Hemodynamic characteristics associated with cerebral aneurysm formation in patients with carotid occlusion

Sophia F. Shakur, MD, Ali Alaraj, MD, Nasya Mendoza-Elias, BS, Muhammad Osama, MD, and Fady T. Charbel, MD

Department of Neurosurgery, University of Illinois at Chicago, Illinois

OBJECTIVE The pathogenesis of cerebral aneurysms in patients with internal carotid artery (ICA) occlusion is hypothesized to be hemodynamic. For the first time, the authors quantify the hemodynamic characteristics associated with aneurysm formation in patients with ICA occlusion.

METHODS Records of patients with unilateral ICA stenosis or occlusion $\geq 90\%$ who underwent hemodynamic assessment before treatment using quantitative MR angiography were retrospectively reviewed. The patients were classified into 2 groups based on the presence or absence of aneurysms. The hemodynamic parameters of flow volume rate, flow velocity, and wall shear stress (WSS) were measured in each vessel supplying collateral flow—bilateral A_1 segments and bilateral posterior communicating arteries—and then compared between the groups.

RESULTS A total of 36 patients were included (8 with and 28 without aneurysms). The mean flow (72.3 vs 48.9 ml/min, $p = 0.10$), flow velocity (21.1 vs 12.7 cm/sec, $p = 0.006$), and WSS (22.0 vs 12.3 dynes/cm², $p = 0.003$) were higher in the A_1 segment contralateral to the side of the patent ICA in patients with versus without aneurysms. All de novo or growing aneurysms in our cohort were located on the anterior communicating artery (ACoA) or P_1 segment.

CONCLUSIONS Flow velocity and WSS are significantly higher across the ACoA in patients who harbor an aneurysm, and de novo or growing aneurysms are often located on collateral vessels. Thus, robust primary collaterals after ICA occlusion may be a contributing factor in cerebral aneurysm formation.

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KEYWORDS aneurysm; carotid occlusion; cerebral; de novo; flow; hemodynamics; shear stress; vascular disorders

CEREBRAL aneurysms are generally thought to be acquired lesions that develop during adulthood.^{6,10} Accordingly, the main risk factors linked to cerebral aneurysm formation and growth are older age, hypertension, and cigarette smoking.^{6,8,12} Hemodynamic stresses are also thought to play a role in the pathogenesis of aneurysms, but this hypothesis is largely based on anecdotal evidence of the high occurrence of de novo aneurysms in patients with internal carotid artery (ICA) occlusion.^{1,4,5,7,13} In this study, we aimed to determine the hemodynamic characteristics associated with cerebral aneurysm formation in patients with ICA occlusion with the aid of quantitative MR angiography (QMRA).

Methods

Patient Selection

After receiving institutional review board approval,

we retrospectively reviewed the records of patients with unilateral ICA stenosis or occlusion $\geq 90\%$ who were evaluated at our institution between 2006 and 2016. Patients were included if they underwent hemodynamic assessment using QMRA before treatment. Patients were classified into 2 groups based on the presence or absence of aneurysms as documented on digital subtraction angiography. The degree of ICA stenosis was determined based on digital subtraction angiography findings using the North American Symptomatic Carotid Endarterectomy Trial criteria.²

Flow Volume Rate, Flow Velocity, and Wall Shear Stress Measurements

In all patients, the quantitative vessel flow volume rate, flow velocity, and diameter of the extracranial and intracranial arteries were measured using QMRA at the time the ICA occlusion was diagnosed. This technique has been

ABBREVIATIONS ACoA = anterior communicating artery; ICA = internal carotid artery; PCoA = posterior communicating artery; QMRA = quantitative MR angiography; WSS = wall shear stress.

