Quantification of Coronary Artery Calcium Using Ultrafast Computed Tomography

ARTHUR S. AGATSTON, MD, FACC, WARREN R. JANOWITZ, MD,
FRANK J. HILDNER, MD, FACC, NOEL R. ZUSMER, MD, MANUEL VIAMONTE, JR., MD,
ROBERT DETRANO, MD, PhD

Miami Beach, Florida and Long Beach, California

Ultrafast computed tomography was used to detect and quantify coronary artery calcium levels in 584 subjects (mean age 48 ± 10 years) with (n = 109) and without (n = 475) clinical coronary artery disease. Fifty patients who underwent fluoroscopy and ultrafast computed tomography were also evaluated. Twenty contiguous 3 mm slices were obtained of the proximal coronary arteries. Total calcium scores were calculated based on the number, areas and peak Hounsfield computed tomographic numbers of the calcific lesions detected.

In 88 subjects scored by two readers independently, interobserver agreement was excellent with identical total scores obtained in 70. Ultrafast computed tomography was more sensitive than fluoroscopy, detecting coronary calcium in 90% versus 52% of patients. There were significant differences (p < 0.0001) in mean total calcium scores for those with versus those without clinical coronary artery disease by decade: 5 versus 132, age 30 to 39 years; 27 versus 291, age 40 to 49 years; 83 versus 462, age 50 to 59 years; and 187 versus 786, age 60 to 69 years.

Sensitivity, specificity and predictive values for clinical coronary artery disease were calculated for several total calcium scores in each decade. For age groups 40 to 49 and 50 to 59 years, a total score of 50 resulted in a sensitivity of 71% and 74% and a specificity of 91% and 70%, respectively. For age group 60 to 69 years, a total score of 300 gave a sensitivity of 74% and a specificity of 81%. The negative predictive value of a 0 score was 98%, 94% and 100% for age groups 40 to 49, 50 to 59 and 60 to 69 years, respectively. Ultrafast computed tomography is an excellent tool for detecting and quantifying coronary artery calcium.

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The detection of coronary artery calcium with fluoroscopy has been shown to be of value in predicting the presence of obstructive coronary artery disease (1–7) and to have prognostic value for future coronary events (8). Recently, digital subtraction fluoroscopy (9) and conventional computed tomographic scanning have been reported (10) to have greater sensitivity than conventional fluoroscopy in detecting coronary calcium. However, quantification of coronary calcium has not been attempted using any of these methods. Ultrafast computed tomographic scanning has the advantages of both rapid image acquisition, allowing the elimination of coronary motion artifacts, and the high contrast and spatial resolution of computed tomography. Accordingly, we studied the ability of ultrafast computed tomography to detect and quantify coronary calcium.

Methods

Study patients. The patient group included 584 consecutive subjects between the ages of 30 and 69 years who underwent scanning in accordance with an ultrafast computed tomographic protocol between September 1, 1988 and January 19, 1989. There were 409 men and 175 women whose average age was 48 ± 10 years. One hundred nine patients had established coronary artery disease defined as a documented history of myocardial infarction (22 patients) or angiographically proved coronary artery disease (>50% diameter narrowing of one or more coronary arteries; 87 patients). Of the 475 subjects without established coronary artery disease, 308 had undergone treadmill exercise testing for suspected coronary artery disease (n = 186) or for
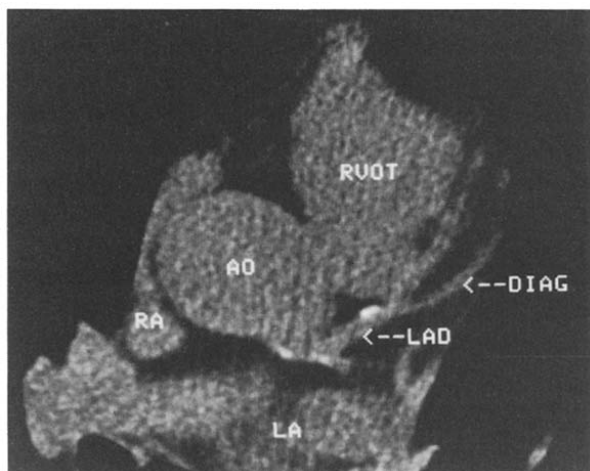
Figure 1. Transverse slice at the level of the proximal left coronary artery. AO = aorta; DIAG = diagonal branch of left anterior descending coronary artery; LA = left atrium; LAD = left anterior descending coronary artery; RA = right atrium; RVOT = right ventricular outflow tract.

