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Detection of Coronary Artery Calcium by Ultrafast Computed Tomography and Its Relation to Clinical Evidence of Coronary Artery Disease

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Ultrafast computed tomography (CT) was used to evaluate the relation of coronary artery calcium, a marker of atherosclerosis, with a reported history of coronary artery disease (CAD) in 928 men and 290 women (mean age 53 ± 10 years; 11% with previous CAD). Total calcium score was calculated as the sum of each lesion-specific score, calculated as the product of pixel area and density >130 Hounsfield units. Total score was 3 to 6 times greater ($p < 0.01$) and the probability of coronary artery calcium 30 to 40% greater ($p < 0.01$) in patients with a reported history of myocardial infarction, positive angiography, bypass surgery or angioplasty. From score cutoffs ranging from 1 to 500 for defining calcium, a negative test was accurate 93 to 98% of the time in ruling out CAD, whereas specificity increased from 43 to 93%; however, sensitivity decreased from 92 to 42%. A score cutoff of 50 showed modest sensitivity (78%) and specificity (71%); however, the predictive value for CAD from a positive test remained low ($\leq 40\%$), regardless of score cutoff. From multiple logistic regression, total score was also an independent indicator of CAD after considering any effects due to age, sex and other CAD risk factors. Further study is needed to document the long-term prognostic use of coronary calcium screening, including criteria that best project future risk of CAD.

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A close correspondence between coronary artery calcium deposits and atherosclerotic plaque has been shown by pathologic studies.¹⁻³ Recently, ultrafast computed tomography (CT) was used to determine the arterial site and relative burden of coronary artery calcium, as a marker of atherosclerosis.^{4,5} Studies in subjects who had both coronary angiography and ultrafast CT have shown a direct relation between the extent of coronary artery calcium present and the number or severity of diseased vessels on angiography.⁴⁻⁶ Those studies have documented a high sensitivity and modest predictive value of ultrafast CT coronary artery scanning in detecting significant coronary artery disease (CAD). The present report evaluates the sensitivity and predictive value of ultrafast CT coronary artery scanning in relation to reported history of CAD, including the impact of age and preexisting risk factors on the ability of this test to identify CAD.

METHODS

Study population and interview: Data obtained in 1,218 men and women, primarily self-referred or referred by their physician for ultrafast CT screening between May 1991 and December 1992 at a private radiology clinic, are included in this report. Reasons for referral included family history of premature CAD, known cardiac risk factors or personal history of documented CAD. The study evaluated data obtained as part of a baseline questionnaire regarding the medical and risk factor history of patients, specifically including history of hypertension, diabetes, hypercholesterolemia, tobacco use, premature family history of myocardial infarction (age ≤ 55 years in parent or sibling), chest pain suggesting angina pectoris (by Rose questionnaire), reported previous myocardial infarction, positive angiography, angioplasty and bypass surgery. Use of medication to control hypercholesterolemia, hypertension or diabetes was also included in the category of a positive history of these conditions, and the number of cigarettes consumed or time since quitting was recorded also.

Procedures for ultrafast computed tomography: All studies were performed by a standard protocol previously described, using an Imatron C-100 Ultrafast CT scanner (South San Francisco).⁴ Briefly, the protocol involved subjects being positioned supine, head first, into the scanning aperture with no couch angulation, and instructed to take 3 deep breaths and hold their breath (at end-expiration) while a preview scan was obtained. Patient positioning was checked, and if necessary,

adjusted, so that scanning began from near the lower margin of the bifurcation of the main pulmonary artery. Coronary visualization was achieved without contrast by using the high-resolution volume mode of the ultrafast CT scanner in conjunction with a 100 ms scan time, 3 mm slice thickness, electrocardiographic triggering (to 80% of RR interval) and breath holding for approximately 45 seconds. Twenty to 30 contiguous slices were obtained with no interslice gaps. Each of the levels (which encompassed the proximal portions of the coronary arteries where nearly all calcium is present) was

evaluated sequentially to determine the presence and quantity of coronary artery calcium. From the established protocol,⁴ the threshold for a calcified lesion was set at a CT density of 130 Hounsfield units in ≥ 1 pixel (area ≥ 0.51 mm²). At each level, all pixels with a CT density ≥ 130 Hounsfield units were displayed. A region of interest was manually encircled around each visible lesion within each coronary artery, and computer-acquired measurements of lesion area in mm² and maximal Hounsfield number of each region of interest were recorded. A density score was determined based on