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TABLE 1. Clinical, aneurysm, and hemodynamic characteristics of patients with and without aneurysms

Variable	Aneurysm Absent (n = 28)	Aneurysm Present (n = 8)
Mean age, yrs (range)	58 (35–74)	59 (36–71)
% of patients		
Male sex	61	38
ICA occlusion	61	63
Hypertension	61	88
Smoking	61	75
Aneurysm location, no.		
Paraclinoid ICA		2
ACoA		3
Basilar tip		1
P ₁		1
PICA		1
Mean aneurysm diameter, mm (range)		6.6 (2.5–12.2)
Hemodynamics		
Mean contralat A ₁ flow, ml/min (range)	48.9 ± 35.0 (7.2–135.0)	72.3 ± 28.6 (30.0–116.7)
Mean contralat A ₁ flow velocity, cm/sec (range)	12.7 ± 7.0 (3.7–35.2)	21.1 ± 4.5 (12.0–26.3)
Mean contralat A ₁ WSS, dynes/cm ² (range)	12.3 ± 7.1 (4.6–18.8)	22.0 ± 5.9 (10.5–30.0)

PICA = posterior inferior cerebellar artery.

described and validated previously^{3,15} and was implemented using the commercially available software Noninvasive Optimal Vessel Analysis (NOVA, VasSol, Inc.). Hemodynamic parameters were measured in all major extracranial and intracranial vessels, including each vessel supplying collateral flow: the bilateral A₁ segments and bilateral posterior communicating arteries (PCoAs).

Once blood flow and vessel diameter were measured, wall shear stress (WSS) was calculated using the Hagen-Poiseuille equation: $WSS = 32\mu Q/\pi D^3$, where WSS is in dynes/cm², Q is the volumetric flow rate in ml/sec, and D is the vessel diameter in cm; μ is the blood viscosity in poise and was assumed to be constant (0.035 poise). This method was previously described by Zhao et al.¹⁶

Statistical Analysis

Hemodynamic parameters were compared between patients with and without aneurysms using the independent 2-tailed Student t-test. Analyses were performed using IBM SPSS (version 24, IBM Corp.); $p \leq 0.05$ was considered statistically significant.

Results

Patient Characteristics

A total of 36 patients were included in this study. Among these patients, there were 28 without and 8 with a cerebral aneurysm. Cohort characteristics are summarized in Table 1.

Aneurysm Characteristics

Aneurysm characteristics are summarized in Table 1, and hemodynamic parameters of patients with aneurysms are provided in Table 2. Among the 8 patients with an-

eurysms, 5 patients were incidentally found to harbor a cerebral aneurysm at the time they were diagnosed with ICA occlusion, and 3 patients (8.3% of study cohort) had de novo or growing aneurysms detected during follow-up.

Of the incidental aneurysms, 2 originated from the paraclinoid ICA, 1 from the anterior communicating artery (ACoA), 1 from the basilar tip, and 1 from the posterior inferior cerebellar artery. Among all patients with aneurysms, ICA flow but not WSS in the patent ICA was the highest in the setting of the 2 paraclinoid ICA aneurysms (441 ml/min and 394 ml/min, mean flow 337 ml/min, range 259–441 ml/min). Basilar artery flow and WSS were not higher in the setting of the basilar tip aneurysm.

Of the de novo or growing aneurysms, 2 originated from the ACoA and 1 from the P₁ segment ipsilateral to the occluded ICA. One patient presented with rupture of a de novo ACoA aneurysm 7 years after ICA coil sacrifice for treatment of a giant cavernous ICA aneurysm, and another patient presented with rupture of a de novo P₁ segment aneurysm 4 years after ICA coil sacrifice. The third patient had atherosclerotic ICA occlusion and an incidental ACoA aneurysm that enlarged from 2 mm to 4 mm over 4 years. Hemodynamic measurements before and after aneurysm development were only available in the patient with the growing aneurysm; the WSS in the contralateral A₁ segment increased from 19.3 dynes/cm² to 21.7 dynes/cm² as the aneurysm doubled in size.

