Arterial Compliance Adds to Conventional Risk Factors For Prediction of Angiographic Coronary Artery Disease

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Abstract and Introduction

Abstract

Background: Arterial compliance is related to left ventricular hypertrophy and risk for cardiovascular disease events; however, its association with coronary artery stenosis remains uncertain. We sought to assess the relation between lower extremity arterial compliance and presence of angiographically defined coronary artery disease.
Methods: Lower extremity arterial compliance was measured with the use of a noninvasive air plethysmography technique in 376 subjects undergoing routine diagnostic coronary angiography.
Results: Measures of calf arterial compliance were significantly associated with the presence of one or more stenoses >/=50% compared with no stenoses, even after adjustment for age, sex, smoking, diabetes, hypertension, hypercholesterolemia, and obesity (P = .03). Measures of thigh arterial compliance were also lower in subjects with disease, although this association did not reach statistical significance (P = .07). Receiver operator curves illustrate the incremental predictive ability of calf arterial compliance over and above age, sex, and conventional risk factors.
Conclusions; Lower extremity arterial compliance is associated with presence of significant coronary stenoses in a cardiac catheterization laboratory referral population. This observation lends support for additional efforts to determine the utility of vascular stiffness measures in both clinical and pre-clinical populations to guide treatment and prevention efforts.

Introduction

Loss of arterial compliance has been studied as both a cause and a consequence of vascular disease.[1] However, its utility as an independent cardiovascular disease risk factor is not yet well established.[2] Aortic stiffness is associated with cardiovascular risk factors,[3] and it is also associated with cardiovascular morbidity and mortality in older subjects[4,5] and in patients with hypertension,[6-9] diabetes,[10] end-stage renal disease,[11] and systolic dysfunction.[12,13] In long-term follow-up of a general population of French men, pulse pressure (a surrogate measure of arterial stiffness) was predictive of total and cardiovascular death.[14]

In animal models[15] and in humans,[16] arterial stiffness correlates with aortic atherosclerosis at necropsy. However, there are relatively few data examining the relation between measures of arterial stiffness and angiographically defined coronary disease. In one study, aortic and carotid arterial stiffness measured by ultrasound was greatest in those with 3-vessel coronary disease.[17] However, no attempt was made to determine if arterial stiffness was predictive after adjusting for other cardiovascular risk factors.

To determine if arterial stiffness is predictive of coronary disease independent of other cardiovascular disease risk factors, we measured lower extremity arterial compliance in a group of 376 subjects undergoing coronary angiography.

Methods

Patients

The study participants were recruited from men and women referred for diagnostic coronary angiography at four different medical centers. All subjects between 25 and 80 years of age with an ejection fraction of >40% who gave written informed consent were eligible. Exclusion criteria included previous coronary bypass, carotid, or lower extremity arterial surgery; significant valvular heart disease; uncontrolled hypertension or hypotension; unstable angina; myocardial infarction, cerebrovascular accident, or transient ischemic event within 30 days before study entry; or if the study physician considered the subject a suboptimal participant for other reasons.

In phase I of the study, 147 patients were recruited from two sites (North Carolina Baptist Hospital, Winston-Salem, NC, and University Hospital

Groningen, Groningen, The Netherlands). An additional 110 patients recruited from four sites (North Carolina Baptist Hospital, University Hospital Groningen, University of Miami [Miami, FL], and University Hospital Leiden, Leiden, The Netherlands) comprised phase II of the study. Phase III, conducted exclusively at the University of Miami, involved 132 patients. The 346 subjects with complete arterial compliance, angiographic, and cardiovascular risk factor data were included for these analyses.

Arterial Compliance

Cardiac cycle-dependent changes in local arterial volume in the thigh and calf were measured with the use of air plethysmography. Measurements were repeated at 12 different cuff pressures ranging from 20 mm Hg to 130 mm Hg, designed to span the range of diastolic pressure. The maximum change in arterial volume that occurred at the cuff pressure closest to but still above diastolic pressure was used to generate an estimate of compliance unbiased by load conditions in the artery. This maximum volume change per unit change in pulse pressure was normalized to a 50-mm Hg pulse pressure to provide a standardized measure of compliance ($MaxV_{50}$). Regulation of cuff pressures and recording of volume changes were made with the use of an internally and externally calibrated air plethysmographic device and PC-based computer interface (Vasogram, New York, NY).

