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Clinical Investigations

Vascular Age: Integrating Carotid Intima-Media Thickness Measurements with Global Coronary Risk Assessment

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Summary

Background: An imaging test that quantifies atherosclerotic burden and that can be integrated with existing risk stratification paradigms would be a very useful clinical tool.

Hypothesis: Measurement of carotid intima-media thickness (CIMT) is feasible in a clinical setting. Such measurements can be integrated into coronary risk assessment models.

Methods: Carotid intima-media thickness was measured by B-mode ultrasound in 82 consecutive patients without manifest atherosclerotic vascular disease. The values were used to determine "vascular age" (VA) based on nomograms from the Atherosclerosis Risk in Communities study. Vascular age was substituted for chronological age and standard and vascular age-adjusted 10-year coronary heart disease (CHD) risk estimates were compared.

Results: The mean chronological age was 55.8 ± 9.0 years. The mean VA using CIMT was 65.5 ± 18.9 years ($p < 0.001$). The Framingham 10-year hard CHD risk estimate was 6.5 ± 4.9%. Substituting CIMT-derived VA for chronological age increased the 10-year CHD risk estimate to 8.0 ± 6.8% ($p < 0.001$). Of 14 subjects initially at intermediate risk, 5 (35.7%) were reclassified as higher risk and 2 (14.3%) were reclassified as lower risk. Significant predictors of reclassification were tobacco use, high-density lipoprotein cholesterol, systolic blood pressure, and low-density lipoprotein cholesterol.

Conclusions: Measurement of CIMT, a noninvasive estimate of current atherosclerotic burden, is feasible in a clinical setting and can be integrated into CHD risk assessment models. Determining VA using CIMT values may help individualize the age component of population-based CHD risk estimates. This strategy should be tested in a large trial with hard clinical endpoints.

Key words: atherosclerosis, cardiovascular diseases, carotid arteries, prevention, risk factors

Introduction

A key challenge in preventing first coronary events is identifying "high-risk" individuals who would be candidates for intensive medical intervention. Cardiovascular risk assessment traditionally has been based on identification of categorical risk factors for coronary heart disease (CHD).[1,2] The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) recommended Framingham global CHD risk assessment to help classify an individual's risk of future coronary events. Framingham CHD risk estimates are influenced strongly by chronological age; however, the atherosclerotic burdens of individuals with the same chronological age and similar risk profiles can differ substantially.[1–3] An imaging test that quantifies atherosclerotic burden and can be integrated with existing risk stratification paradigms could be a very useful clinical tool.[3]

Measurement of carotid intima-media thickness (CIMT) with B-mode ultrasound is a noninvasive and highly reproducible technique for detecting and quantifying subclinical atherosclerosis.[4–7] Several large, prospective epidemiologic and interventional studies have shown that CIMT accurately identifies prevalent and incident cardiovascular disease, independent of traditional risk factors.[4–7] Although it is a well-val-

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idated research tool, CIMT is not used widely as a clinical tool. The purpose of this study was to demonstrate that measurement of CIMT is feasible in a clinical setting and to identify a strategy by which CIMT could be integrated into global CHD risk assessment. Values of CIMT were used to determine "vascular age" (VA). Vascular age was substituted for chronological age in an effort to improve CHD risk prediction potentially by accounting for current atherosclerotic burden.

Methods

Experimental Protocol

The Institutional Review Board of the University of Wisconsin Medical School approved this study. Data were obtained from consecutive patients without manifest atherosclerotic vascular disease, who were referred by their physicians to the University of Wisconsin Vascular Health Screening Program for determination of CIMT from August 2001 through March 2002. Risk factors for CHD included cigarette smoking, diabetes mellitus, hypertension (systolic blood pressure ≥ 140 mmHg or taking antihypertensive medication), hyperlipidemia (low-density lipoprotein cholesterol [LDL-C] ≥ 130 mg/dl or taking lipid-lowering medication, high-density lipoprotein cholesterol [HDL-C] < 40 mg/dl), family history of CHD in a male first degree relative < 55 or a female first degree relative < 65 years old, and chronological age ≥ 45 years in men or ≥ 55 years in women. Fasting laboratory tests used standard serum enzymatic assays in a clinical laboratory. The Framingham global risk algorithm was used to determine the 10-year risk of myocardial infarction or cardiac death.[1]

