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Patterns and Implications of Intracranial Arterial Remodeling in Stroke Patients

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Abstract

Background and Purpose—Preliminary studies suggest intracranial arteries are capable of accommodating plaque formation by remodeling. We sought to study the ability and extent of intracranial arteries to remodel using 3D high-resolution black blood MRI (BBMRI) and investigate its relation to ischemic events.

Methods—42 patients with cerebrovascular ischemic events underwent 3D time-of-flight MRA and contrast-enhanced BBMRI examinations at 3T for intracranial atherosclerotic disease. Each plaque was classified by location (e.g., posterior vs. anterior circulation) and its likelihood to have caused a stroke identified on MRI (culprit, indeterminate, or non-culprit). Lumen area (LA), outer wall area (OWA), and wall area (WA) were measured at the lesion and reference sites. Plaque burden was calculated as WA divided by OWA. The arterial remodeling ratio (RR) was calculated as OWA at the lesion site divided by OWA at the reference site, after adjusting for vessel tapering. Arterial remodeling was categorized as positive if $RR > 1.05$, intermediate if $0.95 \leq RR \leq 1.05$, and negative if $RR < 0.95$.

Results—137 plaques were identified in 42 patients (37% [50] posterior, 63% [87] anterior). Compared with anterior circulation plaques, posterior circulation plaques had a larger plaque burden (77.7 ± 15.7 vs. 69.0 ± 14.0 , $p=0.008$), higher RR (1.14 ± 0.38 vs. 0.95 ± 0.32 , $p=0.002$), and more often exhibited positive remodeling (54.0% vs. 29.9%, $p=0.011$). Positive remodeling was marginally associated with downstream stroke presence when adjusted for plaque burden (OR 1.34, 95% CI: 0.99–1.81).

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Disclosures

Drs. Qiao and Wasserman have a patent pending (no. 13/922,111) for the MR imaging technique used in this study.

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.

Keywords

intracranial stenosis; atherosclerosis; MRI; remodeling

Intracranial atherosclerotic disease (ICAD) is a major cause of ischemic stroke worldwide¹. 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 (Supplemental figure I). Outward remodeling of the coronary artery can preserve the lumen at plaque burdens as high as 40% of the vessel area² 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 vulnerability⁵, clinical symptoms⁷, and poor clinical outcome after coronary intervention⁸. The remodeling patterns of the intracranial arteries, however, have not been studied systematically.

High-resolution black blood MRI (BBMRI) has been used to characterize arterial remodeling in extracranial vessels³. Recently this technique has been optimized as a 3D sequence for imaging the walls of intracranial arteries⁹, 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 high-resolution black blood MRI (BBMRI) and investigate 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 MRA to evaluate known ICAD were prospectively enrolled if (i) there was evidence of ICAD causing stenosis $\geq 50\%$ in a large intracranial artery based on a preceding CTA, MRA, and/or catheter angiogram and (ii) there was a TIA or stroke in the distribution of a narrowed vessel. Exclusion criteria included (i) fewer than two cardiovascular risk factors, (ii) non-atherosclerotic intracranial vascular pathology (e.g., vasculitis, Moya-Moya disease, dissection, reversible cerebral vasoconstriction syndrome), (iii) presence of potential sources of cardioembolism, or (iv) $> 50\%$ stenosis of the extracranial cervical artery proximal to the symptomatic intracranial vessel¹¹. Patients were categorized as acute if they were scanned

within four weeks of the presenting symptoms, subacute if scanned between four and 12 weeks, and chronic if scanned beyond 12 weeks.

MR Imaging

MRI scans were performed on a 3T MRI Achieva scanner (Philips Healthcare, The Netherlands) using an eight-channel head coil. High-resolution intracranial vessel wall imaging was acquired based on a standardized protocol⁹ that included pre- and post-contrast 3D BBMRI and 3D time-of-flight (TOF) MRA sequences. The 3D TOF MRA was acquired in a transverse plane with the following parameters: TR/TE/flip angle, 23 ms/3.5 ms/25°; FOV, 160 mm × 160 mm; acquired resolution, 0.55×0.55×1.1 mm³; reconstructed resolution, 0.55×0.55×0.55 mm³; and scan time of approximately six minutes. The high-resolution 3D BBMRI technique has been previously described¹². Briefly, we used a modified volumetric isotropic TSE acquisition (VISTA) in a coronal plane (40-mm-thick slab) with the following parameters: TR/TE, 2000 ms/38 ms; TSE 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 (FOV, 180×180×40 mm³; matrix, 450×450×100) or 0.45×0.45×0.45 mm³ (FOV, 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 five minutes after contrast administration.