Reproducibility

To estimate the biological and measurement variability in calf $MaxV_{50}$ and thigh $MaxV_{50}$, healthy subjects were studied twice on the same day, separated by 30 minutes, and once more on a different day, separated by >/=7 days. For all subjects, calf $MaxV_{50}$ measurements ranged from 1 to 3 mL, with an intrasubject standard deviation of 0.28 mL, which was 15% of the underlying mean across all subjects. The machine-to-machine standard deviation was 0.063, suggesting strong repeatability across machines. For all subjects, thigh $MaxV_{50}$ measurements ranged from 2.5 to 5.0 mL, with an intrasubject standard deviation of 0.45 mL, which was again ~15% of the underlying mean across all subjects. The machine-to-machine standard deviation thigh $MaxV_{50}$ was 0.078.

Coronary Angiography

Coronary angiograms in phases I and II were analyzed by means of previously validated quantitative coronary angiography techniques.[18-20] The systems determined minimum diameter, percent diameter stenosis, average diameter, and reference diameter for each of 10 standardized segments of the coronary tree. Certified technicians who were blinded to compliance measures interpreted the films at each site. In phase III, stenoses were diagrammed over the same 10 coronary segments, but amount of occlusion was determined visually by trained observers. For the purpose of this analysis, subjects were classified as having coronary artery disease if they had one or more epicardial coronary segments with >/=50% stenosis, based on quantitative coronary angiography or expert visual assessment.

Clinical Risk Factors

Information on patients' cardiac risk factors and demographic data were collected through the use of standardized questionnaires. Demographic data included patient sex (male or female) and patient age (years). Cardiovascular risk factors of interest included the following binary (yes/no) variables: tobacco use (current or previous), diabetes (diet, oral, or insulin-controlled), hyperlipidemia (any documented blood lipid abnormality), hypertension (indicated by prescribed antihypertensives), and presence of obesity (>/=30% above ideal weight).

Statistical Analysis

The Mantel Haentzel χ^2 test and logistic regression models were used to assess the association between individual cardiovascular risk factors or measures of arterial compliance and presence or absence of significant coronary stenoses. The odds ratio for the dichotomous risk factors represents the relative increase in odds of having coronary artery disease when the risk factor is present compared with when the factor is absent. For the continuous variables of calf $MaxV_{50}$ and thigh $MaxV_{50}$, the odds ratio corresponds to the relative increase in odds of disease associated with a 1 unit increase (roughly 25% to 30%) in the measure of arterial compliance. Multivariable logistic regression models were used to examine the association of coronary stenosis with the measures of arterial compliance after adjusting for age, sex, and cardiovascular risk factors.

Receiver operating characteristic (ROC) curves were produced to assess the ability of combinations of risk factors and arterial compliance to predict disease status as measured by coronary angiography. These curves plot the percentage of true-positives against the percentage of false-positives, as predicted by the logistic model for a range of cut-points taken across the continuous measures of arterial compliance. We used the area under these ROC curves across different predictive models to compare the ability of the models to discriminate predicted disease risk.

These analyses were designed to assess and describe the relations among the measures of arterial compliance and angiographically defined disease. As such, nominal 2-sided *P* values are presented for descriptive purposes only.

Results

Of the 346 patients considered in this analysis, 67% were men, 32% had a history of tobacco use, 58% had a history of hypertension, 19% had a history of diabetes, 44% had a history of hyperlipidemia, and 30% were obese (Table I). Significant coronary disease (one or more lesions with >/=50% stenosis) was present in 210 subjects (61%). Sixteen percent of the subjects had 3-vessel disease. The mean thigh $MaxV_{50}$ was 3.3 mL (range, 0.3 to 9.7 mL). The mean calf $MaxV_{50}$ was 1.8 mL (range, 0.2 to 4.8 mL).

The results of the risk factor-specific logistic regression models are presented in Table II. Among the cardiovascular risk factors, hyperlipidemia and smoking were significantly associated with presence of significant coronary artery disease ($P < .05$), and there was a nonsignificant trend toward greater disease prevalence among diabetics as well ($P = .06$). There was a stepwise reduction in prevalence of significant coronary disease across quartiles of calf $MaxV_{50}$ ($P = .02$) (Figure 1), but not thigh $MaxV_{50}$ ($P = .4$, data not shown). After adjusting for other cardiovascular risk factors, a 1-unit increase in calf $MaxV_{50}$ or thigh $MaxV_{50}$ were each associated with a 20% reduction in odds of having a significant coronary stenosis ($P = .03$ and 0.07, respectively). Because thigh $MaxV_{50}$ and calf $MaxV_{50}$ are highly correlated, reliable estimates of their joint effect could not be developed in a single model.

