

Presence and Severity of Noncalcified Coronary Plaque on 64-Slice Computed Tomographic Coronary Angiography in Patients With Zero and Low Coronary Artery Calcium

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How well absence of coronary artery calcium (CAC) predicts the absence of noncalcified coronary artery plaque (NCAP) has not been elucidated. We conducted a cross-sectional study of 554 outpatients to quantify NCAP prevalence as a function of CAC score. All patients underwent CAC scoring followed by 64-slice computed tomographic coronary angiography. Patients were categorized as having 0 CAC (416 patients) or low CAC (138 patients; men with CAC scores from 1 to 50 and women with scores from 1 to 10). Prevalence of detectable NCAP was 6.5% in patients with 0 CAC and 65.2% in those with low CAC. Compared with patients with 0 CAC, those with low CAC had markedly increased rates of NCAP occluding <50% of the arterial lumen (56.5% vs 6.0%, $p < 0.001$) and $\geq 50\%$ of the arterial lumen (8.7% vs 0.5%, $p < 0.001$). In conclusion, in outpatients with a low to intermediate risk presentation and no known coronary artery disease, absence of CAC predicts low prevalence of any NCAP and very low prevalence of significantly occlusive NCAP. Low but detectable CAC scores are significantly less reliable in predicting plaque burden due to their association with high overall NCAP prevalence and nearly a 10% rate of significantly occlusive NCAP. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99:1183–1186)

Clinical utility of coronary artery calcium (CAC) imaging has been supported by evidence showing that its absence dependably excludes obstructive coronary artery stenoses,¹ and that quantification of its presence (CAC score) strongly prognosticates future adverse cardiovascular events.^{1–5} However, only using CAC as a signal of coronary artery disease may mean missing noncalcified coronary artery plaque (NCAP), a finding suggested by 2 small intracoronary ultrasound studies by Baumgart et al⁶ and Schmermund et al.⁷ Recent emergence of 64-slice computed tomographic coronary angiography (CTCA) as a safe, convenient, and accurate technique for visualizing coronary arterial obstruction,^{8–11} particularly in patients low coronary calcium burden,¹² makes it an appealing technique for evaluation of NCAP in a broad range of patients. We conducted this study using 64-slice CTCA to quantify the prevalence and severity of NCAP in patients with 0 and low CAC.

Methods

From January 1, 2005 to December 31, 2005, 1,009 consecutive patients underwent CAC scoring followed imme-

diately by 64-slice CTCA at a Los Angeles metropolitan community medical center. At the time of imaging, a written questionnaire was used to record each patient's medical history (coronary disease, diabetes, hypertension, hypercholesterolemia, smoking history, and family history), symptoms (chest pain and dyspnea), and medication use. Response rates were 78% (family history) to 90% (chest pain). Twenty-five patients with known myocardial infarction or previous coronary revascularization were excluded. We then reviewed CAC and computed tomographic coronary angiographic findings of the remaining 984 patients (299 were self-referrals; 341 were women). All patients gave informed consent for participation in research at the time of CTCA. The study protocol was reviewed and approved by an independent institutional review board.

Patients were categorized by coronary calcium score. The "0-CAC" group contained patients with CAC scores of 0; the "low-CAC" group contained men with CAC scores from 1 to 50 and women with CAC scores from 1 to 10 (ranges were derived from gender- and age-stratified nomograms, using an upper limit age of 75 years, for CAC scores ≤ 25 th percentile of the general population¹³); the remaining 430 patients were not included in this analysis. Computed tomographic coronary angiographic results of each patient were assessed for 2 main findings: presence of any NCAP and quantification of the most severe coronary artery stenosis due to NCAP, expressed as percent underlying luminal diameter. If ≥ 1 coronary artery segment in the American Heart Association 17-segment model was inadequately imaged due to artifact (6 patients in the 0-CAC group and 3 in the low-CAC group), we used results from segments that were adequately assessed.