Carotid Ultrasound Imaging

The carotid arteries were imaged with an 8.0 MHz linear array ultrasound transducer (8L5, Acuson Sequoia, Siemens Medical Solutions, Inc., Mountain View, Calif., USA). The standardized protocol from the Atherosclerosis Risk in Communities (ARIC) study was used to optimize and acquire images of the common, bifurcation, and internal segments of each carotid artery.[8] The common carotid artery segment was defined as the distal 1 cm of the common carotid artery, immediately proximal to the onset of increased spatial separation of the walls of the common carotid artery (i.e., immediately before the origin of the bulb). The carotid bifurcation segment was defined as the distal 1 cm of bulb, the termination of which was characterized by the presence of the flow divider between the internal and external carotid artery. The internal carotid artery segment was defined as the proximal 1 cm of the internal carotid artery, starting immediately beyond the flow divider.

Ultrasound images were recorded on magneto-optical disks using the digital storage and retrieval software of the ultrasound system. The combined thickness of the intimal and medial layers of the far walls of each 1 cm carotid artery segment was measured using proprietary software (Access Point 2000, Freeland Systems, Westfield, Ind., USA). Far wall thicknesses of each carotid segment were averaged to define a segmental score. Composite CIMT was calculated as the mean of the segmental mean scores from all measurable segments (maximum of six). All ultrasound examinations were performed by a single sonographer (S.E.A.) and interpreted by a single reader (J.H.S.). Both the reader and sonographer completed the Sonography Certification Course at the Center for Medical Ultrasound at Wake Forest University School of Medicine, Winston-Salem, North Carolina. Reproducibility of scan images and measurements was determined by blinded, duplicate image acquisition and measurement.

Determination of Vascular Age

Vascular age was determined by linear regression modeling using published nomograms of CIMT percentiles (5th, 10th, 25th, 50th, 75th, 90th, and 95th) according to chronological age, gender, and race.[9, 10] Linear and nonlinear regression models were constructed for each of the CIMT percentile functions for each carotid arterial segment (N = 6, left and right common, bifurcation, and internal carotid arteries), by gender (male and female), race (white and black), and age (5-year increments from 45–65 years old). Composite CIMT values were used to determine VA, defined as the age at which the composite CIMT value for an individual of a given race and gender would represent the median value (50th percentile) in the ARIC study. Specifically, the linear 50th percentile function by chronological age, gender, and race was used to project the age of each subject based on their composite CIMT value. If each of a given subject's segmental CIMT values were at the 50th percentile for their chronological age, gender, and race, then their composite CIMT would be at the 50th percentile and their VA would be equal to their chronological age. For example, a 45-year black female with a composite CIMT of 0.593 mm would have a CIMT percentile of 50% and a VA of 45 years; however, a 45-year black female with a composite CIMT of 0.678 mm would have a CIMT percentile of 71% and a VA of 55 years, representing the age at which a composite CIMT value of 0.678 mm represents the 50th percentile. Finally, VA was substituted for chronological age in the Framingham CHD risk prediction model, resulting in modified CHD risk estimates.[1]

Statistical Techniques

Continuous variables were described by means ± standard deviation and compared using Pearson's correlation and Student's *t*-tests. Noncontinuous variables were described by medians and ranges and compared using point-biserial correlations and chi-square tests. Linear and step-wise regression analyses were performed to identify discriminators of differences between chronological age and VA, actual and adjusted CHD risk estimates, and predictors of changes in ATP III CHD risk classification. For all regression analyses, the odds ratio (OR) for each parameter estimate was reported with the beta (β)-coefficient, standard error (SE), and 95% confidence intervals (CI).