Hemodynamic Characteristics in Patients With Versus Without Aneurysms

Hemodynamic values in the A₁ segment ipsilateral to the side of the patent ICA did not significantly vary between patients with versus without aneurysms (mean flow 165.2 ± 72.5 vs 164.3 ± 92.7 ml/min, $p = 0.98$; flow veloc-

TABLE 2. Hemodynamic characteristics of patients with aneurysms

Case No.	Aneurysm Location	Aneurysm Diameter (mm)	Flow (ml/min)				Flow Velocity (cm/sec)				WSS (dynes/cm ²)			
			Ipsilat A ₁	Contralat A ₁	Ipsilat PCoA	Contralat PCoA	Ipsilat A ₁	Contralat A ₁	Ipsilat PCoA	Contralat PCoA	Ipsilat A ₁	Contralat A ₁	Ipsilat PCoA	Contralat PCoA
1	Paraclinoid ICA	8.6	259.6	116.7	—	45.3	42.1	26.3	—	19.5	33.1	23.3	—	25.3
2	Paraclinoid ICA	3.5	40.2	40.3	—	—	22.4	20.4	—	—	29.9	30.0	—	—
3	ACoA (de novo)	5	—	74.1	—	—	—	22.9	—	—	—	25.1	—	—
4	ACoA (growing)	4	142.5	89.1	—	30.3	34.6	22.6	—	9.1	31.4	21.7	—	9.2
5	ACoA	2.5	175.4	93.0	9.0	—	41.1	23.1	2.7	—	38.7	22.7	3.0	—
6	Basilar tip	12.2	176.4	58.0	—	47.9	23.6	12.0	—	10.1	16.4	10.5	—	8.7
7	P ₁ (de novo)	12	—	30.0	—	82.4	—	—	—	—	—	—	—	—
8	PICA	5	196.9	77.0	—	15.1	29.7	20.3	—	8.2	23.1	20.9	—	11.2

— = hemodynamic parameter not measured.

ity 32.3 ± 8.5 vs 34.9 ± 10.9 cm/sec, $p = 0.59$; and WSS 28.8 ± 7.9 vs 32.6 ± 9.3 dynes/cm², $p = 0.36$). However, A₁ segment hemodynamics contralateral to the side of the patent ICA were higher in patients with aneurysms (mean flow 72.3 ± 28.6 vs 48.9 ± 35.0 ml/min, $p = 0.10$; flow velocity 21.1 ± 4.5 vs 12.7 ± 7.0 cm/sec, $p = 0.006$; and WSS 22.0 ± 5.9 vs 12.3 ± 7.1 dynes/cm², $p = 0.003$) (Table 1 and Fig. 1).

Among patients without aneurysms, PCoA hemody-

namics ipsilateral to the side of the patent ICA were as follows: mean flow 26.1 ± 21.8 ml/min, mean flow velocity 9.9 ± 7.7 cm/sec, and WSS 9.5 ± 6.4 dynes/cm². PCoA hemodynamics contralateral to the side of the patent ICA were as follows: mean flow 45.1 ± 30.1 ml/min, mean flow velocity 17.9 ± 10.3 cm/sec, and WSS 22.3 ± 12.9 dynes/cm². PCoA hemodynamics in patients with aneurysms are provided in Table 2 but were not statistically compared with patients without aneurysms, given the smaller sam-

FIG. 1. Bar graph showing hemodynamic characteristics in patients with versus without aneurysms. The mean flow, flow velocity, and WSS in the A₁ segment contralateral to the patent ICA are higher in patients with aneurysms. * and ** $p \leq 0.05$.

FIG. 2. Illustrative cases. **A and B:** Digital subtraction angiogram (A) and QMRA image (B) obtained in a patient without an aneurysm. The flow in the contralateral A₁ segment is 10.8 ml/min and the WSS is 6.0 dynes/cm². **C and D:** Images obtained in a patient with an ACoA aneurysm. Digital subtraction angiogram (C). The arrow identifies the aneurysm on the digital subtraction angiogram, left ICA injection, oblique projection. QMRA image (D). The yellow arrow and plane indicate the location of the contralateral A₁ segment flow (89.1 ml/min) and WSS (21.7 dynes/cm²) measurements. Figure is available in color online only.

ple size compared with the A₁ segment data set. However, PCoA flow ipsilateral to the de novo P₁ segment aneurysm in our cohort (82.4 ml/min) was the highest among patients with aneurysms and was much higher than mean PCoA flow in patients without aneurysms.

