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Relationship of Peripheral Arterial Compliance and Standard Cardiovascular Risk Factors

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Abnormalities of peripheral arterial compliance are clinically useful markers of atherosclerosis and risk of vascular events. Local peripheral arterial compliance can be easily and accurately assessed in the clinic by computer-controlled pulse volume recordings (air plethysmography). The purpose of this study was to investigate the relationship between clinical cardiovascular risk factors, a surrogate of atherosclerotic burden, and peripheral arterial compliance in the thigh and calf determined by quantification of local pulse volume recordings in patients undergoing coronary angiography. Peripheral arterial compliance in the thigh and calf was measured in 346 patients undergoing diagnostic cardiac catheterization at 4 centers. Demographic and cardiovascular risk factor data were collected, and their relationship to local arterial compliance examined using a new device that assesses maximal local arterial volume change in an extremity segment. Pulse volume recordings detected decreased local arterial compliance in the thigh associated with a history of hypertension ($p < 0.0001$), diabetes mellitus ($p = 0.0001$), and hyperlipidemia ($p = 0.0007$). In the calf, this arterial compliance measure was associated with a history of hypertension ($p < 0.0001$) and diabetes mellitus ($p = 0.002$). Females had lower arterial compliance than males in the thigh ($p = 0.003$) and calf ($p < 0.0001$). Limited evidence of lower arterial compliance in the thigh was found for those with obesity ($p = 0.07$). This procedure also demonstrated that subjects with multiple cardiovascular risk factors had lower arterial compliance in the thigh than subjects with no or 1 risk factor ($p = 0.0001$). Peripheral arterial compliance determined by air plethysmography is strongly associated with standard cardiovascular risk factors. The noninvasive measurement of local arterial compliance by regional pulse volume recording may be a useful adjunct for cardiovascular risk stratification early in the course of the disease as well as for monitoring vascular response to therapy.

Introduction

Atherosclerotic vascular disease remains the leading cause of morbidity and mortality in industrialized societies despite advances in treatment and prevention. In an effort to improve outcomes in this disorder, researchers and clinicians are beginning to focus on interventions in patients with earlier stages of this disease.[1,2] However, a limitation of applying this strategy too broadly is the exposure of patients at low risk to the potential adverse effects and high costs of these thera-

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pies.[3-6] The development of diagnostic techniques that identify patients with preclinical disease or at high risk for future clinical events is desirable. These techniques would enable clinicians to tailor the intensity of preventive strategies to appropriate patient populations. Although several diagnostic methods for risk stratification are being studied, none has achieved widespread clinical acceptance.[7-10]

Peripheral arterial disease is a powerful predictor of future cardiovascular events.[11] Currently, only advanced stages of peripheral arterial disease can be reliably identified clinically or noninvasively with standard office-based techniques. Abnormalities of local peripheral arterial compliance, on the other hand, precede the onset of the clinical manifestations of peripheral arterial disease, and thus may be clinically useful as a marker of early disease and future risk.

A new noninvasive method for directly determining local arterial compliance in the lower extremities using air plethysmography has been developed.

Unlike other techniques that measure systemic arterial compliance, this device directly measures compliance in segments of the thigh and calf. Other advantages of this technique include low cost, ease of performance, portability, and the capacity to be performed at point of care. Measurements based on this approach correlate with the presence and extent of coronary artery disease in a group of 346 patients undergoing coronary angiography.[12] Standard cardiovascular risk factors correlate with atherosclerotic burden,[7,13,14] and are a useful surrogate for testing new diagnostic screening methods. Therefore, as a further step in evaluating this method as a risk stratification tool, we investigated the relationship between local arterial compliance measured by air plethysmography and traditional coronary risk factors obtained by patient history.

Methods

Subjects

The study was a multicenter effort conducted in 3 phases from 1995 to 2000. All patients scheduled by their physicians for diagnostic coronary

Table I. Inclusion/exclusion criteria for Vasogram™ clinical study.

