Abstract

Extracranial internal carotid artery caliber dysregulation is associated with cerebral aneurysms.

Sarah Schimansky, BSc; Samir Patel, BSc; Jason Rahal, MD; Alexandra Lauric, PhD; Adel M. Malek, MD, PhD

Background and Purpose—Flow-induced hemodynamic forces are critical in extra- and intracranial arterial caliber regulation and have been proposed to mediate intracranial aneurysm (IA) formation and rupture. We hypothesized that vascular structural control may be impaired in patients harboring brain aneurysms and sought to examine any differences in extradural internal carotid artery (ICA) caliber profiles.

Methods—Ninety-six catheter 2-dimensional angiograms were divided into 3 subgroups: (1) ICA leading to IA (n=38), (2) matched contralateral ICA (n=25), and (3) ICA from nonaneurysmal controls (n=33). ICA diameter was measured proximally beyond the bulb (D_prox) and distally at the extradural point of maximal dilation (D_maxdist), yielding maximal distal-to-proximal ratio (R_Mdp).

Results—Unlike non-IA controls that tapered smoothly, ICAs leading to IA consistently demonstrated focal sites of abnormal dilation in the distal cervical or petrous extradural segments. R_Mdp was greater in ICAs leading to IA compared with non-IA controls (1.17±0.1 versus 1.0±0.08; P=0.0001). Matched-pair analysis showed R_Mdp to be higher in ICAs leading to IA than the corresponding contralateral ICAs (1.19±0.1 versus 1.07±0.11; P=0.001); R_Mdp from contralateral ICAs was greater than non-IA controls (P=0.005). Among ICAs leading to IA, women showed higher R_Mdp (1.11±0.12 versus 1.05±0.11; P=0.02) with no relationship to intradural IA location.

Conclusions—Measurements of the extradural ICA in patients harboring intradural IA suggest an association with a remote upstream abnormal vascular caliber control consistent with a diffuse flow-mediated structural dysregulation showing laterality and sex dependence.

Key Words: extradural internal carotid artery ■ flow-mediated regulation ■ intracranial aneurysm ■ luminal caliber ■ optimality principle

Intracranial aneurysms (IA) are localized arterial dilations within the cerebrovasculature that, when ruptured, lead to subarachnoid hemorrhage. They remain associated with significant case fatality. Although several local and systemic processes have been correlated with the pathogenesis of IAs, the mechanisms leading to this arteriopathy remain uncertain. Mechanical forces have been well established as important factors contributing to the formation of aneurysms in the absence of significant comorbidities. In particular, wall shear stress has been shown to play a central role in this mechanism because of its importance in controlling vessel caliber in accordance with the vascular optimality principle. This principle, which was previously demonstrated to be at work in the cerebral circulation, posits that vessel geometry has evolved to minimize pumping energy expenditure.

Previous research has primarily focused on arterial branching sites and bifurcations that are designed to optimize workload by preserving physiological wall shear stress. However, the optimality principle also applies to the extradural internal carotid artery (ICA), which under normal pathological circumstances exhibits smooth tapering because of constant blood flow and lack of branches along its extradural course. Pathological geometric alterations of the artery have been implied to occur in patients with aneurysms. Although these abnormalities have been extensively studied in close proximity to the aneurysm, particularly at intradural bifurcations, few studies evaluated the correlation between geometric alterations of the extradural ICA and IA formation.

During diagnostic cerebral angiography, it was subjectively noted that patients with IAs also presented with unexpected focal dilations of the extra- and intracranial ICA (Figure I in the online-only Data Supplement). Invariably, these dilations were noticed upstream of the location of the aneurysms and at considerable distance of what might be considered the vicinity of the lesions. In the region immediately after this focal expansion, the arterial diameter returned to normal. The purpose of...
this study was to evaluate these differences retrospectively in the caliber along the cervical and extradural ICA, as seen on cerebral angiography, between patients with aneurysms and control subjects. Potential variations in vessel caliber at sites upstream of the aneurysm location may have important clinical implications for the understanding of IA formation and possibly form the basis for a screening tool.