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Table 1
Demographic characteristics of patients with zero and low coronary artery calcium scores

Characteristic	0 CAC			Low CAC			p Value*
	All (n = 416)	Men (n = 241)	Women (n = 175)	All (n = 138)	Men (n = 117)	Women (n = 21)	
Age (yrs)	51.7 ± 10.9	48.7 ± 10.5	56.0 ± 10.1	55.4 ± 9.5	54.2 ± 8.9	62.1 ± 10.2	<0.01
Body mass index (kg/m ²)	26.5 ± 5.2	26.9 ± 4.3	26.0 ± 6.2	26.7 ± 5.2	27.3 ± 5.3	23.4 ± 3.3	NS
Diabetes mellitus	6%	5%	8%	9%	10%	0%	NS
Hypercholesterolemia	54%	54%	53%	66%	64%	79%	<0.01
Hypertension	29%	26%	32%	40%	40%	40%	<0.01
Smoker (current or previous)	38%	38%	38%	44%	40%	67%	NS
>2 risk factors	24%	20%	29%	40%	38%	45%	<0.01
Chest pain	51%	45%	59%	34%	37%	19%	<0.01
Dyspnea	16%	16%	15%	10%	9%	13%	NS
Chest pain and dyspnea	13%	12%	13%	5%	5%	5%	<0.01

Values are means ± SDs, or percentages of patients.

* Versus the "All" columns.

All CAC scoring and computed tomographic coronary angiographic studies were performed using the Siemens SOMATOM Sensation 64 Cardiac scanner (Forchheim, Germany). Before imaging, patients with heart rates >60 beats/min were administered intravenous metoprolol (5 mg at a time, up to 30 mg) to decrease the heart rate to ≤60 beats/min. An electrocardiographically gated, unenhanced scan was performed for calcium scoring. Next, 80 ml of contrast (Omnipaque or Visipaque if serum creatinine level was >1.3, GE Healthcare, Princeton, New Jersey) was injected into the antecubital vein at 4.5 ml/s for the first 40 ml and then 3.5 ml/s for the next 40 ml, followed by 50 ml of saline chaser. An injection-to-scan delay of 26 seconds was allowed to elapse before CTCA was performed during a single 9- to 12-second breath-hold. Imaging parameters were 32- × 0.6-mm collimation with 2 slices acquired per detector row, 330-ms rotation time, 3.8-mm table feed per rotation, 120-mV tube voltage, 900-mA tube current without current modulation, and 59-mGy computed tomographic dose index. Estimated radiation doses were 13 mSv for men and 18 mSv for women.

INSIGHT (Neoimager, City of Industry, California) was used to calculate CAC scores (standard Agatston unit) and analyze all computed tomographic coronary angiographic datasets. Image reconstruction was performed with electrocardiographic gating. When heart rate was <65 beats/min, a 1/2-scan reconstruction algorithm was used, decreasing acquisition time to 165 ms. Datasets were reconstructed immediately after image acquisition. First, a single dataset was reconstructed at 65% of the RR interval. If inadequate image quality was noted in ≥1 coronary arterial segment, an additional dataset was obtained at a different operator-determined phase of the RR interval. If poor image quality persisted, ≥3 total reconstructions were made to produce the most optimized images. NCAP was identified by the presence of any coronary arterial wall lesion with a radiodensity detectably lower than injected contrast and higher than surrounding tissue.

Data were transferred from a Microsoft Excel (Microsoft, Redmond, Washington) spreadsheet file to a statistical program (SPSS 11.5, SPSS, Inc., Chicago, Illinois) for analysis. Parametric and nonparametric inferential statistics

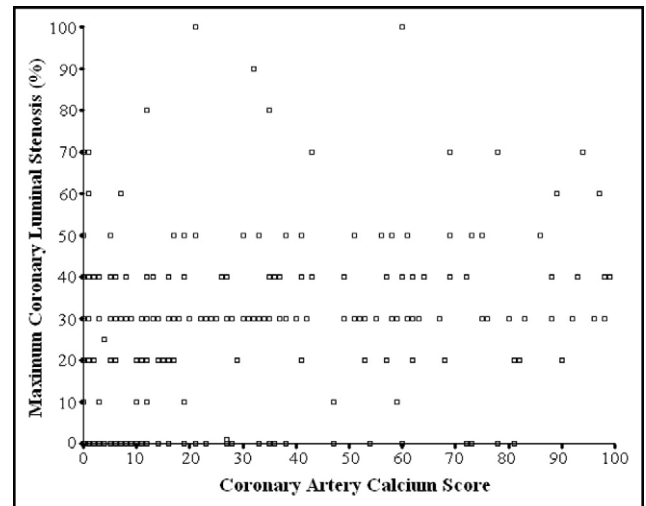


Figure 1. Scatterplot of maximum detected coronary arterial stenosis in each patient with a CAC score from 0 to 100.