screening as part of an industrial medicine program (n = 122). Twenty-one of these 308 subjects had normal or nonobstructive coronary angiograms. Of the remainder, 11 had an abnormal treadmill test by electrocardiographic (ECG) criteria; of these, 6 had a normal thallium scan, 1 had an equivocal thallium scan and 2 had an abnormal thallium scan. In two, thallium imaging was not performed. Of the 167 subjects studied who did not undergo exercise testing, 14 had normal coronary arteries or nonobstructive disease on

coronary angiography. The remainder were asymptomatic and without a history of clinical coronary artery disease.

Fifty patients who underwent fluoroscopy at the time of cardiac catheterization as well as ultrafast computed tomography were also evaluated (30 of these underwent scanning in the September to January interval and are also included in the group described previously). Their average age was 60 ± 10 years, and there were 36 men and 14 women. Eighteen had normal coronary arteries or nonobstructive disease and 32 had obstructive coronary disease on angiography.

Ultrafast Computed Tomographic Protocol

Image acquisition. All studies were performed using an Imatron C-100 ultrafast computed tomographic scanner. Coronary visualization was achieved without contrast by using the high resolution volume mode of the ultrafast computed tomographic scanner in conjunction with a 100 ms scan time, a 3 mm slice thickness, ECG triggering and breath holding (Fig. 1). The image slices were obtained with the patient supine. ECG monitoring electrodes were applied and a scout localization image was obtained to determine the level of the carina as a guide to the location of the main pulmonary artery. The scanner configuration was then switched to the 3 mm, single slice mode. Twenty contiguous slices (60 mm) were acquired with the most cephalad at the lower margin of the bifurcation of the main pulmonary artery. There were no interslice gaps (Fig. 2). Each image slice was triggered at 80% of the patient's RR interval, so
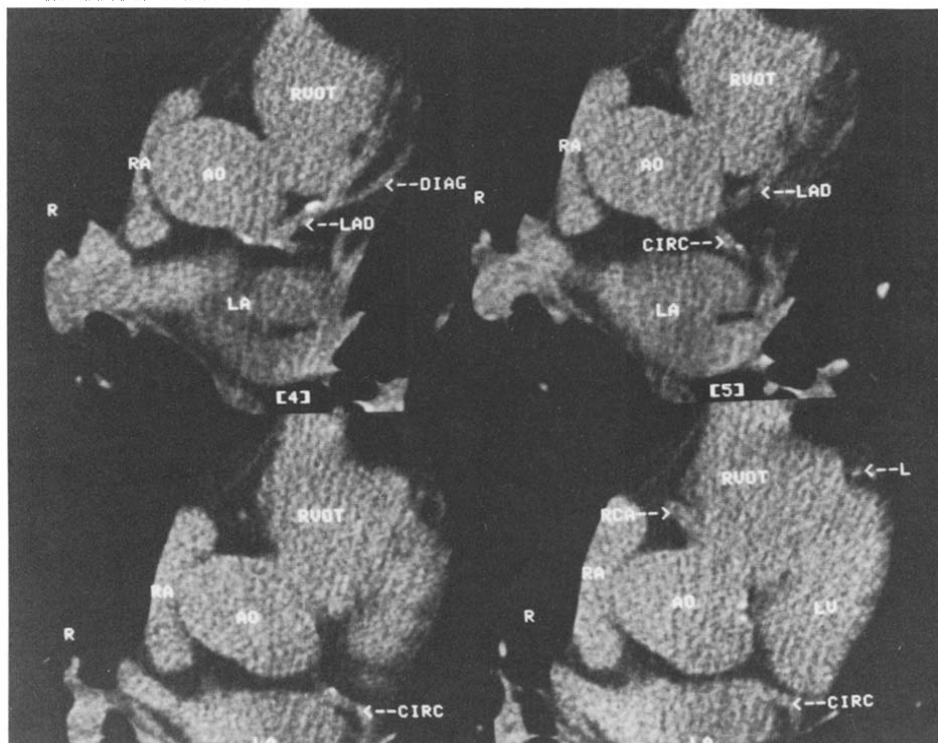