Methods

Patient Selection and Demographics

Two-dimensional (2D) biplane diagnostic cerebral angiograms of the cervical carotid artery were obtained using a calibrated high-resolution flat-panel biplane angiography system (Siemens Artis, Malvern, PA). All angiograms performed by the senior author (A.M.M.) between 2009 and 2012 were considered for the study. To be deemed suitable for inclusion, either the anteroposterior or the lateral x-ray angiographic view captured during acquisition was required to include the entirety of the extradural ICA starting from the common carotid artery bifurcation and to exclude the intracranial ICA to avoid inadvertent aneurysm visualization and consequently measurement bias. In addition, only healthy patients aged >30 years were included to ensure adequate age matching with patients harboring aneurysms.

Where available, bilateral angiograms were also included, resulting in a total of 96 angiograms from 51 patients (66.7% women). Thirty-eight angiograms from 33 patients showed the presence of intradural aneurysms (68.4% women; mean age, 56.2 years). Contralateral data were available for 25 patients (72% women; mean age, 56.7 years). Contralateral data were free of any aneurysmal lesions both in the cervical and extradural ICA.

The control group consisted of 33 angiograms from 18 patients (60.6% women; mean age, 51.3 years) in which the postangiographic diagnosis excluded the presence of aneurysms, dissections, stenoses, or arteriovenous malformations. The indications for angiography performed in the control group included epistaxis (n=3), tumor (n=3), venous sinus thrombosis (n=4), vasculitis (n=2), intracranial hemorrhage (n=3), acute stroke (n=2), and WADA test (n=1).

Morphological Measurements and Validation

Manual 2D measurements of the ICA proximal (D_prox) and widest distal (D_maxDist) diameters were performed by 2 trained medical operators blinded to the presence of aneurysms and to each other measurements, and the average was reported. Either the anteroposterior or lateral view was used depending on which provided the best visualization while including the entirety of the extradural ICA starting from the common carotid artery bifurcation and excluding the intradural ICA to avoid inadvertent aneurysm visualization. D_prox measurement was made along the cervical ICA closest to the carotid bulb where the vessel walls first become parallel at the end of the bulb taper. D_maxDist measurement was made along the cervical, petrous, or extradural cavernous segments of the ICA (Figure 1). The site of each measurement was recorded based on anatomic segments of the ICA, and the corresponding maximal distal-to-proximal ratio was evaluated as \( R_{Mdp} = \frac{D_{MaxDist}}{D_{Prox}} \).

The interobserver variability (2 observers, 96 samples per feature) was analyzed for the proximal and distal measurements using the intraclass correlation coefficient. The intraclass correlation coefficient, taking values between 0 and 1, is a statistical measure used to estimate the methodological reliability and reproducibility, with higher values representing higher agreement between sets of observations (>0.75 implying excellent agreement). The intraclass correlation coefficient for the proximal ICA measurement (\( D_{Prox} \)) was 0.88, whereas the intraclass correlation coefficient for the maximal distal ICA measurement (\( D_{MaxDist} \)) was 0.93.

To evaluate the potential confounding effect of windowing variability, additional measurement validation was performed after application of the Laplacian edge detection filter. Details are available in the online-only Data Supplement.

Statistical Analysis

The data were analyzed using JMP statistical software (version 9.02; SAS Institute, Cary, NC). Data are presented as mean±SD. The Student t-test was performed independently for individual parameters. The Tukey honestly significant difference (HSD) pairwise test was used to evaluate the statistical significance among patient cohorts. Statistical significance was assumed for \( P<0.05 \). Matched-pair analysis was conducted between aneurysmal ICAs and their corresponding contralateral ICAs.

Receiver operating characteristic curve analysis of \( R_{Mdp} \) was performed, and the area under the curve index was computed. The optimal discriminating \( R_{Mdp} \) cutoff, as well as corresponding sensitivity and specificity values, was determined for each patient group.

Results

\( R_{Mdp} \) Is Elevated in Patients With Aneurysms

Univariate statistical analysis for \( R_{Mdp} \) was performed on 4 subgroups: (1) 38 aneurysms versus 58 contralateral data.

