Coronary Artery Calcium Outperforms Carotid Artery Intima-Media Thickness as a Noninvasive Index of Prevalent Coronary Artery Stenosis

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Objective—Increased carotid artery intima-media thickness (IMT) and increased coronary artery calcium (CAC) are noninvasive surrogate indices of prevalent coronary artery disease (CAD). We compared CAC to IMT for noninvasive detection of prevalent CAD in participants whose coronary status was identified by coronary angiography.

Methods and Results—Male and female CAD patients (≥50% stenosis in one or more coronary artery, n = 79) and controls (no lumen irregularities, n = 93) were identified using coronary angiography. Mean maximum carotid IMT was quantified using B-mode ultrasound and total CAC was measured using ECG-gated helical computed tomography (HCT). Carotid IMT was 20% higher in CAD cases compared with controls (P < 0.001), whereas mean CAC was 1000% higher in CAD cases than controls (P < 0.0001). In multivariable models adjusted for age and sex, IMT greater than the median (1.13 mm) was associated with 2-fold increase in likelihood of prevalent CAD compared with scores below that cut point (P = 0.015). CAC scores that exceeded the median score of 92 were associated with 28-fold increase in likelihood of prevalent CAD (P < 0.0001). Although associations of increased IMT with prevalent CAD were similar in males and females, CAC scores above the median in females were associated with 39-fold increase in odds of prevalent CAD, whereas males with elevated CAC had 19-fold risk of CAD.

Conclusion—HCT-measured CAC compares favorably with carotid IMT measured by B-mode ultrasound as a noninvasive index of prevalent CAD. (Arterioscler Thromb Vasc Biol. 2005;25:1723-1728.)

Key Words: calcification ■ computed tomography ■ coronary artery disease ■ intima-media thickness ■ ultrasound

Coronary artery intima-media thickness (IMT) quantified by B-mode ultrasound has proven validity as a noninvasive index of risk for vascular disease.1-7 Recent research suggests that computed tomography (CT) may be used to quantify coronary artery calcification (CAC) as an alternative noninvasive indicator of vascular disease.

Presence and/or extent of CAC is associated with traditional CAD risk factors, including age,8-13 sex,8-13 ethnicity,12,13 cholesterol,8,11,12 hypertension,8,9,12 and history of smoking.8,9,12,13 Cross-sectional studies have also shown that elevated CAC is strongly associated with prevalent CAD identified by coronary angiography and/or with clinically manifest cardiovascular disease (CVD).14-20 The substantial evidence for the association of elevated CAC with prevalent CVD, along with more limited data regarding the association of CAC with incident disease, has been extensively reviewed by 2 expert panels.19,20

Most studies to date have measured CAC using cardiac-gated electron beam CT (EBCT), which was developed and implemented in the mid 1980s.14,15 Recent improvements in more widely available helical CT systems have increased temporal resolution and made CAC measurement possible with this technology. Cardiac-gated helical CT (HCT) has since been validated against EBCT measurement of CAC.21 Because CT directly images the coronary vasculature, it is reasonable for researchers to expect that quantification of CAC would reflect coronary disease better than IMT. Although both B-mode ultrasound and EBCT have been available for more than a decade, only a single small study has directly compared them as noninvasive measures of CAD.22 We compared HCT-quantified CAC to carotid IMT measured by B-mode ultrasound for associations with prevalent CAD in 87 male and 85 female participants whose coronary status was identified at coronary angiography.
Methods

Patient Population
Participants were part of an ongoing longitudinal study of carotid artery atherosclerosis progression measured using B-mode ultrasound in CAD cases and CAD-free controls (Carotid Artery Follow-up Study [CAFUS]).22 Participants were recruited who had undergone coronary angiography predominantly for suspected coronary stenosis, valvular abnormalities, and cardiac arrhythmias. Potentially eligible participants included CAD “cases” (≥50% stenosis of one or more coronary vessels) and “controls” (no coronary lumen irregularities). Patients with nonobstructive CAD (coronary stenoses of <50%) were excluded. Recruitment began in 1991 and ended in 1993 with follow-up B-mode ultrasound measures of carotid artery atherosclerosis continuing through 1996.