were used, as appropriate. For comparison of categorical variables between CAC groups, Pearson's chi-square test was used. Continuous variables were compared using Student's *t* test. Nonparametric Spearman ρ correlations were computed to evaluate the relation between CAC scores and ordinal and continuous variables. Regression analysis using stepwise entry and partial correlation analysis were used to evaluate NCAP findings and control for possible confounding variables. For all analyses, criterion for statistical significance was set at a 2-tailed *p* value ≤0.05.

Results

Of the 554 patients analyzed, 416 (241 men and 175 women) were classified as having 0 CAC, and 138 patients (117 men and 21 women) were classified as low CAC. Table 1 lists demographic characteristics of these patients. Women were older than men in the 2 groups and were more likely to be in the 0-CAC group (51% vs 38%). Patients in the low-CAC group were older and more likely to have traditional risk factors. Patients in the

Table 2
Prevalence of noncalcified coronary artery plaque (NCAP) and mean maximal coronary stenosis due to noncalcified coronary artery plaque

	Zero Coronary Artery Calcium (n = 416)	Low Coronary Artery Calcium (n = 138)	p Value
No. of patients with any detectable NCAP	27 (6.5%)	90 (65.2%)	<0.001
In patients with detectable NCAP, mean maximal percent coronary diameter stenosis due to NCAP	29 ± 13.6	33 ± 16.0	NS

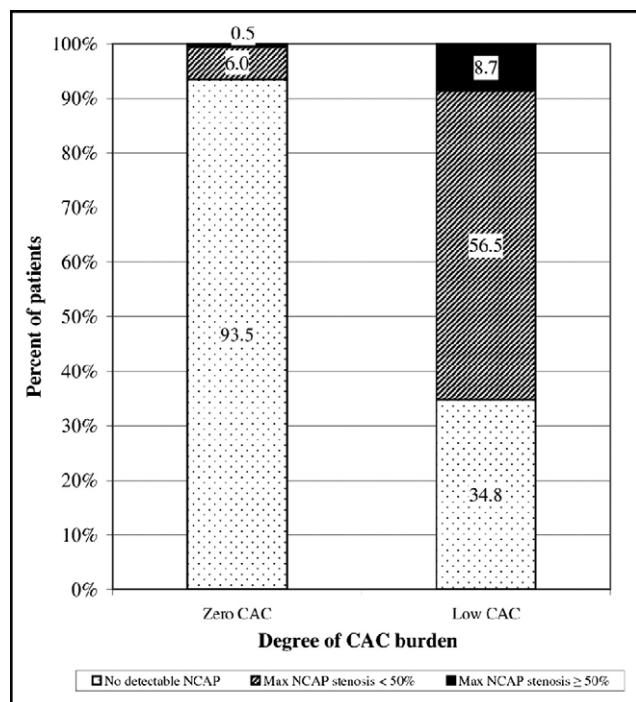


Figure 2. Distribution of maximum coronary luminal diameter stenoses due to NCAP in patients with 0 and low CAC scores. Numerical values on bars represent percentages. Differences between the 2 groups are significant for percentages of patients with <50% maximal luminal stenosis (hatched areas), ≥50% maximal luminal stenosis (black areas), no NCAP (dotted areas), and overall (p values <0.001).

0-CAC group were more likely to report chest pain. None of these differences changed when evaluated separately for men and women.

Figure 1 shows a scatterplot of maximal detected coronary arterial stenosis in each patient with CAC scores up to 100. Although the median CAC score was 9.5 in the low-CAC group, coronary artery plaque severity in these patients varied widely. Prevalence of NCAP on 64-slice computed tomographic coronary angiograms is presented on Table 2. NCAP was detected in 27 patients with 0 CAC (6.5%) and 90 with low CAC (65.2%). In only patients with NCAP, mean maximum coronary arterial stenosis due to NCAP was similar between the 2 groups.