Figure 1. Cervical carotid angiogram of the internal carotid artery (ICA) in a healthy control patient (A) and a patient with an intradural carotid ophthalmic ICA aneurysm (B). For both patients, imaging details are provided for the site of the proximal ICA measurement (\( D_{Prox} \)) and the site of the distal widest ICA measurement (\( D_{MaxDist} \)). The arrow points to the location of the aneurysm. The ratio is computed as maximal distal-to-proximal ratio (\( R_{Mdp} \)).
plus control group, (2) 25 aneurysms versus 25 corresponding contralateral data, (3) 38 aneurysms versus 33 controls, and (4) 25 contralateral angiograms versus 33 controls (Table). The \( R_{Mdp} \) in the aneurysmal group was significantly greater (1.17±0.1) compared with contralateral (1.07±0.11; \( P=0.0008 \)) and control groups (1.0±0.08; \( P<0.0001 \)). Significance was also observed for \( R_{Mdp} \) in the contralateral group compared with non-IA controls (\( P=0.005 \)). Notably, an \( R_{Mdp} \) of <1 (indicating ICA tapering) was not recorded in any of the ICA leading to IA, whereas 5 of 25 contralateral angiograms showed a continuous taper and decrease in ICA diameter distally.

Statistical significance among the patient groups (aneurysm versus contralateral versus control) was assessed using the Tukey HSD pairwise test for comparing \( R_{Mdp} \) (Figure 2A). \( R_{Mdp} \) showed a good discrimination performance between aneurysmal ICA and healthy ICA, with an area under the curve of 0.92 (Figure 2B). Age and sex distribution did not differ significantly between groups (Table I in the online-only Data Supplement).

dependence of \( R_{Mdp} \) on aneurysm location, type, and ruptured status

Of the 38 aneurysmal angiograms, the site of maximal dilation (\( D_{MaxDist} \)) was either in the cervical or petrous segments of the ICA in 31 cases (82%), significantly upstream of the associated aneurysm. In 7 cases (18%), \( D_{MaxDist} \) was measured along the extradural cavernous segment.

Regarding the aneurysm locations, 7 aneurysms originated from the paraclinoid ICA, 4 from the ophthalmic segment, 5 from the posterior communicating artery, 7 from the middle cerebral artery, 13 from the anterior communicating artery, 1 from the anterior cerebral artery, and 1 from the anterior choroidal artery. There was no significant difference in \( R_{Mdp} \) between proximal (ICA, posterior communicating artery, anterior choroidal artery) and distal aneurysms (anterior communicating artery, middle cerebral artery, anterior cerebral artery) at 1.18±0.12 versus 1.15±0.09 (\( P=0.46 \)), respectively, or between bifurcation (n=21) and sidewall (n=17) aneurysms at 1.14±0.09 versus 1.19±0.11 (\( P=0.12 \)), respectively. \( R_{Mdp} \) was not significantly different between ruptured (n=10) and unruptured (n=28) aneurysms (1.18±0.12 versus 1.16±0.10; \( P=0.78 \)).

multivariate analysis

Multivariate analysis for \( R_{Mdp} \) was performed, including patient group (aneurysm versus contralateral versus control), sex, and age as variables. The presence of aneurysm was a highly significant factor affecting \( R_{Mdp} \) (\( P<0.0001 \)). Overall, women were associated with a significantly larger \( R_{Mdp} \) (1.11±0.12) compared with men (1.05±0.11; \( P=0.02 \)). This was also true among ICAs leading to IA, and in this group, women had higher \( R_{Mdp} \) compared with men (1.20±0.11 versus 1.10±0.06; \( P=0.01 \)), with no relationship to intradural IA location. No significant age dependence was observed.

**Table. Univariate Analysis of Maximal Distal-to-Proximal Ratio (\( R_{Mdp} \)) Performed in Patient Subgroups**

<table>
<thead>
<tr>
<th>Aneurysm vs Control</th>
<th>Aneurysm</th>
<th>No Aneurysm</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA leading to IA vs contralateral ICA (all data)</td>
<td>1.17±0.1 (n=38)</td>
<td>1.03±0.1 (n=58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ICA leading to IA vs contralateral ICA</td>
<td>1.17±0.1 (n=38)</td>
<td>1.07±0.11 (n=25)</td>
<td>0.0008</td>
</tr>
<tr>
<td>ICA leading to IA vs healthy ICA</td>
<td>1.19±0.1 (n=25)</td>
<td>1.0±0.08 (n=25)</td>
<td>0.001</td>
</tr>
<tr>
<td>ICA contralateral to aneurysm bearing ICA vs healthy ICA</td>
<td>1.07±0.11 (n=38)</td>
<td>1.0±0.08 (n=33)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Statistics presented as mean±SD. IA indicates intracranial aneurysm; and ICA, internal carotid artery.