In 1998 and 1999, CAFUS participants from the original cohort of 280 were recalled for a study of CAC progression measured using HCT. The present study includes baseline data for CAC from 134 of the original CAFUS participants (70 controls and 64 cases). CAFUS participants were 5 to 8 years after coronary angiography when they underwent HCT for the present study. We recruited another 38 participants between late 1999 and mid 2000 (15 cases, 23 controls) using the same strategy that was used in recruiting the original CAFUS cohort with the exceptions that individuals currently using lipid-lowering medications and those who underwent coronary interventions >6 months before entering the study were not included. The newly recruited subjects included only patients who had undergone coronary angiography within the previous 2 years. HCT and B-mode ultrasonography were performed the same day in newly recruited participants. All patients provided informed consent to participate in the study and the protocol was approved by the institutional review board of Wake Forest University School of Medicine.

Clinical Evaluation
Detailed descriptions of laboratory analyses and clinical evaluations for the present study have been published.25,26 Hypercholesterolemia was defined as use of cholesterol reducing medicines or fasting low-density lipoprotein cholesterol ≥160 mg/dL. Diabetes was coded positive for participants who had diabetes diagnosed, current use of diabetes medicines, or when fasting glucose was >140 mg/dL. Hypertension was defined as present if diagnosed by a physician, if the participant was using current treatment, or if systolic blood pressure was ≥140 mm Hg and/or diastolic blood pressure was >90 mm Hg.

Ultrasound
The ultrasound methodology for this study has been described previously.25,26 Methods and equipment were kept consistent throughout the study. IMT was semi-automatically measured as previously detailed using customized software developed by the California Institute of Technology/Jet Propulsion Laboratory.21 For participants from the original cohort, only the final (ie, the most recent) B-mode ultrasound scan was used.

CAC
CAC was measured using ECG-gated HCT as previously described.21 Paired HCT scans were performed within minutes of each other (coefficient of variation [CV] 12.2% in 119 subjects with measurable CAC). Imaging was performed on 2 systems: the GE CTi single-slice system and, subsequently, the 4-channel GE LightSpeed (General Electric Medical Systems). CAC measurements obtained using the CTi and LightSpeed systems were highly correlated (r²=0.92, n=12). During the entire study, biweekly phantom measurements were made using a calibration phantom (QCT Torso phantom; Image Analysis) to insure stability of the CT systems calibration. The Agatston CAC scoring method, modified to account for slice thickness, was used to quantify CAC using the SmartScore software package developed by General Electric Medical Systems.24 Individual arteries that could not be fully visualized (eg, because of staples from coronary bypass surgery or pacemaker leads that obstructed the view) or contained artifacts (such as stents) were excluded from analysis. For individuals who had undergone coronary bypass, only native arteries (not bypass grafts) were included in analysis.

Statistical Analysis
Mean maximum (mean max) IMT for both far and near carotid walls, all 3 carotid segments, and both right and left sides (12 individual measures), as well as the total CAC score for right, left, and circumflex coronary systems, were calculated. Distribution of CAC was not normal and thus, for data presentation and analysis, IMT and CAC were separately categorized into quartiles by ranking these data without regard to CAD status. Case-control differences were evaluated using t tests (continuous variables) or χ² analysis (discrete variables). Pearson correlation coefficients are presented for relationships of age, IMT, and CAC. CAC was log-transformed before all univariate analyses (1 was added to all CAC scores before transformation). Receiver-operator characteristics (ROC) and area under the curve (AUC) were derived from logistic regression models that included age and sex. Confidence intervals for AUC were calculated as described by Apfel et al.25 Logistic regression models were used to evaluate IMT and CAC associations with the discrete outcome of CAD case-control status. Odds ratios and 95% confidence intervals presented are for risk of prevalent CAD based on various incremental differences in IMT or CAC. Odds ratios are presented per 1-unit difference in IMT or log-CAC (IMT and log-CAC data standardized with mean=0 and SD=1 for comparison purposes), per 1-quartile difference in each of the 2 measures, and the difference between IMT or CAC more than or less than the median value for each of the 2 measures. To allow sex comparisons, data were standardized or categorized into quartiles or by median for all subjects combined before analysis in sex-specific models. Because IMT and CAC in newly recruited cases compared with controls were similar to those of the original CAFUS recruits, data from the original CAFUS population and newly recruited participants were combined for analyses. All analyses were performed using SAS.26

