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Noninvasive Measurement of Carotid Extra-Media Thickness

Associations With Cardiovascular Risk Factors and Intima-Media Thickness

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OBJECTIVES We sought to develop a noninvasive technique to quantify the thickness of a segment of the carotid artery wall that incorporates the adventitia and to identify whether differences in this measure are associated with cardiovascular risk factors.

BACKGROUND There is increasing evidence that the arterial adventitia undergoes extensive structural alteration, including thickening, in response to arterial injury. However, there is currently no widely accepted noninvasive technique for studying the thickness of the arterial adventitia in humans.

METHODS The carotid artery and jugular vein were imaged simultaneously in longitudinal section with the use of high-resolution ultrasound. The distance from the jugular intima-lumen interface to the carotid media-adventitia margin was denominated as the carotid extra-media thickness (EMT). This measure includes the arterial adventitia but not the arterial intima or media. We measured the carotid EMT and intima-media thickness (IMT) in 175 subjects, including 54 with diabetes, 43 with dyslipidemia, 26 with other cardiovascular risk factors, and 52 healthy control subjects.

RESULTS When compared with control subjects, the EMT was increased in both the diabetes ($p < 0.0001$) and dyslipidemia ($p = 0.04$) groups. Multivariate linear regression analyses revealed that diabetes, high-density lipoprotein cholesterol (inverse association), and systolic blood pressure (J-shaped association) were the factors most strongly associated with EMT. These associations appear to be independent of carotid IMT.

CONCLUSIONS Carotid EMT can be assessed by ultrasonography. It is physically distinct from IMT and provides additional information concerning the vascular changes associated with cardiovascular risk factors. As such, the measurement of EMT, in addition to IMT, may provide a more complete indication of the structural modification of the vasculature associated with cardiovascular risk factors than that obtained by the measurement of carotid IMT alone. (J Am Coll Cardiol Img 2009;2:176–82) © 2009 by the American College of Cardiology Foundation

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Experimental evidence suggests that the adventitia undergoes extensive modification, including thickening, in response to arterial injury or in the presence of diabetes or hypercholesterolemia (1–4). Unlike intima-media thickness (IMT), there is currently no readily available technique for studying the arterial adventitia in vivo. However, given the evidence implicating the involvement of the adventitia in atherosclerosis, the ability to assess adventitial thickness may provide important information regarding the extent of atherosclerosis.

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The area between the jugular intima-lumen interface and the carotid media-adventitia margin consists predominantly of arterial adventitia and overcomes the sonographic limitations of defining the external limit of the adventitia. Other components of this "extra-media" region include interstitial tissue, the venous wall, which is unlikely to be altered by cardiovascular risk factors, and perivascular fat, which may be altered by obesity (5).

Thus, we sought to develop a noninvasive technique for imaging and quantifying the carotid extra-media thickness (EMT) in humans. We then examined whether EMT is increased in high-risk subjects with type 2 diabetes or dyslipidemia and attempted to identify the main metabolic determinants of EMT. Finally, we assessed whether the measurement of EMT in addition to IMT, provides additional information concerning vascular disease than that provided by IMT alone.

METHODS

Participant characteristics. We studied 177 subjects, ages 21 to 83 years: 52 had no cardiovascular risk factors and served as control subjects; 55 had type 2 diabetes (average duration 12.0 years [SD 10.2] and HbA1c 7.9% [SD 1.7]); 44 were nondiabetics with dyslipidemia (low-density lipoprotein cholesterol >4.14 mmol/l, triglycerides >2.26 mmol/l or high-density lipoprotein cholesterol [HDL-C] <1.04 mmol/l). To strengthen the power of our analyses examining the associations between EMT and cardiovascular risk factors, we studied a "mixed" cardiovascular risk group of 26 nondiabetic, nondyslipidemic subjects who were obese (body mass index [BMI] ≥30 kg/m^2, waist circumference ≥88 cm for women or ≥102 cm for men), smokers, had a previous myocardial infarct or stroke, or were hypertensive.

