Relationship of Carotid Distensibility and Thoracic Aorta Calcification

Multi-Ethnic Study of Atherosclerosis

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Abstract—Stiffening of the central elastic arteries is one of the earliest detectable manifestations of adverse change within the vessel wall. Although an association between carotid artery stiffness and adverse events has been demonstrated, little is known about the relationship between stiffness and atherosclerosis. Even less is known about the impact of age, sex, and race on this association. To elucidate this question, we used baseline data from the Multi-Ethnic Study of Atherosclerosis (2000–2002). Carotid artery distensibility coefficient was calculated after visualization of the instantaneous waveform of the common carotid diameter using a high-resolution B-mode ultrasound. Thoracic aorta calcification was identified using noncontrast cardiac computed tomography. We found a strong association between decreasing distensibility coefficient (increasing carotid stiffness) and increasing thoracic aorta calcification, as well as a graded increase in the thoracic aorta calcification score ($P<0.001$). After controlling for age, sex, race, and traditional and emerging cardiovascular risk factors, individuals in the stiffest quartile had a prevalence ratio of 1.52 (95% CI: 1.15 to 2.00) for thoracic aorta calcification compared with the least stiff quartile. In exploratory analysis, carotid stiffness was more highly correlated with calcification of the aorta than calcification of the coronary arteries ($\rho=0.32$ versus 0.22; $P<0.001$ for comparison). In conclusion, there is a strong independent association between carotid stiffness and thoracic aorta calcification. Carotid stiffness is more highly correlated with calcification of the aorta, a central elastic artery, than calcification of the coronary arteries. The prognostic significance of these findings requires longitudinal follow-up of the Multi-Ethnic Study of Atherosclerosis cohort. **(*Hypertension*. 2009;54:00-00.)**

Key Words: carotid stiffness ■ carotid compliance ■ subclinical atherosclerosis ■ thoracic aorta calcification ■ coronary calcification

Stiffening of the central elastic arteries is one of the earliest detectable manifestations of adverse change within the vessel wall.[1,2] Accompanying decreased arterial compliance is closely associated with aging[3] and other traditional cardiovascular risk factors.[4,5] Measures of central artery stiffness, including aortic pulse wave velocity,[6] have been associated with coronary artery disease,[7–9] congestive heart failure,[10,11] and stroke,[12] as well as all-cause mortality.[13–15] Although aortic and systemic stiffness have proven difficult to apply in the clinical setting, local stiffening within the carotid artery remains appealing, because it is more directly accessible to measurement.

Mechanical properties of the carotid arteries are most easily visualized using high-resolution ultrasound.[16] On a real-time sweep of the common carotid artery, dynamic measurements of the carotid diameter can be made that enable calculation of several indices of stiffness: distensibility coefficient (DC), Young elastic modulus (YM), β-stiffness index, and carotid distension.[17] These indices have been shown to predict coronary heart disease and stroke among apparently healthy individuals in the Rotterdam[18] and Three-City[19] studies.

Despite the association between carotid stiffness and poor outcomes, little is known about the association between stiffness and atherosclerosis. Even less is known about the impact of age, sex, and race on this association. The little available data correlating carotid stiffness with aortic atherosclerosis used plain radiography of the abdomen as the measure of plaque burden.[20] Definitive conclusions have been limited by the use of this insensitive and difficult-to-quantify measure of atherosclerosis. In contrast, measurement of arterial calcification by computed tomography (CT) allows for quantification of the volumetric burden of atherosclerosis, including that found within the more central ascending and descending thoracic aortas.[21]

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To better describe the association between stiffness and atherosclerosis, we assessed the cross-sectional association between carotid DC measured with ultrasound and thoracic aortic calcification (TAC) measured by CT in a large, multiethnic cohort. In further analysis, we looked for regional variability in the association between carotid stiffness and calcification in the aorta (an elastic central artery) and the coronary arteries (peripheral arteries).

Methods

Study Design and Patient Population

We used baseline data from the Multi-Ethnic Study of Atherosclerosis (MESA; 2000–2002). The MESA study design, patient recruitment, and selection have been described previously.[22] In summary, MESA enrolled 6814 asymptomatic men and women of 4 different ethnic groups (white, Chinese, black, and Hispanic), aged 45 to 84 years, into a population-based, prospective cohort study aimed at describing the prevalence, progression, and significance of subclinical atherosclerosis. Patients were drawn from 6 geographically distinct population centers in the United States. All of the patients were free of known cardiovascular disease at enrollment.

