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Determinants of cerebrovascular remodeling: Do large brain arteries accommodate stenosis?

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Abstract

Objective—It is hypothesized that outward remodeling in systemic arteries is a compensatory mechanism for lumen area preservation in the face of increasing arterial stenosis. Large brain arteries have also been studied, but it remains unproven if all assumptions about arterial remodeling can be replicated in the cerebral circulation.

Methods—The sample included 196 autopsied subjects with a mean age of 55 years; 63 % were men, and 74 % non-Hispanic whites. From each of 1,396 dissected cadaveric large arteries of the circle of Willis, the areas of the lumen, intima, media, and adventitia were measured. Internal elastic lamina (IEL) area was defined as the area encircled by this layer. Stenosis was calculated by dividing the plaque area by the IEL area and multiplying by 100.

Results—Plotting stenosis against lumen area or stratified by arterial size showed no preservation of the lumen in the setting of growing stenosis. We could not find an association between greater IEL proportion and stenosis ($B=0.44$, $P=0.86$). Stratifying arteries by their size, we found that smaller arteries have greater lumen reduction at any degree of stenosis ($B=-23.65$, $P<0.0001$), and although larger arteries show a positive association between IEL proportion and stenosis, this was no longer significant after adjusting for covariates ($B=6.0$, $P=0.13$).

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Conclusions—We cannot confirm the hypothesis that large brain arteries undergo outward remodeling as an adaptive response to increasing degrees of stenosis. We found that the lumen decreases proportionally to the degree of stenosis.

Keywords

remodeling; arterial structure and compliance; stenosis; atherosclerosis; brain

Introduction

Cardiac and cerebral vascular diseases are among the top four causes of mortality and morbidity in the US and the world.^{1,2} Although the mechanisms in cerebrovascular disease are more heterogeneous than in cardiac disease, atherosclerosis can cause both. Most of what we know about atherosclerosis comes from studies of the aorta, extracranial carotid and coronary arteries. Large brain arteries have also been studied, but it remains unproven if many of the assumptions about atherosclerosis and arterial remodeling in the systemic circulation can be applied to the cerebral circulation.

It is believed, for example, that progressive intimal thickening can be accommodated in coronary arteries by outward enlargement of the vessel as an adaptive response to preserve the luminal area, usually until the degree of stenosis reaches approximately 40%.³ This reported outward remodeling does not appear confined to human coronaries as it has been documented also in primates and other animal models of atherosclerosis.^{4,5} However, compensatory dilatation does not occur equally in other non-coronary arteries and to our knowledge, it has not yet been evaluated in brain arteries.⁶ It is unknown whether concentric (or diffuse) vs. eccentric intima thickening induces the same remodeling pattern or if arteries proximal or distal to a bifurcation have a different response.⁷ The need to test prevalent hypotheses about arterial remodeling in brain arteries is further underscored by methodological aspects not yet fully addressed. For example, the fact that larger arteries will have larger plaques by virtue of their size has not been systematically taken into account when plotting the relationships between plaque area and internal elastic lamina (IEL) areas, i.e. larger arteries have logically larger IEL areas and larger plaque areas given the same degree of stenosis.⁸ Furthermore, comparing arteries obtained from different individuals, expected differences in arterial size among taller individuals and between women and men have not always been accounted for, which might lead to biased estimations in cerebral arteries.^{4,9,10}

In this study, we hypothesized that brain arteries are capable of accommodating stenosis by undergoing compensatory outward remodeling as occurs in the coronary system, and that this presumptive dilatatory response varies by arterial size, type, and location. Enhancing the current knowledge about brain arterial remodeling might lead to new views of the pathogenesis of cerebral atherosclerosis and other intracranial arteriopathies.