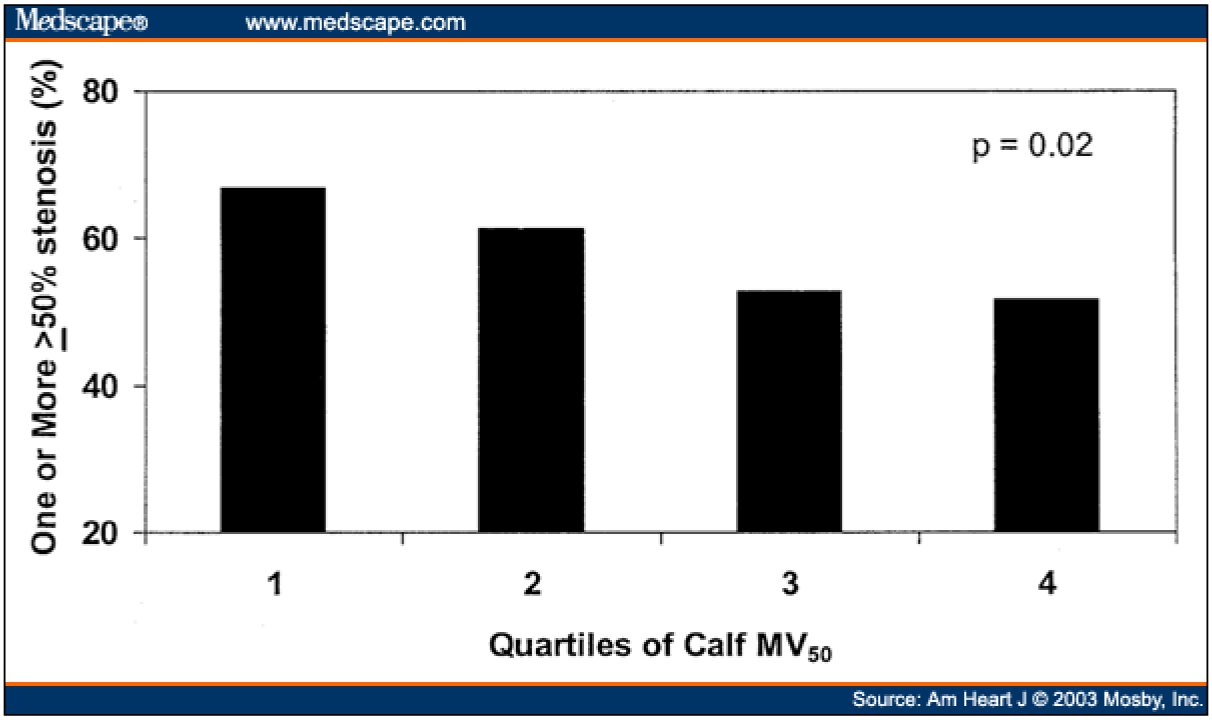

Figure 1. Distribution of significant coronary artery disease (1 or more >/=50% coronary stenoses) across quartiles of calf $MaxV_{50}$. *P* value is for the Mantel-Haenszel χ^2 test.

Predictive Ability of Arterial Compliance

Based on the area-under-the-curve (AUC) estimates generated from the ROC analyses (Table III), calf $MaxV_{50}$ measurement by itself performed roughly the same as the combination of the five cardiovascular risk factors when predicting coronary artery disease. However, it provides a small but significant increase in prediction of significant coronary artery disease not found in the clinical risk factors, as seen by the modest increase (from 0.727 to 0.736) in the AUC between the model containing only the 5 risk factors compared with the model containing both the risk factors and calf $MaxV_{50}$ (Figure 2). Thigh $MaxV_{50}$ was also associated with a small increase in AUC, but this increase was not statistically significant ($P = .07$) (Figure 3).

