Relationship Between Arterial Stiffness and Subclinical Aortic Atherosclerosis

David M. Herrington, MD, MHS; W. Virgil Brown, MD; Lori Mosca, MD, PhD; Warren Davis, MD;
Barry Eggleston, MS; W. Gregory Hundley, MD; Jeffrey Raines, PhD

Background—Noninvasive measures of arterial compliance may be useful for the detection of subclinical atherosclerosis.

Methods and Results—Measures of calf and thigh arterial compliance (MaxV50) were recorded in 267 subjects who also underwent MRI of the distal aorta to quantify distal aorta atherosclerosis. The average of calf and thigh MaxV50 was strongly predictive of extent of aortic atherosclerosis and risk of being in the top quartile of aortic atherosclerosis after adjustment for the Framingham Coronary Risk Score (FCRS) or the combination of the FCRS and C-reactive protein ($P<0.0001$). The areas under the receiver operating curves predicting the top quartile of gender-specific aortic atherosclerosis were 0.57, 0.60, and 0.75 for models containing the FCRS, the FCRS and C-reactive protein, and the FCRS, C-reactive protein, and the average of calf and thigh MaxV50.

Conclusions—Lower-extremity arterial compliance may identify subjects with extensive subclinical atherosclerosis. Further studies examining the potential value of arterial stiffness as a screening tool to guide initiation of more aggressive preventive interventions are warranted. (*Circulation*. 2004;110:432-437.)

Key Words: atherosclerosis ■ aorta ■ magnetic resonance imaging

A substantial number of coronary events occur each year in individuals who currently do not qualify for drug therapy based on The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII)[1] or other primary prevention guidelines.[2] Results from the AFCAPS/TexCAPS study[3] and the Heart Protection Study[4] indicate that many such patients may nevertheless benefit from statin therapy. However, indiscriminate use of statin therapy and other pharmacological interventions in low- or intermediate-risk patients would be prohibitively expensive and would subject large numbers of individuals to unnecessary side effects. Thus, more effective strategies are required to direct drug therapy to those non-ATPIII drug therapy–eligible individuals most likely to benefit from more aggressive treatment. Strategies designed to predict early disease, rather than clinical or anatomic manifestations of advanced disease, would be desirable for the selection of subjects for early or more aggressive preventive interventions.

One potential screening test for consideration is the measurement of arterial compliance. Simple, noninvasive measures of arterial compliance are feasible and correlate with development of experimental atherosclerosis in nonhuman primates.[5] Recently, lower-extremity arterial compliance was shown to be predictive of extent of coronary atherosclerosis in patients undergoing coronary angiography.[6] The purpose of the present study was to examine the association between lower-extremity arterial compliance and extent of abdominal aortic atherosclerosis as determined by MRI and to evaluate the predictive value of these measures above and beyond conventional and novel risk factors. Because atherosclerosis commonly occurs in the abdominal aorta earlier than in other vascular territories,[7] the abdominal aorta is an ideal location for studies designed to identify subjects predisposed to develop atherosclerosis.

Methods

Study Population

This cross-sectional study was conducted at the Atlanta Veterans Administration Hospital, Columbia University Medical Center, Jackson Memorial Hospital at the University of Miami Medical Center, and Wake Forest University Medical Center. The study design was approved by the internal review boards at each of the participating institutions. The study was designed to recruit at least 320 subjects with approximately equal numbers of subjects into 8 blocks cross-classified by gender and 4 levels of cardiovascular risk.