Materials and Methods

Subjects for this study were drawn from the Brain Arterial Remodeling Study, a collection of large and penetrating intracranial arteries assembled with the overall goal of studying

brain arterial remodeling, with particular emphasis on HIV and cerebrovascular disease. The sources of the autopsy cases in the Brain Arterial Remodeling Study are the Manhattan HIV Brain Bank located at the Icahn School of Medicine in New York City, the New York Brain Bank/Alzheimer's Disease Research Center at Columbia University, and the Macedonian/New York Psychiatric Institute Brain collection, which includes brains from Macedonia and New York. The methods used in this study, as well as the characteristics of each brain bank have been previously described.¹¹ For this analysis, we excluded individuals with HIV to facilitate comparisons with prior studies that did not include this specific clinical population. Demographic and clinical information including age, sex, race-ethnicity, hypertension (HTN), diabetes (DM), dyslipidemia (DYS), and smoking prior to death were obtained from medical charts, family and participant interviews, or autopsy reports. Due to various methods and goals of each brain bank, height, weight, heart weight and brain weight were variably obtained. The diagnosis of vascular disease was obtained in the majority of the cases either from medical records or pathological evidence of any of these diseases. Alzheimer dementia was diagnosed prior to death and confirmed pathologically as previously reported.¹²

All arteries were extracted systematically by the lead investigator of the Brain Arterial Remodeling Study (JosG). The circle of Willis was identified either in the whole brain or in one half (on occasions, the other half had been frozen). Each of the large arteries of the circle of Willis was identified, and 5-mm cross sectional segments were cut, fixed in 10% formaldehyde, and then embedded in paraffin for further sectioning. When possible, a proximal and a distal segment from the same artery were obtained with the goal of identifying segments in respect to their bifurcation or origin. Six micron thick sections were obtained from each embedded artery and stained with H&E and elastin van Gieson. Each slices was digitized by JosG in the Histology Shared Resource Facility of the Icahn School of Medicine at Mount Sinai using Olympus Soft Imaging Solutions software and microscope BX61VS with constant illumination, with 10X magnification and scale=0.643 $\mu\text{m}/\text{pixel}$.

Using color segmentation thresholding, areas of the lumen, intima, media and adventitia were obtained. Correction for shrinkage was applied by multiplying each area by a factor of 1.25 and the perimeter by 1.12, as suggested in prior reports.^{3,13} To correct for artery folding, we assumed that the outer perimeter of the adventitia was the least likely to be affected by folding and it would represent the actual perimeter of a fully distended artery (Figure 1, letter a-b). Although adventitia stripping during preparation was a concern; data suggest that this does not significantly change the cross-sectional area.¹⁴ We calculated the total artery area from the measured outer adventitia perimeter, and then subtracted the wall area to obtain the folding-corrected lumen area (Figure 1, letter c), and then derived the interadventitial diameter through standard geometrical formulas, as reported before.¹¹ The IEL area was obtained by adding the intima area plus the derived lumen and the IEL proportion was obtained by dividing the IEL area by the total artery area (Figure 1, letters d and e). Percent stenosis was calculated by dividing the plaque area by the IEL area and multiplying by 100 (Figure 1, letter f). Of note, arterial stenosis calculated in pathology is not the same as the stenosis measurement obtained from lumen-only studies since the former uses plaque area instead of luminal decrements to quantify it. By visual assessment the extent of the intima surface that showed any type of thickening additional to the

endothelium was semi-quantitated into 5 categories: 0= none, 1=1–25 %, 2=26–50 %, 3=51–75 % and > 75 % = 4. A note was made whether the intima thickening appeared diffuse vs. focal to determine if the thickening phenotype appeared concentric or eccentric. The degree of stenosis was not used in this categorization. Visual assessments for all arteries were made by JosG. To obtain reliability of the visual assessment, we obtained kappa values in a random sample of 125 large arteries; the second reader was JamG. The intra- and inter-reader reliability were both $\kappa=0.80$ for intima hyperplasia. The intra-reader reliability for concentric vs. eccentric hyperplasia was $\kappa=0.92$. The intra and inter-reader reliabilities of the color thresholding segmentations have been previously reported as excellent (ICC > 0.90).¹⁵ Although the AHA classification of atherosclerosis was used to rate each artery, we did not use this classification in this analysis to allow a fair comparison with the original report by Glagov et al., who did not use atherosclerosis phenotype other than stenosis percentage.^{3,7,16,17}

We plotted stenosis against IEL and lumen areas, and categorized stenosis into three groups to see if slopes would vary by degree of stenosis, as has been done in prior studies to demonstrate compensatory enlargement.³ The results from these plots would disclose if lumen preservation occurs in the initial stages of stenosis as previously postulated. A second aspect of the remodeling is that as the lumen is preserved with growing stenosis, the artery undergoes compensatory outward remodeling, which would presumably occur through enlargement of the IEL, media and adventitia, which then can be represented by a larger IEL proportion. To test this hypothesis, we created multilevel mixed models using IEL proportion as dependent variable and stenosis as independent variable.