Image Analysis

All BBMRI images were analyzed using Vesselmass software (Leiden University Medical Center, the Netherlands) according to previously described methods⁹. 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 wall¹³. MRI measurements were obtained for all plaques detected in the proximal segments of the intracranial arteries, regardless of the degree of stenosis (i.e., not only for the plaque that qualified the patient for inclusion), including the M1 and M2 segments of the middle cerebral artery (MCA), the A1 and A2 segments of the anterior cerebral artery (ACA), the cavernous (C3) and supraclinoid (C4) segments of the ICA, the P1 and P2 segments of the posterior cerebral artery (PCA), the basilar artery (BA), and the V4 segments of the vertebral arteries.

Wall Area and Thickness Measurements—MRI analyses were performed by three independent readers using Vesselmass software. For each plaque, the entire vessel segment containing the plaque was analyzed (i.e., 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 site¹⁴. Lumen and outer wall contours were traced at the lesion and reference sites as previously described⁹. Quantitative MRI measurements were generated at each site using Vesselmass software and these included lumen area (LA), outer

wall area (OWA), wall area (WA: OWA-LA), plaque burden ((WA/OWA) *100%), mean wall thickness (MWT), and maximum wall thickness (MaxWT) (Supplemental Figure I).

Arterial Remodeling and Luminal Stenosis Measurements—The arterial remodeling ratio (RR) compares the OWA at the lesion site (OWA_{lesion}) to that at the reference site ($OWA_{\text{reference}}$), so $OWA_{\text{reference}}$ must be corrected for the tapering that is expected based on its distance from the lesion (D)¹⁵. 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 (NURBS) surface modeling to contour each vessel segment (Supplemental Figure II). This technique provides semi-automated contour detection of the arterial lumen¹⁶ and performs an iterative linear regression fit of the lumen area over the entire segment. Vessel tapering, represented as the slope (S) of the regression line, was calculated as $S = \text{area (mm}^2\text{)} / \text{distance (mm)}$. RR could then be calculated as $RR = OWA_{\text{lesion}} / (OWA_{\text{reference}} + S * D)$ ¹⁵ (Figure 1). Three remodeling categories were defined as previously described¹⁵: 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_{area}) was calculated as $\% \text{ stenosis}_{\text{area}} = (1 - (LA_{\text{lesion}} - S * D)) / LA_{\text{reference}} * 100$. Diameter-based luminal stenosis (% stenosis_{diameter}) was also measured according to WASID criteria based on the TOF MRA¹¹.

Plaque Classification—Each plaque was classified as non-culprit, indeterminate, or culprit according to its likelihood to have caused a stroke identified on MRI using previously described criteria¹⁰. 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 non-culprit if it was not within the vascular territory of the stroke. For TIA 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 images¹⁷ and confirmed with brain CT 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 two-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 (e.g., 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 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 two-tailed paired t-test. Inter-

reader agreement for plaque measurements was estimated using intraclass correlation coefficient (ICC) 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 Caucasian, 12 African-American, 1 Asian, and 1 Hispanic; mean $\pm$ SD age, 56.3 ± 12.1 years), 37 had ischemic strokes (23 acute, 7 subacute, 7 chronic) and 5 had TIAs. The clinical characteristics of the study population are shown in Table 1. Thirty-one exams were acquired at 0.4 mm^3 and 11 were acquired at 0.45 mm^3 isotropic resolution.

A total of 137 plaques were identified in the 42 patients. Eighty-seven plaques were detected in the anterior circulation (ACA, 11; ICA, 48; and MCA, 28), and 50 in the posterior circulation (BA, 20; PCA, 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 non-culprit, 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 remodeling ratios for each arterial segment are shown in Supplemental Table I. 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 PCA, demonstrated positive remodeling most frequently (53%, 55% and 56%, respectively) (Figure 4). Positive remodeling was associated with culprit plaque classification (versus non-culprit and indeterminate, OR 1.70, 95% 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 non-culprit, OR 1.49, 95% CI: 1.02–2.15), and a trended towards culprit classification when adjusted for plaque burden (OR 1.35, 95% CI: 0.42–2.01).

