Patterns and Implications of Intracranial Arterial Remodeling in Stroke Patients

Ye Qiao, PhD; Zeeshan Anwar, MD; Jarunee Intrapiromkul, MD; Li Liu, MS; Steven R. Zeiler, MD, PhD; Richard Leigh, MD; Yiyi Zhang, PhD; Eliseo Guallar, MD; Bruce A. Wasserman, MD

Background and Purpose—Preliminary studies suggest that intracranial arteries are capable of accommodating plaque formation by remodeling. We sought to study the ability and extent of intracranial arteries to remodel using 3-dimensional high-resolution black blood magnetic resonance imaging and investigate its relation to ischemic events.

Methods—Forty-two patients with cerebrovascular ischemic events underwent 3-dimensional time-of-flight magnetic resonance angiography and contrast-enhanced black blood magnetic resonance imaging examinations at 3 T for intracranial atherosclerotic disease. Each plaque was classified by location (eg, posterior versus anterior circulation) and its likelihood to have caused a stroke identified on magnetic resonance imaging (culprit, indeterminate, or nonculprit). Lumen area, outer wall area, and wall area were measured at the lesion and reference sites. Plaque burden was calculated as wall area divided by outer wall area. The arterial remodeling ratio (RR) was calculated as outer wall area at the lesion site divided by outer wall area at the reference site after adjusting for vessel tapering. Arterial remodeling was categorized as positive if RR>1.05, intermediate if 0.95≤RR≤1.05, and negative if RR<0.95.

Results—One hundred and thirty-seven plaques were identified in 42 patients (37% [50] posterior and 63% [87] anterior). Compared with anterior circulation plaques, posterior circulation plaques had a larger plaque burden (77.7±15.7 versus 69.0±14.0; P=0.008), higher RR (1.14±0.38 versus 0.95±0.32; P=0.002), and more often exhibited positive remodeling (54.0% versus 29.9%; P=0.011). Positive remodeling was marginally associated with downstream stroke presence when adjusted for plaque burden (odds ratio 1.34, 95% confidence interval: 0.99–1.81).

Conclusions—Intracranial arteries remodel in response to plaque formation, and posterior circulation arteries have a greater capacity for positive remodeling and, consequently, may more likely elude angiographic detection. Arterial remodeling may provide insight into stroke risk. (Stroke. 2016;47:434-440. DOI: 10.1161/STROKEAHA.115.009955.)

Key Words: atherosclerosis ◼ intracranial arteriosclerosis ◼ MRI ◼ stroke ◼ vascular remodeling

Intracranial atherosclerotic disease (ICAD) is a major cause of ischemic stroke worldwide.1 Traditional ICAD diagnosis has depended on stenosis measured by angiography; however, lumen narrowing is a poor indicator of plaque burden when vessels accommodate plaque formation by compensatory remodeling.2,3 Remodeling can vary in degree and direction depending on the vessel involved (Figure I in the online-only Data Supplement). Outward remodeling of the coronary artery can preserve the lumen at plaque burdens as high as 40% of the vessel area,2 whereas internal carotid artery (ICA) remodeling has been shown to preserve the lumen at even higher plaque burdens approximating 62%.3,4 Remodeling can also be inward with a constricting vessel area during plaque formation and hastening stenosis.5,6 Understanding a vessel’s pattern of remodeling might provide insight into our ability to detect plaque by angiography and better characterize its risk. For example, although outward remodeling limits the hemodynamic impact, coronary plaques with outward remodeling may be associated with increased plaque vulnerability,5 clinical symptoms,7 and poor clinical outcome after coronary intervention.8 The remodeling patterns of the intracranial arteries, however, have not been studied systematically.

High-resolution black blood magnetic resonance imaging (BBMRI) has been used to characterize arterial remodeling in extracranial vessels.1 Recently, this technique has been optimized as a 3-dimensional (3D) sequence for imaging the walls of intracranial arteries,9 enabling reliable measurements of thickness and burden of ICAD.9,10 We sought to determine the ability and extent of intracranial arteries to accommodate...
plaque formation by remodeling using 3D BBMRI and investigates its relation to ischemic events.

**Materials and Methods**

The institutional review board approved this study and provided an exemption to allow the inclusion of de-identified data for patients from whom we did not receive written consent.