Statistical analysis

For the simple plots, we used percentage stenosis and interadventitial diameter expressed in millimeters (mm) without transformation. Because we used parametric tests to evaluate predictors IEL proportion, we verified the distribution normality with stem and leaf and Q.Q plots, skewness and kurtosis. We found that IEL proportion was not normally distributed mainly due to large kurtosis (>2). We used exponential transformation for IEL proportion resulting in normalization of the distributions as verified by the Kolmogorov test. Since vascular risk factors affect all arteries in one individual and they are not independent among themselves, we used univariate and multivariate multilevel mixed models to account for this. The only case where we used simple linear regression was to calculate the slope of scatter plots. Our group and others have previously demonstrated that arterial size and location are important determinants of arterial phenotypes.^{8,11,18} Aware of this, we tested with a simple linear regression whether IEL proportion varies by arterial size, independent of stenosis. We found that arterial size explains 40 % (R^2) of the IEL proportion variability. Based on this, we decided to include arterial size as a mandatory covariate in our models. Additional to arterial size, we also included artery type and location to the models to account for differences in arteries studied by subject. Type III effects from transformed variables were used to confirm the statistical significance at a P value of < 0.05. The analysis was carried out with SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

Results

The sample in this study included 196 subjects with a mean age of 55 years (± 17 SD, median 51, range 21–102 years); 63 % were men, 74 % non-Hispanic whites, 14 % Hispanics and 12 % non-Hispanic blacks. Smoking was the most common vascular risk factor (49 %), followed by HTN (38 %), DYS (19%) and DM (15%). Vascular disease was self-reported or abstracted from autopsy in 38% of the sample: 31% reported cardiac ischemic disease, 15% were found to have myocardial infarctions, 17 % had ischemic stroke, 2 % had peripheral vascular disease and 4% had intracranial hemorrhage.

a) Pathology of large brain arteries

Pathological data was available in 1,392 large brain arteries, with an average of 7 arterial segments per case (median 6, range 1–17, 70% with > 6 segments, 38% with arteries from both hemispheres and 64% with arteries from both the anterior and posterior circulations). The intima was not thickened in 16% of the arteries and demonstrated at least some degree of hyperplasia in 84 %. Among arteries with some degree of hyperplasia, the hyperplasia was eccentric in 82%. Luminal stenosis ranged from 3 to 99 %, with a mean of 17 ± 13 %, median 13 %. Thirteen percent of the arteries had stenosis of 30% or more. Arterial size, as defined by interadventitial diameter, ranged from 1.1 to 7.2 mm and varied across arterial types. We identified tapering of arterial size of about 1 mm in size between arteries in the anterior circulation (mean interadventitial diameter of the ICA $\pm$ SD: 3.9 ± 0.8 mm, MCA: 2.7 ± 0.7 mm, and ACA: 2.3 ± 0.5 mm), and of about 0.5 mm in the posterior circulation (mean interadventitial diameter of the BA $\pm$ SD: 3.7 ± 0.9 mm, VA: 3.0 ± 0.9 mm, and PCA: 2.5 ± 0.6 mm). We also found tapering of between 0.1–0.2 mm in size from proximal to distal within the same artery.

b) Relationship between stenosis, plaque area, and arterial size

To investigate whether brain arteries undergo enlargement in the presence of stenosis as has been reported in coronary arteries, we plotted the same parameters used by Glagov et al. to describe coronary artery remodeling.³ First, we found a linear relationship between IEL area and intima area (Figure 2a), suggesting larger IEL areas with growing intima area (i.e. plaque burden). Then we plotted the lumen area against stenosis to evaluate whether the lumen area was preserved in the initial process of stenosis. This plot failed to show an evident inflection at 40% stenosis similar to what had been demonstrated in coronary arteries (Figure 2b). Because the variance of luminal areas in our cohort was significantly broader than that seen in coronary arteries, we stratified the lumen areas into quintiles and looked to see whether a more homogenous arterial size would demonstrate a biphasic relationship. We found that dividing arteries into quintiles of size rendered more homogenous groups. In both the highest and lowest quintiles, the slopes appeared linear throughout the full range of stenosis, and suggested a constant linear decline in luminal area with growing degrees of stenosis (Figure 2c and d). We then stratified arteries by posterior vs. anterior circulation and by eccentric vs. concentric intimal hyperplasia, but the same linear pattern appeared (Figure 3). Finally, we stratified stenosis into three groups: 0–20%, 21–40%, and > 41 % and plotted the lumen area against stenosis in arteries in the highest

and lowest quintiles of arterial size. Again, fully linear relationships emerged, with a slightly higher slope for the smaller arteries (Figure 4).