**Figure 2. A**, Mean distal-to-proximal ratio (\( R_{Mdp} \)) in internal carotid arteries (ICAs) leading to aneurysms (IAs), ICAs contralateral to the aneurysm-bearing vessel, and control arteries in patients without IAs. **B**, Receiver operating characteristic (ROC) curve of \( R_{Mdp} \) as a detector for the presence of intracranial aneurysms (area under the curve=0.92).
Discussion
To our best knowledge, this is the first study to demonstrate a clear correlation between abnormal caliber changes of the extradural ICA and presence of intradural cerebral aneurysms. The aneurysmal group displayed a significantly greater $R_{\text{dmax}}$ which exhibited sex dependence but did not vary with age. Importantly, the widest measurement used to compute $R_{\text{dmax}}$ was consistently recorded at a location significantly proximal to the IA. Notably, the extradural ICA dilations, while not observed in controls, were also present to a lesser extent in the ICAs contralateral to the aneurysmal side. These observations are in line with other studies reporting morphological and structural changes in the common carotid artery and extradural ICA, which were also prominent on the contralateral side. Spallone et al. reported significant changes in the extradural ICA morphology in patients with aneurysms compared with matched controls. Variations in the vasculature, namely kinks, coils, and stenosis, were also commonly noted along the extradural ICA on the side contralateral to the aneurysm. Maltete et al. related a specific extradural ICA phenotype, characterized by hypertrophic remodeling and altered elasticity, to IA formation. Previously, it has been proposed that failure of the vasculature to adhere to the optimality principle is reflected in locally altered bifurcation geometry.

Our data suggest that pathological alterations in vasculature geometry also occur along the extradural ICA at locations remote from branching points and bifurcations in patients with aneurysms. Despite the localized appearance of the dilation, its presence in the artery contralateral to the IA implies a possible global defect at a histomorphological level within the vessel walls. This indicates the need for future research to examine hemodynamic forces and biomechanical vascular properties outside the immediate vicinity of the aneurysm at a more systemic level.

Additional research is required to validate the effect of artery caliber dysregulation on hemodynamic forces and aneurysm formation and to examine this particular effect in correlation with other possible risk factors. Given that the inclusion criteria required that patients have separate cervical angiograms, this selection methodology may introduce unknown bias and is a limitation of the study. Furthermore, this study is retrospective in nature, and its conclusions will require validation by prospective randomized studies with a larger sample size; only then can its use be determined with respect to prediction of the presence of aneurysm in a clinical setting.

Conclusions
Although flow-related forces have been previously implicated in the genesis of IAs, these correlations focused on cerebral bifurcation sites in the vicinity of the aneurysm. The current study suggests an association between localized dysregulation of the cervical ICA diameter and presence of downstream distal intradural IAs. The results suggest a focally impaired vascular regulatory response with local deviation from the vascular optimality principle at sites significantly distant and upstream from the cerebral aneurysm.

Sources of Funding
This work was supported by a grant from the National Institutes of Health (NIH-R21HL102685). The first author was financially supported by the German National Academic Foundation and the Royal College of Surgeons in Ireland Alumni Fund.

Disclosures
The senior author has received unrestricted research funding from Codman Neurovascular, Stryker Neurovascular, Microvention Inc, Siemens Inc, Ansyst Inc, and CD-Adapco Inc for research that is unrelated to the submitted work. The other authors report no conflicts.

References
Extradural Internal Carotid Artery Caliber Dysregulation Is Associated With Cerebral Aneurysms
Sarah Schimansky, Samir Patel, Jason Rahal, Alexandra Lauric and Adel M. Malek

Stroke. published online October 3, 2013;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2013/10/03/STROKEAHA.113.001762

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/10/03/STROKEAHA.113.001762.DC1

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

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

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
Extradural Internal Carotid Artery Caliber Dysregulation Associated with Intradural Cerebral Aneurysms

Supplemental content

Focal Dilatations of the Extradural ICA

During diagnostic cerebral angiography, it was subjectively noted by the senior author (AMM) that patients with IAs also presented with unexpected focal dilations of the extradural internal carotid artery (Supplemental Figure 1). Invariably, these dilations were noticed upstream to the location of the aneurysms and at considerable distance of what might be considered the vicinity of the lesions. In the region immediately after this focal expansion the arterial diameter returned to normal. This study attempts to quantify these differences in the caliber along the cervical and extradural ICA, as seen on cerebral angiography, between patients with aneurysms and control subjects.