Each MESA participant underwent 2 baseline cardiac CT scans for the evaluation of coronary and extracoronary calcification. In 6529 participants (96%), baseline carotid ultrasound imaging was sufficient to calculate DC. Patients without sufficient carotid imaging were more likely to be women and black but did not differ in age or any other measured covariate. All of the participants gave informed consent for the study protocol, which was approved by the institutional review boards of all 6 of the MESA field centers.

Carotid Imaging and DC

The right and left carotid arteries were imaged according to a common scanning protocol using high-resolution B-mode ultrasonography with a Logiq 700 machine (General Electric Medical Systems). Carotid IMT was measured in the common carotid artery, and reported as the mean of the maximum intima-media thickness (IMT) measured in the right and left sides for both the near and far walls. Data necessary for calculating DC were obtained from a separate 20-second–long acquisition of longitudinal images of the right distal common carotid artery. All of the images were interpreted at a central MESA ultrasound reading center (Tufts Medical Center) by readers blinded to all of the clinical information.

For each participant, an edge detector was used to process the images and to extract carotid arterial diameter curves. Diastolic and systolic diameters were determined as the smallest and largest diameter values during a cardiac cycle. Blood pressure measurements were taken by upper arm sphygmomanometry (DINAMAP System; GE Medical Systems) at the time of the carotid artery ultrasound.

These data were used to calculate a simplified DC via the following equation described by Gamble[23]:

$$DC = \frac{2\Delta D}{\Delta P D_s}$$

where ΔD is the change in systolic/diastolic diameter, ΔP is the brachial pulse pressure, D_s is the systolic diameter, D is the average common carotid artery diameter, and h is the mean wall thickness (IMT) measured 10 mm proximal to the carotid bulb.

Reproducibility studies were performed in 221 participants; 211 were intraobserver repeated-image analyses, and 10 were interobserver correlations. For DC and YM, the intraobserver class correlation coefficients were 0.71 and 0.69, respectively. The interobserver intraobserver class correlation coefficients were 0.85 and 0.84, respectively. The intraobserver variability in reading exams was assessed in 204 patients, revealing an intraobserver class correlation coefficients of 0.68 for DC and 0.80 for YM. This reflects good-to-excellent agreement.

Cardiac CT Protocol

Cardiac CT was performed at 3 sites using a cardiac-gated, electron-beam CT scanner (Imatron C-150XL; GE-Imatron) and at 3 sites using a 4-section multidetector CT. All of the participants were scanned over phantoms of known physical calcium concentration. Images were read at the MESA CT reading center (Harbor-University of California Los Angeles).

The MESA scanning protocol has been described previously.[24] Image sections were obtained with the participant supine, with no couch angulation, during a single breath hold. A minimum of 35 contiguous images was obtained, beginning above the left main coronary artery and proceeding below both ventricles. Section thickness of 3 mm, field of view of 35 cm, and matrix 512×512 were used to reconstruct the raw data. Nominal section thickness was 3.0 mm for electron beam CT and 2.5 mm for 4-detector row CT. Spatial resolution, expressed as the smallest voxel able to be discriminated, was 1.38 mm^3 (0.68×0.68×3.00 mm) for electron beam CT and 1.15 mm^3 (0.68×0.68×2.50 mm) for 4-detector row CT.

The ascending and descending thoracic aortas were visualized from the lower edge of the pulmonary artery bifurcation to the cardiac apex on each cardiac CT. TAC is defined as total calcification in the ascending plus the descending portions. For this study, TAC was considered both as a binary measure (present versus not present) and a continuous measure (Agatston score).

The reproducibility of extracoronary measures of calcification within MESA has been discussed in detail previously.[25] To summarize for TAC, among 1729 randomly chosen participants undergoing rescanning on dual scanners, the intrascan κ statistic for agreement on presence of TAC was 0.95 (95% CI: 0.94 to 0.97). This varied slightly by scanner type, with multidetector CT outperforming electron beam computerized tomography (0.97 versus 0.94). The mean rescan percentage of absolute difference in Agatston score for measurement of TAC >0 was 10.2%. This variability is most likely attributed to slightly different starting points for the 2 scans, such that that slightly different anatomy may be examined in scan 1 and scan 2. The reproducibility of coronary artery calcium (CAC) within MESA has also been thoroughly described.[26] The κ statistic for agreement on the presence of CAC was 0.92, and the mean rescan percentage absolute difference in CAC >0 was 20.1%.