Participants were recruited by word of mouth, and from the outpatients' clinics at the Cardiovascular Hospital Louis Pradel and Hôpital Edouard Herriot, Lyon, France. All patients provided written informed consent, and the project was undertaken in accordance with French legislation (Huriet law).

Ultrasonography: IMT and EMT. Participants rested in a supine position for 10 min before bilateral examination of the carotid arteries with high-resolution ultrasound (Acuson Sequoia S512, Siemens, Mountain View, California) with a 8L5 linear-array transducer (8 MHz). Settings were kept constant for all scans. Carotid IMT was assessed just proximal to the carotid bulb as previously described (6). This technique has been previously demonstrated to have good reproducibility in our laboratory (7). All scans were measured by an experienced IMT reader, blinded to subject group, with the use of validated edge detection software.

EMT was assessed at the segment of the carotid artery where the distance between the jugular vein and carotid artery is smallest and readily imaged (approximately 1 to 1.5 cm proximal to the carotid bulb). The vessels were scanned such that the jugular wall-lumen interface and the carotid wall-lumen interface were both in focus (Fig. 1). The distance between the carotid media-adventitia interface and the jugular lumen was measured along a 0.3- to 1.0-cm long segment using semiautomated software (M'ATH SR version 2.0, Metris, France), such that the carotid media-adventitia interface was traced manually and the jugular lumen interface was automatically selected (Fig. 1).

ABBREVIATIONS AND ACRONYMS

BMI = body mass index
EMT = extra-media thickness
HDL-C = high-density lipoprotein cholesterol
IMT = intima-media thickness
SBP = systolic blood pressure

All scans were analyzed by 1 of 3 observers, with 90 (60%) of the scans being analyzed by at least 2 observers for analysis of interobserver variability. The 3 observers measured a total of 50 scans a second time, to calculate the intraobserver variability. Eleven participants were scanned twice for the assessment of interscan variability, with the repeat scan being conducted by a second sonographer, immediately following the first scan.

The mean EMT was calculated as the average from the left and right carotid arteries, and the maximum EMT was the single thickest point from the left and right carotid arteries. These were then averaged for all available measures from the 3 observers. Images suitable for offline, blinded anal-

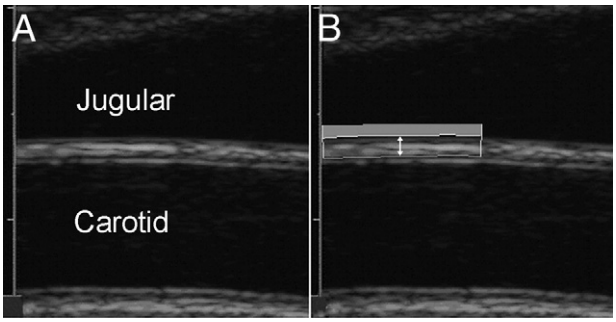

Figure 1. High-Resolution Ultrasound Image of the Carotid Extra-Media Thickness

(A) A longitudinal section of the carotid artery and jugular vein showing the **(B)** site and measurement of the carotid extra-media thickness, extending from the jugular intima-lumen interface through to the carotid media-adventitia margin, between 1 and 1.5 cm proximal to the carotid bifurcation. The carotid extra-media thickness includes the arterial adventitia yet is structurally distinct from the components of the arterial wall assessed by carotid intima-media thickness.

ysis of EMT were obtained from 175 subjects (52 control subjects, 54 diabetic subjects, 43 dyslipidemia, 26 "mixed" cardiovascular risk). One further subject was excluded from analyses involving IMT because of poor scan quality.

Statistical analysis. Carotid EMT was compared between the left and right sides by the use of paired *t* test. Graphical presentation of the distribution of EMT and IMT indicate that these measures are normally distributed. Associations between EMT, lumen diameter, and IMT were determined with the use of Pearson's correlation coefficient. Comparisons between group/controls were assessed for continuous variables by Student *t* test and by analysis of variance with post-hoc comparisons with Dunnett's *t* test, and for nominal variables by chi-square tests. Comparisons in which we used the Student *t* test and chi-square test were not corrected for multiple comparisons. The relationship between number of cardiovascular risk factors and EMT was assessed by regression analysis, and sex-heterogeneity was tested with an interaction term.

