Systemic Atherosclerosis Relate to Brain Arterial Diameters: The Northern Manhattan Study

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Key Words

Dolichoectasia · Atherosclerosis · Carotid artery disease · Intracranial arterial stenosis

Abstract

Background: Phenotypic expressions of arterial disease vary throughout the body and it is not clear to what extent systemic atherosclerosis influences brain arterial remodeling. We aim to test the hypothesis that systemic atherosclerosis is associated with brain arterial diameters. **Methods:** Stroke-free participants in the Northern Manhattan Study MRI sub-cohort in whom carotid ultrasound, transthoracic echocardiogram, and brain MRA ($n = 482$) were performed were included in this analysis. Brain arterial diameters were measured with semi-automated software as continuous and categorical variables. Ultrasound and echocardiography provided the sum of maximum carotid plaque thickness (sMCPT) and aortic plaque thickness. Associations between brain arterial diameters and aortic and carotid plaque thickness were assessed with semi-parametric generalized additive models. **Results:** Aortic plaque thickness was inversely and linearly associated with brain arterial diameters (B per mm = -0.073 ± 0.034 , $p = 0.03$), while sMCPT was associated

nonlinearly in a u-shaped curve with anterior brain arterial diameters (spline regression $\chi^2 = 9.19$, $p = 0.02$). Coexisting carotid and aortic atherosclerosis were more prevalent in participants with small luminal diameters (40%) compared with participants with average (30%) or with large (13%) luminal diameters, while carotid atherosclerosis without aortic atherosclerosis was more prevalent among participants with large luminal diameters (31%) compared with those with average (12%) or small luminal diameters (2%, $p < 0.001$ for both trends). **Conclusions:** We confirmed the hypothesis that systemic arterial disease is associated with brain arterial diameters. Gaining knowledge about the origin of these phenotypic expressions of atherosclerosis in the human body may lead to a better understanding of the cerebrovascular consequences of the systemic arterial disease.

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Introduction

Phenotypic expressions of atherosclerosis have varied manifestations throughout the body in each individual and it is not entirely understood why atherosclerosis has such a heterogeneous distribution. For example, greater

severity of coronary atherosclerosis is associated with greater severity of aortic atherosclerosis, but about a third of individuals with a high Agatston coronary artery calcium score (>300) do not have evidence of aortic calcification [1, 2]. In pathology studies, individuals with aortic atherosclerosis involving $>50\%$ of the aorta have various degrees of carotid atherosclerosis but about a tenth of these individuals lack significant evidence of carotid atherosclerosis [3].

An even greater variability has been noted regarding the distribution of atherosclerotic lesions between extracranial and intracranial atherosclerosis. While a majority of individuals with severe intracranial atherosclerosis defined by histopathology have advanced aortic or coronary atherosclerosis, only half of the cases with advanced aortic or coronary atherosclerosis will have severe intracranial atherosclerosis [3, 4]. Although coronary and aortic atherosclerosis are associated with carotid atherosclerosis, there is no meaningful relationship of either coronary or aortic atherosclerosis with vertebral artery plaques [3]. Furthermore, intracranial plaques are associated with coronary plaques while intracranial stenosis is not associated with coronary plaque [5], further emphasizing the heterogeneous relationship between local and systemic atherosclerosis. Brain arterial diameters, used as biomarkers of intracranial large artery disease, have also been associated with extracranial vascular events [6]. While large basilar artery diameters have been associated with an increased risk of coronary events [7], the incidence of vascular events is higher in individuals with either very small or very large brain arterial diameters, and this is suggestive of a nonlinear relationship among extracranial carotid, aortic atherosclerosis, and intracranial arterial diameters [6].

Understanding the interplay between systemic arterial health, presumably modified by atherosclerosis, and brain large artery health may lead to a better learning of the physiopathology of cerebrovascular outcomes such as vascular dementia and stroke. With this in mind, we tested the hypothesis that systemic atherosclerosis is associated with brain arterial diameters.

Methods

The Northern Manhattan Study (NOMAS) is a racially and ethnically diverse, population-based sample of stroke-free community dwellers followed since 1993. In 2003, all surviving participants were invited to participate in a brain MRI substudy if they were 50 years or older, remained stroke or TIA-free, and were available for a brain MRI. All participants signed written informed

consent and the study was approved by the institutional review boards at Columbia University and the University of Miami. Information related to age, gender, ethnicity, and smoking status was self-reported. Hypertension was defined as self-reported diagnosis, self-reported use of antihypertensives, or a systolic blood pressure/diastolic blood pressure $\geq 140/90$ mm Hg. Hypercholesterolemia was defined as self-reported high cholesterol, use of cholesterol-lowering medications, or a total cholesterol ≥ 240 mg/dL. Diabetes was defined by self-report diagnosis or glucose-lowering medications, or a fasting glucose ≥ 126 mg/dL.

