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The Association of Brachial Artery Diameter with Noncalcified Coronary Plaque Burden in Apparently Healthy Individuals

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Abstract

Objective—Coronary atherosclerosis has been associated with systemic arterial remodeling even in non-atherosclerotic vessels. However it is not known whether systemic remodeling is differentially associated with the cumulative atherosclerotic process, reflected by putatively quiescent calcified plaque (CP) or with active atherosclerosis consisting of non-calcified plaque (NCP). We thus examined the association of brachial artery diameter (BAD), an artery which does not suffer clinical atherosclerosis, with the presence and the extent of coronary CP and NCP.

Methods—We studied 688 apparently healthy, asymptomatic participants from 350 families with a history of early-onset coronary artery disease (<60 years of age) measuring CAD risk factors and coronary plaque using dual-source CT angiography. Plaque volumes were quantified using a validated automated method. BAD was measured during diastole using B-mode ultrasound. The association of resting BAD with any detectable plaque, and log-transformed CP and NCP volumes if detectable, was tested using Generalized Estimating Equations (GEE) adjusted for age, sex, race, current smoking, diabetes, hypertension, body mass index, non-HDL and HDL-cholesterol.

Results—Higher quintiles of BAD were associated with greater age and male sex (both $p < 0.001$). In fully adjusted analysis, CP volume was not associated with BAD ($p = 0.65$) but 1 ml greater NCP volume was associated with 0.65 mm larger BAD ($p = 0.027$).

Conclusion—Our results suggest that systemic arterial remodeling of non-atherosclerotic arteries is a dynamic process that is correlated with the extent of putatively active atherosclerotic processes in distant beds, but not inactive accumulated plaque burden.

Keywords

Brachial Artery; Remodeling; CT Angiography

Introduction

Although the brachial artery does not develop clinically obstructive atherosclerosis,[1] autopsy studies demonstrate low-grade atherosclerotic lesions concomitant with more severe atherosclerotic disease in other vascular beds such as the coronary arteries.[2] The external remodeling and arterial enlargement of atherosclerotic vascular segments, e.g., of the coronary arteries[3] is thought to be adaptive for the maintenance of localized shear rate.[4] There is also evidence that atherosclerosis in one arterial bed may be associated with systemic arterial remodeling, including the brachial artery.[5-7] Greater brachial artery diameter (BAD) has been shown to be associated with the Framingham risk score[8] and with cardiovascular events.[9] With aging, larger BAD is accompanied by a maladaptive lower shear rate.[10] It is currently unknown whether the cumulative atherosclerotic process or currently active level of atherosclerosis is associated with systemic arterial remodeling.

We hypothesized that localized active coronary atherosclerosis may result in maladaptive remodeling of arteries throughout the vascular system including the brachial arteries. Early active stages of coronary atherosclerosis are characterized by noncalcified plaques composed of lipid, inflammatory cells, and fibrous tissue[11, 12] that may be prone to rupture, thrombosis and coronary artery disease events,[13, 14] whereas later stages show plaque calcification, reflecting a relative quiescence of the pathogenic process.[15] Thus, we further hypothesize that BAD should be associated with non-calcified plaque (NCP) rather than calcified plaque (CP).

Methods

Sample Population

The sample population (n=688) was drawn from the ongoing GeneSTAR (Genetic Study of Atherosclerosis Risk) cohort. Proband with early-onset CAD prior to 60 years of age (myocardial infarction, unstable angina requiring revascularization, or acute angina with angiographic evidence of >50% stenosis in any coronary artery) were identified in 10 Baltimore-area hospitals. Apparently healthy, asymptomatic family members of the proband were invited to participate, including siblings of the proband and offspring of the proband or the siblings. Persons with known CAD, systemic autoimmune disease, chronic kidney failure, or allergy to iodinated dyes were excluded. The study was approved by the Johns Hopkins Institutional Review Board, and all participants gave informed consent.

Risk factor assessment

Participants underwent a comprehensive risk factor assessment following a 12-hour overnight fast. Medical history and current medication use were elicited, and a physical exam was performed by a study cardiologist. Medication use was confirmed by examining prescription medication containers brought in by the participants. Current cigarette smoking behavior was assessed by self-report and verified by expired carbon monoxide (CO) levels of ≤ 8 ppm. Height and weight were measured with light clothing and without shoes on a stadiometer. Body Mass Index (BMI) was calculated as $\text{weight}/\text{height}^2$. Seated blood pressure was obtained using JNC VI guidelines[16] as an average of three readings over the

course of the screening day. Hypertension was defined as a mean blood pressure of ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic, and/or the use of antihypertensive medication. Blood was obtained for measurement of lipid and glucose levels. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured using the United States Centers for Disease Control standardized methods [17]. Low-density lipoprotein (LDL) cholesterol was estimated using the Friedewald formula [18] for persons with triglyceride levels up to 400 mg/dl. Diabetes was defined as a measured fasting glucose level of ≥ 126 mg/dL and/or use of hypoglycemic medication.