**Study Population**

Patients referred to Neurovascular Imaging Center for high-resolution BBMRI and magnetic resonance angiography (MRA) to evaluate known ICAD were prospectively enrolled if (1) there was evidence of ICAD causing stenosis ≥50% in a large intracranial artery based on a preceding computed tomography angiography, MRA, or catheter angiogram and (2) there was a transient ischemic attack or stroke in the distribution of a narrowed vessel. Exclusion criteria included (1) fewer than 2 cardiovascular risk factors, (2) nonatherosclerotic intracranial vascular pathology (eg, vasculitis, Moyamoya disease, dissection, reversible cerebral vasospasm syndrome), (3) presence of potential sources of cardioembolism, or (4) >50% stenosis of the extracranial cervical artery proximal to the symptomatic intracranial vessel. Patients were categorized as acute if they were scanned within 4 weeks of the presenting symptoms, subacute if scanned between 4 and 12 weeks, and chronic if scanned beyond 12 weeks.

**Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) scans were performed on a 3 T MRI Achieva scanner (Philips Healthcare, The Netherlands) using an 8-channel head coil. High-resolution intracranial vessel wall imaging was acquired based on a standardized protocol that included pre- and post-contrast BBMRI and 3D time-offlight (TOF) MRA sequences. The 3D TOF MRA was acquired in a transverse plane with the following parameters: repetition time/echo time/dip angle, 23 ms/3.5 ms/25°; field of view, 160 mm×160 mm; acquired resolution, 0.55×0.55×1.1 mm²; reconstructed resolution, 0.55×0.55×0.55 mm³; and scan time of 6 minutes. The high-resolution 3D BBMRI technique has been previously described. Briefly, we used a modified volumetric isotropic turbo-spin-echo acquisition (VISTA) in a coronal plane (40-mm-thick slab) with the following parameters: repetition time/echo time, 2000 ms/38 ms; turbo-spin-echo factor, 56 echoes; echo spacing, 6.1 ms; sense factor, 2; number of averages, 1. The acquired resolution was 0.4×0.4×0.4 mm³ (field of view, 180×180×40 mm³; matrix, 450×450×100) or 0.45×0.45×0.45 mm³ (field of view, 180×180×40 mm³; matrix, 400×400×100), with scan times of 7.2 or 5.5 minutes, respectively. Gadolinium (gadopentetate dimeglumine, Magnevist, Schering) was administered intravenously (0.1 mmol/kg), and the BBMRI images were repeated 5 minutes after contrast administration.

**Image Analysis**

All BBMRI images were analyzed using Vesselmass software (Leiden University Medical Center, The Netherlands) according to previously described methods. An atherosclerotic plaque on MRI was defined as an eccentric wall thickening identified on both pre- and post-contrast BBMRI images with or without luminal stenosis. Postcontrast images were used for wall measurements because gadolinium-contrast administration improves the delineation of the outer wall. MRI measurements were obtained for all plaques detected in the proximal segments of the intracranial arteries, regardless of the degree of stenosis (ie, not only for the plaque that qualified the patient for inclusion), including the M1 and M2 segments of the middle cerebral artery, the A1 and A2 segments of the anterior cerebral artery, the cavernous (C3) and supraclinoid (C4) segments of the ICA, the P1 and P2 segments of the posterior cerebral artery, the basilar artery (BA), and the V4 segments of the vertebral arteries.

**Wall Area and Thickness Measurements**

MRI analyses were performed by 3 independent readers using Vesselmass software. For each plaque, the entire vessel segment containing the plaque was analyzed (ie, beyond the margins of the plaque). 3D BBMRI images were first reconstructed orthogonal to the vessel axis at 2.0 mm thick slices throughout each vessel segment with plaque. For each segment, the cross section with the thickest plaque was selected as the lesion site. The cross section that contained the thinnest wall was chosen as the reference site. Lumen and outer wall contours were traced at the lesion and reference sites as previously described. Quantitative MRI measurements were generated at each site using Vesselmass software, and these included lumen area (LA), outer wall area (OWA), wall area (OWA–LA), plaque burden ([(wall area/OWA)×100%]), mean wall thickness, and maximum wall thickness (Figure I in the online-only Data Supplement).