Risk Group 1 was composed of healthy subjects free of cardiovascular disease with a body mass index <40 kg/m² and a 10-year risk for a future coronary heart disease (CHD) event of <10% based on the Framingham Coronary Risk Score (FCRS). Subjects were classified as free of cardiovascular disease if they had no history of CHD and a normal resting ECG, a negative Rose Angina Questionnaire, and an ankle/brachial index >0.90. Risk Group 2 was defined as subjects free of cardiovascular disease but with a Framingham 10-year risk for CHD ≥10% but ≤20%. Risk Group 3, the CHD-equivalent group, included individuals free of cardiovascular disease but with a Framingham CHD 10-year risk of >20%, diabetes, an ankle/brachial index <0.90, or evidence of cerebrovas-
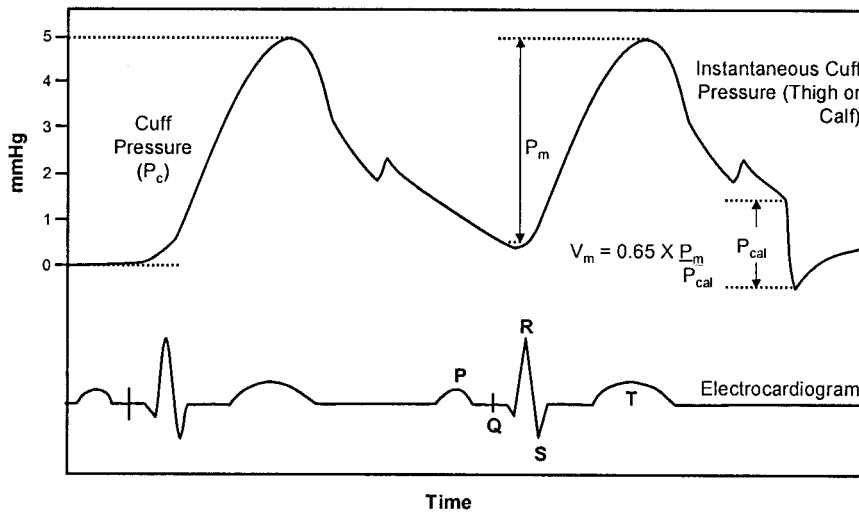
Figure 1. Cuff pressure (P_c) is measured on instantaneous basis. During early diastole, system rapidly expands cuff volume by 0.65 mL, which produces step reduction (P_{cal}) in instantaneous cuff pressure. Maximum pressure change in cuff for cardiac cycle is also measured (P_m). Knowing P_{cal}, P_m, and expansion volume, it is possible to calculate maximum volume change (V_m) associated with cardiac cycle.

cular disease. Risk Group 4 included subjects with coronary artery disease documented by cardiac catheterization (at least 1 lesion with a diameter >50% stenosis) in a major epicardial coronary artery, a prior Q-wave myocardial infarction, or history of coronary revascularization.

The age range for subjects in all risk groups was 35 to 69 years for males and 45 to 79 years for females. Subjects were excluded from the study if they had active infections (excluding skin infections); if they were taking antibiotics, immunosuppressive drugs, or steroids; or if the site's principal investigator considered them to be inappropriate for the study.

Subject Evaluation

All eligible subjects signed a consent form. At the baseline visit, cardiovascular risk status was established on the basis of physical examination and responses to standardized questionnaires, an ECG was obtained, and blood samples were taken for measurement of plasma lipids, C-reactive protein (CRP), and other blood analytes. The Emory Lipid Research Laboratory, a participant in the CDC/NHLBI Lipid Standardization Program, performed all analyses from freshly isolated EDTA plasma on the Beckman CX7 chemistry autoanalyzer. Total triglycerides and cholesterol were determined by enzymatic methods (Beckman Coulter Diagnostics). Direct HDL and direct LDL cholesterol levels were obtained with homogeneous assays (Equal Diagnostics). The high-sensitivity CRP assays were performed on a Beckman LX-20 analyzer (Beckman Coulter) with an "Ultra CRP" assay manufactured by Polymadco, Inc. The assay range available is from 0 to 5 or 0 to 15 mg/L. Calibrators are traceable to international reference preparations.

Measurements of arterial compliance were obtained during visits 1 through 3. At visit 4, an MRI of the abdominal and thoracic aorta was performed. The protocol required visits 1 through 3 be completed within a 3-week window and visit 4 be completed within 6 weeks of Visit 1.