We repeated the same analyses of stenosis by lumen area substituting IEL area by IEL proportion. We found a linear relationship between IEL proportions and stenosis, but a broad variability was observed in IEL proportions (Figure 5a) similar to that found in lumen areas. We stratified IEL proportions in quintiles to allow more homogenous groups. We found that in arteries in the highest quartile of size, there appears to be a positive relationship between stenosis and IEL proportion ($B=16.7$, $P<0.001$). The slopes rapidly become flat and turn clearly negative in the smallest arteries ($B=-24.6$, $P<0.0001$, Figure 5b–f). However, after successive control of covariates, we could only confirm a negative association between stenosis and IEL proportion for the smallest arteries ($B=-23.65$, $P<0.0001$, Table 1). Although in univariate analysis there was a strong relationship between stenosis with IEL proportions, after adjusting for covariates, particularly arterial size, the point estimate was reduced by about 64% and the association became non-significant ($B=5.99$, $P=0.13$, Table 1).

DISCUSSION

Compensatory enlargement of arteries in the context of progressive stenosis is the current paradigm in the understanding of atherosclerosis of the coronary arteries. We attempted to examine whether large cerebral arteries undergo the same compensatory outward remodeling in the context of stenosis as do extracranial arteries. However, we could not find evidence to support the hypothesis that compensatory outward remodeling occurs in cerebral arteries. Our results suggest instead that for any degree of stenosis, the lumen area decreases linearly, and this decrement is sharper in small arteries compared to large arteries. Specifically we cannot support with our data the notion that the IEL area expands as stenosis ensues.

Various explanations for the discrepancy of our finding with the current literature can be offered. The first explanation is that the biology of arteries varies by anatomical locations – coronary versus cerebral circulation. Evidence for these arguments come from prior work investigating remodeling in various arteries, which included the coronaries as well as the common carotid, renal, and lower extremity arteries.^{6,19} For example, it was found that arterial luminal narrowing occurs in the setting of progressive stenosis in arteries of the lower extremities compared with coronary, common carotid, and renal arteries in which compensatory outward remodeling was the most common remodeling phenotype.^{6,18} Nonetheless, paradoxical inward remodeling has also been described in coronary arteries, more frequently in those with severe stenosis, with clinical symptoms, or in plaques deemed responsible for the syndrome.^{4,18,20} In the extracranial carotid artery, the pattern of arterial remodeling was clearly different depending on the flow patterns and circumferential wall stress.²¹ More important, the risk of vascular events varied by remodeling phenotype.²² These results and others highlight the importance of studying arterial remodeling in each system since responses might vary depending on the local arterial biology, architecture and flow dynamics.^{21,23,24}

A possible reason for why we failed to produce evidence supporting the hypothesis that cerebral arteries undergo outward remodeling as a response to a growing intima is because cerebral arteries are unique. The first and most outstanding difference in the arterial walls of brain versus other vessels is the lack of external elastic lamina in adult cerebral arteries compared to systemic arteries.^{25,26} Although present at birth, the external elastic lamina eventually dissipates at about 2 years of age when the sutures of the skull fuse and the intracranial pressure rises.²⁶ Another important difference between cerebral and systemic arteries is the thickness of the media. In normal coronary arteries (i.e. < 5% stenosis), the proportion of the wall composed of the media is about 35% vs. an average of 45% reported in brain arteries, 55 % in femoral arteries, and 62% in carotid arteries.^{15,27,28} Thinning of the media has been associated with compensatory outward remodeling of coronary arteries and it is presumably a step required for subsequent dilatation.²³ The thicker media of brain arteries and femoral arteries might be an obstacle for compensatory outward remodeling, although a thicker media does not appear to be obstacle in common carotid arteries for expansion.^{21,29} Arterial size is another determinant of remodeling. Smaller arteries might have less ability to undergo enlargement as large arteries do. Our results support this hypothesis as well as does evidence that distal coronary arteries with lumen areas < 6 mm² have less outward expansion compared to more proximal, larger segments of the same artery.²³ In our sample, 78% of the studied arteries had lumen areas smaller than 6 mm² so it could be that smaller arteries dominated the overall estimates. However, stratifying into quintiles of arterial size failed to show definitive evidence of enlargement even in the largest brain arteries.