Study Covariates

Hypertension, smoking, diabetes mellitus, and family history of heart attack are presented as binary variables. Hypertension was defined as the use of antihypertensive medication or baseline sphygmomanometric measurements of blood pressure fulfilling the Joint National Committee guidelines (≥140/90 mm Hg identifying hypertension). Smoking was defined as previous or present use of tobacco cigarettes. Diabetes mellitus was defined according to American Diabetes Association guidelines (fasting blood sugar >126 mg/dL) or the use of hypoglycemic medications. Replacement of hypertension, smoking, and diabetes mellitus with absolute systolic and diastolic blood pressures, pack-years of smoking, and fasting blood glucose in the study models resulted in minimal change with no overall impact on study conclusions. Medication use was defined as the present use of prescription medications for the treatment of hypertension or hypercholesterolemia. Family history was positive if an immediate family member (parents, siblings, or children) had suffered a heart attack.

Statistical Analysis

Baseline characteristics of the study participants are presented over decreasing quartiles of DC (increasing carotid stiffness). The fourth quartile (most distensible) is used as the reference group for subsequent analyses. Frequencies and proportions are reported for caegorical variables, and either means with SDs or medians with interquartile ranges are reported for continuous variables on the basis of the normality of distribution. χ^2 tests, Fisher exact tests, 1-way ANOVA, or Kruskal-Wallis tests were used for the comparison of variables between groups.

Table 1. Characteristics of the Study Participants

Characteristic	Total (N=6526)	DC Quartile 4 (≥3.02)	DC Quartile 3 (2.36 to 3.01)	DC Quartile 2 (1.78 to 2.35)	DC Quartile 1 (≤1.77)	*P*
Age, y	62±10	55±8	60±9	64±9	69±9	<0.001
Sex, women, %	53	51	50	54	56	0.001
Race, %						
White	39	46	42	37	29	<0.001
Chinese	12	11	14	12	12	
Black	27	23	32	29	35	
Hispanic	22	21	21	23	24	
Heart rate, bpm	63±10	61±9	63±9	64±10	65±11	<0.001
BMI, kg/m^2	28.3±5	27.3±5	28.1±5	28.9±6	28.8±5	0.022
Systolic blood pressure, mm Hg	127±22	114±16	122±17	129±19	142±23	<0.001
Diastolic blood pressure, mm Hg	72±10	69±10	71±9	73±10	75±11	<0.001
Hypertension, %	45	22	35	51	71	<0.001
Fasting glucose	104±31	99±29	102±26	106±32	110±35	<0.001
Diabetes mellitus, %	14	8	12	15	22	<0.001
Cr, mg/dL	0.95±0.3	0.93±0.2	0.94±0.3	0.95±0.3	0.99±0.3	<0.001
Smoking, %						<0.001
Former	37	34	36	38	39	
Current	13	21	13	10	8	
LDL, mg/dL	117±32	117±32	112±31	118±32	116±32	0.61
HDL, mg/dL	51±15	51±15	50±14	51±15	51±15	0.27
Triglycerides, mg/dL	111 (77 to 161)	102 (72 to 152)	115 (79 to 166)	113 (80 to 163)	114 (81 to 162)	<0.001
Family history of heart attack, %	40	40	41	41	39	0.67
Medications for hypertension, %	37	22	32	42	53	<0.001
Medications for cholesterol, %	16	11	15	18	19	<0.001
hsCRP, mg/L	1.90 (0.83 to 4.19)	1.56 (0.66 to 3.88)	1.71 (0.76 to 3.80)	2.07 (0.94 to 4.46)	2.25 (0.99 to 4.61)	<0.001
CAC, %	50	36	47	53	63	<0.001
Log-normal (CAC+1), score	2.19±2.5	1.42±2.2	2.03±2.5	2.38±2.6	2.94±2.6	<0.001
Carotid IMT, mm	0.87±0.19	0.80±0.16	0.84±0.18	0.89±0.19	0.95±0.21	<0.001
10-y FRS, %	8.2±7	5.6±6	7.3±7	8.7±7	12±8	<0.001

Data are mean±SD or median (interquartile range) unless otherwise specified. BMI indicates body mass index; Cr, creatinine; hsCRP, high-sensitivity C-reactive protein; FRS, Framingham risk score; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Because the prevalence of CAC in our cohort was >10%, odds ratios overestimate the relative risk. Therefore, prevalence ratio estimates are presented from the regression model $y=\exp(X^T\beta)$, with the exponentiated parameter β interpreted as the relative risk or prevalence ratio. Using this method, we assessed the relationship between DC and the presence of TAC in a hierarchal fashion. Model 1 adjusts for key demographic variables: age, sex, and race. Model 2 adds traditional and emerging cardiovascular risk factors: body mass index, heart rate, low-density lipoprotein cholesterol, hypertension, diabetes mellitus, cigarette smoking, family history of heart attack, and lipid-lowering medication use. Model 3 adds the inflammatory variable C-reactive protein and baseline measures of subclinical vascular disease: CAC and carotid IMT.