Inclusion Criteria	Exclusion Criteria
Male or non-pregnant female	Previous coronary bypass, carotid, or lower extremity arterial surgery
25–80 yr of age*	Significant valvular heart disease‡
Ejection fraction > 40%†	Uncontrolled hypertension or hypotension
Written informed consent	Unstable angina altering cardiac function‡
Approval of treating physician	Cerebrovascular accident, MI or TIA within last 30 days prior to study entry, if determined to alter cardiac function at study entry (phases I and II only)
Coronary angiography, Vasogram™ testing and carotid ultrasound (phases I and II only) completed within 60 days with no intervening events	Previous cardiac transplantation
	Considered an inadequate participant for this study by the study physician (due to medication, systemic alteration, etc)

MI = myocardial infarction; TIA = transient ischemic attack.
*Both genders and a wide range of ages were included to simulate the population to be tested with this device.
†Eliminates subjects with severe myocardial damage and associated advanced coronary artery disease.
‡Significant valvular heart disease and unstable angina known to affect peripheral arterial waveforms.

angiography at an investigational site and meeting the established inclusion/exclusion criteria (Table I) were eligible for recruitment into the study.

In phase I, 147 patients were recruited from 2 sites (Wake Forest University, Winston-Salem, NC; and University Hospital Groningen, Groningen, the Netherlands). An additional 110 patients were recruited from 4 sites (Wake Forest University; Groningen University; University of Miami, Miami, FL; and Leiden University Medical Center, Leiden, the Netherlands) and comprised phase II. Phase III, conducted exclusively at the University of Miami, involved 132 patients. Due to technical difficulties and missing data, 43 patients were excluded, and the total cohort available for analysis was 346. All patients with complete demographic and coronary risk factor data, compliance measurements, and angiography were included in the analyses. Coronary artery disease was assessed by quantitative angiography in phases I and II and by standard coronary angiography in phase III. Inclusion and exclusion criteria, clinical data collection, and measurements of compliance were the same in all 3 phases. The institutional review boards of all 4 centers approved the protocol.

Clinical and Demographic Risk Factors

Cardiovascular risk factors and demographics were collected by questionnaire. Demographic data included subject gender (male or female) and age in years. Cardiovascular risk factors of interest included the following dichotomous variables: history of tobacco use (current or previous), history of hypertension (indicated by prescribed antihypertensives), history of diabetes mellitus (diet, oral, or insulin-controlled), history of hyperlipidemia (any documented increased blood lipid levels), and obesity status (≥ 30% above ideal weight).

Patient demographics and clinical risk factors are shown in Table II. Hypertension and obesity were significantly more common in females, while more men had a history of tobacco use.

Coronary Angiography

Sixty-one percent of patients had coronary artery disease, defined as at least 1 coronary artery with ≥ 50% diameter stenosis. The results of coronary angiography by gender and number of diseased vessels are shown in Table III.

Determination of Peripheral Arterial Compliance

Peripheral arterial compliance at the thigh and calf levels was measured with the Vasogram (Vasocor, Inc.). The Vasogram system is a computer-controlled air plethysmograph designed for clinical use. The device consists of an air pump, calibration chamber, and high-resolution pressure transducer. The interface with the patient is via standard blood pressure cuffs (Figure 1).

The cuffs are placed at the thigh and calf, and measurements at these levels are taken indepen-

Table II. Demographics and risk factors (%).

Characteristics	Total (n = 346)	Males (n = 230)	Females (n = 116)
Mean age (yr)	57.0 (SD 10.0)	56.7 (SD 10.4)	59.9 (SD 9.7)
Tobacco use	74	84	56
Hypertension	58	54	66
Diabetes mellitus	19	18	22
Hyperlipidemia	44	43	46
Obesity	30	27	37

SD = standard deviation.

Table III. Coronary angiography: distribution of disease.

NDV	Total N (%)	Males N (%)	Females N (%)
0	136 (39)	68 (30)	68 (59)
1	79 (23)	55 (24)	24 (20)
2	74 (21)	60 (26)	14 (12)
3	57 (17)	47 (20)	10 (9)

Diseased vessel = ≥ 50% diameter stenosis; NDV = number of diseased vessels.