Distribution of maximal coronary arterial stenosis caused by NCAP is shown in Figure 2. Of patients with 0 CAC, 93.5% had no detectable NCAP, 6.0% had NCAP occluding <50% of arterial diameter, and 0.5% had NCAP occluding ≥50% of arterial luminal diameter. Of patients with low CAC, distributions were 34.8%, 56.5%, and 8.7% respectively (p <0.001 for all comparisons).

We evaluated the effect that underlying demographic differences may have had on our findings. CAC score showed a much higher ρ correlation to number of arteries with NCAP ($\rho = 0.64$) and maximum stenosis due to NCAP ($\rho = 0.63$) than to patient age ($\rho = 0.15$) and number of risk factors ($\rho = 0.16$). However, maximum stenosis showed a similar correlation to age ($\rho = 0.1$). After partial correlation between CAC and maximum stenosis was performed controlling for age, number of risks factors, and body mass index, CAC still showed a significant correlation to maximum stenosis (partial correlation 0.52). A stepwise multiple regression with maximum stenosis as the dependent variable entered CAC score as the strongest predictor ($R = 0.53$, $p < 0.001$), with age, number of risk factors, and body mass index not showing any significant predictive value.

In the 0-CAC group, there was no difference in risk factors, body mass index, and rates of chest pain and dyspnea between the 27 patients with detectable NCAP and the 389 patients with 0 CAC without detectable NCAP. Anatomic distribution of NCAP was 22 in the left anterior descending artery (19 in proximal and 3 in mid arteries), 5 in the right coronary artery (2 in proximal, 2 in mid, and 1 in distal arteries), 2 in the left circumflex artery (proximal), and 2 in the left main coronary artery. Of the 2 patients with radiographically obstructive NCAP, 1 was a 58-year-old man with smoking and a family history found to have 50% NCAP in the mid-right coronary artery, and the other was a 38-year-old woman with no risk factors found to have 70% NCAP in the proximal left anterior descending artery.

Discussion

Our study represents the largest reported experience to date with 64-slice CTCA in outpatients with 0 and low CAC and is the first study to report prevalence of detectable NCAP in this population. We believe that using 64-slice CTCA to quantify NCAP burden was acceptable for 2 reasons beyond its safety as a noninvasive test. First, CTCA has the capability to capture the early phases of atherosclerotic coronary disease, when sensitivity of conventional coronary angiography may be compromised by compensatory vascular remodeling that often preserves visualized luminal dimensions.^{14,15} Second, a recent study has shown that 64-slice CTCA demonstrates promising correlation when compared with intravascular ultrasound in detecting coronary artery plaque occupying <50% of artery lumen.¹⁶

When CAC was absent, NCAP prevalence was low (6.5%) and obstructive NCAP prevalence was extremely low (0.5%), confirming the high negative predictive value of a 0 CAC score shown in previous studies.^{1,17} Although we used a more stringent scoring range than published guidelines (that consider CAC scores from 1 to 100 as

minimal to mild^{17,18}) to define low CAC, 64-slice CTCA still detected NCAP in nearly 66% of these patients, including an 8.7% rate of radiographically obstructive plaque. This dramatic NCAP burden increase in patients with low CAC suggests a threshold-like relation between coronary calcium and plaque. Acceleration of the intimal hydroxyapatite accumulation process (resulting in visible coronary calcium) may occur when a certain plaque “load” is reached, or development of macroscopic coronary calcification may mark acceleration in the atherosclerotic process. Such hypotheses would need evaluation in histologic studies. It is almost certain that factors not addressed in our study further affect the interplay between coronary calcium and plaque, as evidenced by the substantial number of patients in our study with detectable CAC but no NCAP on CTCA.

We conclude that in outpatients with low to intermediate risk, although a 0 CAC score is quite predictive of very low NCAP burden, low CAC scores are significantly less predictive of prevalence or severity of underlying NCAP. Whether NCAP presence in patients with 0 and low CAC scores indicates an increased cardiovascular event risk, and whether detection of NCAP beyond CAC yields any clinical benefit in these patients, can only be answered by future prognostic studies.

There are several limitations in our study. Our data were retrospectively derived from a single center, whose patients were subject to referral bias. Our criteria for low CAC score, although based on population data, were still arbitrary. We lacked inter- and intrareader variability data. Significant risk factor differences between the 2 CAC groups may have confounded our results, although statistical analyses controlling for such differences still supported our primary findings.

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