Results

Descriptive Statistics
As shown in Table 1, patients with CAD were older, more likely to be male, diabetic, and have hypertension than were disease-free controls. The interval in time between CAC and IMT determinations was not significantly different for CAD cases compared with controls. Mean-max carotid IMT was 26% higher in CAD cases than controls (P<0.001). Total CAC was =10-fold greater in CAD cases than controls (P<0.001 based on log-transformed values). Mean max IMT values for 23 newly recruited controls (1.10±0.20) and 15 cases (1.44±0.32) whose IMT and CAC data were obtained contemporaneously were similar to IMT for 70 controls (1.08±0.27) and 64 cases (1.35±0.43) that were recalled from the original CAFUS cohort. CAC for newly recruited controls and cases [65±184 (median 1) versus 864±1018 (median 400), respectively] was comparable to CAC for controls and cases in the original CAFUS cohort [76±161 (median 6) versus 967±905 (median 615), respectively].

Determinants of CAC and IMT

Age
Both carotid IMT (r=0.34, P<0.001) and log-transformed CAC (r=0.41, P<0.001) were strongly associated with age. Among CAD cases, associations of age with IMT and CAC were similar (r=0.34, P=0.02 and r=0.31, P=0.03, respectively). In disease-free controls, the association of age with
IMT ($r=0.49, P=0.001$) was somewhat stronger than the association of age with CAC ($r=0.37, P=0.02$).

Sex
CAC was greater in males than females after adjusting for CAD status and age (661 ± 75 versus 409 ± 77, respectively; $P=0.015$ based on log-transformed values). In females, CAC was 837 ± 802 in CAD cases versus 408 ± 1188 in controls compared with 121 ± 199 in controls ($P<0.0001$). Carotid IMT was also greater in male compared with female participants (1.29 ± 0.03 versus 1.14 ± 0.03 mm, respectively; $P=0.004$, adjusted for age and CAD status). In females, IMT was significantly greater in CAD cases than controls (1.27 ± 0.42 versus 1.05 ± 0.24 mm; $P=0.007$, in cases and controls, respectively). In males, mean IMT was 1.42 ± 0.40 mm in cases versus 1.12 ± 0.25 mm in controls ($P<0.0001$).

Smoking
CAC was positively associated with pack-years history of smoking ($r=0.20, P=0.03$) and, likewise, was increased in participants who were current or former smokers compared with those who had never smoked ($P=0.03$; age, sex, and CAD status adjusted). IMT was also positively correlated with pack-years smoking ($r=0.21, P=0.02$), and current or former smokers had thicker IMT than participants who had never smoked ($P=0.04$; age, sex, and CAD status adjusted).

Hypercholesterolemia
Carotid IMT was significantly elevated in participants with a history of hypercholesterolemia ($P=0.04$) compared with normcholesterolemic participants after adjustment for age, sex, and CAD status. CAC was nonsignificantly increased among hypercholesterolemic ($P=0.2$) versus normal participants.

Diabetes Mellitus and Hypertension
Neither history of diabetes nor history of hypertension was significantly associated with carotid IMT or CAC in the present analysis.

### Inter-relationship of CAC and IMT
Log-transformed CAC was positively correlated with IMT among all participants ($r=0.38, P<0.001$). The associations of CAC with IMT were of similar magnitudes in CAD cases and controls. However, CAC and IMT were somewhat better correlated in males ($r=0.46, P<0.0001$) than in females ($r=0.31, P=0.004$).

### Distributions of IMT and CAC in CAD Cases and Disease-Free Controls
The distributions of CAD cases and controls by quartiles of IMT and CAC are presented separately in Figures 1 and 2 for males and females, respectively. Both figures suggest that CAC distinguishes CAD status more effectively than IMT.

### ROC
Figure 3 shows ROC curves depicting the relationships of the 2 noninvasive measures, CAC and IMT, each adjusted for age and sex, with prevalent CAD. AUC for the curve describing the relationship between CAC and prevalent CAD was 0.91 (95% CI, 0.85 to 0.97) compared with AUC of 0.73 (0.63 to 0.83) for the IMT-prevalent CAD association.
Logistic Regression Models for Noninvasive Measures of CAD

Logistic regression models for associations of IMT and CAC with CAD are presented in Table 2. Models are presented, separately for males and females, and for all participants combined. Overall, regardless of the regression model, odds ratios associated with prevalent CAD were greater for CAC than IMT. For example, among all participants, the odds ratio for prevalent CAD increased 1.7-fold with each quartile increase in carotid IMT, whereas each quartile increase in CAC was associated with an 8-fold increase in odds of CAD. CAC greater than the median score of 92 was associated with a 28-fold increase in the likelihood of being a CAD case, whereas IMT above the median of 1.13 mm approximately doubled the risk of CAD.