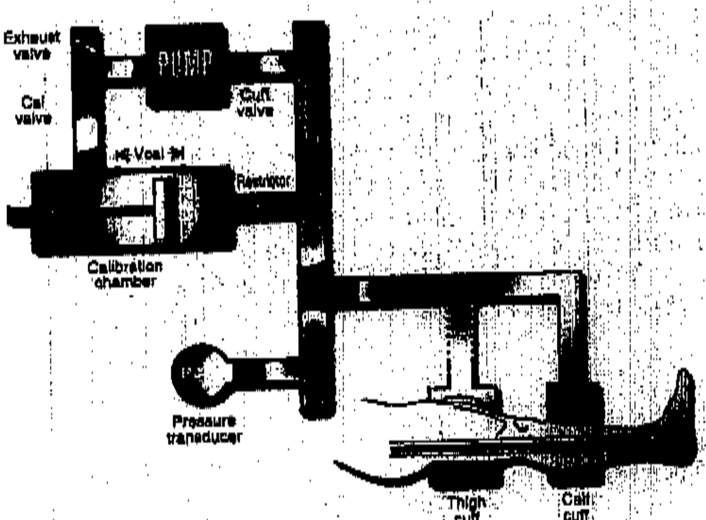
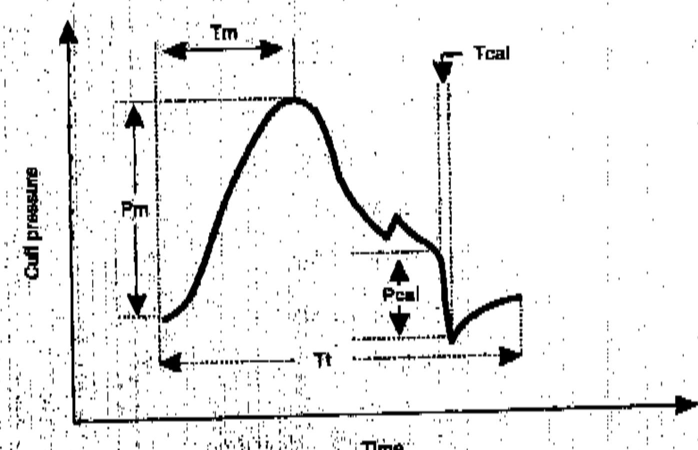


Figure 1. Diagram of Vasogram components, which include standard blood pressure cuffs, pump, valving, calibration chamber and high-resolution pressure transducer.

How it works. By producing a relationship between maximum segmental arterial volume change (Vm) for each mean cuff pressure (Pc), the following endpoint can be measured directly: MaxV50, maximum arterial volume change per 50 mm Hg pulse pressure. Reduction in this parameter suggests loss of arterial compliance. This parameter is normalized to allow comparisons between patients.

dently. For this study, cuff pressures were changed from 20 to 130 mm Hg in 10-mm Hg increments. At each pressure, the Vasogram measures segmental limb volume change as a function of time during the cardiac cycle. During the early stages of diastole, a calibration volume (Vcal) of 0.65 mL rapidly expands the system volume. This introduction of volume produces an abrupt change in pressure (Pcal). With the measurement of the maximum pressure change (Pm) during the cardiac cycle of interest and Pcal, it is possible to determine the local volume change during that cycle (Figure 2). This procedure is performed for the cuff pressure range previously mentioned. With this information the peak volume change (Vm) at each cuff pressure is plotted as a function of mean cuff pressure (Pc). This is illustrated in Figure 3. To determine the local arterial compliance, the maximum volume change (MaxV) is identified from this curve and divided by the subject's systemic pulse pressure. We normalize this value to a 50-mm Hg pulse pressure to facilitate comparison among patients and quote the compliance as MaxV50 in millimeters. Higher scores for MaxV50 correspond to more compliant arteries. Testing, which takes approximately 20 minutes to complete, is fully automated and may be performed in virtually any examining room.

Figure 2. Cuff pressure (Pc) as function of time during the cardiac cycle. Introduction of 0.65 mL (Vcal) in early diastole causes a pressure change (Pcal) that, along with the maximum pressure change (Pm), is used to calculate local volume change.