Patient Demographics

Ninety-six cerebral angiograms (from 51 patients) were included in this study. A total of thirty-eight were aneurysmal angiograms (from 33 patients). Twenty-five contralateral angiograms were also available. Thirty-three angiograms represented control data (from 18 patients). Details about the age and gender of patients in each group are available in Supplementary Table I.

Measurement Validation using Laplacian Edge Detection

To evaluate the potential confounding effect of windowing variability, a test subset of twenty angiograms was measured following application of the Laplacian edge detection filter. This algorithm highlights vessel edges independent of other visualization settings such as
window center or width. The measurements showed excellent correlation with corresponding data obtained without Laplacian edge detection with an ICC of 0.95.

While two-dimensional measurements may potentially offer room for observation error, the excellent ICC indicates that the measurements are both reliable and reproducible. Furthermore, 2-dimensional DSA is still the standard for diagnosing aneurysms and our results demonstrate that caliber changes along the ICA can be easily and reliably assessed by blinded medical operators in a clinical setting.

**Continuous ICA Caliber Measurements in a Subset of Angiograms**

Out of the 97 angiograms available, fourteen angiograms (7 aneurysms, 7 controls) were randomly chosen for a series of fifteen sequential 2D measurements carried out at equidistance along the ICA from the end of the carotid bulb (D_{Prox}) to the end of the cavernous segment. The measurements were performed using the line measurement tool in OsiriX software (Version 4.1.2, Pixmeo, Bernex, Switzerland) at default visualization settings (Window Level: 128; Window Width: 256). For each angiogram, a series of distal to proximal ratios were obtained by dividing each of the fifteen measurements by D_{Prox}.

The continuous measurements along the extradural ICA in a subset of 14 angiograms displayed a marked trend whereby the arterial caliber in the control group gradually decreased distally, as expected. In stark contrast, the ICA diameter in the aneurysmal group revealed a non-characteristic pattern with regional increases and an overall less pronounced downward trend. Despite the small number of data used for these initial measurements, statistical significance between the two groups was observed by paired t-test analysis (Supplemental Figure I).
The angiographic diameter of the 7 control non-aneurysmal ICA measured at 15 equidistant steps from the cervical origin to the cavernous segment displayed a steady downward trend in the consecutive distal to proximal ratios as expected with the normal ICA caliber decreasing distally (Supplemental Figure II). In stark contrast, similar measurements from the 7 ICA leading to an intradural IA not only failed to demonstrate the expected gentle taper but instead showed a relative increase in width progressing distally with a prominent widening of the ICA in the region of the carotid canal. Paired t-test of the two sets of average measurements (p = .001) confirmed a statistically significant difference between the ICA leading to IA and non-IA controls.
**Supplemental Table I:** Sample size and patient demographics by subgroup. Age is presented as mean ± Standard Deviation.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Gender (female %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysm (n = 33)</td>
<td>56.2 ± 10.9</td>
<td>68.4</td>
</tr>
<tr>
<td>Contralateral (n = 25)</td>
<td>56.7 ± 11.9</td>
<td>72.0</td>
</tr>
<tr>
<td>Controls (n = 18)</td>
<td>51.3 ± 15.9</td>
<td>60.6</td>
</tr>
</tbody>
</table>
**Supplemental Figure I:** Cervical carotid digital subtracted angiography (DSA) in three patients harboring intracranial aneurysms. White arrows indicate the proximal and distal extents of the observed high cervical dilations not seen in control patients.
Supplemental Figure II: Graph showing the average of 15 consecutive measurements of the internal carotid artery distal-to-proximal ratio ($R_{dp}$) in 7 ICA leading to intracranial aneurysms (red line) and 7 control non-aneurysm harboring controls (black line). Equidistant measurements progress from the end of the carotid bulb to the location of the petrolingual ligament.