To better discern the influence of important study covariates, additional stratified analyses were conducted, with results expressed as the prevalence ratio of having TAC per 1-SD increase in DC. Finally, to explore differential correlations between DC and calcification of the thoracic aorta and coronary arteries, we constructed a Spearman correlation coefficient matrix among DC, TAC, and CAC. We used logarithmically transformed values of TAC and CAC (log-normal [score+1]) to normalize their distributions.

All of the analyses used a 5% 2-sided significance level. Calculations were performed using Stata software, version 8.2 (Stata Corp).

Results

Baseline Characteristics of the MESA Participants

The mean age of the 6526 study participants was 62±10 years. Approximately 53% were men, with mean calculated 10-year Framingham risk for the entire cohort of 8.2±7.0%. Mean DC for the study cohort was 2.51 mm Hg, with a SD of 1.1×10^{-3} mm Hg. Median DC was 2.36×10^{-3} mm Hg reflecting a slight rightward skew. The mean and median DC values are similar to those reported in other studies after adjusting for differences in calculation.[18]

Patients were divided into 4 categories on the basis of their values for DC (see Table 1). Across decreasing DC quartiles (increasing carotid stiffness), patients were, on average older, more likely to be women, and enriched in the black and Hispanic ethnicities. Most traditional and emerging cardiac risk factors were associated with decreasing DC, including body mass index, blood pressure, diabetes mellitus, smoking, and C-reactive protein. In addition, decreasing DC was associated with a higher prevalence of CAC, a higher CAC score, and higher carotid IMT (all $P<0.001$).

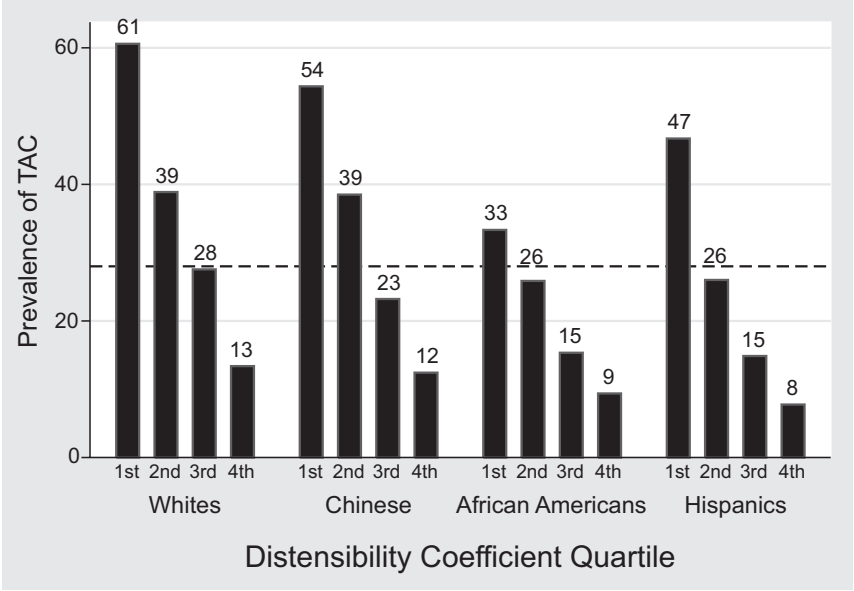

Figure 1. Unadjusted prevalence of TAC by increasing DC quartile, stratified by race. Calcification of the aorta decreased with increasing carotid distensibility. Overall prevalence of TAC is 28% (dotted line). $P<0.001$ in each race for the trend across DC quartiles.

Prevalence of TAC by DC Quartile

The prevalence of TAC was 28% for the study cohort. Across all 4 of the ethnicities, there was a graded association between increasing DC quartile and decreasing prevalence of TAC ($P<0.001$; see Figure 1). The prevalence of TAC reached 61% among whites for quartile 1, the group with the stiffest arteries. The association between DC and TAC remained strong among blacks, the ethnicity known to have the lowest incidence of TAC.

Association Between DC and TAC Score

Considering only patients with a prevalent TAC (score >0), there remains a "dose-response" relationship between the DC quartile and TAC score (see Figure 2). From the least to the most distensible carotid artery quartile, the median TAC scores were 367, 275, 187, and 133, respectively ($P<0.001$). To better demonstrate this graded relationship, we examined median DC over quartiles of TAC score, retaining the large TAC=0 group as a distinct category (see Figure 3). Across all of the races, mean DC was higher among patients with no TAC ($P<0.001$), with a modest threshold effect for lower DC among individuals in the highest TAC score quartile. In linear aggression analysis adjusting for age, race, and sex, 1 SD decrease in DC corresponded with a 12% relative increase in log-transformed TAC score ($P=0.008$).