Brain MRI Measurements

Imaging was performed on a 1.5-T MRI system (Philips Medical Systems) at the Columbia University Medical Center. We used a standardized protocol to obtain 2-dimensional time-of-flight MRA in each participant, with FOV of 15 cm, 1 mm effective slice thickness, acquisition matrix interpolated to 256×228 matrix, flip angle of 25 degrees, and TR/TE 20 and 2.7 ms, respectively. The brain MRA images were systematically evaluated to obtain the diameters of all the large intracranial arteries as described earlier [8]. If an artery was not visualized in the axial images of the MRA sequences, the diameter was set to zero for that artery. We created a normalized average arterial diameter for the 13 brain large arteries measured called the global brain arterial remodeling (BAR score) [6]. A high BAR score reflects a greater number of arteries with larger lumina, whereas a low score implies a greater number of arteries with smaller lumina. The anterior BAR score comprised the normalized average diameter of the bilateral internal, anterior, and middle cerebral arteries. The posterior BAR score comprised the normalized average diameter of the vertebral arteries, the basilar artery, and the posterior cerebral arteries. The posterior communicating arteries (Pcomm) were used separately to assess the integrations based on the degree of connectivity between the anterior and posterior circulations through Pcomm (or fetal PCA).

Carotid Doppler Measurement

Standardized carotid ultrasonography was performed using a high-resolution B-mode ultrasound and a GE LogIQ 700 system with a multi-frequency 9–13 MHz linear-array transducer. With the participant in a supine position, right and left common carotid artery (CCA), external and internal carotid arteries were evaluated in the longitudinal and transverse planes. Maximum carotid plaque thickness (MCPT) was measured for each plaque from the base of a plaque to its greatest peak with good to excellent reliability [9]. For this analysis, we defined bilateral MCPT as the sum of the right and the left MCPT (sMCPT) and used it continuously or categorically as “no plaque” versus “any plaque” in the analyses. CCA diastolic diameter was measured by identifying the intima-lumen boundaries in the best 10 heart cycles of a real-time clip of the CCA with an inter-reader correlation coefficient of 0.96.

Aortic Arch Atherosclerosis Measurements

Aortic plaque was assessed with 2-dimensional transthoracic images of the aortic arch with real-time 3D confirmation from a suprasternal window. The study was performed by a registered cardiac sonographer protocol using a commercially available system (iE33; Philips Medical Systems, Andover, MA, USA) equipped with a 2.5–3.5-MHz transducer and interpreted by a single experienced echocardiographer (MDT) blinded to demographic, clinical, and radiographic characteristics. A plaque was defined as a discrete pro-

Table 1. Demographics of the subsample of the NOMAS MRI substudy included in this analysis compared to the excluded sample

	Included (<i>n</i> = 486)	Excluded (<i>n</i> = 808)	<i>p</i> value
Age, years	69±10	71±8	<0.001
Gender, male, %	36	42	0.051
Ethnicity, %			
Non-Hispanic white	13	19	0.003
Non-Hispanic black	16	18	
Hispanic	71	62	
Hypertension, %	80	71	<0.001
Diabetes, %	25	26	0.736
Hypercholesterolemia, %	71	68	0.360
Current smoking, %	17	15	0.375
Prior cardiac disease, %	25	26	0.356

trusion of the intimal surface of the vessel at least 1 mm in thickness, different in appearance and echogenicity from the adjacent intact intimal surface. For this study, we used aortic plaque thickness continuously and categorized into the following groups: no-plaque, 1–3 mm plaque, and ≥4 mm plaque. Compared with transesophageal echocardiogram, transthoracic echocardiography has positive and negative predictive values of 91 and 98%, respectively [10].