TABLE 1 Prevalence by Coronary Artery Calcium Score Cutoff and Mean Calcium Score ($\pm$ SD) by Presence of Coronary Artery Disease in 1,218 Subjects

	Prevalence			Mean Score $\pm$ SD
	Score > 0	Score > 50	Score > 250	
Previous myocardial infarction				
Yes (n = 72)	90%*	79%*	54%*	630 $\pm$ 891*
No (n = 1,136)	58%	31%	15%	170 $\pm$ 451
Previous positive angiogram				
Yes (n = 57)	97%*	83%*	61%*	911 $\pm$ 928*
No (n = 1,129)	58%	32%	15%	162 $\pm$ 434
Previous bypass surgery				
Yes (n = 37)	89%*	84%*	68%*	1,087 $\pm$ 1,032*
No (n = 1,165)	59%	33%	16%	166 $\pm$ 439
Previous angioplasty				
Yes (n = 49)	94%*	76%*	50%*	570 $\pm$ 474*
No (n = 1,153)	59%	32%	16%	178 $\pm$ 753
Previous CAD				
Yes (n = 128)	92%*	78%*	57%*	746 $\pm$ 928*
No (n = 1,090)	57%	29%	13%	137 $\pm$ 389

*p < 0.01 compared with subjects without prevalent end point.
 tp values based on Student's *t* test performed on natural log-transformed data to improve normality of compared distributions.
 CAD = coronary artery disease.

FIGURE 1. Screening test values for coronary artery disease by calcium score cutoff. Pred. = predictive.

maximal Hounsfield number, as follows: 1 = 130 to 199; 2 = 200 to 299; 3 = 300 to 399; and 4 = >400 Hounsfield units. A score for each region of interest was calculated by multiplying density score by area. A total calcium score was determined by adding each score for all lesions across all slices.

Statistical analysis: The prevalence of coronary artery calcium (defined as the prevalence of subjects with a total calcium score >0, 50 or 250), and the mean total calcium score were calculated and compared (by the chi-square test of proportions to compare prevalence, or Student's *t* test comparing the mean natural logarithm of [total score plus 1] to normalized data) between men and women with and without history of myocardial infarction, bypass surgery, angioplasty and positive angiography. Total CAD was defined as a reported history of ≥1 of the following: myocardial infarction, bypass surgery, angioplasty and positive angiography. Reported chest pain was not included in the aforementioned definition, because of its nonspecificity as an indicator of CAD. Analyses were performed also by age group (<50, 50 to 59, and ≥60 years) and sex. Sensitivity, specificity, and positive and negative predictive values of ultrafast CT-detected coronary artery calcium (using cutoff points of total score of 1, 50, 100, 250 and 500) in relation to CAD were plotted for the overall sample, and analyzed by age/gender group for a cutoff score of 500 (arbitrarily chosen on the basis of maximized overall sensitivity and specificity). Finally, the independent value of the natural log of [calcium score plus 1] in predicting prevalent CAD was examined by multiple logistic regression after allowing for adjustment of known reported risk factors of CAD.

RESULTS

In all, 928 men and 290 women (age range 22 to 85 years, mean 53 ± 10) were included in this report; 83% had ≥1 and 49% had ≥2 reported risk factors among the following: past or current smoking (43%), diabetes mellitus (8%), hypercholesterolemia (55%), hypertension (29%), and premature (parent or sibling aged <55 years) family history of myocardial infarction (20%).

Overall, 6.1% (*n* = 56) of men and 5.5% (*n* = 16) of women had a reported history of myocardial infarction, and including bypass surgery, angioplasty, and positive angiography, CAD was reported in 11% (*n* = 102) and 9% (*n* = 26), respectively.

Table I shows comparisons by prevalence using different score cutoffs and mean calcium scores, comparing patients with and without each coronary end point. The prevalence of coronary artery calcium and mean total calcium scores were significantly greater in patients with than in those without each coronary end point (*p* < 0.01). Although 90.3% of patients with history of myocardial infarction had coronary artery calcium defined by a score >0, 58% of those without this history were positive for coronary artery calcium. In patients (*n* = 128) with any manifestation of CAD, 92.2% were positive for coronary artery calcium by a score criterion >0 and 57% by a score >250, which are substantially greater than in those without previous CAD (56.5 and

TABLE II Prevalence and Mean Score ($\pm$ SD) of Coronary Artery Calcium by Presence of Coronary Artery Disease in 1,218 Subjects by Age/Gender Group