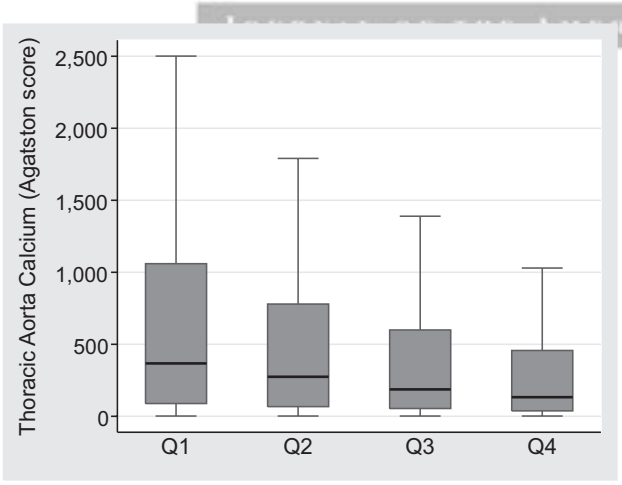

Figure 2. Median, interquartile range, and adjacent values of TAC by DC quartile in those with TAC>0. In those with TAC, the mean TAC score decreased with increasing distensibility of the carotid artery. $P<0.001$ for the association across DC quartiles.

Multivariable Regression Models

The results from 3 different regression models are presented in Table 2. Adjusted for demographic variables, the prevalence ratio for having TAC among the least distensible compared with the most distensible quartile was 1.79 (95% CI: 1.41 to 2.26). Adding cardiovascular risk factors to the model, the prevalence ratio was slightly attenuated to 1.52 (95% CI: 1.19 to 1.96). Adding measures of subclinical vascular disease resulted in little change, with a prevalence ratio of 1.52 (95% CI: 1.15 to 2.00). Further analyses including creatinine and fasting glucose in the model did not change these results.

Table 3 shows the results of stratified multivariable analyses examining the prevalence ratio for TAC with 1-SD change in DC (see Table 3). For the entire cohort, a 1-SD decrease in DC resulted in a 25% increase in TAC prevalence (95% CI: 1.12 to 1.41). In stratified analyses, individual risk factors did not have a major impact on this association, with numerous statistically significant associations and overlapping CIs. Associations between DC and TAC remained strong in middle-aged participants and individuals in the lower Framingham risk categories.

Correlation Between DC and Regional Calcification

Table 4 displays a stratified Spearman correlation matrix among DC, TAC, and CAC. All of the individual correlation coefficients were statistically significant at $P<0.001$. In general, the correlation between DC and calcification was the

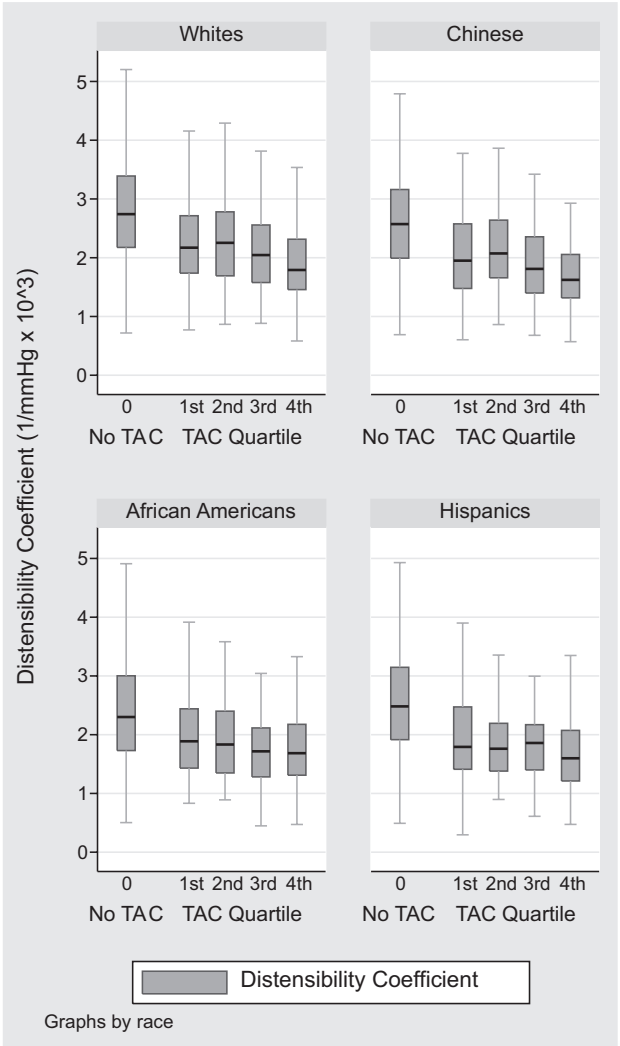

Figure 3. Median, interquartile range, and adjacent values of DC by absence/quartiles of thoracic aortic calcium carotid distensibility is greatest in those with no TAC, with a threshold effect for decrease distensibility among individuals in the highest TAC score quartile. $P<0.001$ for the association across all of the TAC groups.