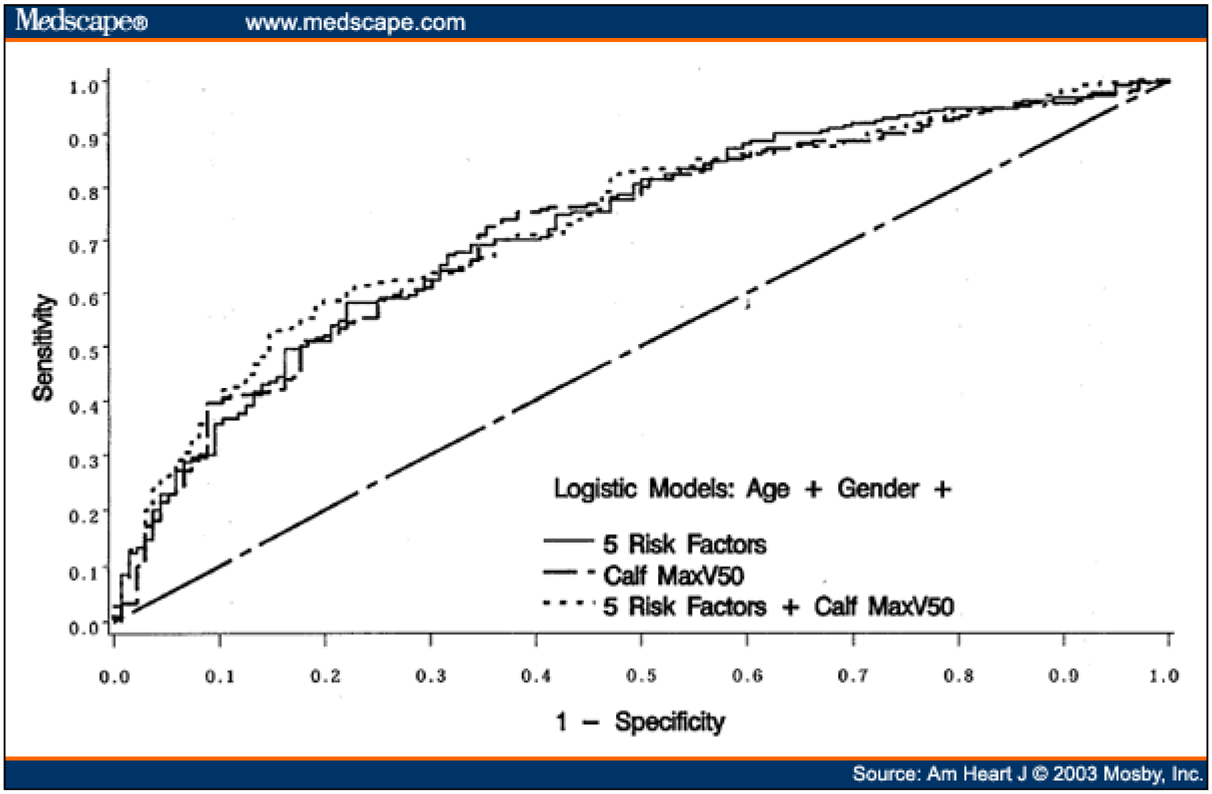

Figure 2. Receiver operator curves comparing predictive ability of 5 cardiovascular risk factors (diabetes, hypercholesterolemia, hypertension, obesity, and smoking), calf $MaxV_{50}$, and their combination to predict the presence of one or more significant coronary stenoses. Area under the curve for calf $MaxV_{50}$ plus age, sex, and the 5 cardiovascular risk factors was significantly greater than the model with age, sex, and the 5 factors alone (*P* = .03).