Age- and sex-adjusted linear regression analyses were used to predict EMT and IMT. The linearity of associations was examined with the use of centered quadratic variables. Variables with p values <0.05 in analyses of EMT or IMT, and those related to our primary hypothesis (diabetes and lipids), were included in a fully adjusted regression model. The residuals of the multivariate linear model are normally distributed, as determined by a Kolmogorov-Smirnov test. Because waist circumference was missing for 18 subjects, it was not used in the multivariate analysis. The relationship between cardiovascular risk factors and EMT was adjusted for IMT to determine the additional information concerning the variance in vascular structure captured by measuring EMT, compared with measuring IMT alone.

Statistical analyses were performed with SPSS software (version 15.0, SPSS Inc., Chicago, Illinois). Post-hoc power calculations indicate that we had >99% power to detect a statistically significant difference between control/diabetes groups, and 54% power for control/dyslipidemia. The regression analyses had 92% power to detect associations with a standardized β-coefficient of 0.250.

RESULTS

Carotid EMT. Patient characteristics for the 175 subjects are displayed in Table 1. In combined analyses of all subjects, the mean and maximum EMT were 722 μm (SD 122) and 804 μm (SD 142), respectively, for the left carotid, and 747 μm (SD 134) and 830 μm (SD 157), respectively, for the right carotid (mean $p = 0.044$ and maximum $p = 0.065$ for left vs. right). The combined left/right carotid EMT was mean 737 μm (SD 112) and maximum 880 μm (SD 158). The Pearson correlation coefficient between EMT and carotid artery diameter was 0.211 ($p = 0.009$) for mean thickness and 0.271 ($p = 0.0008$) for maximum thickness.

The combined intraobserver coefficient of variation from 50 scans measured twice by the same observer was 0.052 for mean EMT and 0.061 for maximum EMT. The combined interobserver coefficient of variation, calculated from 91 comparisons, was marginally lower for mean than maximum measures (0.078 for mean EMT and 0.107 for maximum EMT). Interscan variability was generally low (0.061 for mean EMT and 0.068 for maximum EMT).

EMT and cardiovascular risk factors. Carotid EMT was greater in the diabetes and dyslipidemia groups than in the healthy controls (Figs. 2A and 2B). This difference remained significant for the diabetes group after adjustment for age and sex (vs. controls: mean $p = 0.001$, maximum $p = 0.002$), but not for the dyslipidemia group (vs. controls: mean $p = 0.092$, maximum $p = 0.27$). EMT in the "mixed" cardiovascular risk group (obese, smokers, previous cardiovascular disease or hypertensive, without diabetes or dyslipidemia) was similar to controls (Table 1). The sum of cardiovascular risk factors (age ≥55 years, male sex, current smoker, obesity, dyslipidemia, hypertension, diabetes) was strongly,

Table 1. Patient Characteristics for Study Population

	Control (n = 52)	Diabetes (n = 54)	Dyslipidemia (n = 43)	"Mixed" CV Risk (n = 26)
Age, yrs	49.9 (8.5)	61.2 (9.2)§	51.2 (10.7)	49.1 (6.8)
Male sex, %	46	54	74†	50
Waist, cm	80.5 (9.6)	101.3 (11.9)§	98.4 (15.8)§	87.4 (13.0)
BMI, kg/m^2	22.8 (2.4)	28.4 (5.2)§	27.4 (5.0)§	25.4 (5.2)
Smoking status, %		*	†	§
Nonsmoker	77	76	51	46
Smoker	0	11	21	35
Ex-smoker	23	13	28	19
Glucose, mmol/l¶‖	4.95 (4.68, 5.32)	7.90 (6.90, 11.00)§	5.30 (5.00, 5.76)	5.06 (4.70, 5.42)
Triglycerides, mmol/l ¶‖	0.79 (0.58, 0.99)	1.66 (1.09, 2.27)§	1.54 (0.92, 2.28)§	0.95 (0.79, 1.06)
HDL-C, mmol/l	1.86 (0.47)	1.37 (0.40)§	1.30 (0.37)§	1.77 (0.43)
LDL-C, mmol/l	2.88 (0.65)	2.82 (0.99)	3.86 (1.12)§	3.02 (0.78)
Lipid-lowering treatment, %	0	69	65	0
SBP, mm Hg	113 (12)	130 (16)§	124 (14)‡	118 (15)
DBP, mm Hg	72 (7)	71 (10)	77 (11)	73 (10)
Hypertension, %	0	59	33	19
Previous CV disease, %	0	33	17	4
Mean IMT, μm	656 (86)	798 (114)§	753 (139)§	642 (91)
Maximum IMT, μm	848 (118)	1017 (131)§	980 (166)§	861 (160)
Mean EMT, μm	693 (99)	788 (108)§	736 (104)	724 (121)
Maximum EMT, μm	828 (161)	941 (135)‡	887 (161)	843 (154)