**Arterial Remodeling and Luminal Stenosis Measurements**

The arterial remodeling ratio (RR) compares the OWA at the lesion site (OWAlesion) to that at the reference site (OWAreference), so OWAlesion must be corrected for the tapering that is expected based on its distance from the lesion (D). The tapering of the LA was used to represent tapering of the OWA based on the assumption that circumferential wall thickness is uniform over the length of a normal arterial segment. To accomplish this, the TOF-MRA was analyzed using LAVA software (LAVA, Leiden University Medical Center, the Netherlands), which uses a deformable tubular model based on Non-Uniform Rational B-Splines surface modeling to contour each vessel segment (Figure II in the online-only Data Supplement). This technique provides semi-automated contour detection of the arterial lumen and performs an iterative linear regression fit of the LA over the entire segment. Vessel tapering, represented as the slope (S) of the regression line, was calculated as S=ΔA area/(mm²)/D distance (mm). RR could then be calculated as RR=OWAlesion/(OWAreference+4SxD) (Figure 1). Three remodeling categories were defined as previously described: positive (outward expansion of the wall) if RR>1.05; intermediate if 0.95≤RR≤1.05; and negative (vessel wall shrinkage) if RR<0.95. Percent luminal area stenosis ( % stenosis LA) was calculated as % stenosis LA=1−[LAlesion−4SxD]/LA reference×100. Diameter-based luminal stenosis (% stenosis LA) was also measured according to the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) study criteria based on the TOF MRA.

**Plaque Classification**

Each plaque was classified as nonculprit, indeterminate, or culprit according to its likelihood to have caused a stroke identified on MRI using previously described criteria. A plaque was considered culprit if it was the only lesion within the vascular territory of the stroke or the most stenotic lesion when multiple plaques were present within the same vascular territory of the stroke. A plaque was considered indeterminate if it was not the most stenotic lesion within the same vascular territory of the stroke. A lesion was considered nonculprit if it was not within the vascular territory of the stroke. For transient ischemic attack cases, plaque classification was adjudicated if symptoms could be localized to an arterial territory. Plaque calcification was identified as hypointense on TOF and pre- and post-contrast BBMRI images and confirmed with brain computed tomographic scans when available.

**Statistical Analysis**

Data were analyzed using Stata 12.1 (Stata Inc, College Station, TX). Comparison of continuous variables was performed by a 2-sample Student’s t tests for normally distributed data. The chi-square test was used to compare the frequency of occurrences. Multilevel mixed-effects linear regression models were used to compare the differences in MRI measurements (eg, area, thickness, vessel tapering, plaque burden, RR, calcification) between anterior and posterior circulations by including random intercept terms to account for measurements of multiple arterial segments within.
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patients. The association (odds ratio) of positive remodeling with lesions categorized as culprit was estimated using mixed-effects logistic regression. For participants with coexistent anterior and posterior circulation plaques, average RR was compared between circulations by a 2-tailed paired t-test. Inter-reader agreement for plaque measurements was estimated using intraclass correlation coefficient based on repeat readings of all detected lesions from 3 readers. Reliability estimates below 0.4 were characterized as poor, 0.4 to 0.75 as fair to good, and above 0.75 as excellent.

Results

Patients

A total of 45 consecutive patients were studied. Three exams were excluded because of motion. Of the remaining 42 patients (29 male; 28 white, 12 black, 1 Asian, and 1 Hispanic; mean±SD age, 56.3±12.1 years), 37 had ischemic strokes (23 acute, 7 subacute, and 7 chronic), and 5 had transient ischemic attacks. The clinical characteristics of the study population are shown in Table 1. Thirty-one exams were acquired at 0.4 mm³, and 11 were acquired at 0.45 mm³ isotropic resolution.

A total of 137 plaques were identified in the 42 patients. Eighty-seven plaques were detected in the anterior circulation (anterior cerebral artery, 11; ICA, 48; and middle cerebral artery, 28) and 50 in the posterior circulation (BA, 20; posterior cerebral artery, 9; and VA, 21). Thirty patients had multiple plaques (mean, 3.3; range, 1 to 14; Table 1), and 24 patients had plaques coexisting in the anterior and posterior circulations. Among the 137 plaques, 26 were culprit, 77 were nonculprit, and 34 were indeterminate. There was no difference between culprit plaque frequencies in the anterior and posterior circulations (P=0.34).

Intracranial Arterial Tapering, Remodeling, and Calcification

The average vessel tapering and RRs for each arterial segment are shown in Table 1 in the online-only Data Supplement. Among the 137 plaques studied, 56 exhibited positive remodeling, 53 negative remodeling, and 28 intermediate remodeling. Plaques exhibiting negative and positive remodeling are shown in Figures 2 and 3, respectively. The VA, BA, and posterior cerebral artery demonstrated positive remodeling most frequently (53%, 55%, and 56%, respectively; Figure 4). Positive remodeling was associated with culprit plaque classification (versus nonculprit and indeterminate; odds ratio [OR] 1.70, 95% confidence interval [CI]: 1.0–2.8) and was marginally associated (OR 1.34, 95% CI: 0.99–1.81) when adjusted for plaque burden. The association was reassessed after excluding indeterminate plaques (n=34). Positive remodeling remained associated with culprit plaque classification (culprit versus nonculprit; OR 1.49, 95% CI: 1.02–2.15) and a trended toward culprit classification when adjusted for plaque burden (OR 1.35, 95% CI: 0.42–2.01).