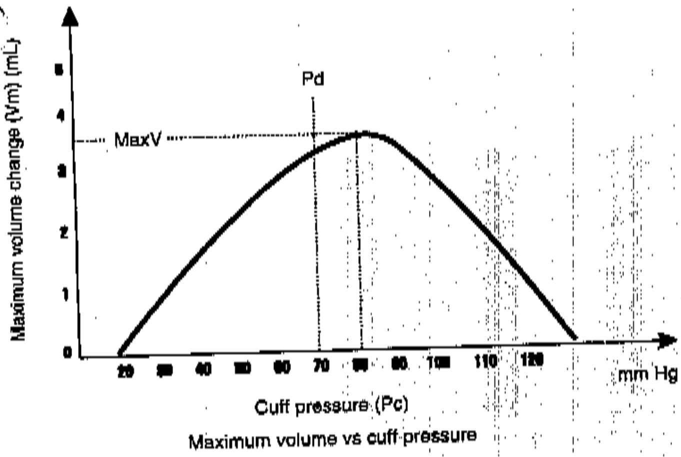


Figure 3. Peak volume change (Vm) as a function of mean cuff pressure (Pc). The maximum volume change (MaxV) occurs when mean cuff pressure is just above the diastolic pressure (Pd).

Statistical Analysis

We first examined the relationship of each individual clinical risk factor with thigh MaxV50 and calf MaxV50. Differences in mean thigh and calf MaxV50 between populations with a specific risk factor and those without were tested using a two-sample t test.

We next used a series of general linear regression models, including models for all subjects and gender-specific models, to examine which of these risk factor relationships remained significant in the presence of other demographic and clinical variables. Because this is an exploratory analysis, p values are considered descriptive and no multiple comparison adjustments were made.

Results

The mean thigh MaxV50 for the cohort was 3.3 mL with a range of 0.3 to 9.7 mL. The mean calf MaxV50 was 1.8 mL with a range of 0.2 to 4.8 mL.

Relationship of Individual Risk Factors to Thigh and Calf MaxV50

The mean thigh MaxV50 and calf MaxV50 by presence (+) or absence (–) of each of the risk factors are presented in Figures 4 and 5. For a specific risk factor, an asterisk indicates differences in mean MaxV50 with p values of 0.05 or less. Standard error bars represent the upper 95% confidence limit. These t tests show a significant difference in mean thigh MaxV50 for gender ($p = 0.003$), hypertension ($p < 0.0001$), diabetes mellitus ($p = 0.0001$), and hyperlipi-

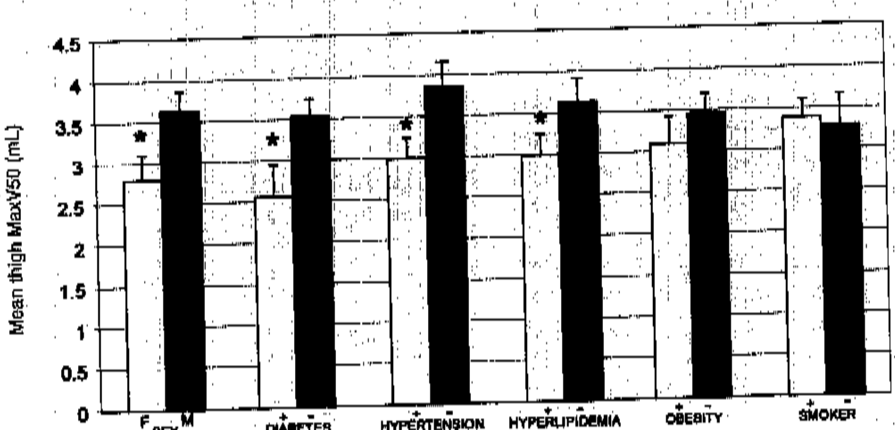


Figure 4. Mean thigh MaxV50 in males, females, and in subjects with and without a history of diabetes mellitus, hypertension, hyperlipidemia, obesity, and smoking. (+) = presence of risk factor, (–) = absence of risk factor. *Significant p value (≤ 0.01) from t test. Error bars represent 95% confidence limit.