Computed tomography methods

Computed tomographic angiography (CTA) was performed using the newest generation dual-source multidetector scanner (SOMATOM Definition Flash, Siemens Medical Solutions, Forchheim, Germany). Both non-contrast and contrast enhanced imaging were acquired. The volume of CP was measured on a workstation (Leonardo Multimodality Workstation, Syngo, Siemens Medical Solutions, Malvern, PA) using noncontrast images. Regions of interest were placed over each of the coronary arteries and a threshold of >130 HU was used for determining per vessel volumes of CP (mm^3) using standard validated methods.[19, 20] Vessel CP volumes were summed for a total CP volume. NCP volumes were quantified from contrast enhanced images using well-validated automated software (AUTOPLAQ, Cedars-Sinai Medical Center, Los Angeles, CA) as described previously.[21]

Ultrasound methods

Brachial artery 2-D B-mode ultrasound imaging was performed using the Philips CX50 Ultrasound machine with a 12-3MHz linear probe (Philips Healthcare, Bethesda, MD). Video images were digitized at 29 frames/sec. The brachial artery interadventitial diameter was measured in a 5-mm region of interest using automated edge detection software (Brachial Tools, Medical Imaging Applications, Coralville, IA) for a period of 20 seconds. Diastolic frames were identified as local minima in the diameter vs. time signal. The average diastolic diameter was used for this analysis.

Statistical methods

Descriptive analysis

We tabulated demographic and risk factor characteristics by quintile of BAD. In addition to unadjusted tests using analysis of variance for continuous variables and chi2 tests for categorical variables, we tabulated age, sex and race adjusted p-values using generalized estimating equation (GEE) models to correct for intrafamilial correlation. We examined the tetrachoric correlation coefficient between the dichotomized variables of any CP and any NCP, and the Spearman correlation between CP and NCP volumes in the subset of individuals with any detectable plaque.

Association analysis

For association of linear trend, the sample was divided into 6 groups by plaque volume. Separate groups were defined for CP and NCP. The groups were (group 1) no detectable plaque and (groups 2-6) quintiles for the NCP or CP if any plaque was detectable. The group

ranges for NCP volume were 0, 3-50.5, 50.7-98.7, 98.9-168.2, 173.9-310.6, 315.4-1063.6 mm³. The group ranges for CP volume were 0, 0.1-8.0, 8.1-26.9, 27.4-69.5, 70.4-227.6, 239-1909.7 mm³. Medians and interquartile ranges were graphed by sex, and age and race adjusted trends were tested using GEE.

Multivariable adjusted analysis with both CP and NCP volumes in the same model was performed using GEE adjusting for sex, age, race, smoking, hypertension, diabetes, BMI, HDL-cholesterol and nonHDL cholesterol.

Sensitivity analysis

We performed multivariate analysis (a) adjusting for systolic blood pressure and blood pressure medication use (b) aspirin use (c) adjustment for height and weight as separate covariates and (d) a spline model with a different covariate for any plaque and the volume of plaque subtype if any plaque was present.

Results

Sample characteristics

In this sample, 385 (56%) individuals had no detectable coronary plaque, 8 (1%) had exclusively NCP, 41 (6%) had exclusively CP, and 254 (37%) had mixed plaque. The tetrachoric (dichotomous) correlation between the prevalence of CP and NCP was 0.98 ($p<0.001$) while the Spearman correlation between NCP and CP volumes among those with detectable plaque was 0.66 ($p<0.001$). The distribution of demographic and cardiovascular risk factor characteristics in the sample population are shown in table 1. Older ages and male sex were associated with higher quintiles of brachial artery diameter. After adjustment for age and sex, hypertension, lower levels of HDL-C, and greater BMI were associated with higher quintiles of BAD.

Association of Plaque and Plaque Volumes with Brachial Artery Quintiles

Figure 1 and Figure 2 show the median and interquartile ranges of BAD by NCP and CP groups. Although the unadjusted trend of greater BAD with greater plaque volume was significant for NCP and CP in both sexes ($p<0.002$ for all), after age and race adjustment, only higher levels of NCP remained significantly associated with larger BAD (women, $p = 0.032$ and men, $p = 0.023$), whereas CP levels were no longer associated with BAD (women, $p = 0.50$ and men, $p = 0.15$).

Multivariate regression analysis

Table 2 shows the multivariable GEE regression analysis for BAD. Male sex, older age and higher BMI were significantly associated with larger BAD. Additionally, every 1 ml greater volume of NCP was associated with 0.67 mm larger brachial artery diameter ($p=0.027$). No significant association was found between BAD and CP volume.