Figure 2. Four consecutive slices 3 mm apart without interslice gaps. Note that part of the circumflex (CIRC) and left anterior descending (LAD) coronary arteries can be seen on more than one level. LV = left ventricle; R = right; RCA = right coronary artery. Other abbreviations as in Figure 1.

Figure 3. Four nonconsecutive 3 mm slices in a 56 year old man who required coronary bypass surgery for three vessel disease. There is dense calcification (white specks) in the left anterior descending (LAD), diagonal (DIAG), left circumflex (CIRC) and right (RCA) coronary arteries. AO = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RVOT = right ventricular outflow tract.
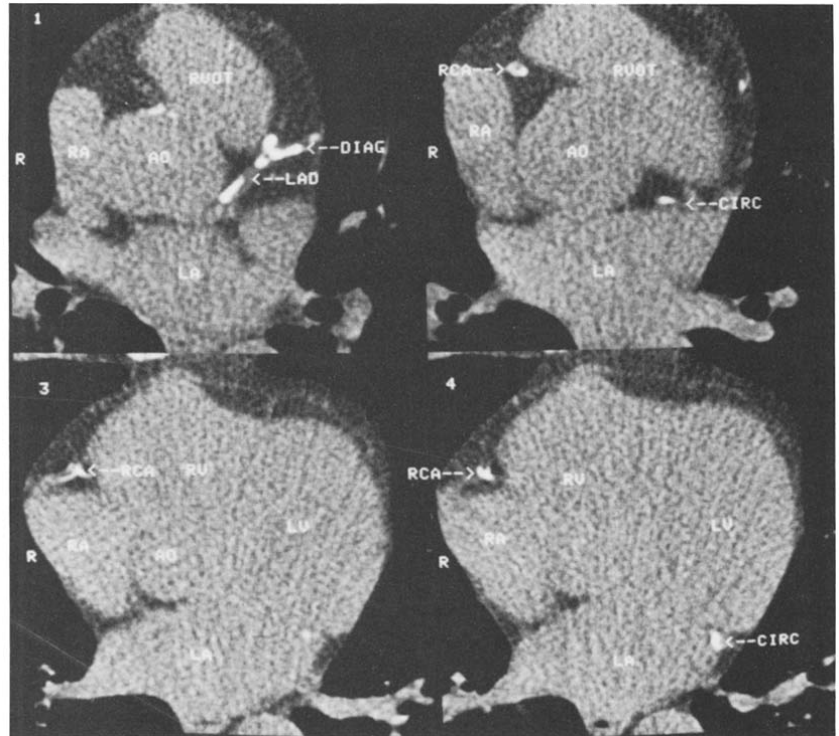
that slices were obtained at the same point in diastole during a single breath hold. This required approximately 40 heartbeats (a duration of 30 to 45 s). The scanner skipped one heartbeat between slices to allow for table incrementation.

After acquisition of the study, the first and last images were reviewed to check patient positioning; if this was found to be adequate, the study was terminated. Additional slices were acquired as needed. Radiation exposure was always <500 mrem. Total procedure time averaged 10 min.

Coronary calcification score determination. To determine the presence and quantity of coronary calcium, each of the 20 levels was evaluated sequentially. The threshold for a calcific lesion was set at a computed tomographic density of 130 Hounsfield units having an area ≥ 1 mm^2. This eliminated single pixels with a computed tomographic density >130 units due to noise. At each level, all pixels with a computed tomographic density ≥ 130 units were displayed. A "region of interest" was placed around all lesions found within a coronary artery. Automated measurements of the lesion area in square millimeters and the maximal computed tomographic number of each region of interest were recorded.