Statistical Analysis

We restricted this analysis arbitrarily to individuals in whom the carotid ultrasound, the echocardiogram, and the brain MRI were performed within 6 years of each other (*n* = 482, median and interquartile range for time between MRI and echocardiogram was 0, 0–2 months and for time between MRI and carotid Doppler was 0, 0–36 months). We used chi-square and Student *t* tests to assess differences between categorical and continuous variables respectively. The main outcome of the study was the BAR score, which was analyzed both continuously and categorized into small luminal diameters (first decile), large luminal diameters (tenth decile), and average luminal diameters (second to ninth deciles). To test our hypotheses, we used semi-parametric generalized additive models to obtain beta estimates for the association between extracranial (carotid and aortic) plaque thickness with brain arterial diameters, adjusted for the time between the tests using a spline assumption for atherosclerosis and parametric (linear) assumption for demographic and clinical covariates. We considered evidence of nonlinearity, a *p* value ≤0.05 for the regression of the spline with 3 degrees of freedom. Finally, we used statistical interactions between carotid or aortic atherosclerosis and demographic and vascular risk factors to determine differential associations with smaller or larger brain arterial diameters. The statistical analysis was carried out with SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Sample

From the 1,290 participants in the NOMAS MRI study, 482 had a brain MRA, carotid Doppler, and echocardiogram

done within 6 years of each other. Compared with the NOMAS MRI study participants excluded from this analysis, participants in this analysis were younger, more likely to be women or Hispanic, and had a higher prevalence of hypertension (Table 1).

Aortic and Carotid Atherosclerosis Associations with Brain Arterial Diameters

Aortic plaque thickness was inversely and linearly associated with brain arterial diameters ($B = -0.073 \pm 0.035$, $p = 0.03$). The sMCPT was associated nonlinearly with anterior brain arterial diameters (chi-square value for the regression of the spline = 9.19, $p = 0.02$): participants with greater sMCPT had either small or large anterior luminal diameters (Table 2). Stratifying based on anterior and posterior circulation changed little the direction of the associations. There were no statistical interactions between the posterior BAR score and the degree of collateral connection with the anterior circulation, as recorded by the average Pcomm diameter, with aortic plaque thickness ($p = 0.54$) or carotid plaque thickness ($p = 0.53$).

Plotting the brain arterial diameters (expressed continuously and categorically) against the carotid and aortic plaque thickness metrics showed a more heterogeneous relationship. Figure 1, for example, shows a progressive rise in the BAR score as the sMCPT increased in value, while the opposite trend is noted when aortic plaque increased in severity. This was more evident for arteries in the anterior circulation. There was also a U-shaped relationship between aortic atherosclerosis and higher posterior circulation BAR scores (Fig. 1), but this trend did not reach statistical significance (spline regression $\chi^2 = 5.88$, $df = 3$, $p = 0.11$). A sensitivity analysis done only in participants who had the brain MRI, carotid Doppler, and

Table 2. Relationship between aortic and carotid atherosclerosis with brain arterial diameters

	Global BAR score		Anterior circulation BAR score		Posterior circulation BAR score	
	linear term B ± SE	spline regression (chi-square value)*	linear term B ± SE	spline regression (chi-square value)*	linear term B ± SE	spline regression (chi-square value)*
Aortic plaque thickness	-0.073±0.034 <i>p</i> = 0.03	5.52, <i>p</i> = 0.14	-0.068±0.034 <i>p</i> = 0.05	6.12, <i>p</i> = 0.10	-0.026±0.034 <i>p</i> = 0.44	5.88, <i>p</i> = 0.11
Maximum bilateral carotid plaque thickness	-0.014±0.039 <i>p</i> = 0.71	5.05, <i>p</i> = 0.16	0.009±0.038 <i>p</i> = 0.872	9.19, <i>p</i> = 0.02	-0.038±0.037 <i>p</i> = 0.31	3.23, <i>p</i> = 0.36

All estimates were obtained adjusting for sex, age, ethnicity, hypertension, diabetes, hypercholesterolemia, active smoking, prior cardiac disease, head size, body surface area, and time between brain MRI, transthoracic echocardiogram, and carotid Doppler.

* *p* value is calculated as a chi-square test with *df* = 3.

Fig. 1. Relationship between carotid and aortic plaque thickness and brain arterial diameters.

TTE within 1 year from each other (*n* = 245) changed little the direction or significance of these result.

Categorizing the BAR score confirmed the results showed using the continuous BAR score. For example, 92% of participants with small brain luminal diameters had any aortic atherosclerosis compared to 75% of participants with average brain luminal diameters and 26% of those with large brain luminal diameters (*p* < 0.001 for trend). Coexisting carotid and aortic atherosclerosis were more prevalent in participants with small brain luminal

diameters (40%) compared to participants with average (30%) or large (13%) brain luminal diameters (*p* < 0.001 for trend). Carotid atherosclerosis without aortic atherosclerosis was more prevalent among participants with large brain luminal diameters (31%) compared to those with average (12%) or small brain luminal diameters (2%, *p* < 0.001 for the trend). These results were independent of the variables listed in Table 2.