In sex-specific logistic regression models, compared with IMT, CAC was again more strongly associated with prevalent CAD. As suggested by Figures 1 and 2, each 1-quartile increase in CAC was associated with increased risk of prevalent CAD in both females (odds ratio = 10) and males (odds ratio = 6.7) alike. Odds ratio point estimates for the association of increased IMT with prevalent CAD were similar in magnitude for males and females, although CAC odds ratios tended to be larger in females than males.

Discussion

The present study demonstrates that HCT-quantified CAC compares favorably with carotid artery IMT measured by B-mode as a noninvasive index of prevalent CAD in both male and female patients. Although this finding may not be surprising, the magnitude of the difference has not previously been described, nor have sex-specific comparisons of these indices been presented.

We compared CAC with carotid IMT for their associations with prevalent CAD in participants selected by coronary angiography to include only those with documented CAD and those with “normal” arteries free from any stenosis. In age-adjusted logistic regression models, a single quartile increase in IMT was associated with a 1.7-fold increase in the odds of being a CAD case, whereas the risk of CAD increased 8-fold with each quartile increase in CAC score among all participants. Moreover, the odds of being a CAD case were ≈2-fold higher when IMT exceeded the median, whereas the odds ratio was 28 for CAC scores greater than the median score of 92. Odds ratios calculated in the present study agree well with those reported in similarly designed studies of CAC; a recent review of the EBCT literature estimated an overall odds ratio of 21.3 (95% CI, 4 to 106 for 16 studies) for CAD when CAC was present.²⁰

We further compared CAC to IMT in the present study by plotting ROC curves to assess the performance of the 2 noninvasive indices as predictors of CAD case or control status. ROC analysis allows direct comparison of the predictive power of the 2 indices plotted as sensitivity (true-positive rate) versus 1 specificity (the false-positive rate). The ROC curves shown in Figure 3 suggest that, compared with IMT, CAC has better sensitivity and specificity for identifying prevalent CAD. Moreover, AUC calculated from ROC argues strongly that CAC (AUC 0.91) is superior to IMT (AUC...
TABLE 2. Logistic Regression Models

<table>
<thead>
<tr>
<th>Females</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1-unit difference†</td>
<td>2.0</td>
<td>1.1–3.6</td>
</tr>
<tr>
<td>Per 1-quartile difference</td>
<td>1.5</td>
<td>1.0–2.3</td>
</tr>
<tr>
<td>IMT &gt; vs. &lt; 1.06 mm (median)</td>
<td>1.9</td>
<td>0.8–4.7</td>
</tr>
<tr>
<td>CAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1-unit difference in log-CAC</td>
<td>18.7</td>
<td>5.2–66.8</td>
</tr>
<tr>
<td>Per 1-quartile difference</td>
<td>10.1</td>
<td>4.0–25.9</td>
</tr>
<tr>
<td>CAC &gt; vs. &lt; 60 units (median)</td>
<td>38.9</td>
<td>9.8–154.4</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1-unit difference</td>
<td>2.4</td>
<td>1.3–4.5</td>
</tr>
<tr>
<td>Per 1-quartile difference</td>
<td>1.8</td>
<td>1.1–3.1</td>
</tr>
<tr>
<td>IMT &gt; vs. &lt; 1.17 mm (median)</td>
<td>1.7</td>
<td>0.6–4.7</td>
</tr>
<tr>
<td>CAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1-unit difference in log-CAC</td>
<td>8.5</td>
<td>3.5–20.4</td>
</tr>
<tr>
<td>Per 1-quartile difference</td>
<td>6.7</td>
<td>3.1–14.7</td>
</tr>
<tr>
<td>CAC &gt; vs. &lt; 232 units (median)</td>
<td>19.2</td>
<td>5.9–62.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All Participants</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1-unit difference</td>
<td>2.3</td>
<td>1.5–3.5</td>
</tr>
<tr>
<td>Per 1-quartile difference</td>
<td>1.7</td>
<td>1.3–2.4</td>
</tr>
<tr>
<td>IMT &gt; vs. &lt; 1.13 mm (median)</td>
<td>1.9</td>
<td>1.0–3.8</td>
</tr>
<tr>
<td>CAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1-unit difference in log-CAC</td>
<td>11.3</td>
<td>6.0–23.8</td>
</tr>
<tr>
<td>Per 1-quartile difference</td>
<td>8.0</td>
<td>4.4–14.6</td>
</tr>
<tr>
<td>CAC &gt; vs. &lt; 92 units (median)</td>
<td>27.9</td>
<td>11.4–38.0</td>
</tr>
</tbody>
</table>

