Male ICA harboring an aneurysm on the ophthalmic segment: C_{distal_mean}=0.20, C_{distal_max}=0.34. (B) Control male ICA: C_{distal_mean}=0.14, C_{distal_max}=0.24. (C) Female ICA harboring an aneurysm on the ophthalmic segment: C_{distal_mean}=0.19, C_{distal_max}=0.43. (D) Control female ICA: C_{distal_mean}=0.16, C_{distal_max}=0.28.

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reported here. In addition, the analysis is retrospective in character and thus can only imply a predilection for aneurysm formation based on curvature analysis. Our study will require validation in prospective randomized studies before its performance can be validated for any risk assessment in clinical practice.

Related to the above limitation, the degree to which the presence of aneurysms affects the geometry of the parent vessels is unknown. Although not statistically significant, our results showed a trend in which larger aneurysms were associated with lower curvature, which suggests that vessel deformation due to aneurysm size may be possible. In this population the aneurysms were relatively small (only six aneurysms <10 mm), with a mean size of 5.45±3.79 mm, thus decreasing the likelihood of severe vessel deformation due to aneurysm presence. This is an issue that can only be conclusively addressed by prospective studies in which follow-up data are available prior to aneurysm formation.

The control group of non-aneurysmal patients was matched by age with the aneurysmal group; while some clinical risk factors such as hypertension, high cholesterol and smoking have been taken into consideration, others such as alcohol and drug use, use of oral contraceptives and family history have not. Although we share this limitation with similar research,[9 12] additional studies are necessary to evaluate the interplay between the proposed curvature parameters and known risk factors for aneurysm formation and rupture.

CONCLUSION

This study evaluated the effect of vessel curvature on sidewall aneurysm formation on the ICA. The presence of an aneurysm was associated with high curvature both on the intracranial ICA and also on the distal ICA. Non-aneurysmal ICAs showed less variation in curvature than aneurysmal ICAs for both genders. Non-aneurysmal ICAs in men were less curved than in women, which may explain the gender predisposition to aneurysm formation. High mean curvature and high curvature peaks may be indicative of an increased risk of aneurysm initiation.

Contributors AL: analysis and interpretation of data, drafting and final approval of the manuscript. MGS: acquisition of data, critical revision of the manuscript. JH: acquisition of data. AMM: conception, design, analysis and interpretation of data, critical revision and final approval of the manuscript.

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Ethics approval This research was approved by Tufts Health Sciences Campus Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

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