	Prevalence (score > 0)/Mean Score $\pm$ SD			
	Men		Women	
	< 50 Years	50–59 Years	< 60 Years	≥ 60 Years
Previous myocardial infarction				
Yes (<i>n</i> = 72)	100%*/399 $\pm$ 449† (<i>n</i> = 4)	100%†/290 $\pm$ 306† (<i>n</i> = 20)	94%/962 $\pm$ 1,122*† (<i>n</i> = 32)	57%/333 $\pm$ 641 (<i>n</i> = 7)
No (<i>n</i> = 1,136)	40%/142 $\pm$ 164 (<i>n</i> = 373)	72%/163 $\pm$ 367 (<i>n</i> = 274)	87%/530 $\pm$ 782 (<i>n</i> = 216)	33%/180 $\pm$ 196 (<i>n</i> = 180)
Previous positive angiogram				
Yes (<i>n</i> = 57)	100%†/747 $\pm$ 734† (<i>n</i> = 5)	100%*/459 $\pm$ 472† (<i>n</i> = 14)	93%/1,220 $\pm$ 1,069† (<i>n</i> = 28)	100%†/992 $\pm$ 966† (<i>n</i> = 4)
No (<i>n</i> = 1,129)	39%/138 $\pm$ 134 (<i>n</i> = 364)	73%/159 $\pm$ 355 (<i>n</i> = 277)	87%/501 $\pm$ 776 (<i>n</i> = 214)	34%/123 $\pm$ 126† (<i>n</i> = 179)
Previous bypass surgery				
Yes (<i>n</i> = 37)	100%*/1,543 $\pm$ 640† (<i>n</i> = 3)	100%†/770 $\pm$ 329† (<i>n</i> = 7)	86%/1,258 $\pm$ 1,105*† (<i>n</i> = 21)	100%†/1,238 $\pm$ 1,021† (<i>n</i> = 3)
No (<i>n</i> = 1,165)	41%/134 $\pm$ 97 (<i>n</i> = 374)	74%/157 $\pm$ 329 (<i>n</i> = 285)	88%/516 $\pm$ 781 (<i>n</i> = 226)	33%/124 $\pm$ 125 (<i>n</i> = 183)
Previous angioplasty				
Yes (<i>n</i> = 49)	100%*/773 $\pm$ 431† (<i>n</i> = 3)	100%*/301 $\pm$ 290† (<i>n</i> = 16)	91%/813 $\pm$ 945 (<i>n</i> = 21)	100%†/510 $\pm$ 835† (<i>n</i> = 4)
No (<i>n</i> = 1,153)	40%/144 $\pm$ 169 (374)	72%/164 $\pm$ 368 (<i>n</i> = 277)	88%/551 $\pm$ 825 (<i>n</i> = 224)	33%/133 $\pm$ 187 (<i>n</i> = 182)
Previous CAD				
Yes (<i>n</i> = 128)	100%†/710 $\pm$ 808† (<i>n</i> = 8)	100%†/414 $\pm$ 549† (<i>n</i> = 34)	93%/1,083 $\pm$ 1,086† (<i>n</i> = 60)	70%*/441 $\pm$ 738† (<i>n</i> = 10)
No (<i>n</i> = 1,090)	40%/143 $\pm$ 230 (<i>n</i> = 372)	70%/142 $\pm$ 320 (<i>n</i> = 265)	86%/426 $\pm$ 679 (<i>n</i> = 189)	32%/121 $\pm$ 123 (<i>n</i> = 177)
				81%/395 $\pm$ 673† (<i>n</i> = 16)
				71%/129 $\pm$ 298 (<i>n</i> = 87)

**p* < 0.05, †*p* < 0.01, ‡*p* < 0.1; compared with subjects without prevalent end point.
CAD = coronary artery disease.

TABLE III Multiple Logistic Regression for Coronary Artery Calcium (total score) as Indicator of Coronary Artery Disease

	Coefficient	Odds
Intercept	-5.74	
Natural logarithm of total score	0.43	1.53*
Age (10 years)	0.32	1.38*
Sex (female)	0.21	1.12

*p < 0.01.

12.9%, respectively) ($p < 0.01$). Total calcium score was nearly 5 times greater in patients with than in those without previous CAD (mean 746 vs 137; $p < 0.01$). From the negative predictive value plotted by calcium score cutoff (Figure 1), regardless of cutoff, a negative calcium scan was found to be associated with the absence of CAD 93 to 98% of the time. Sensitivity, however, decreased from 92% at a score cutoff of 1 to below 70% after score cutoffs exceeding 100 for defining a positive test. Specificity (absence of calcium in the absence of CAD) increased to nearly 90% using a score cutoff of 250. A score cutoff of 50 appeared to yield modest levels of both sensitivity and specificity in the study population as a whole. The predictive value of a positive test, however, remained low (<40%), regardless of score cutoff used.