Determination of Peripheral Arterial Compliance

Peripheral arterial compliance was measured with a fully automated, computer-controlled air plethysmograph designed for clinical use (Vasogram, Vasocor Inc.). 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 placed at the thigh and calf, with measurements at these levels taken independently. For this study, cuff pressures were inflated to 30 mm Hg below diastolic pressure, and segmental limb volume change as a function of time during the cardiac cycle was recorded (Figure 1). The cuff pressure was then increased in 10-mm Hg increments and the process repeated until the peak cardiac cycle dependent volume change was reached. At each cuff pressure, during early diastole, a calibration volume of 0.65 mL was rapidly introduced to calibrate the system. To determine the local arterial compliance, the maximum volume change (MaxV) was divided by the subject's brachial pulse pressure. This value was normalized to a 50-mm Hg pulse pressure (MaxV50) to facilitate comparison among patients. Higher scores for MaxV50 correspond to more compliant arteries. Additional normalization for body size (height or body surface area) did not alter the associations between calf and thigh MaxV50 and the outcomes of interest; therefore, results are expressed as change in volume (in milliliters) per 50-mm Hg change in pressure.

The correlations between paired measures of calf and thigh MaxV50 obtained during the first and second visits were 0.77 ($P<0.0001$) and 0.79 ($P<0.0001$), respectively. For the purpose of these analyses, the mean results from visit 1 through visit 3 were used.

Determination of Atherosclerotic Burden by MRI

Images of the wall of the abdominal aorta were acquired with fast-spin echo double-inversion recovery techniques[8,9] with 1.5-Tesla full-body imaging systems (2 GEMS, 1 Picker, and 1 Philips) with torso array coils wrapped around the abdomen. Axial images were acquired from the renal arteries to the aortic bifurcation in 1-cm increments (5-mm-thick slice with 5-mm gap). Both T2 and proton-density–weighted (PDW) images were acquired according to previously published techniques with ECG gating and respiratory compensation incorporating a 2-cm field of view and a 256×256 acquisition matrix with no phase wrap.[8,9] Other imaging parameters included: repetition time equal to 2 RR intervals, echo time equal to 12 ms (PDW) and 60 ms (T2-weighted), 2 excitations, 32 to 64 echo-train length, ±64-kHz receiver bandwidth, and chemical shift suppression. The total time for imaging of the abdominal aorta was ≈30 minutes.

On acquisition, images were archived in DICOM II format and transferred to the core imaging reading center by FTP transfer or optical disk. With software approved for beta testing by the Food and Drug Administration,[10,11] the lumen and outer wall boundary of the abdominal aorta were identified and manually traced in each slice on both the T2 and PDW image.[12] For all but 14 of the cases, the tracing resulting from the T2-weighted scan was used for subsequent analysis. In 14 cases, the outer boundary or luminal surface could not be accurately identified in >25% of its circumference. In these cases, clear identification of the lumen surface occurred on the PDW image and therefore was selected for subsequent analysis. This technique has been shown to be the most accurate in identifying the true wall boundary compared with ex vivo and in vivo plaque morphology.[13] The area of the lumen was identified as the total number of pixels within the lumen circumference multiplied by the pixel dimensions (200/256=0.78 mm on side). The total vessel area was defined as the
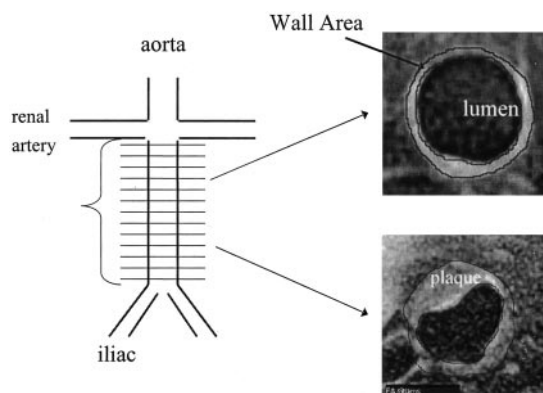
Figure 2. Schematic of image slice acquisition strategy and MRI images of 2 distal aortic cross sections. Outer boundary indicates adventitial surface, whereas inner boundary represents blood-intimal interface. % Wall area is 54% in image on left and 28% in image on right.

total number of pixels within the circumference of the outer wall multiplied by the pixel dimensions.