Sensitivity analyses—The association of NCP volume with BAD remained significant and the association of CP volume with BAD remained non-significant in multivariate analysis (a) adjusting for systolic blood pressure and blood pressure medication use (b)

aspirin use (c) adjustment for height and weight as separate covariates and (d) a spline model with a different covariate for any plaque and the volume of plaque subtype if any plaque was present.

Discussion

To our knowledge, this is the first study to show the association between noncalcified but not calcified coronary plaque volumes and BAD, after adjustment for age, sex and race. We found that the unadjusted association of BAD with the presence of any plaque and CP was explained successively by age and cardiovascular risk factors, suggesting that the associations of BAD with these plaque characteristics are cumulative over a long period, and are not specific. However, we also found that the association of BAD with NCP was only partially explained with age, and was not attenuated further on adjustment for cardiovascular risk factors, suggesting that the degree of active coronary atherosclerosis may have systemic effects on other arterial beds.

NCP volume represents a measure of currently active and vulnerable atherosclerotic processes,[11-14] thus this independent association with BAD likely represents a current and dynamic systemic process. A recent study showing that maladaptive BAD enlargement in severe obesity was reversible with weight loss supports the suggestion that arterial remodeling is a dynamic process.[22] Other studies have found associations of BAD with CAD phenotypes. Larger BAD has been associated with atherosclerotic risk factors including age and the Framingham Risk Score.[8, 10] In longitudinal studies BAD has been associated with cardiovascular events.[9] Rohani et al found that BAD was associated with angiographically determined extent and severity of coronary stenoses in symptomatic individuals.[7] In the Cardiovascular Health Study, BAD was associated with the presence, but not the extent, of coronary calcification measured using the Agatston score.[6] This is consistent with our findings demonstrating an extremely high correlation between the presence of calcified and noncalcified plaque, but the correlation between the extent of NCP and CP plaque volumes, if present, was low.

External remodeling at the site of atherosclerotic plaque is an adaptive response to prevent local stenoses.[3] Although autopsy studies show that brachial arteries do undergo early stage atherosclerosis,[2] lesions in the brachial artery do not develop into clinically significant stenoses.[1] Additionally, these early stage brachial artery lesions have been correlated with more severe carotid lesions,[2] supporting the concept that severe lesion progression may depend on local hemodynamics but other arterial beds may be affected by systemic changes that occur from the atherosclerotic process. Larger carotid artery diameter has also been shown to be associated with aging and cardiovascular risk factors.[23] Other studies that have shown that BAD is associated with carotid artery diameter and left ventricular mass[24] as well as right ventricular mass.[25]

Atherosclerosis is now known to be an inflammatory process, with evidence of circulating inflammatory mediators and activated inflammatory cells, especially monocytes. External remodeling of non-atherosclerotic arterial segments are dependent on macrophage activation and the action of proteases such as MMPs on the adventitial extracellular matrix.[26] It is

not known if brachial artery remodeling occurs because of cell activation and protease secretion in distant active atherosclerotic lesions or because of local cell activation. Our study shows that BAD is correlated with the volume of putatively active NCP in a different vascular bed, suggesting that inflammatory atherosclerotic processes in one vascular bed may affect the whole circulatory system. Alternatively, even though the brachial artery does not show lesions, there may be low-grade inflammatory processes within these arteries as well, and that larger BAD may signify a general systemic vasculopathy.

We found that BAD is not associated with the volume of CP, which is presumably quiescent as compared to NCP. The volume of CP represents the cumulative burden of atherosclerotic processes throughout the lifetime. This suggests that systemic arterial remodeling is a dynamic phenomenon that depends on currently active atherosclerotic processes. This warrants a future longitudinal study to determine whether the BAD regresses or progresses along with the atherosclerotic activity in clinically relevant vascular beds.

The advanced CTA imaging technology that makes it possible to distinguish calcified and non-calcified plaque and the reproducible automated quantitation of plaque volumes are strengths of our study, as is the wide age range of men and women in this biracial sample. The ascertainment of our sample from families with a history of premature CAD may be responsible for adequate prevalence of coronary plaque to be able to perform association analyses. This strength could be a partial limitation in generalizing our findings to non-high risk family population. However, our study recapitulates BAD associations with age and other risk factors seen in prior studies. Thus we believe that our findings may be cautiously applicable to the general population.

Conclusions

We have found that the diameter of the brachial artery, which is a measure of the extent of external remodeling of systemic arteries not undergoing local clinical atherosclerosis, is associated with putatively active plaque burden in the distant coronary arterial beds, but not the volume of quiescent calcified plaque. This suggests that the atherosclerosis is a process with systemic effects in terms of remodeling, and that such remodeling is likely to be dynamic and not cumulative over the lifetime.