Data presented as mean (SD), unless otherwise stated. Analysis of variance with Dunnett's *t* test for multiple comparisons was used for continuous variables and the chi-square test was used for nominal variables, for comparisons with the control group. *$p < 0.05$ versus control group. †$p < 0.01$ versus control group. ‡$p < 0.001$ versus control group. §$p < 0.0001$ versus control group. ¶Log transformation was used for statistical analysis. ‖Data presented as median (25th, 75th percentile).
BMI = body mass index; CV = cardiovascular; DBP = diastolic blood pressure; EMT = extra-media thickness; HDL = high-density lipoprotein; IMT = intima-media thickness; LDL = low-density lipoprotein; SBP = systolic blood pressure.

and positively associated with EMT (Fig. 2C). This association was not modified by gender ($p_{heterogeneity} > 0.10$).

Participants in the thickest quartile of mean EMT were older; had greater waist circumferences, BMI, triglycerides and systolic blood pressure (SBP); decreased HDL-C; and increased prevalence of diabetes, cholesterol treatment, hypertension, and previous cardiovascular events (all $p < 0.05$ vs. lowest quartile, data not shown).

Age and male sex were associated with EMT, and after adjusting for these 2 factors, measures of adiposity (waist circumference, BMI, and obesity), smoking, diabetes, lipid-lowering treatment and triglycerides were all positively associated and HDL-C negatively associated with EMT (Table 2). Systolic blood pressure was associated with EMT in a nonlinear, J-shaped manner (Table 2) ($p > 0.10$ all other quadratic terms). A multivariate linear regression model indicated that diabetes, HDL-C, and SBP were the strongest determinants of EMT (Table 3), and that these were independent of other major cardiovascular risk factors. A model including lipid-lowering treatment, hypertension (yes/no), and previous cardiovascular disease showed similar associations for diabetes, HDL-C, and SBP, in addition to some evidence for an association between lipid-lowering treatment and mean EMT ($p = 0.031$).

Carotid IMT and cardiovascular risk factors. The results of age- and sex-adjusted linear regression analyses for IMT are shown in Table 2. A multivariate model identified age and BMI as the only independent determinants of IMT (Table 3).

EMT: relationship with carotid IMT. The Pearson correlation coefficient between carotid EMT and carotid IMT was 0.419 ($p < 0.0001$) for mean measures, and 0.358 ($p < 0.0001$) for maximum measures.

Further adjustment for IMT of the multivariate model (detailed in Table 3) did not greatly alter the associations of diabetes, HDL-C, and SBP with EMT (results not shown). The associations of cardiovascular risk factors with a combined "IMT + EMT" measure are shown in Table 2. The associations of this combined measure with some risk factors, most notably HDL-C, diabetes, triglycerides, and SBP, were stronger than that obtained by the measurement of IMT alone.