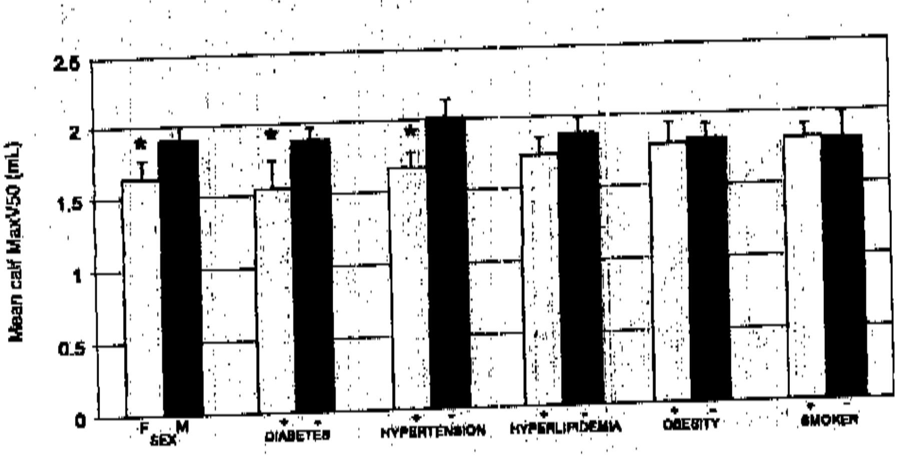


Figure 5. Mean calf MaxV50 in males, females and in subjects with and without a history of diabetes mellitus, hypertension, hyperlipidemia, obesity and smoking. *Significant p value (≤0.01) from t test. Error bars represent 95% confidence limit.

demia ($p = 0.0007$). A difference in mean calf MaxV50 was observed for gender ($p < 0.0001$), hypertension ($p < 0.0001$), and diabetes ($p = 0.002$). Obesity was not significantly related to either thigh MaxV50 or calf MaxV50, but non-obese patients had more compliant arteries on average in the thigh ($p = 0.07$).

Relationship of Arterial Compliance to Multiple Risk Factors

Two multiple regression type models were used to examine the joint effect of different risk factors on arterial compliance.

Each model used either the thigh MaxV50 or the calf MaxV50 as outcome variables and all five risk factors, along with gender and age as joint predictors. The relationships described previously were consistently replicated in these models.

The estimates obtained from the regression models, shown in Tables IV and V, represent the mean increase or decrease in thigh MaxV50 or mean calf MaxV50 for each level of the predictor while controlling for all other predictors in the model. For example, the estimate of 0.71 mL for the predictor of gender (Table IV) represents the mean increase in thigh MaxV50 for males, controlling for the other risk factors in the model. Similarly, the estimate of 1.90 mL is the increment in mean calf MaxV50 for each year of life, controlling for the other risk factors in the model

Table IV. Thigh MaxV50 vs demographic and clinical risk factors.

	Thigh MaxV50 (mL)	
Predictor	Estimate (SE)	p Value
Male	0.71 (0.189)	0.0002
Hx diabetes mellitus	−0.73 (0.230)	0.0018
Hx elevated lipids	−0.45 (0.182)	0.0127
Hx hypertension	−0.66 (0.183)	0.0004

Hx = history of; SE = standard error.

Table V. Calf MaxV50 vs demographic and clinical risk factors.

	Calf MaxV50 (mL)	
Predictor	Estimate(SE)	p Value
Age − 55	−0.01 (0.004)	0.0129
Male	0.22 (0.086)	0.0120
Hx diabetes mellitus	−0.25 (0.10)	0.0190
Hx hypertension	−0.29 (0.084)	0.0006

Hx = history of; SE = standard error.