Outward remodeling itself is presumably a compensatory response to plaque formation, and plaque formation is thought to be induced, among other things, by unique flow patterns in atherosclerosis-prone regions.⁷ The flow resistance is lower in the brain arteries than in the coronaries, which makes the brain vessels more susceptible to the pulsatility energy of the cardiac cycle.³⁰ Additionally, the increasing aortic stiffness seen with aging and in the setting of vascular risk factors exacerbates the transmission of pulsatile energy to the brain large arteries.^{30,31} Whether this might or not play a role in the capacity to undergo dilatatory changes in the setting of stenosis is uncertain. The complex collateral network of the Circle of Willis and the unique branching pattern of the proximal large arteries have an important influence on the brain arterial diameters.^{32–34} As a consequence, the stimuli to expand may not only be due to a nascent plaque, but possibly a result of competing factors which include brain oxygen demand, collateral phenotype, central hemodynamics and possibly a permissive genome. Additionally, it has been described that in the setting of intracranial stenosis, distal arterioles are capable of dilatation. This reduces the resistance which leads to a compensatory increased blood flow to the distal capillary beds.^{35,36} This phenomenon, called cerebral autoregulation, represents an extra layer of physiological compensation to secure a stable brain blood flow, but by decreasing resistance and increasing the flow, this compensatory mechanism might dampen the hemodynamics effects of growing stenosis that would otherwise stimulate outward remodeling at the level of the circle of Willis. Contextualizing the reported particularities of the brain circulation into our results, it is plausible to postulate that in brain large arteries, plaque formation with subsequent stenosis is not usually well accommodated by enlargement of brain arteries and the failure to

accommodate a plaque leads to a directly proportional lumen narrowing. However, it is well documented that outward remodeling of brain arteries does occur in certain circumstances, for example in the form of saccular aneurysm or dolichoectasia.^{37–39} One can therefore infer that other factors not related to atherosclerosis might play a role in physiological and pathological outward remodeling seen in brain arteries. Investigating in detail the mechanisms of large artery remodeling in the brain might lead to fresh ideas in how to incorporate arterial phenotypes in risk stratification for vascular events and perhaps newer therapeutic targets.

However, other explanations can be invoked to account for why evidence of compensatory outward remodeling in brain arteries could not be found in this study. For example, a major source of discrepancy between our results and those of others include the methods used to study remodeling using pathology specimens. The two most common methods used include a) using scatter plot and linear regression to evaluate associations between lumen and IEL areas with the degree of stenosis, and b) using adjacent segments of the same artery as a referent for “normal” arterial size after tapering correction.^{3,6} These approaches are not perfect. In the first case, using scatter plots assumes that the areas are independent among themselves, which we do not believe is the case. A large artery will always have large IEL and intima areas compared to smaller arteries, given the same degree of stenosis. Also, we have previously shown that the degree of stenosis in brain arteries is associated with artery locations.¹¹ The susceptibility of large arteries to develop more stenosis might be linked to oscillating wall shear stress that the complex branching pattern of brain arteries undergo, presumably greater in larger areas.^{40–42} A second approach to study remodeling assumes that the contiguous segment of the artery should be used as referent. But this assumes the rest of the artery is healthy and untouched by the effects of the studied stenosis, which might not always be the case since atherosclerosis is a systemic rather than a local cerebral disease.⁴³ However, some think that this method leads to a more accurate estimation of referent normal than using the local IEL area as the referent for stenosis.⁶ There is a chance that outward remodeling could be reported by applying this method, but we did not attempt using this method to compare results because the distance between proximal and distal segments of each artery was not systematically recorded and would prohibit size tapering correction and because we rarely found a significant degree of stenosis contiguous to a healthy, normal appearing vessel.