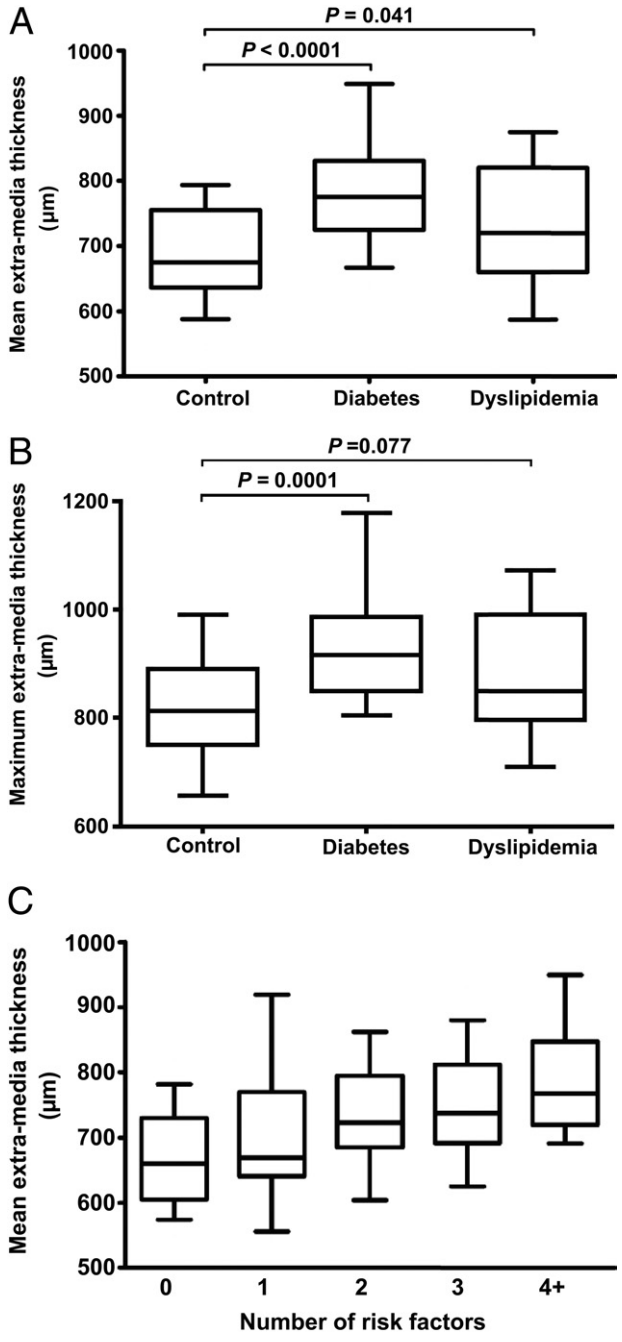

Figure 2. Extra-Media Thickness and Cardiovascular Risk Factors

Box plots of **(A)** mean and **(B)** maximum extra-media thickness in control, diabetes, and dyslipidemia groups. **(C)** Box plot of the mean extra-media thickness with increasing number of cardiovascular risk factors in subjects without evidence of previous cardiovascular disease (β-coefficient = 25.1, $p < 0.0001$). Risk factors were: male sex, age ≥55 years, diabetes, dyslipidemia, obesity, current smoking, and hypertension. **Box, line, and error bars** represent 10th, 25th, 50th (median), 75th, and 90th percentiles.

DISCUSSION

Our findings show that carotid EMT is increased in subjects with dyslipidemia and type 2 diabetes and is strongly associated with the total number of cardiovascular risk factors. The strongest individual factors associated with carotid EMT are age, diabetes, waist circumference, cigarette smoking, SBP (J-shaped association), and HDL-C (inverse association). Furthermore, some of the associations between EMT and cardiovascular risk factors appear to be independent of carotid IMT, most notably for diabetes, SBP, and HDL-C.

EMT is generally not able to be measured on images previously captured for quantification of carotid IMT, primarily because of the differences in the site (0 to 1 cm and 1 to 1.5 cm proximal to the carotid bifurcation for carotid IMT and EMT, respectively) and the necessity for the EMT scan to be focused on the venous far wall and arterial near wall. The layers of the vascular wall included in the EMT assessment are physically distinct from those measured with carotid IMT. In addition to the arterial adventitia, the other components of the EMT include the venous wall, perivascular and interstitial tissue, and perivascular fat deposits. The venous wall undergoes fibrous thickening (phlebosclerosis) in response to experimental stimuli (8). However, the venous wall does not appear to be altered by cardiovascular risk factors, with the exception of long-term exposure to venous hypertension, which may result in localized nonobstructive wall thickening (9).