Wall area was defined as the difference between total vessel area and lumen area. Percent wall area was defined as the ratio of wall area to total area (% wall area $=100\times$wall area/total vessel area). The mean % wall area was defined as the mean of the slice-specific % wall area across all slices of the abdominal aorta (Figure 2). Twenty-two subjects underwent repeat scanning of the abdominal aorta on separate days at 1-week intervals and subsequent measurement of % wall area. The correlation coefficient was 0.98 for these repeated measures. Limited imaging of the ascending and descending thoracic aorta was also performed; however, significant thickening of the aortic wall was so infrequent that analysis was uninformative (data not shown).

Statistical Analysis

The primary objective was to evaluate whether calf MaxV50 and thigh Max V50 are associated with atherosclerotic burden as measured by mean % wall area in the abdominal aorta. A secondary objective was to compare the predictive ability of the calf and thigh MaxV50 to that of conventional measures of cardiovascular risk, including the FCRS and plasma level of CRP.

Simple descriptive statistics were used to describe the characteristics of the study population and the distribution of the raw measures of arterial compliance. General linear models were used to describe the association between the measures of arterial compliance and extent of aortic atherosclerosis. These models were performed in the total cohort and the subset of low- and intermediate-risk subjects (FCRS $<20\%$, n=208). Additional models were developed to further adjust for conventional cardiovascular risk factors or the FCRS and CRP. Risk factors included are age, gender, current smoking status, history of hypertension, history of diabetes, body mass index, LDL/HDL ratio, family history of CHD, and current statin use. Additional secondary analyses were generated with a series of logistic regression models. These models used a binary outcome, defined as being above or below the upper quartile of mean % wall area. These models were adjusted for the same set of conventional cardiovascular risk factors used in the linear models. Receiver operating curves were constructed to graphically illustrate the ability of the average of calf and thigh MaxV50 to estimate the likelihood of an individual being in the highest quartile of aortic atherosclerosis. Nested models were compared with the likelihood ratio test.[14] All statistical analyses were performed with SAS version 8.02.

Results

Study Population

The study enrolled 343 subjects, of whom 282 underwent abdominal MRI. Of these, 268 (95%) had sufficient quality

TABLE 1. Characteristics of the Study Population

Characteristic	Value
N	256
Gender	
Male, n (%)	130 (51)
Female, n (%)	126 (49)
Risk group, n (%)	
1	74 (29)
2	65 (25)
3	63 (25)
4	54 (21)
Age, y, mean (range)	57.8 (35–79)
Hypertension, n (%)	93 (36)
Diabetes, n (%)	72 (28)
Smoker, n (%)	56 (22)
BMI >30 kg/m^2, n (%)	72 (28)
Family history of CVD, n (%)	138 (54)
Statin use, n (%)	63 (25)
Total cholesterol, mg/dL, mean (SD)	191.0 (38.9)
LDL cholesterol, mg/dL, mean (SD)	124.5 (36.4)
FCRS, mean (SD)	11.9 (7.8)
CRP, mg/dL, mean (SD)	3.5 (4.9)

BMI indicates body mass index; CVD, cardiovascular disease.

MRI scans to be included for analysis. An additional 12 subjects were excluded because of missing arterial compliance, cardiovascular risk factor, or CRP data (Table 1). The baseline characteristics of the subjects that had incomplete MRI or arterial compliance data were not significantly different from the final cohort (data not shown).