least strong among men and blacks. There was a tighter correlation between DC and TAC than between DC and CAC ($\rho=0.315$ versus 0.221; $P<0.001$ for comparison of coefficients across the entire study population). This difference remained statistically significant in both sexes (women: $P<0.001$; men: $P=0.01$) and all races (white: $P<0.001$; Chinese: $P=0.03$; black: $P=0.03$; Hispanic: $P=0.008$).

Supplementary Analysis

To facilitate comparison with existing literature, we subsequently conducted exploratory analyses using YM, a measure of arterial elasticity, as well as a parameter indicating "distension" that was achieved by adjusting our primary analysis for pulse pressure. Results were similar to those seen with the analysis using DC. For YM quartile 4 (most elastic), there was a statistically significant 35% increase in TAC prevalence (95% CI: 1.02 to 1.80). After adjusting for pulse pressure, there remained a strong association between carotid distention and TAC. Point estimates of the association were slightly attenuated but remained statistically significant (Figures S1 and S2, please see the online Data Supplement, available athttp://hyper.ahajournals.org).

Discussion

In this large multiethnic cohort, we demonstrate a strong association between decreasing carotid distensibility (increasing carotid stiffness) and increasing prevalence of TAC, as well as a graded increase in TAC score. This association is independent of age, sex, race, and traditional and emerging cardiovascular risk factors, and importantly remains broadly applicable to low and intermediate Framingham risk groups. In addition, we demonstrate regional variability in the association with calcific atherosclerosis, with carotid DC more highly correlated with TAC than CAC.

Distensibility Coefficient

We chose the DC as a measure of stiffness because of its intuitive calculation, its common use in the epidemiological literature,[27] and its use in the Rotterdam studies enabling a direct comparison of results.[18,20] Prespecified analysis with a single index also avoids problems with "multiple looks" seen in studies that test every index of stiffness. We did subsequently conduct an exploratory analysis using YM, a measure of arterial elasticity, which revealed similar associations although less strong point estimates of risk (please see http://hyper.ahajournals.org). This pattern is consistent with previous studies relating these 2 indices.[11]

Indices such as DC that rely on blood pressure have been criticized because of their reliance on pulse pressure, which is itself an independent predictor of cardiovascular risk.[28] To adjust for the influence of pulse pressure, we repeated our analyses adjusting for this variable, resulting in attenuated but continued statistically significant associations (see http://hyper.ahajournals.org). After adjustments for pulse

Table 2. Multivariable-Adjusted Prevalence Ratio (95% CI) for TAC by Decreasing Quartile of DC

	DC, Decreasing Quartiles, in 1/mm Hg×10^3			
Prevalence Ratio for TAC	Quartile 4 (≥3.02)	Quartile 3 (2.36 to 3.01)	Quartile 2 (1.78 to 2.35)	Quartile 1 (≤1.77)
Model 1	1 (ref group)	1.15 (0.90 to 1.47)	1.50 (1.19 to 1.89)	1.79 (1.41 to 2.26)
Model 2	1 (ref group)	1.17 (0.91 to 1.50)	1.43 (1.13 to 1.83)	1.52 (1.19 to 1.96)
Model 3	1 (ref group)	1.24 (0.95 to 1.64)	1.43 (1.09 to 1.87)	1.52 (1.15 to 2.00)

Model 1 was adjusted for age, sex, and race. Model 2 was model 1+body mass index, heart rate, low-density lipoprotein cholesterol, hypertension, diabetes mellitus, cigarette smoking, family history of heart attack, and cholesterol-lowering medications. Model 3 was model 2+log-transformed C-reactive protein, log-transformed CAC+1, and carotid IMT. ref indicates reference.