Additionally, in multivariate regression models, we found that BMI is not independently associated with EMT, suggesting that perivascular fat deposits are not a major contributor to the variance of EMT. In contrast, there is a growing body of experimental evidence indicating that cardiovascular risk factors and mechanical injury are associated with structural changes to the adventitia and periadventitial tissue. This includes evidence that adventitial structure is modified in response to experimental hypercholesterolemia and diabetes in animal models (1,4,10). Changes in adventitial thickness also have been observed in response to arterial injury (3) and associated arterial remodeling, such that negative remodeling is associated with increases in adventitial thickness (11). However, the site chosen for assessment of EMT (1 to 1.5 cm proximal to the carotid bulb) is not a high-risk area for arterial plaque formation and, indeed, there were no subjects in this study with plaques at this site. Changes

in adventitial vaso vasorum, extracellular matrix, and cellular components may contribute to the differences in EMT observed in our study (1,4,12). It has been proposed that adventitial responses to stimuli are not merely markers of pathology, but rather influence arterial wall structure and function (13,14). These responses include the production by activated adventitial fibroblasts of reactive oxygen species, including superoxide, and the potent vasoconstrictor endothelin-1, which mediates medial smooth muscle cell tone (4).

We and others have previously inferred changes to carotid adventitial thickness in humans by comparing measurements of the entire arterial wall (including the arterial intima, media, and adventitial layers) by using magnetic resonance imaging with measurement of IMT alone (15). Others have used intraoperative high-frequency epicardial echocardiography to obtain detailed images of the coronary arteries (2), where the interface between the arterial adventitia and the surrounding tissue is more distinct. They demonstrated that the adventitial thickness of the left anterior descending coronary artery is increased in subjects with atherosclerosis; however, the number of patients was limited to 18, and the role of specific cardiovascular risk factors was not examined (2). To our knowledge, the present study is the first to simultaneously assess the thickness of the adventitial/peri-adventitial region and IMT in a large number of patients.

We compared EMT with IMT, an established noninvasive marker of atherosclerosis. The 2 measures were moderately correlated, and both were associated with cardiovascular risk factors. However, the proportion of variability due to modifiable cardiovascular risk factors was more marked for EMT (approximately 20%) than for IMT (approximately 10%). Furthermore, diabetes, HDL-C, and

Table 2. Linear Regression Analyses, Age- and Sex-Adjusted, for Associations Between Cardiovascular Risk Factors and Carotid EMT and IMT

	β-Coefficient				
	Mean EMT	Maximum EMT	Mean IMT	Maximum IMT	Mean EMT + Mean IMT
Age	2.52†	2.64*	7.18§	8.09§	9.77§
Male sex	25.2	63.8†	45.7†	68.7‡	76.1†
Waist	1.90†	3.00†	3.16§	3.54§	5.32§
BMI	3.34	5.34*	7.58§	8.08§	11.4§
BMI categories					
Healthy weight	0.000	0.000	0.000	0.000	0.000
Overweight	30.9	33.8	43.2*	71.6†	76.7*
Obese	49.0*	78.3*	95.3§	98.4‡	148§
Smoking status					
Nonsmoker	0.000	0.000	0.000	0.000	0.000
Smoker	51.0*	73.6*	22.2	17.9	56.6
Ex-smoker	4.84	−5.75	−2.82	−2.18	1.68
Diabetes	61.4†	82.4†	43.4*	42.4	108‡
Log glucose	16.1	94.2	54.6	20.0	92.3
Log triglycerides	77.6*	119*	81.7†	121†	162†
HDL-C	−58.9†	−89.2‡	−61.3‡	−77.1‡	−123§
LDL-C	−2.72	−5.83	0.183	13.8	−1.32
Lipid-lowering	48.9†	41.3	54.2†	67.6†	106‡
Hypertension	36.1	47.5	48.6†	45.8	87.0†
SBP	1.11	1.18	1.66†	1.51*	3.10‡
SBP^2	0.070†	0.072*	0.013	0.021	0.066
Previous CVD	20.0	43.6	29.1	53.6	50.7

*$p < 0.05$. †$p < 0.01$. ‡$p < 0.001$. §$p < 0.0001$.
CVD = cardiovascular disease; other abbreviations as in Table 1.