Association of Arterial Compliance With Aortic Atherosclerosis

The mean % wall area averaged over all the subjects was 36.8 (range 29.04 to 49.56). Figure 3 shows mean % wall area among participants stratified by quartile of calf or thigh MaxV50. Mean % Wall Thickness and Mean (calf, thigh) MaxV50 were split on their respective medians and the positive value calculated for low arterial compliance to predict increased aortic atherosclerosis. Among the entire cohort, the positive predictive value was 0.71, whereas in the subset of subjects with FCRS $<20\%$ it was 0.70. In regression models of mean % wall area, both calf and thigh MaxV50 were significantly associated with extent of aortic atherosclerosis ($P<0.0001$ for each). After adjustment for age, gender, diabetes, hypertension, LDL/HDL ratio, family history of premature coronary disease, body mass index, and current statin use, both calf and thigh MaxV50 remained independently associated with aortic atherosclerosis ($P<0.0001$ and <0.0001 respectively). Similar results were obtained when the analyses were limited to subjects with FCRS $<20\%$.

To compare the relative ability to predict extent of aortic atherosclerosis, calf and thigh MaxV50 and their average were compared with the FCRS and the FCRS combined with CRP as predictors of extent of aortic atherosclerosis. Calf and
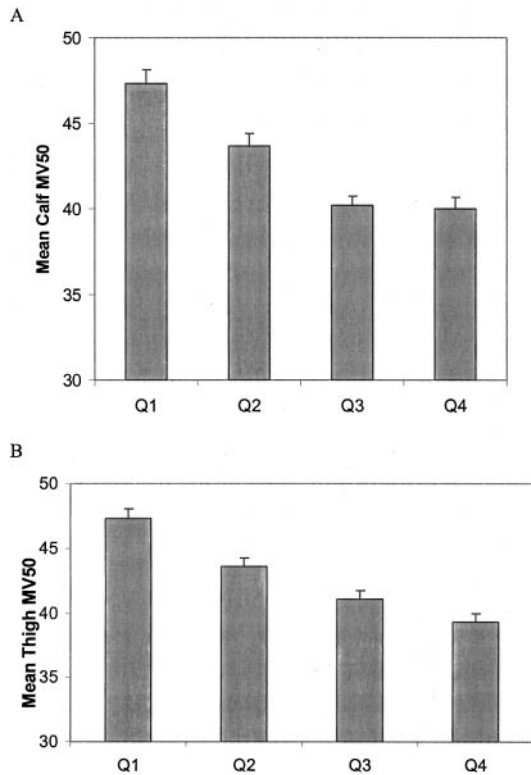
Figure 3. Mean calf (A) or thigh (B) Max V50 stratified by quartile (Q) of mean % wall area. P_{trend} <0.0001 for each.

thigh MaxV50 or their average accounted for 17% to 22% of the variance in mean % wall area (P<0.0001). In contrast, the FCRS only accounted for 1% of the variability in mean % wall area (P=0.22), and the FCRS in combination with CRP accounted for only 3% of the variance (P=0.02). The relative ability of arterial compliance to predict aortic atherosclerosis compared with FCRS and CRP remained the same when the analyses were limited to subjects with FCRS <20% (Table 2).

Finally, a series of logistic models were fit to asses the value of arterial compliance to predict extensive atherosclerotic burden, defined as the highest quartile of mean % wall area of the aorta. To determine the incremental value of arterial compliance over conventional strategies, models that included the FCRS and the FCRS and CRP were compared with a model that also included the average of calf and thigh MaxV50. The results of these models can be summarized using the area under the receiver operating curve (Figure 4.).The model containing gender-adjusted measures of arterial compliance was significantly more predictive of extensive aortic atherosclerosis than the FCRS and CRP model (P<0.0001) or the FCRS-only model (P<0.0001), with areas under the receiver operating curves of 0.75, 0.60, and 0.57, respectively.