When the analysis was performed only for patients with acute stroke (23 patients, 90 plaques), positive remodeling again was associated with culprit plaque classification (culprit versus non-culprit, OR 1.64, 95% CI: 1.06–2.54). When adjusted for plaque burden, a marginal association was seen (OR 1.43, 95% CI: 0.90–2.27).

Calcification was identified in 42 of 135 (31%) plaques (30 anterior circulation, 12 posterior circulation) after excluding two plaques exhibiting artifacts on TOF MRA. There was no difference in the frequency of calcified plaques between anterior and posterior circulations

(35% vs. 24%, respectively, $p=0.17$). Calcification was not associated with positive remodeling.

Comparisons between Anterior and Posterior Circulation Plaques

There were no significant differences in the degree of diameter stenosis, lumen area, outer wall area, or mean and maximum wall thickness values between anterior and posterior circulation plaques (Table 2). However, compared to anterior circulation lesions, posterior circulation plaques had a larger plaque burden (posterior vs anterior: 77.7 ± 15.7 vs. 69.0 ± 14.0 , $p=0.008$) and a higher RR (posterior vs anterior: 1.15 ± 0.38 vs. 0.95 ± 0.32 , $p=0.013$) (Table 1), and more often exhibited positive remodeling (posterior vs. anterior: 58.0% vs. 31.0%, $p=0.007$).

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 vs anterior: 1.15 ± 0.41 vs. 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 (i.e., remodeling can no longer preserve the lumen) when plaque burden reached 55.3% (95% CI: 51.6, 60.0) (Supplemental Figure IIIA). Compared to anterior circulation lesions, posterior circulation plaques accommodated a higher plaque burden before stenosis occurred (posterior vs anterior: 57.6% [95% CI: 52.6, 62.6] vs. 58.9% [95% CI: 55.0, 60.0]) (Supplemental Figure IIIB).

MRI Measurement Reproducibility

Inter-reader reliability (ICC) estimates for the LA, OWA, MWT, and maxWT 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 approximately 55.3%. Our 3D volumetric, high-resolution MRI technique allowed us to extend prior reports describing the occurrence of intracranial arterial remodeling^{18–21} 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^{18–21}. These 2D techniques are limited to an inherently lower, nonisotropic resolution that leads to overestimation of thickness measurements of intracranial arteries since these vessels are typically small relative to an optimized 2D voxel size²². This overestimation is exacerbated by the difficulty of positioning contiguous 2D slices orthogonal to these inherently curving arteries¹⁸. 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 lumen area over an entire vessel segment, and with our 3D postprocessing software, characterize vessel tapering in order 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 (i.e. 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^{3, 15}. Astor et al³ examined 3,348 common carotid arteries and 1,064 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 approximately 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 to 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 (i.e., BA) compared to the anterior circulation (i.e., ICAs)²³. This may impose different hemodynamic forces (e.g., endothelial shear stress) on the vessel wall and mediate arterial remodeling²⁴. The relatively sparse sympathetic innervation of the posterior circulation, specifically the VA and BA, compared to the anterior circulation^{25, 26} might be another reason for the greater capacity for positive remodeling in the posterior circulation since cerebral autoregulation depends on sympathetic innervation, and impaired autoregulation could lead to a passive over-distention of the vessel²⁷. In addition, some genetic factors that affect atherogenicity appear to be site-specific and are associated with variable plaque development in different arterial beds²⁸. 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 remodeling²⁹. Of note, intracranial arterial dolichoectasia also has a predilection for the posterior circulation³⁰ suggesting it could share a common etiology with positive remodeling. However, ICAD is infrequently found in ectatic intracranial arteries in symptomatic patients^{31, 32} 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^{5, 7, 33}. 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 (i.e., 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 lumen area, 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. 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 techniques³⁴.

In conclusion, we have described significant regional differences in arterial remodeling of intracranial arteries. Compared to 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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$$RR = OWA_{lesion} / Expected_OWA_{lesion}$$

$$Expected_OWA_{lesion} = OWA_{reference} + S \cdot D$$

S: slope of vessel tapering (area)
D: distance between lesion and reference

Figure 1.

