Fast Computed Tomography Detection of Coronary Calcification in the Diagnosis of Coronary Artery Disease

Comparison With Angiography in Patients <50 Years Old

James A. Fallavollita, MD; Alan S. Brody, MD; Ivan L. Bunnell, MD; Krishna Kumar, MD; John M. Canty, Jr, MD

Background The predominant cause of coronary artery calcification is atherosclerosis. Although fast x-ray computed tomography (CT) has been demonstrated to be a sensitive technique to detect coronary calcification, the increasing prevalence of calcification with age has been associated with a low specificity for identifying obstructive atherosclerosis. We hypothesized that the specificity of this test would be improved in a younger patient population, making it more useful in the diagnosis of coronary artery disease.

Methods and Results We compared fast CT-detected calcification with coronary angiography in 106 patients under the age of 50 years. Nonenhanced fast CT scans consisting of 20 contiguous 3-mm tomograms of the proximal coronary arteries were obtained during a single breath hold. A positive scan was defined as 4 contiguous voxels (≥1 mm³) of density >130 Hounsfield units in the region of the epicardial coronary arteries. Calcification detected by fast CT had an 85% sensitivity to predict patients with significant coronary artery disease (≥50% diameter stenosis), with a specificity of 45%. Although the sensitivity to detect multivessel disease was 94%, the sensitivity to detect single-vessel disease was 75%. Changing the threshold for defining a positive fast CT scan from 4 to 2 contiguous voxels produced a small improvement in sensitivity, to 88%, but reduced specificity to 36%.

Conclusions Although the specificity to detect angiographically significant coronary disease with fast CT improves in a younger patient population, it continues to be relatively low. In contrast to older patient populations, a small but significant number of patients <50 years old with angiographically significant coronary artery disease do not have coronary calcification demonstrated by fast CT. Thus, caution should be used in excluding significant coronary artery disease on the basis of a negative fast CT study. (Circulation. 1994;89:285-290.)

Key Words • tomography • atherosclerosis • coronary calcification

A number of previous investigations have established a strong association between proximal coronary artery calcification and atherosclerosis. 1-3 Initial studies using conventional fluoroscopy have shown that the detection of calcium was highly specific but only moderately sensitive in predicting the presence of angiographically significant stenosis at cardiac catheterization. 4-8 This has raised speculation that more sensitive methods of detection could potentially be useful in the noninvasive diagnostic evaluation of patients with suspected coronary artery disease (CAD). Results with improved fluoroscopic detection techniques have been encouraging in this regard. 9-11

Several recent investigations have capitalized on the potentially improved densitometric sensitivity of x-ray computed tomography (CT) to detect coronary calcification. 12-15 Fast CT appears to be the most promising CT approach, since it is able to obtain contiguous gated diastolic tomograms of the proximal coronary arteries during a single breath hold and avoid misregistration of tomograms because of motion artifacts. Initial studies with fast CT have indicated that the presence of calcification increases dramatically as age exceeds 50 years. Thus, although the sensitivity of fast CT to detect disease was very high (ranging between 96% and 100%), its specificity was low (28% to 28%). 14

Since the prevalence of CT-detected calcium appears to increase markedly with age, we hypothesized that fast CT would be more suitably applied to evaluating younger patients, provided that the sensitivity to detect disease remained high. To test this, we compared the results of calcification detected by fast CT with those by coronary angiography in patients <50 years of age.

Methods

The protocol was approved by the investigational review committee of the State University of New York at Buffalo.

Patient Population

The study group consisted of 108 patients <50 years of age (range, 25 to 49 years) who underwent coronary angiography for the clinical evaluation of CAD. Patients were contacted by telephone after angiography and, after informed consent was obtained, underwent fast CT. The fast CT scans were obtained 59±29 days after angiography.

Coronary Angiography

Coronary angiograms were performed by each patient's cardiologist for routine clinical indications. All coronary an-
TABLE 1. Study Population Characteristics (n=106)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
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<tbody>
<tr>
<td>Male</td>
<td>78</td>
<td>74</td>
</tr>
<tr>
<td>White</td>
<td>96</td>
<td>91</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Family history of coronary artery disease</td>
<td>67</td>
<td>63</td>
</tr>
<tr>
<td>Cholesterol ≥200 mg/dL</td>
<td>67</td>
<td>63</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46</td>
<td>43</td>
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<tr>
<td>Tobacco abuse</td>
<td>57</td>
<td>54</td>
</tr>
</tbody>
</table>

giograms were reviewed by an observer blinded to the results of the CT study. One hundred of the angiograms were available for review by a second blinded observer. Each coronary artery was visually categorized as being normal, insignificantly stenosed, or significantly diseased. Normal arteries were defined as those having no luminal irregularities on angiography. Insignificant stenoses were defined as those involving <50% of the normal luminal diameter. Significant CAD was defined as a ≥50% diameter stenosis. Caliper measurements were used to confirm categorization of lesions. In cases of disagreement between observers, the lesions were reviewed by a third blinded observer, and final categorization was determined by consensus.