Table II compares the prevalence and mean calcium scores of patients with and without each CAD end point by age/gender group. In men aged <50 years and women aged <60, good discrimination in coronary artery calcium prevalence is shown in patients with compared with those without each end point; however, after age 60, calcium prevalence is high regardless of history of event. Mean coronary artery calcium score, however, remains much higher in patients with than in those without each end point, irrespective of age.

When comparisons of sensitivity, specificity, and positive and negative predictive values were evaluated by age and gender group (with a total score cutoff of 500 arbitrarily chosen based on Figure 1), both specificity and the predictive value of a negative test to confirm absence of CAD were best in younger subjects. Sensitivity was best in older subjects (aged >60 years) who had adequate data for analysis.

Multiple logistic regression showed that the natural log of [calcium score plus 1] remained an important indicator ($p < 0.01$), discriminating between patients with and without CAD (Table III). Only score and age were associated independently with CAD status, with no other risk factors entering in the model by stepwise selection.

DISCUSSION

This report confirms a prevalence of coronary artery calcium that is generally in the 90 to 95% range for subjects with a reported history of CAD, which is substantially higher than in those without reported CAD. Mean calcium score is also considerably higher in patients with a positive versus negative history of CAD. The data also suggest that if total calcium score is used as a criterion for defining CAD, a score cutoff of 50 units appears to provide modest (>70%) specificity and sensitivity for discriminating CAD end points, although

this criterion may be too strict for women or younger subjects who have a lower prevalence of coronary calcium. The use of age- and sex-matched isopercentile score cutoffs to risk stratify patients was examined recently by other investigators.⁷ However, longitudinal investigation in relation to future clinical events in a larger population will be required to confirm the use of such an approach.

Although the predictive value of a negative test for excluding clinical CAD remains high regardless of the score cutoff used, the predictive value of a positive coronary artery scan for documenting a positive history of CAD remains low (<50%). This is not surprising, because coronary calcium or atherosclerosis does not necessitate clinically significant CAD, and many subjects with low or moderate levels of coronary calcium may never develop symptomatic CAD. However, the large number of asymptomatic middle-aged subjects in this population who have not developed clinical CAD may underestimate the positive predictive value and overestimate the negative predictive value that would eventually be realized.

The findings from this large study population corroborate those from a previous report of a decreasing sensitivity and increasing specificity with respect to calcium score.⁴ Furthermore, in angiographic subsets, a perfect or nearly perfect sensitivity documenting positive calcium in subjects with significant angiographic obstruction is observed, as well as a high negative predictive value to rule out significant CAD.^{4,6} However, if the presence of any calcium is used to define a positive test, it has been shown that almost half of patients negative for obstructive CAD will remain positive for coronary artery calcium (low specificity).⁶ In these cases, CAD sufficiently significant to result in infarction cannot be ruled out, because these events frequently occur in the presence of mild angiographic CAD.

A possible explanation for lower levels of sensitivity in women and younger subjects, who in general have less calcium, may relate to partial volume effects on identifying calcified pixels, or patient movement that may result in missing smaller lesions, especially if only 1 scan is performed, as in this study. Furthermore, the finding of an increased sensitivity, but reduced positive predictive value with age for higher amounts of calcium suggests that older, highly calcified vessels may not necessarily reflect the severity of stenosis or threat of acute events, but may largely be a reflection of increased calcium prevalence with age. The lower sensitivity in women suggests that calcium could be less important in the pathogenesis of CAD in women, although overreporting of myocardial infarction by women could be an explanation also. However, underreporting of CAD status would tend to result in underestimated specificity.

A role of coronary artery calcium as a marker for coronary risk is also implicated from studies showing its association with coronary risk factors⁸⁻¹⁰ and from earlier fluoroscopic studies showing that coronary artery calcium predicts subsequent prognosis,^{11,12} although not all reports show an association.¹³

The present data show important differences between subgroups of patients with and without a reported his-

tory of CAD in the distribution and quantity of coronary artery calcium. Further refinement of scoring criteria, and improved scanning methodology to minimize technical error are needed to best define the role of coronary artery calcium screening in the diagnosis of CAD. Furthermore, investigations involving longitudinal follow-up of asymptomatic subjects with and without coronary artery calcium, and evaluation of threshold levels and patterning of coronary calcium in relation to clinical events are warranted.

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