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Figure 1. Median and interquartile ranges of brachial artery diameter by noncalcified plaque volume (volume ranges of groups: 0, 3-50.5, 50.7-98.7, 98.9-168.2, 173.9-310.6, 315.4-1063.6 mm³). Age and race adjusted trend for women, $p = 0.032$; men, $p = 0.023$.

Figure 2. Median and interquartile ranges of brachial artery diameter by calcified plaque volume (volume ranges of groups: 0, 0.1-8.0, 8.1-26.9, 27.4-69.5, 70.4-227.6, 239-1909.7 mm³). Age and race adjusted trend for women, $p = 0.50$; men, $p = 0.15$.

Table 1

Demographic and risk factor characteristics by quintile of Brachial Artery Diameter (GeneSTAR study 2009-2013)

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Unadjusted p	Adjusted p
N	138	138	137	138	137		
Age (years)	46.5 (10.3)	50.9 (10.5)	51.5 (11.6)	51.4 (9.6)	54.8 (10.2)	<0.001	.
Male Sex, n (%)	20 (14.5)	25 (18.1)	42 (30.7)	89 (64.5)	124 (90.5)	<0.001	.
Black race, n (%)	53 (38.4)	55 (39.9)	44 (32.1)	59 (42.8)	49 (35.8)	0.43	.
Current Smoking, n (%)	32 (23.2)	31 (22.5)	24 (17.5)	26 (18.8)	22 (16.1)	0.50	0.64
Hypertension, n (%)	35 (25.4)	57 (41.3)	66 (48.2)	66 (47.8)	80 (58.4)	<0.001	0.004
Diabetes, n (%)	13 (9.4)	15 (10.9)	14 (10.2)	22 (15.9)	17 (12.4)	0.47	0.49
Total-C (mg/dL)	193.4 (39.0)	200.3 (45.9)	193.1 (33.9)	192.1 (41.5)	184.1 (38.2)	0.031	0.41
Non-HDL-C (mg/dL)	137.2 (45.8)	135.6 (36.5)	136.0 (41.8)	135.2 (38.2)	135.1 (37.5)	0.99	0.95
LDL-C (mg/dL)	110.4 (36.3)	119.1 (41.5)	111.1 (30.6)	116.0 (40.0)	109.1 (32.9)	0.16	0.10
HDL-C (mg/dL)	62.6 (20.7)	58.5 (15.1)	58.7 (17.0)	52.4 (14.0)	51.2 (16.4)	<0.001	0.001
Triglycerides (mg/dL)	103.4 (51.9)	112.1 (67.9)	114.2 (64.1)	118.3 (64.5)	120.5 (83.9)	0.26	0.82
Systolic BP (mmHg)	118.4 (13.5)	126.1 (15.8)	124.1 (13.7)	125.2 (12.9)	128.9 (14.2)	<0.001	0.002
Diastolic BP (mmHg)	74.8 (8.0)	77.5 (8.4)	77.3 (8.4)	78.8 (9.2)	80.5 (8.5)	<0.001	0.005
BMI (kg/m²)	28.5 (6.4)	30.8 (6.6)	30.8 (6.6)	30.7 (5.3)	30.6 (4.5)	0.002	<0.001

Total C - Total cholesterol, LDL-C - LDL cholesterol, HDL-C - HDL cholesterol, BP - blood pressure, BMI - body mass index, BAD quintile ranges in mm: 1 - <3.569, 2 - 3.572 to 4.051, 3 - 4.052 to 4.534, 4 - 4.539 to 5.067, 5 - >5.072; Unadjusted p using χ^2 tests for categorical variables and ANOVA for continuous variables, Age, sex and race adjusted p using Generalized Estimating Equations (GEE) logistic or linear regression correcting for intrafamilial correlations.

Table 2

Multivariable association of brachial artery diameter with noncalcified and calcified plaque volumes
(GeneSTAR study 2009-2013)

Variable	Comparator	Coefficient (mm of BAD/comparator) [95% Confidence Interval]	P-value
Sex	Male vs. Female	1.02 [0.88-1.15]	<0.001
Race	Black vs. Nonblack	0.07 [−0.07-0.2]	0.35
Current smoking	Smoker vs. Nonsmoker	−0.14 [−0.29-0.01]	0.074
Hypertension	Hypertensive vs. Normotensive	0.07 [−0.07-0.2]	0.34
Diabetes	Diabetes vs. non-Diabetes	−0.03 [−0.22-0.16]	0.74
Age	per year	0.02 [0.01-0.02]	<0.001
NonHDL-C	per 10 mg/dL	0.00 [−0.01 – 0.02]	0.076
HDL-C	per 10 mg/dL	−0.03 [−0.07 – 0.01]	0.17
BMI	per kg/m ²	0.02 [0.01-0.03]	<0.001
Noncalcified plaque	per ml volume	0.65 [0.08-1.23]	0.027
Calcified plaque	per ml volume	0.11 [−0.35-0.57]	0.65