Table 3. Prevalence Ratio (95% CI) for TAC With 1-SD Decrease in DC

Characteristic	N	No. With TAC>0	Relative Risk (95% CI)	*P*
Age				
Tertile 1 (45 to 56 y)	2239	107	1.58 (0.70 to 3.57)	0.27
Tertile 2 (57 to 67 y)	2125	480	1.15 (0.97 to 1.36)	0.10
Tertile 3 (68 to 84 y)	2162	1239	1.33 (1.14 to 1.55)*	<0.001
Sex				
Women	3427	992	1.30 (1.10 to 1.54)*	0.002
Men	3099	834	1.21 (1.03 to 1.41)*	0.017
Race				
White	2517	814	1.27 (1.10 to 1.47)*	0.001
Chinese	783	252	1.24 (0.89 to 1.73)	0.21
Black	1779	401	1.17 (0.85 to 1.61)	0.34
Hispanic	1447	359	1.32 (0.96 to 1.82)	0.09
Risk factor status				
Normotensive	3613	651	1.34 (1.14 to 1.58)*	<0.001
Hypertension	2913	1175	1.21 (1.02 to 1.43)*	0.03
Nondiabetic	5605	1482	1.23 (1.09 to 1.39)*	0.001
Diabetes mellitus	921	334	1.46 (1.10 to 1.94)*	0.008
Nonsmoker	5681	1602	1.27 (1.12 to 1.45)*	<0.001
Smoking	845	224	1.22 (0.97 to 1.54)	0.09
Framingham risk score†				
Low (0% to 6%)	2890	414	1.30 (1.05 to 1.63)*	0.02
Intermediate (6% to 20%)	2570	806	1.21 (1.03 to 1.44)*	0.03
High (≥20%)	1066	606	1.12 (0.85 to 1.47)	0.42
Total	6526	1826	1.25 (1.12 to 1.41)*	<0.001

SD=1.1×10^{-3} mm Hg. Data were adjusted for age tertile, sex, race, body mass index, heart rate, low-density lipoprotein cholesterol, hypertension, diabetes mellitus, smoking, family history of heart attack, cholesterol-lowering medications, transformed C-reactive protein, log-transformed CAC+1, and carotid IMT when not first stratifying by these variables.

*Association was statistically significant ($P<0.05$).

†Data were adjusted for age tertile, sex, race, body mass index, heart rate, diabetes mellitus, family history of heart attack, cholesterol-lowering medications, transformed C-reactive protein, log-transformed CAC+1, and carotid IMT.

pressure, the stiffness parameter becomes more similar to a measure of carotid distention.[20]

Although inversely correlated ($\rho=-0.25$), our study demonstrates that DC provides information that is independent of carotid IMT (see Table 2, model 3). This is consistent with previous studies.[18,20] Both DC and carotid IMT can be calculated from the same longitudinal scanning sequence using a high-resolution ultrasound. This raises the possibility of combining these noninvasive measures for a more comprehensive evaluation of vascular disease.[29]

Table 4. Correlation Among DC, CAC, and TAC

	Correlation Coefficients [ρ] Between		
Characteristic	ρ DC, TAC	ρ DC, CAC	ρ TAC, CAC
Women	−0.349	−0.271	0.487
Men	−0.275	−0.214	0.441
White	−0.374	−0.279	0.450
Chinese	−0.361	−0.261	0.441
Black	−0.243	−0.172	0.387
Hispanic	−0.358	−0.269	0.454

CAC and TAC are defined as continuous variables by the following equation: natural log (calcification score+1). All of the individual correlations are significant at $P<0.001$. $P<0.001$ for ρ DC, TAC vs ρ DC, CAC for the entire population ($\rho=-0.315$ vs -0.221). Difference remains significant across both sexes ($P<0.01$) and all races: whites ($P<0.001$), Chinese ($P=0.03$), black ($P=0.03$), and Hispanic ($P=0.008$).

Carotid Distensibility and Arterial Calcification

Why is DC more highly correlated with TAC than CAC? There is increasing evidence that the determinants of calcification and atherosclerosis are different for different vascular beds.[30] For example, studies by Nasir et al[31] within MESA have shown that, whereas whites have more CAC than Chinese subjects, their burden of TAC is similar. Sex associations are reversed: although men have more CAC than women, women appear to have more TAC than men.[31] This observation has been corroborated by Post et al[32] with data from the Pennsylvania Amish, showing that male sex is associated with CAC and not TAC. In the Amish population, aging is more highly associated with TAC. CAC and TAC are in fact loosely correlated before the age of 50 years ($\rho=0.135$).

There are likely distinct features characterizing the pathophysiology of calcification within the thoracic aorta versus the coronary arteries. Histological studies demonstrate that calcification of the coronary arteries is largely confined to the intimal layer. However, within the large arteries, including the aorta, calcification can be present both in the intima and tunica media.[33] Medial calcification is more strongly associated with aging, diabetes mellitus, and severe renal disease.[34] Structural features of different vascular beds likely also play a role. The elastic carotid artery can be considered structurally more similar to central arteries (such as the aorta[35]) than the nonelastic predominantly conduit coronary arteries, perhaps contributing to the tighter correlation.