Among participants with carotid atherosclerosis, small brain arterial diameters were more common among those

Table 3. Differential associations between aortic and carotid atherosclerosis with large and small brain arterial diameters compared with individuals with average brain arterial diameters*

	Among participants with carotid atherosclerosis		Among participants with aortic atherosclerosis	
	small brain arterial diameters OR (95% CI)	large brain arterial diameters OR (95% CI)	small posterior circulation arterial diameters OR (95% CI)	large posterior circulation arterial diameters OR (95% CI)
Age, years	1.04 (0.97–1.11)	1.00 (0.95–1.06)	1.00 (0.96–1.10)	1.05 (1.01–1.10)
Gender, male	0.14 (0.03–0.72)	1.14 (0.32–3.98)	0.62 (0.19–1.98)	2.00 (0.69–5.82)
Ethnicity				
Non-Hispanic white	Ref	Ref	Ref	Ref
Non-Hispanic black	1.13 (0.19–6.84)	6.77 (0.61–75.31)	1.31 (0.30–5.75)	1.52 (0.38–6.10)
Hispanic	0.29 (0.06–1.35)	2.13 (0.21–21.34)	0.87 (0.26–2.94)	0.97 (0.31–3.01)
Hypertension	15.47 (1.53–156.5)	5.47 (0.93–32.07)	0.88 (0.35–2.24)	1.72 (0.60–4.90)
Diabetes	2.98 (0.79–11.25)	1.77 (0.59–5.34)	0.80 (0.30–2.13)	1.27 (0.51–3.20)
Hypercholesterolemia	1.17 (0.29–4.69)	1.41 (0.42–4.75)	4.35 (1.25–15.03)	1.57 (0.64–3.86)
Current smoking	1.57 (0.29–8.57)	3.54 (1.04–12.07)	1.45 (0.55–3.84)	1.49 (0.58–3.82)
Aortic atherosclerosis (per mm of plaque)	1.53 (1.06–2.21)	1.28 (0.91–1.80)	1.06 (0.73–1.56)	0.85 (0.54–1.35)
Carotid Atherosclerosis (per mm of plaque)	4.26 (2.53–7.18)	3.37 (2.12–5.36)	0.94 (0.81–1.12)	0.83 (0.66–1.05)

Ref, referent group.

* Multivariate analysis included all the variables listed in this table PLUS head size, body surface area, and time elapsed between both the carotid Doppler and the transthoracic echocardiogram.

with hypertension (OR 15.47, 95% CI 1.53–156.5) and in those who also had aortic atherosclerosis (per mm of plaque, OR 1.53, 95% CI 1.06–2.21), while large brain arterial diameters were more common in active smokers (OR 3.54, 95% CI 1.04–12.07; Table 3). Greater severity of carotid atherosclerosis was associated with both small brain arterial diameters (OR 4.26, 95% CI 2.53–7.18) and large arterial diameters (OR 3.37, 95% CI 2.12–5.36). Among participants with aortic atherosclerosis, small brain arterial diameters were more common among those with hypercholesterolemia (OR 4.35, 95% CI 1.25–15.03), while large brain arterial diameter were more common with older age (OR 1.05 per year, 95% CI 1.01–1.10).

Aortic and Carotid Plaque Thickness Associations

In the univariate linear regression model, aortic plaque thickness was associated with bilateral sMCPT (B per mm = 0.07, $p < 0.001$). The linear association persisted after controlling for age, gender, ethnicity, vascular risk factors, and time elapsed between the 2 studies ($B = 0.05$, $p = 0.008$). Not all participants with aortic atherosclerosis had carotid atherosclerosis, however. Among participants with large aortic plaques (i.e., >4 mm), 20% had no

evidence of carotid atherosclerosis (Fig. 2). Conversely, among participants with advanced carotid atherosclerosis (i.e., sMCPT >4 mm), 23% had no evidence of aortic atherosclerosis.

Discussion

In this report, we confirmed the hypotheses that systemic atherosclerosis is associated with the diameters of brain arteries and that the association between extracranial carotid atherosclerosis and brain arterial diameters is not linear. Based on these findings, the previously reported higher risk of vascular events associated with large and small brain arterial diameters in this population may be partially explained by the extracranial atherosclerotic phenotypes accompanying the extremes of brain arterial remodeling [6].