Results

Clinical Parameters and Carotid Intima-Media Thickness Measurements (Table I)

There were 82 subjects in this study (45 men, 37 women, average age 55.8 ± 9.0 years, range 26–74 years). On average, subjects had 2.8 ± 1.1 cardiac risk factors (median 3.0, range 1–5). Subjects tended to be overweight and had elevated non-HDL cholesterol, but were normotensive and normoglycemic. The mean 10-year hard CHD risk estimate was 6.5 ± 4.9%, indicative of low to intermediate risk. On average, subjects had 4.6 ± 1.0 carotid segments measured (median 5.0, range 2–6). The mean composite CIMT was 0.806 ± 0.198 mm (range 0.421–1.287 mm). The CIMT correlated positively with chronological age ($r = 0.526$, $p < 0.0001$) and systolic blood pressure ($r = 0.255$, $p = 0.021$). On duplicate scanning, the reproducibility of composite CIMT values was 0.004 ± 0.087 mm ($r = 0.983$, $p < 0.001$) and of VA it was 0.2 ± 2.6 years ($r = 0.981$, $p < 0.001$).

Vascular Age (Fig. 1)

The mean VA was 65.5 ± 18.9 years (range 29–120 years), which represented an average increase of 9.6 ± 5.9 years over chronological age ($p < 0.001$). Vascular age was greater than chronological age in 58 subjects (70.7%) and less than chronological age in 24 subjects (29.3%). It was greater than chronological age by ≥ 10 years in 40.2% of subjects and less than chronological age by more than 10 years in 6.1% of subjects.

TABLE I Subject characteristics (n = 82)

Parameter	Mean (± standard deviation)
Sex (% female)	43.9
Chronological age (years)	55.8 ± 9.0
Total cholesterol (mg/dl)	215.4 ± 42.2
Triglycerides (mg/dl)	126.6 ± 59.3
High-density lipoprotein cholesterol (mg/dl)	53.3 ± 11.6
Low-density lipoprotein cholesterol (mg/dl)	137.8 ± 39.1
Non-high-density lipoprotein cholesterol (mg/dl)	162.1 ± 42.2
Systolic blood pressure (mmHg)	128.0 ± 15.4
Fasting blood glucose (mg/dl)	98.3 ± 15.5
Body-mass index (kg/m^2)	27.7 ± 4.7
Composite CIMT (mm)	0.806 ± 0.198
Vascular age (years)	65.5 ± 18.9
10-year hard CHD risk (%)	6.5 ± 4.9
CIMT adjusted 10-year hard CHD risk (%)	8.0 ± 6.8

Abbreviations: CIMT = carotid intima-media thickness, CHD = coronary heart disease.

Change in age correlated positively with systolic blood pressure ($r = 0.239$, $p = 0.031$). Systolic blood pressure was a weak predictor of VA being greater than chronological age by ≥ 10 years (OR 1.03, β 0.029, SE 0.012, 95% CI 1.00–1.06, $p = 0.070$).

Effects of Vascular Age on Coronary Heart Disease Risk Prediction (Fig. 2)

Substituting VA for chronological age increased the 10-year CHD risk estimate to 8.0 ± 6.8% ($p < 0.001$). Substituting VA for chronological age increased the Framingham 10-year CHD risk estimate in 37 subjects (46.2%) and decreased it in 17 subjects (20.0%), with a ≥ 5% change in 29.2% of subjects. Change in CHD risk correlated positively with LDL-C ($r = 0.346$, $p = 0.020$) and non-HDL-C ($r = 0.265$, $p = 0.017$). Predictors of a ≥ 5% increase in adjusted 10-year CHD risk resulting from the use of VA in place of chronological age were LDL-C and an HDL-C < 40 mg/dl (Table II).

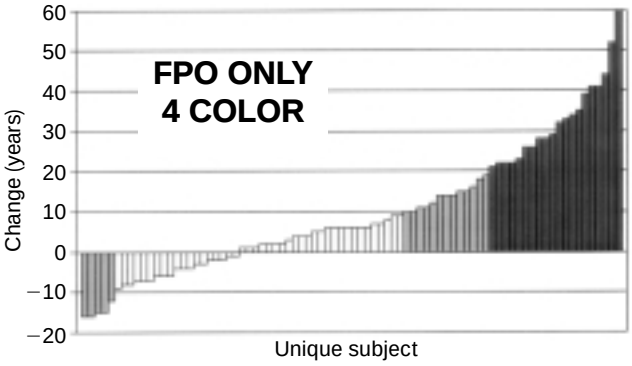

FIG. 1 Vascular age derived from carotid intima-media thickness: Change from chronological age. Each vertical bar represents the difference between an individual subject's chronological and vascular age, as determined by carotid ultrasound. Color changes denote differences of < 10 years (yellow), 10–20 years (orange), or > 20 years (red).