Discussion

In this study, noninvasive measures of peripheral arterial compliance were strongly and independently associated with presence and extent of aortic atherosclerosis as measured by abdominal MRI. Reduced arterial compliance was more strongly associated with aortic atherosclerosis than the FCRS

TABLE 2.   Association of Arterial Stiffness, FCRS, and CRP With Aortic Atherosclerosis*

	Total Cohort (n=256)		FCRS <20% (n=208)	
	Partial R^2	$P*$	Partial R^2	$P*$
Calf MaxV50	0.17	<0.0001	0.17	<0.0001
Thigh MaxV50	0.20	<0.0001	0.19	<0.0001
Mean (calf, thigh)	0.22	<0.0001	0.21	<0.0001
Framingham	0.01	0.22	0.02	0.05
Framingham+CRP	0.03	0.02	0.05	0.008
Mean (calf, thigh)† (after adjustment for FCRS and CRP)	0.20	<0.0001	0.19	<0.0001

*Models with calf or thigh MaxV50 or their average are adjusted for gender.
†Model R^2=0.22 for each.

or the combination of FCRS and CRP. These data, coupled with results of earlier work demonstrating an association between peripheral arterial compliance and coronary atherosclerosis,[6] suggest these measures could be used as an additional means to identify individuals with extensive atherosclerosis burden who are at high risk for coronary events and who may therefore benefit from more aggressive intervention. Despite the considerable strengths of alternate screening tests, such as measurement of coronary calcium by computed tomography or flow-mediated vasodilation as an indicator of endothelial function, these tests are limited because they are costly or difficult to perform with precision. Additionally, coronary calcium is focused on detection of a later stage of atherosclerosis. Newer strategies, such as changes in digital skin perfusion after a period of transient ischemia, continue to be evaluated.[15]
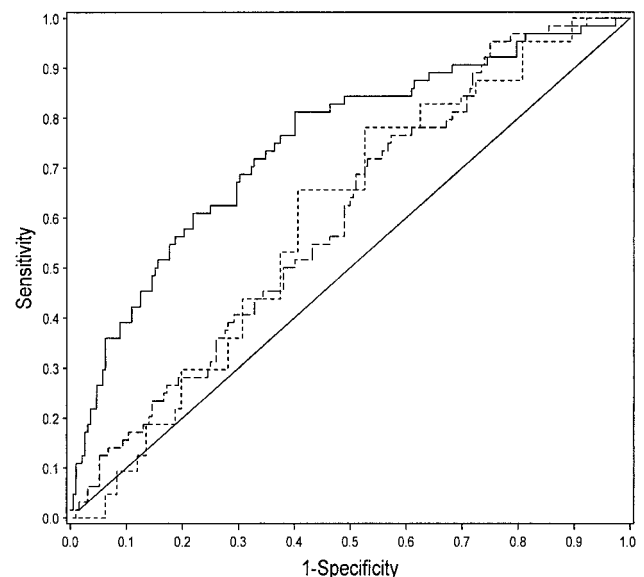

Figure 4. Receiver operating curves for prediction of highest quartile of gender-specific mean % wall area. Solid line indicates FCRS, CRP, average of calf and thigh Max V50; dashed line, FCRS; short dashed line, FCRS and CRP; and diagonal line, receiver operating curve for test that is unrelated to outcome of interest.

The data in the present study are consistent with earlier work linking similar measures of vascular compliance with aortic atherosclerosis and its progression in animal models,[5] as well as extent and severity of coronary atherosclerosis in humans.[6] Other indirect measures of vascular compliance, including pulse pressure and pulse wave velocity, have been shown to be associated with extent or progression of aortic and carotid atherosclerosis[16–21]as well as risk for myocardial infarction,[22,23] congestive heart failure,[24–26] stroke,[26,27] restenosis after percutaneous coronary intervention,[28] and total mortality.[27,29,30]

Both the FCRS[31,32] and CRP[33,34] are also associated with extent of atherosclerosis and risk for future cardiovascular events; however, data from the present study suggest measures of arterial compliance may be a superior predictor of extent of subclinical aortic atherosclerosis. Additional studies are needed to determine whether this improved ability to predict extent of aortic atherosclerosis translates into improved ability to prevent cardiovascular events in intermediate-risk subjects. Conventional or phase-encoded magnetic resonance images can also be used to measure cardiac cycle–dependent changes in aortic dimensions or local flow velocity as other indicators of arterial stiffness.[35,36] However, currently, MRI is expensive and logistically difficult to implement on a wide-scale basis for screening.