Table 1. Patient and Plaque Characteristics

<table>
<thead>
<tr>
<th>Patient characteristics, N (%)*</th>
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<tbody>
<tr>
<td>Male</td>
<td>29 (69.1)</td>
</tr>
<tr>
<td>Active smoker</td>
<td>8 (19.1)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (26.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (69.1)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>23 (54.8)</td>
</tr>
<tr>
<td>Stroke</td>
<td>37 (88.1)</td>
</tr>
<tr>
<td>Acute</td>
<td>23 (54.8)</td>
</tr>
<tr>
<td>Subacute</td>
<td>7 (16.7)</td>
</tr>
<tr>
<td>Chronic</td>
<td>7 (16.7)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>5 (11.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plaque characteristics, N (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of plaques per patient</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>≥5</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Vessel segment, Number of plaques per segment (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cerebral artery</td>
</tr>
<tr>
<td>Internal carotid artery</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
</tr>
<tr>
<td>Basilar artery</td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
</tr>
<tr>
<td>Vertebral artery</td>
</tr>
</tbody>
</table>

N indicates number of patients.
*Percentages based on 42 patients.
†Percentages based on 137 plaques.
When the RR differences between the anterior and posterior circulations were restricted to participants who had co-existing anterior and posterior plaques (n=22), the results were similar to those observed in the overall sample (posterior versus anterior: 1.15±0.41 versus 0.98±0.28; \( P=0.01 \)).

**Compensatory Arterial Enlargement and Plaque Accumulation**

A linear regression fit between plaque burden and diameter-based stenosis using WASID criteria revealed that the lumen begins to narrow (ie, remodeling can no longer preserve the lumen) when plaque burden reached 55.3% (95% CI: 51.6, 60.0; Figure IIIA in the online-only Data Supplement). Compared with anterior circulation lesions, posterior circulation plaques accommodated a higher plaque burden before stenosis occurred (posterior versus anterior: 57.6% [95% CI: 52.6, 62.6] versus 58.9% [95% CI: 55.0, 60.0]; Figure IIIB in the online-only Data Supplement).

**MRI Measurement Reproducibility**

Inter-reader reliability (intraclass correlation coefficient) estimates for the LA, OWA, mean wall thickness, and maximum wall thickness measurements were 0.95, 0.98, 0.89, and 0.91, respectively.

**Discussion**

We observed that intracranial arteries remodel in response to plaque formation, that posterior circulation arteries have a greater capacity for positive remodeling than arteries in the anterior circulation, and that stenosis occurs when the plaque burden reaches \( \approx 55.3\% \). Our 3D volumetric, high-resolution MRI technique allowed us to extend prior reports describing the occurrence of intracranial arterial remodeling by determining the threshold for luminal narrowing and identifying regional differences in the extent of remodeling.

Until now, characterization of intracranial arterial remodeling has relied on in vivo MRI using 2D imaging. These 2D techniques are limited to an inherently lower, nonisotropic resolution that leads to overestimation of thickness measurements of intracranial arteries because these vessels are typically small relative to an optimized 2D voxel size. This overestimation is exacerbated by the difficulty of positioning contiguous 2D slices orthogonal to these inherently curving arteries. Our high isotropic resolution 3D technique minimized errors caused by partial volume averaging, enabling us to determine the threshold for intracranial arterial remodeling. We could also quantify wall thickness and LA over an entire vessel segment and, with our 3D postprocessing software, characterize vessel tapering to correct for OWA reference, an important step in the calculation of the intracranial arterial RR. Finally, 3D acquisition achieved a broad coverage enabling a comprehensive survey of the intracranial circulation for ICAD lesions, facilitating a comparison of co-existing anterior and posterior circulation plaques (ie, occurring within the same patient). It also enabled the study of low-grade ICAD lesions along with the high-grade plaques that led to inclusion into this study.
As demonstrated previously, arterial remodeling varies in degree for different extracranial vessels. Astor et al examined 3348 common carotid arteries and 1064 ICAs and found that common carotid arteries compensated for a greater degree of wall thickening than ICAs. The threshold for stenosis detected in ICAs occurred when plaque burden reached \( \approx 62\% \), which was similar to what we observed in intracranial arteries.