Table 3. Multivariate Linear Regression Model Examining the Associations Between Cardiovascular Risk Factors and Carotid EMT and IMT

	Mean EMT		Maximum EMT		Mean IMT		Maximum IMT	
	β-Coefficient	p Value	β-Coefficient	p Value	β-Coefficient	p Value	β-Coefficient	p Value
Age	0.789	0.35	1.07	0.34	6.24	<0.0001	7.09	<0.0001
Male sex	−3.96	0.82	8.12	0.72	13.1	0.46	26.2	0.26
BMI	1.23	0.47	3.43	0.13	5.99	0.0009	5.66	0.015
Smoker	25.6	0.27	57.7	0.053	12.4	0.60	13.3	0.67
Ex-smoker	10.3	0.60	0.006	1.00	−2.28	0.91	−2.97	0.91
Diabetes	54.5	0.009	77.9	0.005	7.67	0.72	11.0	0.69
Log triglycerides	−29.1	0.45	−56.9	0.26	−16.2	0.68	19.8	0.70
HDL-C	−49.3	0.023	−81.9	0.004	−31.7	0.15	−35.3	0.22
LDL-C	5.8	0.45	8.07	0.43	3.45	0.66	16.0	0.12
SBP	0.370	—*	–0.678	—*	0.938	0.11	0.789	0.30
SBP^2	0.066	0.003*	0.098	0.002*	—	—	—	—

A SBP^2 term was statistically significant for the association with EMT in crude analyses (adjusted only for age and sex), and consequently included in the EMT models. Two subjects were removed from each of the EMT models because of outlying residual values; n = 161 for EMT models and n = 162 for IMT models. *Combined p value for SBP and SBP^2 derived from the change in R^2 with the addition of these 2 variables to the model. Model fit characteristics for model including age and sex alone: mean EMT R^2=0.089; maximum EMT R^2=0.087; mean IMT R^2=0.380; maximum IMT R^2=0.329. Model fit characteristics for full model including all variables: mean EMT R^2= 0.272; maximum EMT R^2=0.302; mean IMT R^2=0.485; maximum IMT R^2= 0.422.
Abbreviations as in Table 1.

SBP were associated with EMT independent of IMT, which is consistent with EMT providing information concerning vascular structure that is otherwise not captured by the assessment of IMT alone. Although EMT and IMT may share a common etiology, they appear to represent different aspects of the vascular changes due to atherosclerosis. Whether or not EMT provides further information concerning the risk of future cardiovascular events remains unknown.

This study was designed to provide preliminary data concerning the associations of EMT with cardiovascular risk factors, specifically diabetes and dyslipidemia. Whether the observed associations were due to differences in age between these groups remains unknown; however, regression analyses suggest that diabetes is associated with increased EMT independent of concurrent risk factors including aging. Interaction terms suggest that the associations between cardiovascular risk factors and EMT were similar among all subject groups (data not shown). Further research is required to fully explore these and other associations.

The technique that we have developed for measuring carotid EMT requires little additional time or skill than that involved in a standard carotid IMT assessment. The portion of the vascular wall that is measured consists of the adventitia, is physically distinct from carotid IMT, and is associated with the prevalence of cardiovascular risk factors. As such, the assessment of carotid EMT, in addition to carotid IMT, may provide a more complete indication of the structural modifications to the vasculature associated with cardiovascular risk factors than that obtained by the measurement of carotid IMT alone.

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Key Words: adventitia ■ atherosclerosis ■ high-density lipoprotein cholesterol ■ diabetes ■ imaging ■ ultrasound ■ intima-media thickness ■ cardiovascular risk.