The present study has several limitations. Although the study was designed to include individuals with a wide range of risk for coronary disease and extent of atherosclerosis, blacks and other ethnic minorities are not adequately represented. Thus, the results of this study may not be applicable to other racial or ethnic subgroups. Second, the study participants were volunteers and may not be truly representative of the general population. Larger studies that include a more representative selection of individuals would be useful. Finally, a low percentage of subjects were excluded from the analysis because of poor-quality MRI results. This may be the result of an increased amount of intra-abdominal fat immediately adjacent to the aorta that obscured the location of the external elastic lamina, leading to less accurate or unusable results. Selective exclusion of individuals with increased intra-abdominal fat could therefore introduce bias in the observed associations, although the direction of the bias is difficult to predict. There were no significant differences in any of the baseline characteristics between subjects with and without MRIs or complete arterial compliance data.

Conclusions

These data demonstrate a strong and independent association between calf and thigh arterial compliance and extent of aortic atherosclerosis as measured by MRI. The extent to which these measures will correlate with future risk for cardiovascular events is not yet well established. Nevertheless, the fact that these measures were more strongly associated with aortic atherosclerosis than either the FCRS or the combination of the FCRS and CRP suggests that prospective studies are warranted to determine whether arterial stiffness would be a useful adjunct for screening subjects for aggressive primary preventative interventions.

References

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
2. Wierzbicki AS, Reynolds TM, Gill K. A comparison of algorithms for initiation of lipid lowering therapy in primary prevention of coronary heart disease. *J Cardiovasc Risk*. 2000;7:63–71.
3. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. *JAMA*. 1998;279:1615–1622.
4. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.
5. Farrar DJ, Bond MG, Riley WA, et al. Anatomic correlates of aortic pulse wave velocity and carotid artery elasticity during atherosclerosis progression and regression in monkeys. *Circulation*. 1991;83:1754–1763.
6. Herrington DM, Kesler K, Reiber JHC, et al. Arterial compliance adds to conventional risk factors for prediction of angiographic coronary artery disease. *Am Heart J*. 2003;4:662–667.
7. Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking: a preliminary report from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *JAMA*. 1990;264:3018–3024.
8. Corti R, Fayad ZA, Fuster V, et al. Effects of lipid-lowering by simvastatin on human atherosclerotic lesions: a longitudinal study by high-resolution, noninvasive magnetic resonance imaging. *Circulation*. 2001;104:249–252.
9. Fayad ZA, Nahar T, Fallon JT, et al. In vivo magnetic resonance evaluation of atherosclerotic plaques in the human thoracic aorta: a comparison with transesophageal echocardiography. *Circulation*. 2000;101:2503–2509.
10. Hamilton CA, Link KM, Salido TB, et al. Is imaging at intermediate doses necessary during dobutamine stress magnetic resonance imaging? *J Cardiovasc Magn Reson*. 2001;3:297–302.
11. Tan P, Hamilton CA, Link KM, et al. Automated analysis of phase-contrast magnetic resonance images in the assessment of endothelium-dependent flow-mediated dilation. *J Cardiovasc Magn Reson*. 2003;5:325–332.
12. Luo Y, Polissar N, Han C, et al. Accuracy and uniqueness of three in vivo measurements of atherosclerotic carotid plaque morphology with black blood MRI. *Magn Reson Med*. 2003;50:75–82.
13. Zhang S, Hatsukami TS, Polissar NL, et al. Comparison of carotid vessel wall area measurements using three different contrast-weighted black blood MR imaging techniques. *Magn Reson Imaging*. 2001;19:795–802.
14. Agresti A. *An Introduction to Categorical Data Analysis: Wiley Series in Probability and Statistics*. New York, NY: Wiley & Sons; 1996:124–125.
15. Binggeli C, Spieker LE, Corti R, et al. Statins enhance postischemic hyperemia in the skin circulation of hypercholesterolemic patients: a monitoring test of endothelial dysfunction for clinical practice? *J Am Coll Cardiol*. 2003;42:71–77.
16. Witteman JCM, Grobbee DE, Valkenburg HA, et al. J-shaped relation between change in diastolic blood pressure and progression of aortic atherosclerosis. *Lancet*. 1994;343:504–507.