This is the first report documenting that the posterior circulation seems more capable of positive remodeling compared with the anterior circulation. The exact mechanism is not clear, though we suspect blood flow, sympathetic vascular innervation, and genetic factors may affect the remodeling response. There are regional differences in cerebral blood flow, with markedly lower flow in the posterior circulation (ie, BA) compared with the anterior circulation (ie, ICAs). This may impose different hemodynamic forces (eg, endothelial shear stress) on the vessel wall and mediate arterial remodeling. The relatively sparse sympathetic innervation of the posterior circulation, specifically the VA and BA, compared with the anterior circulation might be another reason for the greater capacity for positive remodeling in the posterior circulation because cerebral autoregulation depends on sympathetic innervation, and impaired autoregulation could lead

Figure 3. Positive remodeling of an intracranial plaque in a 62-year-old man. A, Time-of-flight (TOF) magnetic resonance angiography maximum intensity projection shows a patent basilar artery without significant luminal narrowing. B, Long-axis image reconstructed from the 3D contrast-enhanced black blood magnetic resonance imaging (BBMRI) scan (0.4 mm isotropic resolution) reveals a large plaque along the right wall of the proximal and midsegments of the basilar artery (arrows). Short-axis 2-mm-thick images are reconstructed from the 3D BBMRI volume acquisition orthogonal to the basilar artery using semi-automated software (VesselMass; Leiden University, The Netherlands). C, These images are used for the analysis of the reference site (left-most image) and lesion (4 contiguous images on the right). D, Contours were drawn to delineate the outer wall (green) and lumen (red) of the reference site selected as the slice showing the thinnest wall (left) and the lesion selected as the slice showing the thickest plaque (middle). A 3D view of the vessel segment is generated by integrating contours over contiguous slices (D, right), and lesion and reference positions are indicated.

Figure 4. Frequency of positive, intermediate, and negative remodeling for each vessel segment. ACA indicates anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; and PCA, posterior cerebral artery.
Atherosclerotic lesions could provide more insight into the natural history of ICA remodeling. Finally, our BBMRI images of ICAD lesions lack histologic validation, although there is no reason to suspect that image interpretation would differ from carotid artery techniques.14

In conclusion, we have described significant regional differences in arterial remodeling of intracranial arteries. Compared with anterior circulation arteries, posterior circulation arteries have a greater capacity to remodel in response to plaque formation. This has important clinical implications for relying on angiography for ICAD lesion detection and highlights the importance of 3D BBMRI for this purpose.

Sources of Funding
This study was supported by National Institutes of Health (NIH) RO1HL105930, K99HL106232, and R00HL106232.

Disclosures
Drs Qiao and Wasserman have a patent pending (no 13/922,111) for the 3D black blood MR imaging technique used. The other authors report no conflicts.

References

Table 2. Comparison Between Anterior and Posterior Circulation MRI Measurements

<table>
<thead>
<tr>
<th>Lesion Site</th>
<th>Anterior Circulation (63 Plaques)</th>
<th>Posterior Circulation (50 Plaques)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis (diameter, WASID)</td>
<td>35.2±25.4</td>
<td>41.9±27.0</td>
<td></td>
</tr>
<tr>
<td>Arterial remodeling ratio (RR)</td>
<td>0.95±0.32</td>
<td>1.15±0.38</td>
<td>0.002</td>
</tr>
<tr>
<td>Lesion site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen area, mm²</td>
<td>0.07±0.10</td>
<td>0.05±0.05</td>
<td>0.20</td>
</tr>
<tr>
<td>Outer wall area, mm²</td>
<td>0.18±0.09</td>
<td>0.21±0.12</td>
<td>0.41</td>
</tr>
<tr>
<td>Plaque burden, %†</td>
<td>69.0±14.0</td>
<td>77.7±15.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum wall thickness, mm</td>
<td>1.79±0.68</td>
<td>1.97±0.81</td>
<td>0.45</td>
</tr>
<tr>
<td>Mean wall thickness, mm</td>
<td>1.15±0.53</td>
<td>1.31±0.59</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Reference site

| Lumen area, mm²                                 | 0.10±0.10                         | 0.08±0.05                         | 0.15     |
| Outer wall area, mm²                            | 0.17±0.09                         | 0.18±0.08                         | 0.26     |

All values are mean±SD. MRI indicates magnetic resonance imaging; RR, remodeling ratio; and WASID, the Warfarin–Aspirin Symptomatic Intracranial Atherosclerosis Disease study.