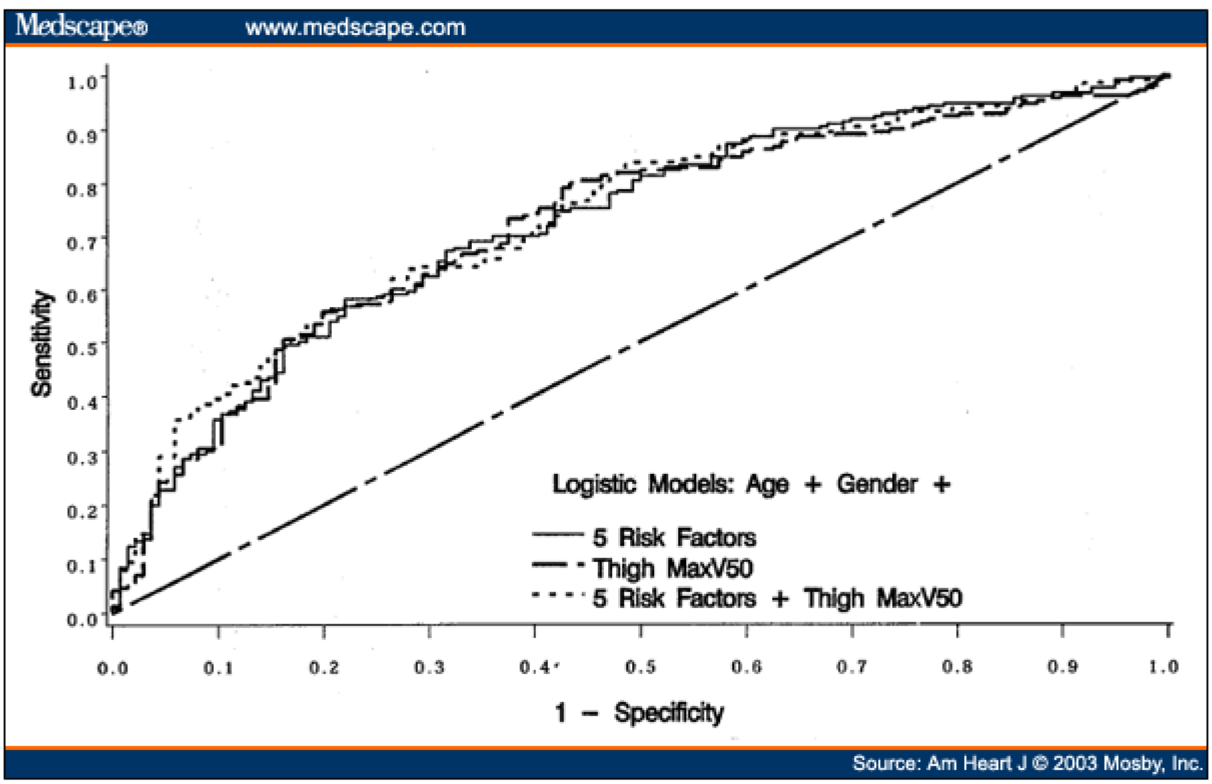

Figure 3. Receiver operator curves comparing predictive ability of 5 cardiovascular risk factors (diabetes,

hypercholesterolemia, hypertension, obesity, and smoking), thigh $MaxV_{50}$, and their combination to predict the presence of one or more significant coronary stenoses. Area under the curve for thigh $MaxV_{50}$ plus age, sex, and the 5 cardiovascular risk factors was greater than the model with age, sex, and the 5 factors alone, although this difference did not reach statistical significance (P = .07).

Discussion

Recently, the National Cholesterol Education Program Adult Treatment Panel issued revised guidelines concerning strategies for treatment of dyslipidemia for the prevention of cardiovascular disease (ATP III).[21] These new guidelines focus on recognition of the metabolic syndrome and diabetes as entities in need of more aggressive treatment. Based on these guidelines, millions more individuals may be considered eligible for drug therapy. Nevertheless, a critical appraisal of recent clinical trials of lipid lowering for primary and secondary prevention indicates that a large percentage of cardiovascular events will still occur in subjects who do not meet ATPIII criteria for drug treatment.[22] Furthermore, the AFCAPS/TexCAPS results indicate that even healthy subjects with normal total cholesterol but below-average HDL cholesterol can benefit from statin therapy.[23] Unfortunately, if statin use were extended to all US subjects who met eligibility criteria for AFCAPS/TexCAPS, the societal cost would be prohibitive. Therefore, a considerable challenge for physicians is to identify subjects who do not yet meet ATP III criteria for drug therapy but would nevertheless benefit from more aggressive treatment.

Various competing technologies offer promise to identify non-ATP III-eligible high-risk subjects. Certain biochemical markers (including C-reactive protein,[24] possibly homocysteine[25,26] or small, dense LDL particles[27,28]) may provide additional cardiovascular risk discrimination among otherwise apparently healthy subjects. Computerized tomographic scanning to detect coronary calcium[29,30] or ultrasound[31] to detect intima-media thickening of the carotid arteries are other strategies under consideration. A third class of technology involves measurement of vascular stiffness as an indicator of early or preclinical disease.