17. van Popele NM, Grobbee DE, Bots ML, et al. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke*. 2001; 32:454–460.

18. Zureik M, Touboul PJ, Bornithon-Knopp C, et al. Cross-sectional and 4-year longitudinal associations between brachial pulse pressure and common carotid intima-media thickness in a general population: the EVA Study. *Stroke*. 1999;30:550–555.

19. Sutton-Tyrrell K, Lassila HC, Meilahn E, et al. Carotid atherosclerosis in premenopausal and postmenopausal women and its association with risk factors measured after menopause. *Stroke*. 1998;29:1116–1121.

20. Franklin SS, Sutton-Tyrrell K, Belle SH, et al. The importance of pulsatile components of hypertension in predicting carotid stenosis in older adults. *J Hypertens*. 1997;15:1143–1150.

21. Zanchetti A, Crepaldi G, Bond MG, et al. Systolic and pulse blood pressures (but not diastolic blood pressure and serum cholesterol) are associated with alterations in carotid intima-media thickness in the moderately hypercholesterolaemic hypertensive patients of the Plaque Hypertension Lipid Lowering Italian Study. *J Hypertens*. 2001;19:79–88.

22. Madhavan S, Ooi WL, Cohen H, et al. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension*. 1994;23:395–401.

23. Mitchell GF, Moye LA, Braunwald E, et al. Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. *Circulation*. 1997;96:4254–4260.

24. Chae CU, Pfeffer MA, Glynn RJ, et al. Increased pulse pressure and risk of heart failure in the elderly. *JAMA*. 1999;281:634–639.

25. Vaccarino V, Holford TR, Krumholz HM. Pulse pressure and risk for myocardial infarction and heart failure in the elderly. *J Am Coll Cardiol*. 2000;36:130–138.

26. Vaccarino V, Berger AK, Abramson J, et al. Pulse pressure and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program. *Am J Cardiol*. 2001;88:980–986.

27. Blacher J, Staessen JA, Girerd X, et al. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. *Arch Intern Med*. 2000;160:1085–1089.

28. Nakayama Y, Tsumura K, Yamashita N, et al. Pulsatility of ascending aortic pressure waveform is a powerful predictor of restenosis after percutaneous transluminal coronary angioplasty. *Circulation*. 2000;101: 470–472.

29. Glynn RJ, Chae CU, Guralnik JM, et al. Pulse pressure and mortality in older people. *Arch Intern Med*. 2000;160:2765–2772.

30. Domanski MJ, Norman J, Wolz M, et al. Cardiovascular risk assessment using pulse pressure in the first National Health and Nutrition Examination Survey (NHANES I). *Hypertension*. 2001;38:793–797.

31. Greenland P, Smith SC Jr, Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. *Circulation*. 2001;104:1863–1867.

32. Jaffer FA, O'Donnell CJ, Larson MG, et al. Age and sex distribution of subclinical aortic atherosclerosis: a magnetic resonance imaging examination of the Framingham Heart Study. *Arterioscler Thromb Vasc Biol*. 2002;22:849–854.

33. Ridker PM, Buring JE, Shih H, et al. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation*. 1998;98:731–733.

34. Haverkate F, Thompson SG, Pyke SDM, et al. Production of C-reactive protein and risk of coronary events in stable and unstable angina. *Lancet*. 1997;349:462–466.

35. Hundley WG, Kitzman DW, Morgan TM, et al. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *J Am Coll Cardiol*. 2001;38:796–802.

36. Rogers WJ, Hu YL, Coast D, et al. Age-associated changes in regional aortic pulse wave velocity. *J Am Coll Cardiol*. 2001;38:1123–1129.