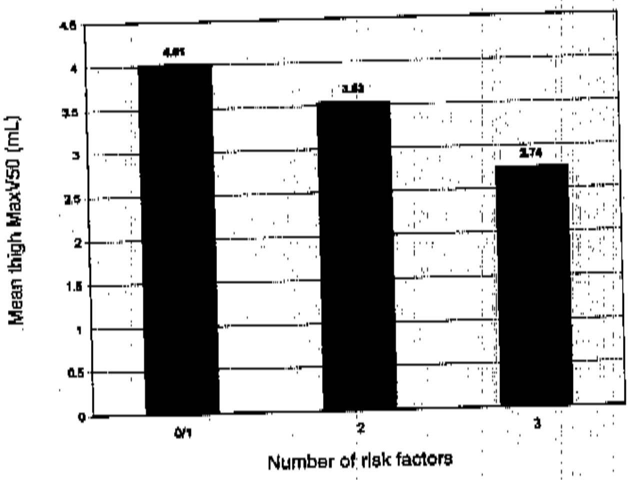


Figure 6. Mean thigh MaxV50 as function of the number of risk factors.

(Table V). The demographic factor of gender and the clinical risk factors of hypertension and diabetes mellitus are strongly associated with both thigh MaxV50 and calf MaxV50. In addition, the clinical risk factor of hyperlipidemia is strongly associated with thigh MaxV50, and the demographic factor of age is strongly associated with calf MaxV50. Tobacco use and obesity are not associated with thigh or calf arterial compliance in this multivariable analysis.

Figure 6 demonstrates mean thigh MaxV50 as a function of the number of risk factors. The data indicate that as persons have increasing numbers of risk factors, the mean thigh MaxV50 decreases, suggesting that patients with multiple risk factors tend to have lower arterial compliance in the thigh. An analysis of variance model showed strong evidence of linear decreases in mean arterial compliance in the thigh with an increasing number of risk factors. There was a statistically significant difference between subjects with 0 or 1 and 3 risk factors ($p = 0.0001$).

Discussion

Modification of reversible cardiovascular risk factors has been shown to reduce cardiovascular mortality in primary and secondary prevention trials.[2,15] An important goal of preventive cardiology is to optimally match the intensity of risk reduction therapies in patients to an accurate estimate of their future incidence of vascular events.[16] Several diagnostic methods that attempt to achieve this risk stratification are currently in use or under investigation. These include clinical multivariable risk factor assessment,[7] carotid intima-media thickness measured by B-mode ultrasound,[8] electron beam computed tomography of the coronary arteries (EBCT),[9] and ankle-brachial blood pressure index (ABI).[10] Each of these methods has limitations, and none has achieved widespread acceptance. Although relatively inexpensive and convenient for the office practitioner, clinical algorithms, such as the Framingham Risk Profile and the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) guidelines, fail to identify all patients at risk.[17] Furthermore, because of the increasingly recognized complex and multifactorial pathogenesis of atherosclerosis, a significant number of patients experiencing coronary events do not have any of the traditional risk factors.[18] However, these patients have been recently shown to benefit from lipid lowering.[19] Incorporation of emerging risk factors into algorithms may improve accuracy but at the cost of increased complexity and expense.[20] Direct assessment of plaque morphology or arterial function may conceivably overcome this problem by integrating the combined effects of established, emerging, and yet to be discovered risk factors. For this to be effective it must be low cost and available in physician's offices.

Carotid intima-media thickness measurements may be too technically demanding for office-based use. EBCT is expensive, cannot be performed at point of care, and has diminished specificity in the elderly.[21] The ABI detects advanced peripheral arterial disease and thus may not identify patients at the stage of their disease when risk management can be optimally initiated.

Peripheral arterial compliance has been shown to correlate with atherosclerosis in humans and experimental models of atherosclerosis.[22,23] As atherosclerosis develops, there is generalized thickening of the walls of the large peripheral arteries, particularly the intima and media. This thickening is associated with a localized decrease in compliance in these large arteries. These changes in peripheral arterial compliance may precede the development of hemodynamically significant lesions and abnormalities of ABI. Therefore, measuring peripheral arterial compliance may identify patients with early stages of atherosclerosis, when risk reduction strategies are most effective. Pulse volume recordings or air plethysmography is an established modality for noninvasively diagnosing and localizing hemodynamically significant peripheral arterial disease.[24] Air plethysmography can be adapted to measure local peripheral arterial compliance by converting changes in pulsatile pressure in a limb detected by a cuff to segmental limb volume changes. This direct measurement of local compliance differs from other methods that measure systemic arterial compliance and may be a superior indicator of atherosclerosis. Other advantages of this technique include reproducibility, portability, technical ease of performance, modest operator training requirements, and low cost. Therefore, the measurement of arterial compliance by air plethysmography has the potential to be an office-based tool for cardiovascular risk stratification by primary care providers.