*Odds Ratio adjusted for age at scan.
†Odds Ratio per 1-unit difference in IMT (SD=0.36 mm) or log-CAC (SD=2.80 CAC units) standardized with mean=0 and SD=1.

0.73) in correctly identifying subjects with prevalent CAD. Aside from the present study, EBCT-derived CAC and B-mode ultrasound identified carotid plaques were previously compared as markers for prevalent CAD in a single study of 80 participants (59 with CAD) that also found CAC was superior to carotid plaques for identifying case subjects.25

In the present study, we were able to compare carotid IMT with CAC as indices of prevalent CAD, separately, in males and females. In female participants, a single quartile increase in CAC was associated with 10-fold increase in odds of CAD, whereas in males, each quartile increase in CAC was associated with a 6.7-fold increase in odds of prevalent CAD. For each sex-specific model tested, the odds ratio for the association of CAC score with CAD was of greater magnitude in females compared with males. This observation is consistent with prior studies suggesting that presence of CAC is highly indicative of prevalent CAD in females.18

Despite the association of elevated CAC with prevalent CAD, questions remain about its usefulness in both clinical and research settings.19,20 Some individuals with angiographically documented CAD have virtually undetectable CAC (<5% of CAD cases in the present study) and, conversely, individuals with no detectable coronary stenosis may have elevated CAC scores thought to be indicative of atherosclerotic lumen narrowing.19,20

Study Limitations

The measurements of IMT and CAC were not performed at the same time as coronary angiography, thus it is possible that the relationship between coronary angiography and IMT or CAC measures is overestimated in the present analysis. The interval between coronary angiography and noninvasive measures was, however, similar in CAD cases and controls as shown in Table 1, and the main purpose of the present communication was to compare the relative discriminatory power of CAC with that of IMT for coronary stenosis. The overall study findings are supported within the subset of participants who underwent IMT and CAC measures at the same clinic visit and whose angiography was performed within 2 years before the noninvasive measures. However, we cannot rule out the possibility that our findings were biased by the time that elapsed between angiography and both the IMT and CAC scans.

Reliability of the 2 noninvasive indices could also contribute to some of the findings for the present study. Kanters et al have reviewed reliability of IMT measures and reported that coefficient of variation for duplicate IMT scans ranged from 13% to 18% in large studies using methods comparable to the present analysis.27 In the present study in which replicate measures of CAC were available for our participants, coefficient of variation for HCT was 12.2% in subjects with CAC scores thought to be indicative of atherosclerosis change in intervention studies in atherosclerosis, B-mode ultrasound could prove more useful in identifying subclinical atherosclerosis compared with HCT, which, by definition, identifies complex, calcium-containing plaques. Moreover, these data do not address the potential use of CAC as an index of atherosclerosis progression or of atherosclerosis change in intervention studies in which IMT has proven to be extremely useful.

Conclusions

CAC was more strongly associated with CAD case-control status than carotid artery IMT in the present study. CAD presence was strongly associated with prevalent CAD in both males and females. The present analysis supports the use of HCT-derived CAC in cross-sectional, patient-based studies of coronary artery atherosclerosis. In population-based studies of atherosclerosis, B-mode ultrasound could prove more useful in identifying subclinical atherosclerosis compared with HCT, which, by definition, identifies complex, calcium-containing plaques. Moreover, these data do not address the potential use of CAC as an index of atherosclerosis progression or of atherosclerosis change in intervention studies in which IMT has proven to be extremely useful.

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