*Lesion-level analysis was adjusted for patient effects using a random effects model.

†P<0.05

...to a passive over-distention of the vessel. In addition, some genetic factors that affect atherogenicity appear to be site-specific and are associated with variable plaque development in different arterial beds. In contrast, recent studies indicate that the vertebrobasilar and the coronary systems may share similar genetic factors, leading to similar patterns of arterial dilation and remodeling. Of note, intracranial arterial dolichoectasia also has a predilection for the posterior circulation, suggesting that it could share a common pathogenesis with positive remodeling. However, ICAD is infrequently found in ectatic intracranial arteries in symptomatic patients, so the mechanism for strokes in these patients likely differs from that in patients with atherosclerotic lesions with positive remodeling.

The association we observed between positive remodeling and culprit lesion classification supports reports of positive remodeling related to acute coronary events and stroke. Larger studies are warranted to validate these preliminary observations for the intracranial circulation.

Limitations of our study included the nature of our patient population, specifically that all patients enrolled in this study were symptomatic (ie, inclusion based on having had a cerebrovascular ischemic event). Therefore, we were unable to compare plaques between symptomatic and asymptomatic patients, and future studies that include asymptomatic patients are needed to validate our observations. Furthermore, culprit lesions were identified based on stenosis, limiting our ability to relate positive remodeling, which preserves LA, with stroke. Second, although we studied low-, intermediate-, and high-grade plaques, our inclusion criteria required the presence of at least one high-grade (≥50% stenosis), culprit ICAD lesion, so our estimated threshold of remodeling might not be applicable to the general population. A population-based study that includes solitary early and intermediate stages of atherosclerosis could provide more insight into the natural history of ICA remodeling.


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Supplemental Table I: Average Vessel Tapering and Remodeling Ratios for Each Arterial Segment

<table>
<thead>
<tr>
<th></th>
<th>ACA (n=11)</th>
<th>ICA (n=48)</th>
<th>MCA (n=28)</th>
<th>BA (n=20)</th>
<th>PCA (n=9)</th>
<th>VA (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel Tapering (%)</td>
<td>18.5±4.03</td>
<td>17.7±3.71</td>
<td>7.79±2.60</td>
<td>5.91±2.22</td>
<td>11.7±3.31</td>
<td>7.71±1.60</td>
</tr>
<tr>
<td>Remodeling Ratio</td>
<td>0.87±0.41</td>
<td>0.93±0.31</td>
<td>1.00±0.32</td>
<td>1.12±0.26</td>
<td>1.02±0.42</td>
<td>1.22±0.45</td>
</tr>
</tbody>
</table>

ACA (A1 and A2 segments), ICA (C3 and C4 segments), MCA (M1 and M2 segments), PCA (P1 and P2 segments), VA, V4 segment, all values are represented as mean ± SD.
Figure I: Categories of remodeling. Positive (outward) remodeling is characterized by expansion of the outer wall delineated by the green circle with relative preservation of the lumen. Constriction of the outer wall during plaque development with a reduction in lumen size constitutes negative (inward) remodeling. Variables of interest include lumen area (LA, area shown in black), outer wall area (OWA, area circumscribed by the green outer wall), and wall area (WA, area shaded in grey).
Figure II: Calculation of Vessel Tapering based on the TOF-MRA. A centered pathline is automatically detected between manually-placed proximal (red circle) and distal (blue circle) points by a front propagation method using LAVA software (LAVA, Leiden University Medical Center, the Netherlands) (A). A three-dimensional lumen surface is rendered using a deformable tubular model (B). The tapering of the lumen area is calculated using an iterative linear regression fit, represented as the slope $(S) = \Delta \text{area (mm}^2)/\Delta \text{distance (mm)}$. 

Slope (S): 0.26mm$^2$/mm
Figure III: Linear regression for plaque burden as a function of stenosis measurements. A stenosis of 0% corresponded to a plaque burden of 55.3% (95% CI: 51.6, 60.0) for all ICAD lesions (A). The Pearson correlation coefficient was 0.47. A stenosis of 0% corresponded to plaque burdens of 57.6% (95% CI: 52.6, 62.6) and 58.9% (95% CI: 55.0, 60.0) for the posterior and anterior circulations, respectively (B). The Pearson correlation coefficients were 0.80 and 0.58, respectively.