Discussion

An understanding of the formation and growth of cerebral aneurysms is imperative, given the high morbidity and mortality rates associated with ruptured aneurysms. While hemodynamic stresses have been implicated in the pathogenesis of aneurysms, not all de novo aneurysms are associated with ICA occlusion, and not all patients with ICA occlusion develop aneurysms.^{1,4–8,11–13} Thus, our current understanding of the pathogenesis of cerebral aneurysms remains incomplete.

The hemodynamic perspective has been investigated using computational fluid dynamics and has yielded conflicting conclusions regarding WSS.^{7,9} In this study for the first time we used QMRA to quantify and compare hemodynamic parameters in ICA occlusion patients with and without aneurysms. We found that flow velocity and WSS are significantly higher across the ACoA in patients who harbor an aneurysm. Additionally, all de novo or growing aneurysms in our cohort were located on vessels providing collateral blood supply, namely the ACoA and P₁ segment. Illustrative cases depicting one patient without an aneurysm and another patient with an aneurysm are shown in Fig. 2.

Our results suggest that increased WSS can lead to cerebral aneurysm formation, corroborating previous studies that cite WSS as an important biomechanical stimulus for molecular changes associated with aneurysm development.¹⁴ Our findings also support a multifactorial model for aneurysm formation since patients with aneurysms in our cohort had a higher prevalence of hypertension and smoking in addition to elevated flow velocity and WSS (Table 1). We also demonstrated that patients with ICA occlusion are a subgroup at higher risk for de novo or growing aneurysms (3/36 patients [8.3%], present study vs 26/2153 patients [1.2%], Wang et al.¹²). Consequently, screening for de novo aneurysms may be appropriate in this patient subset. Further studies may identify a WSS threshold indicative of a hyperdynamic state susceptible to aneurysm formation among patients with ICA occlusion.

Limitations of this study are its retrospective design and small sample size. Only 3 de novo or growing aneurysms were identified, and hemodynamic measurements before and after aneurysm development were only available in the patient with the growing aneurysm; the WSS of the contralateral A₁ segment increased from 19.3 dynes/cm² to 21.7 dynes/cm² as the aneurysm doubled in size. Another limitation is that PCoA hemodynamics were not statistically compared between patients with and without aneurysms given that the sample size was smaller than that of the A₁ segment data set. PCoA hemodynamics measured using QMRA are less consistently obtained than those measured in other vessels, particularly when the PCoA is small or absent. Our small sample size yields preliminary

results that require confirmatory investigation. Potential variability in the data reflects the fact that blood flow, flow velocity, and WSS are physiological parameters. Ipsilateral and contralateral hemodynamics were examined to account for potential confounders, such as age, heart rate, and blood pressure. Finally, while the Hagen-Poiseuille equation assumes steady, laminar flow of a newtonian fluid in straight rigid vessels, it provides a useful estimate of WSS.

Conclusions

Flow velocity and WSS are significantly higher across the ACoA in patients who harbor an aneurysm, and de novo or growing aneurysms are often located on collateral vessels. These preliminary results suggest that robust primary collaterals after ICA occlusion may be a contributing factor in cerebral aneurysm formation.

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Disclosures

Dr. Alaraj: consultant for Cordis-Codman. Dr. Charbel: consultant for Transonic Inc.

Author Contributions

Conception and design: Charbel, Alaraj. Acquisition of data: Shakur, Mendoza-Elias, Osama. Analysis and interpretation of data: Shakur. Drafting the article: Shakur. Critically revising the article: Charbel, Shakur, Alaraj. Reviewed submitted version of manuscript: all authors. Statistical analysis: Shakur. Administrative/technical/material support: Charbel. Study supervision: Charbel.

Correspondence

Fady T. Charbel: University of Illinois at Chicago, IL. fcharbel@uic.edu.