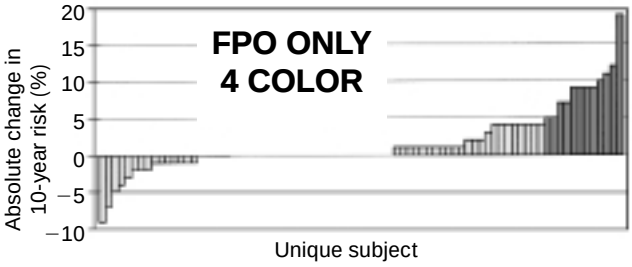

FIG. 2 Modified 10-year hard coronary heart disease risk by substituting carotid intima-media thickness-derived vascular age for chronological age. Each vertical bar represents the difference in 10-year hard coronary heart disease risk estimated using an individual subject's chronological age and vascular age, as determined by carotid ultrasound. Color changes denote risk differences of < 5% (yellow), 5–10% (orange), or > 10% (red). The space in the center of the figure represents subjects with no predicted change in 10-year risk.

TABLE II Predictors of 10-year CHD risk changing by ≥ 5% after substituting vascular age for chronological age

Variable	OR	95% Confidence interval	p Value
Continuous			
Chronological age (years)	0.96	0.90–1.02	0.160
Total cholesterol (mg/dl)	1.01	1.00–1.02	0.213
Triglycerides (mg/dl)	1.00	0.99–1.01	0.743
HDL-C (mg/dl)	0.96	0.91–1.00	0.072
LDL-C (mg/dl)	1.02	1.00–1.03	0.018
Non-HDL-C (mg/dl)	1.01	1.00–1.02	0.065
Waist circumference (inches)	0.99	0.84–1.16	0.865
Weight (pounds)	0.99	0.99–1.02	0.480
Binary NCEP ATP III CHD risk factors (present/absent)			
Tobacco use	2.46	0.38–15.99	0.346
Family history of CHD	3.08	0.91–10.40	0.071
Age	0.83	0.25–2.74	0.766
Hypertension	1.38	0.48–3.97	0.545
Low HDL-C	3.93	1.12–13.80	0.033
Metabolic syndrome	1.68	0.45–6.28	0.439

Abbreviations: CHD = coronary heart disease, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, NCEP = National Cholesterol Education Program, ATP = Adult Treatment Panel.

Effect of Carotid Intima-Media Thickness on Adult Treatment Panel III Risk Classification

Adjusted 10-year CHD risk estimates were calculated after substituting VA for chronological age, leading to reclassification of 12 (15%) subjects into a higher hard CHD risk group and 3 (3.8%) subjects into a lower risk group. Of 14 subjects initially at intermediate risk, 5 (35.7%) were reclassified as higher and 2 (14.3%) as lower risk. Predictors of reclassification to a higher risk category were as follows: HDL-C (OR 0.87, β-0.142, SE 0.048, 95% CI 0.79–0.95, p = 0.003), LDL-C (OR 1.02, β-0.016, SE 0.008, 95% CI 1.00–1.03, p = 0.050), non-HDL-C (OR 1.02, β-0.153, SE 0.007, 95% CI 1.00–1.03, p = 0.040), systolic blood pressure (OR 1.06, β-0.054, SE 0.024, 95% CI 1.01–1.11, p = 0.024). In binary stepwise regression that excluded non-HDL-C, these variables and tobacco abuse predicted reclassification (chi-square goodness of fit = 38.2, degrees of freedom = 70, p = 0.999) (Table III).