The heterogeneity of atherosclerosis in different arterial systems has been consistently reported in the literature, but few reports have operationalized brain arterial diameters as a spectrum in which the extremes may be biomarkers of vascular risk. We used brain arterial (luminal) diam-

Fig. 2. Carotid and aortic atherosclerosis phenotypes and their associations with small, large, or average brain arterial diameters.

eters as surrogates of arterial wall disease. Small luminal diameters may be the result of intracranial atherosclerosis or hypotrophic brain arteries [11, 12]. Because the BAR score represents an average of 13 large brain arteries and because we explicitly avoided measuring the brain diameters in areas of focal stenosis, a small BAR score represents diffuse (rather than focal) inward remodeling. Given the pathological evidence that brain arterial lumina decrease in diameter linearly as cerebral atherosclerosis increases in severity [5, 13], diffuse atherosclerosis is a plausible pathological correlate of a small BAR score. There is no pathological data suggestive of atherosclerosis as the principal driver of brain arterial outward remodeling [14]. This issue remains controversial given the radiological evidence that is suggestive of brain arterial outward remodeling in patients with intracranial atherosclerosis using high resolution MRI [15, 16]. As we have argued before, the discrepancy in methods, particular pixel resolution, as well as problems with the “normal referent” used to define outward remodeling may explain the discrepancy of results [17, 18]. Because of the generalized predisposition of the brain arteries and the lack of a clearly defined etiology, “primary dolichoectasia” has been proposed as a term to define this dilatative process [19].

The number of possible phenotypes shown in Figure 2 appears daunting, but a few patterns that emerge from this data should be considered. The first conspicuous pattern is the increasing prevalence of atherosclerosis as the BAR score decreases, with a strong negative association between the BAR score and aortic plaque thickness. If a small BAR score indeed represents diffuse cerebral atherosclerosis, then this trend replicates data from pathological studies in which it has been clearly demonstrated that in the presence of aortic atherosclerosis, the brain arteries can be either free of atherosclerosis or have severe atherosclerosis. But when there is severe cerebral atherosclerosis, it is exceedingly rare to have an aorta free of atherosclerosis, which suggests that atherosclerosis tends to start in the aorta [4, 20]. Clinical data also support the fact that there is an association between aortic atherosclerosis and intracranial arterial disease. For example, there exists a high prevalence of aortic calcifications or plaques among lacunar or non-lacunar, non-embolic strokes (presumably due to large artery atherosclerosis), or with intracranial atherosclerosis defined with cerebral angiography [21–23].

The second conspicuous pattern is the association of isolated carotid atherosclerosis (in the absence of aortic

atherosclerosis) with large brain luminal diameters. Plausible, yet unproven, explanations include the production of chemical signals in the atherosclerotic carotid plaque that travel distally to the brain that could stimulate dilatation, flow-related changes in the extracranial carotids as a consequence of atherosclerosis, or greater carotid stiffness that could facilitate the transmission of pulsatility to the more proximal segments of the circles of Willis [24, 25]. The fact that the association is stronger in arteries from the anterior circulation than for arteries in the posterior circulation also supports downstream effects of the extracranial carotid to their intracranial segments. From these results, it can also be deduced that there is dissociation between carotid atherosclerosis and aortic atherosclerosis. Such dissociation has been evident in a large autopsy series with systematic evaluation of the coronary, carotid, vertebral, cerebral arteries, the aorta, and in more recent clinical data showing that while aortic plaque measuring 1.0–3.9 mm was significantly associated with a high degree of carotid stenosis, plaques of more than 4 mm were not [20, 26].

The strength of this study is the concomitant study of 3 arterial systems in an unselected sample obtained from the community. The measurement of brain arterial diameters is reliable as they are obtained semi-automatically and it takes into account the head size, which is the most important anthropomorphic predictor of brain arterial diameters [27]. Our measurements of aortic and carotid atherosclerosis have been validated and obtained reliably in this study. The major limitation of this study is the cross-sectional nature of the analysis, which precludes us from confirming the directionality of the reported associations. Whether these results are applicable to popula-

tions with a different demographic composition is unclear, but this is something that needs to be investigated. The sample size is small given the exclusion of subjects who did not have the required data for this analysis or whose studies were done with greater intermittent gaps between the studies.

In summary, the extremes of the brain arterial diameter spectrum are associated with systemic arterial disease: while aortic atherosclerosis is associated with small brain arterial diameters, carotid atherosclerosis is associated with small brain arterial diameters typically in the setting of coexisting aortic atherosclerosis while in the absence of aortic atherosclerosis, isolated carotid atherosclerosis is a marker of large brain arterial diameters. Gaining knowledge about the various phenotypic expressions of atherosclerosis in the human body may result in a better understanding of the cerebrovascular consequence of systemic arterial disease.

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