Although CAC is a well-established predictor of cardiovascular events,[36] TAC has been less thoroughly studied with regard to cardiovascular outcomes. TAC measured by plain radiography and transesophageal echocardiography has a well-established correlation with obstructive coronary disease.[37,38] TAC measured by CT is highly correlated with CAC and predicts the incidence and progression of CAC.[39] Among patients with stable angina pectoris, TAC is an independent predictor of adverse cardiovascular events.[40] However, among 2304 asymptomatic self-referred adults, TAC failed to predict events beyond the Framingham risk score and beyond CAC.[41] A total of 31% of patients (724 total patients) had measurable TAC in this study, likely limiting its discriminatory power. It has not been explored whether TAC predicts adverse aortic outcomes, such as aortic aneurysm, dissection, or rupture, although aortic atherosclerosis is closely associated with ischemic stroke.[34]

Limitations

Before clinical use of this application of carotid ultrasound can be established, the chicken-and-egg question remains paramount: does carotid stiffness precede the development of aortic calcification, or is calcinosis a generalized phenomenon that alters the elastic properties of the artery wall? The first major limitation of this study is its cross-sectional nature. Although we are able to describe the association of carotid stiffness with calcific atherosclerosis, we are unable to establish a temporal relationship. The use of measures of carotid stiffness would be augmented if early vascular disease was identified, in anticipation of the development of measurable calcification and atherosclerosis. We have planned follow-up studies within MESA to help address this question.

The second major limitation is the use of brachial pulse pressure rather than a direct measurement of carotid pulse pressure. Peripheral arteries, such as the brachial artery, have pressure wave reflection sites that are closer than for central arteries. Reflected waves travel faster on peripheral arteries, which are stiffer, than on the elastic central arteries, which, in asymptomatic patients, are more elastic. Because of this "amplification phenomenon," the pulse pressure in the brachial artery will be higher than in the carotid artery, which may lead to systematic underestimation of true carotid distensibility.[42] MESA participants did not undergo carotid applanation tonometry, which would be required for direct measurement of local carotid pressure. However, it has been suggested that the use of brachial blood pressure would in fact lead to systematic underestimation of the association between stiffness and adverse events.[43]

Perspectives

The results of this study suggest that noninvasive ultrasound measures of carotid artery stiffness demonstrate a dose-response association with calcification of the thoracic aorta. The independence of this relationship from carotid IMT, in addition to the greater association with TAC compared with CAC, raises important mechanistic questions and highlights the complexity of the interplay among stiffening, calcinosis, and atherosclerosis. In the future, a combination of these measurements may provide the most comprehensive evaluation of subclinical vascular disease. To evaluate the prognostic significance of these relationships, we have planned longitudinal studies within MESA.

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Disclosures

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SUPPLEMENTAL DATA FOR ONLINE PUBLICATION

SUPPLEMENTAL TABLES

S1.

Prevalence Ratio for TAC	**Young's Modulus** *(increasing quartiles)*			
	Quartile 1 (<897)	**Quartile 2** (897-1176)	**Quartile 3** (1176-1532)	**Quartile 4** (>1532)
Model	1 (ref group)	1.13 (0.90-1.42)	1.13 (0.90-1.42)	1.25 (1.00-1.56)

Model: Adjusted for age, gender, and race, body mass index, heart rate, LDL cholesterol, hypertension, diabetes mellitus, cigarette smoking, family history of heart attack, cholesterol-lowering medications, log transformed C-reactive protein, log transformed CAC+1, carotid IMT

Young's modulus: $\frac{D\,\Delta P}{\Delta D\,h}$

S2.

Prevalence Ratio for TAC	**Distensibility Coefficient** *(decreasing quartiles, in 1/mmHg x 10^3)*			
	Quartile 4 (≥3.02)	**Quartile 3** (2.36-3.01)	**Quartile 2** (1.78-2.35)	**Quartile 1** (≤1.77)
Model	1 (ref group)	1.20 (0.91-1.59)	1.37 (1.04-1.79)	1.35 (1.02-1.80)

Model 1: Adjusted for **pulse pressure**, age, gender, race, body mass index, heart rate, LDL cholesterol, hypertension, diabetes mellitus, cigarette smoking, family history of heart attack, cholesterol-lowering medications. log transformed C-reactive protein, log transformed CAC+1, carotid IMT