There are several reasons to consider vascular stiffness, especially in the peripheral arteries, as an ideal tool to identify high-risk individuals or individuals with early disease. First, there are simple, noninvasive, and inexpensive strategies to measure vascular stiffness that could easily be used in primary-care settings—precisely where prevention efforts would be maximally effective. The device used in the current study is a small, portable, fully automated, computer-assisted device, and testing takes ~20 minutes to complete. Second, evidence suggests that peripheral vascular atherosclerosis, especially in the distal aorta, may occur long before the development of occlusive coronary disease.[32] Third, numerous studies have shown correlations between measures of vascular stiffness and cardiovascular events.[4-14] In addition, decreased central aortic compliance causes systolic hypertension, left ventricular hypertrophy, and diastolic dysfunction[33] that together are responsible for nearly half the cases of congestive heart failure in this country. Nevertheless, the current data demonstrating the value of measures of vascular stiffness as a predictor of existing disease are limited by small studies, imprecise measures of compliance, and a failure to demonstrate an incremental value of the measure of vascular stiffness beyond conventional cardiovascular risk factors.

In the current study, lower-extremity arterial compliance measured with an automated air plethysmography technique was independently associated with presence of coronary disease measured by angiography. This association remained significant even after accounting for hypercholesterolemia and other cardiovascular risk factors. The incremental value of this simple test beyond conventional risk factors was further illustrated by examination of the ROC curves. These data are consistent with earlier work demonstrating the correlation between these measures and accumulation of aortic atherosclerosis in a nonhuman primate model of vascular disease.[15]

Our sample size was modest, thereby limiting the precision of our estimates of the strength of the association. Furthermore, the data were collected from a clinical catheterization laboratory referral cohort, which could have introduced selection bias with unpredictable effects on the results. Assessment of extent of disease may have varied among the participating centers. In 3 of the 4 centers, angiograms were analyzed by means of standardized quantitative coronary angiography techniques. However, in the fourth center, only visual estimates of disease were available. This heterogeneity in classification of the outcome may have introduced additional variance, making it more difficult to detect an association. The fact that an association was evident despite this limitation lends credence to the validity of the finding. Finally, no data are available on the subsequent clinical outcomes in these subjects. More data are needed linking these measures to future risk of disease events.

This study indicates that lower-extremity arterial compliance is significantly inversely associated with coronary disease independent of conventional cardiovascular risk factors in a cardiac catheterization laboratory referral cohort. These data provide proof-of-principle that peripheral measures of vascular stiffness may be another indicator of extent of coronary disease and suggest that additional efforts are warranted to examine the potential utility of such measured in preclinical and clinical populations to help guide treatment decisions for primary and secondary prevention of coronary heart disease.

Tables

Table I. Demographics, cardiovascular risk factors, and measures of arterial compliance in subjects with and without coronary artery disease (CAD)

	CAD(-)	CAD(+)
Demographics	n = 136	n = 210
Age (y)	54 ± 10	57 ± 10
Female (%)	68 (50)	55 (26)

CAD risk factors (%)		
1.6	92 (68)	61 (77)
Hypertension	76 (56)	43 (54)
Diabetes	19 (14)	14 (18)
Elevated lipids	50 (37)	31 (39)
Obese	46 (34)	23 (29)
Arterial compliance		
Calf max V_{50} (mean ± SD) (mL)	1.9 ± 0.8	1.8 ± 0.8
Thigh max V_{50} (mean ± SD) (mL)	3.5 ± 1.8	3.3 ± 1.6

Table II. *P* values from logistic regression models predicting presence or absence of significant coronary stenosis using measures of arterial compliance[*]

Risk factors	**OR**	**95% CI**	***P***
Calf max V_{50}	0.7	0.52-0.97	.03
Thigh max V_{50}	0.9	0.76-1.01	.07

[*]Adjusted for age, sex, tobacco use (current or previous), diabetes (diet, oral, or insulin-controlled), hyperlipidemia (any documented elevated blood lipids), hypertension (indicated by prescribed antihypertensives), and obesity status (>/=30% above ideal weight). *OR,* Odd ratio.

Table III. Area under the ROC curve (AUC) from logistic regression models predicting coronary artery disease using measures of arterial compliance and cardiovascular risk factors[*] (after adjusting for age and sex)

Predictor variables	**AUC**
5 Risk factors	0.727
Calf max V_{50}	0.721
5 Risk factors + calf max V_{50}	0.736
Thigh max V_{50}	0.722
5 Risk factors + thigh max V_{50}	0.734

[*]Risk factors include tobacco use (current or previous), diabetes (diet, oral, or insulin-controlled), hyperlipidemia (any documented elevated blood lipids), hypertension (indicated by prescribed antihypertensives), and obesity status (>/=30% above ideal weight).

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