Strengths of our study include the systematic and reproducible measurements performed in this study. The sample size is larger than some of the samples used in prior studies to demonstrate remodeling. This makes likely a low power as the potential explanation for the negative results. Our study also has weaknesses, however. It is possible that by analyzing remodeling with a linear regression, we could have missed more detailed remodeling phenotypes as others have carefully described.^{21,44} However, one of our main goals was to be able to compare our results to those used by Glagov et al. using similar techniques (tissue rather than Doppler data). Our conclusion is thus limited to the lack of outward remodeling in the setting of plaque growth, but we have not yet excluded that other arterial remodeling phenotypes might be present in the brain not disclosed by the method used in this study. This will certainly be the subject of future research. Additionally, some degree of error is expected in vessel measurements used for this study despite attempted correction for

fixation, processing and folding of the brain arteries. Our results should also be interpreted in the context of the study's cross-sectional design, without reference to causality. Prospective and in-vivo studies have confirmed remodeling in animal and human carotid and coronary arteries, which supports the hypothesized natural history of brain arterial remodeling documented here.^{20,29,45–47} Because the completeness of the circle of Willis varied by brain bank, there exist a chance that selective sampling of the circle of Willis could have introduced bias. Using mixed models that clustered the data by subjects could have reduced this potential bias, but we can't completely rule out residual bias attributed to each brain bank. Finally, pathology studies are not necessarily representative of the general population, and thus the results should be interpreted with caution with respect to generalization to the full populations. We think that pathological studies should be used to understand the physiopathology of brain arterial remodeling, but generated hypotheses will need to be validated in living individuals.

In summary, our results do not confirm the hypothesis that large brain arteries undergo outward remodeling as an adaptive response to early progression of atherosclerosis. We found that the arterial lumen decreases proportionally to the degree of stenosis and that smaller brain arteries might in fact shrink with growing stenosis. The failure to replicate what has been assumed about remodeling in extracranial arteries underscores the importance of studying brain arterial biology with brain arteries so we can improve methods of diagnosis and treatment of cerebrovascular disease.

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- This work addresses for the first time whether brain arterial can undergo compensatory enlargement to accommodate stenosis
- Contrary to what is believed to occur in systemic arteries, brain arteries do not enlarge to accommodate for stenosis
- Filling research gaps in brain arterial biology can open new ways to treat brain arterial disease

Figure 1.
Definition of the terms used in this study.

Figure 2. Scatter plots of the internal elastic lamina (IEL) and lumen areas against plaque area and stenosis.

Figure 3.
Scatter plots of lumen area against stenosis by anterior vs posterior circulation and by eccentric vs. concentric intima hyperplasia.

Figure 4.

Scatter plots of lumen area (y axis) against stenosis (x axis) by degree of stenosis in the upper and lower quintiles of arteries size.

Figure 5. Scatter plots of internal elastic lamina (IEL) proportion against stenosis in all arterial sizes and by quintiles of arterial size.

Table 1

Arterial stenosis as determinant of the internal elastic lamina (IEL) proportion*

	Arterial size (mm)	Model 0 Beta coefficient (P-value)	Model 1 Beta coefficient (P-value)	Model 2 Beta coefficient (P-value)	Model 3 Beta coefficient (P-value)
All arteries N=1,392	1.09–7.29	0.44 (0.86)	-1.85 (0.47)	-1.85 (0.48)	-2.96 (0.14)
By Quintiles					
First (lowest)	1.09–2.20	-24.6 (<0.0001)	-28.01 (<0.0001)	-27.3 (<0.0001)	-23.65 (<0.001)
Second	2.21–2.63	-1.12 (0.82)	-0.53 (0.91)	-0.28 (0.95)	1.23 (0.81)
Third	2.63–3.10	-6.26 (0.21)	-6.72 (0.19)	-7.24 (0.15)	-6.14 (0.23)
Fourth	3.11–3.74	2.01 (0.57)	1.81 (0.63)	1.95 (0.60)	0.07 (0.98)
Fifth (highest)	3.74–7.29	16.7 (<0.001)	13.4 (0.006)	12.4 (0.003)	5.99 (0.13)

Model 0: Univariate.

Model 1: Adjusting for age, sex, and race/ethnicity.

Model 2: Adjusting for age, sex, and race/ethnicity, hypertension, diabetes, dyslipidemia, and smoking.

Model 3: Adjusting for age, sex, and race/ethnicity, hypertension, diabetes, dyslipidemia, smoking and arterial size and location.

* Exponential transformation was used to achieve normalization.