A lesion score was determined based on the maximal computed tomographic number in the following manner: 1 = 130 to 199, 2 = 200 to 299, 3 = 300 to 399 and 4 $\geq$400 Hounsfield units. A score for each region of interest was calculated by multiplying the density score and the area. A total coronary calcium score was determined by adding up each of these scores for all 20 slices. The readers of the ultrafast computed tomographic scores were blinded to the

clinical, fluoroscopic and angiographic data. To evaluate the limitations of scanning only the proximal coronary arteries, 58 subjects had studies using 40 rather than 20 slices (120 versus 60 mm), requiring an additional scan and breath hold for the distal segments.

Fluoroscopy protocol. Cardiac fluoroscopy was performed just before coronary angiography in 50 patients. All fluoroscopic observations were immediately recorded to avoid bias due to angiographic findings. Fluoroscopy was performed in the 30° right anterior oblique and 60° left anterior oblique projections. Other views were used if necessary. The presence or absence of calcium was recorded for the left main–left anterior descending, circumflex and right coronary artery distributions.

Statistical analysis. Statistical analyses were performed on the log transformed total score and on the square root of the number of lesions to normalize the experimental data. Two-way unbalanced analysis of variance was carried out on the log total calcium scores by group (with and without clinical coronary artery disease) and by age (grouped by decade). Because the differences in total calcium scores between the two clinical groups were uniform over all age groups, a two-sample unpaired t test was used to compare the two groups at each decade using a Bonferroni inequality ($\alpha = 0.05$).

Two-way analysis of variance was also carried out on the square roots of the number of lesions. Differences in this analysis between the two clinical groups were not uniform over all age groups (interaction was present). Therefore,

Table 1. Calcification in Coronary Disease Versus No Coronary Disease by Age in 584 Subjects

	Age Group (yr)			
	30 to 39	40 to 49	50 to 59	60 to 69
No. of patients				
No CAD	110	181	116	68
CAD	3	17	54	35
Prevalence				
No CAD	25%	39%	73%	74%
CAD	100%	88%	96%	100%
Total calcium score (raw)				
No CAD	5 ± 2	27 ± 9	83 ± 14	187 ± 38
CAD	132 ± 91	291 ± 93	462 ± 95	786 ± 115
Total calcium score (LN)*				
No CAD	0.24 ± 0.05	0.42 ± 0.05	1.14 ± 0.09	1.43 ± 0.13
CAD	1.80 ± 0.42	1.87 ± 0.24	2.04 ± 0.13	2.66 ± 0.09
Lesion number (raw)				
No CAD	0.6 ± 0.15	1.6 ± 0.33	4.6 ± 0.55	7.1 ± 1.07
CAD	6.7 ± 1.2	11.4 ± 2.5	14.4 ± 2.0	25.3 ± 2.7
Lesion number (SQRT)				
No CAD	0.8 ± 0.05	1.1 ± 0.07	1.9 ± 0.11	2.3 ± 0.19
CAD	2.6 ± 0.22	3.0 ± 0.40	3.4 ± 0.25	4.8 ± 0.27
	p < 0.01	p < 0.0001	p < 0.0001	p < 0.0001

*p < 0.0001 over all ages. Values are expressed as mean values ± SEM; CAD = clinical coronary artery disease; Lesion number = number of coronary calcific densities reported; LN = logarithmic transformed data; Prevalence = prevalence of reported coronary calcium by computed tomography; raw = raw data; SQRT = square root transformed data.