Calculation of Remodeling Ratio (RR). Outer wall area is measured at a reference point free of plaque within the vessel segment ($OWA_{reference}$). The slope of the lumen tapering (S) and the distance between the lesion and reference site (D) are then used to estimate the expected outer wall area at the lesion site ($Expected_OWA_{lesion}$). This is then divided into the true outer wall area at the lesion site (OWA_{lesion}) to determine the RR.

Figure 2.

Negative remodeling of an intracranial plaque in a 61-year-old woman. TOF MRA MIP shows moderate stenosis of the M1 segment of the right MCA (A, arrows). Long-axis image reconstructed from the 3D contrast-enhanced BBMRI scan (0.4 mm isotropic resolution) demonstrates wall thickening responsible for luminal narrowing (B, arrows). Short-axis 2mm thick images are reconstructed from the 3D BBMRI volume acquisition orthogonal to the right M1 segment using semi-automated software (VesselMass, Leiden University, the Netherlands). These images are used for the analysis of the reference site (C, left-most image) and lesion (C, 4 contiguous images on the right). Contours were drawn to delineate the outer wall (green) and lumen (red) of the reference site selected as the slice showing the thinnest wall (D, left) and the lesion selected as the slice showing the thickest plaque (D, 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 3.

Positive remodeling of an intracranial plaque in a 62-year-old man. TOF MRA MIP shows a patent basilar artery without significant luminal narrowing (A). Long-axis image reconstructed from the 3D contrast-enhanced BBMRI scan (0.4 mm isotropic resolution) reveals a large plaque along the right wall of the proximal and mid segments of the basilar artery (B, arrows). Short-axis 2mm thick images are reconstructed from the 3D BBMRI volume acquisition orthogonal to the basilar artery using semi-automated software (VesselMass, Leiden University, the Netherlands). These images are used for the analysis of the reference site (C, left-most image) and lesion (C, 4 contiguous images on the right). Contours were drawn to delineate the outer wall (green) and lumen (red) of the reference site selected as the slice showing the thinnest wall (D, left) and the lesion selected as the slice showing the thickest plaque (D, 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.

Table 1**Patient and Plaque Characteristics**

Patient Characteristics		N (%)[*]
Male		29 (69.1)
Active smoker		8 (19.1)
Diabetes mellitus		11 (26.2)
Hypertension		29 (69.1)
Hyperlipidemia		23 (54.8)
Stroke		37 (88.1)
Acute		23 (54.8)
Subacute		7 (16.7)
Chronic		7 (16.7)
Transient ischemic attack		5 (11.9)
Plaque Characteristics		
Number of plaques per patient		N (%) [*]
1		12 (28.6)
2		7 (16.7)
3		9 (21.4)
4		4 (9.5)
5		10 (23.8)
Vessel segment	Number of plaques per segment (%) [†]	
Anterior cerebral artery		11 (8.0)
Internal carotid artery		48 (35.0)
Middle cerebral artery		28 (20.4)
Basilar artery		20 (14.6)
Posterior cerebral artery		9 (6.6)
Vertebral artery		21 (15.3)

N: number of patients.

^{*} percentages based on 42 patients.

[†] percentages based on 137 plaques

Table 2

Comparison between Anterior and Posterior Circulation MRI Measurements

	Anterior circulation (87 plaques)	Posterior circulation (50 plaques)	p[†]
Stenosis (diameter, WASID)	35.2 ± 25.4	41.9 ± 27.0	0.10
Arterial remodeling ratio (RR)	0.95 ± 0.32	1.15 ± 0.38	0.002
Lesion site			
Lumen area (mm ²)	0.07 ± 0.10	0.05 ± 0.05	0.20
Outer wall area (mm ²)	0.18 ± 0.09	0.21±0.12	0.41
Plaque burden (%) [*]	69.0 ± 14.0	77.7 ± 15.7	<0.001
Maximum wall thickness (mm)	1.79 ± 0.68	1.97 ± 0.81	0.45
Mean wall thickness (mm)	1.15 ± 0.53	1.31 ± 0.59	0.56
Reference site			
Lumen area (mm ²)	0.10 ± 0.10	0.08 ± 0.05	0.15
Outer wall area (mm ²)	0.17 ± 0.09	0.18±0.08	0.26

All values are mean ± SD.

[†] Lesion-level analysis was adjusted for patient effects using a random effects model.^{*} p<0.05