In this study of 346 patients undergoing diagnostic coronary angiography, female gender, hypertension, diabetes mellitus, and hyperlipidemia were independently associated with decreased local arterial compliance in the thigh. In the calf female gender, hypertension and diabetes mellitus were independently associated with decreased compliance. Local arterial compliance in the calf decreased with advancing age while thigh arterial compliance showed no relationship to age. In males, a history of tobacco use and obesity were independently associated with decreased arterial compliance in the thigh.

Several features and findings of this study merit further comment. The population studied was a serial group of patients who were assessed for CAD by angiography and had a high probability of having active disease. Although 39% of the patients had no vessels with greater than a 50% stenosis, most had lumenal irregularities and therefore documented evidence of coronary artery disease. It seems highly probable that virtually all of these patients would have been found to have intimal-medial disease assessed by intravascular ultrasound or other devices that measure properties of the arterial wall rather than the lumen. Therefore, the relationships with risk factors in this study are best considered as being drawn from a population with atherosclerotic disease.

The finding of a lower arterial compliance in women compared to men confirms the work of other investigators using different methods to record arterial compliance.[25,26] These findings suggest that once women develop atherosclerosis in the coronary distribution, it is also expressed in the periphery and that smaller arteries and stature or other gender-specific factors further reduce compliance.[25,26]

It is also possible that because of the well-known gender bias in catheterization referral, women were required to have more risk factors than men before being referred for an invasive evaluation.[27-29] In our study, females had significantly more hypertension and obesity than males. Thus, a more dense clustering of risk factors may have contributed to the lower arterial compliance observed in females in this study. The current data suggest that arterial compliance for assessing atherosclerotic risk will require separation by gender.

Hyperlipidemia was assessed by questionnaire, and quantitative lipid analysis was not performed. However, self-reporting of coronary risk factors has been shown to correlate with outcomes.[30] Also, a history of hyperlipidemia may be representative of the information available to primary care providers during an initial evaluation. Because we foresee air plethysmography as a diagnostic tool for primary care providers, we thought correlating arterial compliance with historical risk factors that are obtained during an initial patient interview by primary care providers was important. Studies examining the relationship of peripheral arterial compliance and detailed lipoprotein analysis are ongoing.

The lack of a stronger association between smoking and arterial compliance in the lower leg is initially surprising in view of the known association of peripheral arterial disease with tobacco use.[31] However, this must be considered in the context of the select nature of our patients who had been referred for coronary angiography. Several thrombolytic trials have also observed a "smokers paradox."[32] In these trials, smokers presenting with myocardial infarction had less extensive coronary artery disease than their nonsmoking counterparts.

The proposed explanation is that smoking is more thrombogenic than atherogenic, and may thus cause symptoms in the presence of less advanced atherosclerosis.[33] Because we hypothesize that arterial compliance measured by air plethysmography predominantly reflects a more generalized disease activity intrinsic to the artery walls with scarring and reduced elasticity, a similar explanation may account for our results.

Conclusion

The relationship of standard cardiovascular risk factors with decreased peripheral arterial compliance as measured by air plethysmography parallels the relationship of these risk factors to atherosclerotic burden and cardiovascular events. These findings, in conjunction with the findings of a correlation between arterial compliance and extent of coronary artery disease[12] suggest that the measurement of local arterial compliance is an important and potentially useful clinical parameter. The ease and low cost of measuring peripheral arterial compliance by air plethysmography compared to other modalities make it an attractive office-based device for risk stratification. Ongoing studies are currently under way to determine average compliance values for age and gender. Further studies are needed to determine if this device will be useful in following vascular response to effective treatment of risk factors.

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