Table 2. Sensitivity, Specificity and Predictive Value by Total Calcium Score by Age Group in 584 Subjects

Calcium Score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Age 40 to 49 years				
1	88	61	17	98
25	71	87	34	97
50	71	91	41	97
100	47	94	42	95
200	41	96	50	95
300	18	97	60	93
500	—	—	—	—
700	—	—	—	—
Age 50 to 59 years				
1	96	28	38	94
25	80	55	45	85
50	74	70	53	85
100	56	75	51	78
200	50	86	63	79
300	35	90	63	75
500	28	94	68	74
700	19	100	100	73
Age 60 to 69 years				
1	100	26	41	100
25	97	46	47	97
50	91	51	49	92
100	89	63	55	91
200	77	71	57	86
300	74	81	67	86
500	60	85	68	81
700	49	91	74	78

NPV = negative predictive value; PPV = positive predictive value.

differences between the clinical groups by decade were analyzed using simple effects analysis (11).

Results

Prevalence of calcification. The prevalence of coronary calcification (total calcium score >0) by ultrafast computed tomography in the 109 subjects with clinical coronary artery disease was 96%. The prevalence of coronary calcium in those without clinically established coronary artery disease increased with age (Table 1).

Distal calcification. Of the 58 subjects in whom 40 levels were scanned, 26 had calcium reported. Only one of these subjects had calcium found exclusively in the distal 20 slices. Four had both proximal and distal calcification and 21 had only proximal calcification.

Coronary calcium score. The total calcium score and lesion number in those with and those without clinical coronary artery disease by age are shown in Table 1. The score and lesion number increased with age for those with and without coronary artery disease. In each age group there was a statistically significant difference in calcium score and lesion number between those with and those without clinical disease. The sensitivity, specificity and the positive and negative predictive values for clinical coronary artery dis-

ease were calculated for a range of total calcium scores in each age group (Table 2). A score of 50 appeared to be the best cut score for those in their 40s and 50s, and a score of 300 was the best cut score for those in their 60s. The four subjects who had an abnormal ECG treadmill test (two with an abnormal thallium scan) without angiography were included in the group without established coronary artery disease, but all four had calcium present. Their average total calcium score was 423 (range 30 to 613).

Interobserver variability. Interobserver variability was evaluated by having two physicians independently score 88 consecutive studies. Of these studies, there were 48 with no calcium detected by both observers (total score = 0). Of the remaining 40 studies with evidence of calcification reported by at least one observer, scores ranged from 1 to 815. Identical total calcification scores were obtained by both readers for 22 of these 40 studies. Thus, 70 (80%) of 88 studies were scored identically. Three sources of interobserver disagreement were identified. The most common was a variation in computed tomographic number on recall of the study at different times (12 of 18). This caused an average error of 5 points and was eventually traced to a computer

hardware error. Four discrepancies with an average error of 44 points were due to a motion artifact that obscured the true border of the lesion, leading to inconsistent scoring. This was most often seen in the distal images of the right coronary artery. A third potential source of disagreement included ostial calcifications (two subjects) that bordered the aorta and the origin of the left main or right coronary artery and had to be judged to be in one or the other. Overall, the mean error was 2.5%, with a standard deviation of 5% between the two observers.

Sensitivity of computed tomography versus fluoroscopy. Forty-five (90%) of the 50 patients undergoing both tests and coronary angiography had calcium reported by ultrafast computed tomography in at least one vessel compared with 26 patients (52%) by fluoroscopy (p < 0.001). Of the 150 vessels examined in the 50 patients, calcium was detected in 98 (65%) by ultrafast computed tomography versus 57 (38%) by fluoroscopy (p < 0.001). Calcium was detected in 20 patients only by ultrafast computed tomography and in 1 patient only by fluoroscopy. Sixty-one vessels had calcium detected only by ultrafast computed tomography, and 20 vessels had calcium detected only by fluoroscopy. The mean total calcium score by ultrafast computed tomography in those with normal versus abnormal fluoroscopic results was 99 and 546, respectively. The sensitivity and specificity for obstructive disease were 100% and 28%, respectively, by ultrafast computed tomography (for a total calcium score >0) and 75% and 56%, respectively, by fluoroscopy.