TABLE III Predictors of ATP III reclassification by substituting vascular age for chronological age

Variable	OR	95% CI	p Value
Constant			0.230
HDL-C (mg/dl)	0.81	0.71–0.92	0.001
LDL-C (mg/dl)	1.02	1.00–1.05	0.052
Systolic blood pressure (mmHg)	1.09	1.00–1.18	0.046
Tobacco use	19.83	1.13–398.53	0.041

Abbreviations: OR = odds ratio, CI = confidence interval. Other abbrevations as in Table II.

Discussion

This study demonstrated that measurement of CIMT is feasible in a clinical setting and that the age component of CHD risk assessment can be modified by incorporating CIMT, an assessment of current atherosclerotic burden. The CIMT measurements can be used in conjunction with well-validated and previously published population norms to determine VA.[9] Vascular age represents atherosclerotic burden, which varies between individuals with the same chronological age despite similar CHD risk profiles. Thus, population-based risk estimates can be modified by this direct assessment of an individual's current atherosclerotic burden. When VA replaced chronological age in CHD risk prediction algorithms, estimated CHD risk was altered substantially; however, the accuracy of the modified risk estimates could not be determined in this study. These changes reflect the characteristics of the referral population used in this demonstration study. In this study, use of CIMT-adjusted 10-year hard CHD event estimates altered ATP III risk classification in one-half of intermediate-risk individuals, suggesting that evaluating atherosclerotic burden using CIMT may help individualize therapy for the primary prevention of CHD events.

Like all ultrasound techniques, determining CIMT requires training of sonographers and readers, as well as strict attention to quality control. Training programs for determining CIMT in research and clinical settings have been established. The reproducibility of this test in our clinical laboratory is similar to that reported in the literature.[6,7,9] Because high-resolution vascular ultrasound transducers, modern ultrasound machines, and sonographers are available in most active clinical environments, assessment of CIMT appears to be ready for mainstream use.[11] Indeed, the American Heart Association Prevention Conference V concluded that CIMT "can now be considered for further clarification of CHD risk assessment."[7]

Limitations

We have not demonstrated that CHD risk assessment using VA is more accurate than traditional CHD risk assessment; however, the concept of replacing chronological age with an individualized measure of atherosclerotic burden recognizes that age-related CHD risk is not the same for everyone.[3] The Framingham risk algorithm estimates incident CHD events using established CHD risk factors by assigning "points" or weight to the presence or absence and magnitude of risk factor abnormalities and statistically adjusting for other risk factors, including chronological age.[2] It is not known whether the co-

efficients of the equations used in the Framingham CHD risk estimation algorithm would be the same if VA were used in place of chronological age. This report should be regarded as "proof of concept" that CIMT measurements can be used clinically, and as an example of a strategy to integrate noninvasive imaging with existing risk stratification paradigms.

Because of the small sample size, the models predicting risk reclassification identified in this study should be regarded as exploratory, rather than definitive. Similarly, the regression models for determining vascular age using CIMT measurements were based on data acquired from subjects in the ARIC study and may not be applicable to subjects from ethnic groups or in age ranges not represented in this study. Since VA is determined by incorporating ultrasound image measurements into a predictive model with an expected median value that is based on chronological age, race, and gender, there is an inherent variance in this parameter that is not present for an individual's chronological age. This variance could have contributed to some of the change in risk classification observed in this study.

Conclusions

We have identified a strategy by which a noninvasive estimate of an individual's current atherosclerotic burden—CIMT—could be integrated into global CHD risk assessment models and potentially alter CHD risk prediction. To accomplish this, we have demonstrated that measurement of CIMT is feasible in a clinical setting and that using CIMT- derived VA can alter CHD risk assessment. Determining VA using CIMT values potentially could improve the applicability of population-based CHD risk estimates to the management of an individual patient by accounting for age-related variation in atherosclerotic burden. Measuring CIMT might help identify previously unrecognized high-risk individuals and could help clinicians better tailor primary prevention strategies to an individual patient's risk of a first CHD event. The effects of using CIMT-derived VA measurements to alter risk prediction models could be assessed in large epidemiological cohorts, such as ARIC. Additional studies with hard clinical endpoints are needed to determine whether incorporating CIMT-derived VA into risk assessment models improves CHD risk prediction.

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