Discussion

The presence of calcium in the coronary arteries is invariably an indication of intimal atherosclerosis (4), and postmortem studies have shown the extent of coronary calcification to correlate with the severity of coronary stenosis and the frequency of myocardial infarction (12–15). Most fluoroscopic studies (1–7) of coronary calcium have related its presence or absence to angiographically documented obstructive coronary artery disease. Although some studies (3,4) have semiquantified coronary calcium, none have attempted its precise quantification and no fluoroscopic study has reported interobserver variability.

Other methods of coronary calcium detection. Because of the demonstrated value of coronary calcium detection in predicting significant coronary disease, particularly in the young, and because of its independent predictive value for coronary events (8), it is important to explore the potential of newer techniques that may better detect and quantify coronary calcium. Detrano et al. (9) have shown digital subtraction fluoroscopy to be superior to conventional fluoroscopy for detecting coronary calcium. Reinmuller et al. (10) used conventional computed tomography and Tanenbaum et al. (16) used the cine (low resolution) mode of the ultrafast computed tomographic scanner to detect coronary calcium.

In none of these studies was precise quantification attempted. Good interobserver agreement for detection of coronary calcium was demonstrated with ultrafast computed tomography (16). Because of its slow acquisition time, the advantage of the improved resolution of conventional computed tomography over fluoroscopy is limited when moving structures such as coronary arteries are imaged. Ultrafast computed tomographic scanning overcomes this limitation because of rapid acquisition times (≤100 ms) that freeze coronary motion and result in sharper images (Fig. 1). The protocol described in this report was developed to exploit the advantages of ultrafast computed tomography for detecting and quantifying coronary calcium. In contrast to the protocol used by Tanenbaum et al. (16) (eight 8 mm cuts with 4 mm gaps between every other level), a high spatial resolution mode was used that included twenty 3 mm cuts with no gaps between slices.

Fluoroscopy versus ultrafast computed tomography. Ultrafast computed tomography was superior to fluoroscopy at detecting coronary calcium (96% versus 57% by patient and 65% versus 38% by vessel, respectively). Because distal as well as proximal scanning indicated that exclusive distal calcification is rare, it is likely that the 20 vessels with calcium detected only by fluoroscopy represented false positive studies. This may be due to misinterpretation of overlapping structures, which is not a problem with a tomographic imaging technique. The marked difference in the mean calcium score between the patients with calcium detected only by ultrafast computed tomography and the patients with calcium detected by both methods (99 versus 546) indicates that it is generally subjects with milder calcification who are undetected by fluoroscopy.

Compared with ultrafast computed tomography, fluoroscopy has less sensitivity and several other limitations. A physician must be present for the examination, and the results obtained depend on the skill and experience of the examiner as well as on the number of views and the duration of the study. False positive and negative readings may be caused by overlapping structures and by failure to achieve correct angulation for a particular coronary artery. In contrast, the ultrafast computed tomographic examination does not require a physician to be present and the results using the automated method described have minimal interobserver variability.

Sensitivity, specificity and prognostic value of ultrafast computed tomography. The high sensitivity of ultrafast computed tomography for subjects with clinical coronary artery disease and the high negative predictive value for its absence (Table 2) are superior to those of fluoroscopy, exercise testing and exercise thallium scanning. The range of ultrafast computed tomography total calcium scores allows the choice of threshold values of sensitivity, specificity and predictive values to be tailored to the population to which a subject belongs. Although a combination of fluoroscopic detection

of calcium and treadmill exercise has been found to be of value in screening an asymptomatic population (5), separately neither one has been determined to be cost effective for this task (17,18). Ultrafast computed tomographic scanning may prove superior to these modalities in screening asymptomatic populations.

Although the specificity of low calcium scores for clinical coronary artery disease is poor, detection of minimal calcification may still be of value. Because the presence of calcium indicates intimal atherosclerosis (4), its detection may have prognostic significance, as does the detection of coronary calcium by fluoroscopy even in subjects with a normal exercise test (8). Further studies using this new diagnostic tool to determine the prognostic value of precise coronary calcium quantification are in progress.

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