Fast CT Scans

Nonenhanced fast CT scans were performed on an Imatron C-100 CT scanner (Imatron Inc, South San Francisco, Calif) in the high-resolution mode with a 100-millisecond scan time and a 3-mm slice thickness. The field of view was 26 cm, with a resultant voxel size of 0.5×0.5×3 mm. A scout image was obtained to identify the area of interest, and 20 consecutive tomograms were obtained in a single breath hold. Scans began 1 cm caudal to the carina and encompassed the proximal left and right coronary arteries. The slices were electrocardiographically triggered to obtain each image at the same point in diastole for each of 20 consecutive heart beats as previously described.14 Total radiation exposure was <0.005 Gy per patient.

Each CT study was interpreted by two independent observers. Significant coronary calcification was defined as ≥1 mm² (4 voxels) of contiguous area of CT density >130 Hounsfield units (Hu). A lesion score was calculated by multiplying the area in square millimeters by a “density factor” as previously described.14 The density factor was determined from the peak density within the area of calcification and was equal to 1 for lesions of 131 to 199 Hu, 2 for lesions of 200 to 299 Hu, 3 for lesions of 300 to 399 Hu, and 4 for lesions that were ≥400 Hu. Calcific lesions were assigned to the distribution of the left main, left anterior descending, left circumflex, or right coronary artery by their anatomic orientation. A total calcium score was calculated by summing the lesion scores in all 20 tomograms.14 The results reflect the average scores of the two observers. When there was disagreement regarding the presence or absence of significant calcification within an individual vessel, scans were subjected to review by a third blinded observer and settled by consensus.

Data Analysis

Standard estimates of sensitivity, specificity, and positive and negative predictive value were obtained by use of two-by-two contingency tables.16 All values are the mean±SD. Baseline characteristics between study groups were compared by χ² and ANOVA,16 with significance defined at the 0.05 level.

Results

Technically adequate fast CT studies were obtained in 106 of the 108 patients. One study had a respiratory motion artifact, and another was reconstructed with an inappropriate field of view. Demographic variables are summarized in Table 1. There were 78 men and 28 women, with an average age of 43.6±5.4 (SD) years. Ninety-one percent of the population was white. Risk factor data were obtained from official catheterization reports and from review of each patient’s medical record. There was an average of 2.4±1.2 coronary risk factors per person.

The results of coronary angiography and the distribution of fast CT--detected coronary calcification are summarized in Table 2. Significant CAD was identified in 59 patients (56%). Of the remaining 49 patients without significant disease, 20 (19%) had luminal irregularities (<50% diameter reduction) and 27 (25%) had smooth, luminally normal coronary arteries. There was no significant difference in the age of patients with and without angiographically significant disease (44.1±5.0 versus 42.9±5.8 years). Coronary calcification was detected in 76 (72%) of the patients. Those having coronary calcification were more likely to be older (P=.002), male (P=.001), and hypercholesterolemic (P=.015). The prevalence of smoking and hypertension was similar in each group. The overall sensitivity of coronary calcification to detect significant CAD was 85%, with a specificity of 45% (Fig 1). The positive predictive value of coronary calcification for detecting significant CAD was 66%. The negative predictive value was 70%. Subgrouping patients by sex or by age (<40 versus ≥40 years) revealed no statistically significant differences.

TABLE 2. Detection of Coronary Calcification With Fast Computed Tomography vs Angiographic Disease

<table>
<thead>
<tr>
<th>Coronary Calcification</th>
<th>Number</th>
<th>%</th>
<th>Present</th>
<th>Absent</th>
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<tbody>
<tr>
<td>Significant coronary artery disease</td>
<td>59</td>
<td>56</td>
<td>50</td>
<td>9</td>
</tr>
<tr>
<td>One-vessel disease</td>
<td>28</td>
<td>26</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>Two-vessel disease</td>
<td>14</td>
<td>13</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>17</td>
<td>16</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Insignificant coronary artery disease</td>
<td>47</td>
<td>44</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Luminal irregularities</td>
<td>20</td>
<td>19</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Normal coronary arteries</td>
<td>27</td>
<td>25</td>
<td>13</td>
<td>14</td>
</tr>
</tbody>
</table>
Nine of the 59 patients with significant CAD had false-negative fast CT studies. Fig 2 shows the prevalence of calcification in angiographic subsets. The sensitivity of CT was particularly low in patients with single-vessel disease and averaged 75%. This group accounted for seven of the nine false-negative CT studies. The sensitivity to detect multivessel disease was higher and averaged 94% for patients with two- and three-vessel disease combined. Fig 3 shows the effect of reducing the number of contiguous voxels required to define a positive CT study on calculations of sensitivity and specificity. When this was reduced from 4 to 2 voxels, there was an increase in sensitivity from 85% to 88%, but specificity fell from 45% to 36%. A 1-voxel threshold increased sensitivity to 93%, but specificity was only 17%.

Fig 4 shows the prevalence of fast CT-detected calcification in individual vessels subgrouped into normal, insignificant disease, and significant disease. Two left main arteries were too short to be accurately categorized. Of the remaining 422 vessels, 106 (25%) were significantly diseased, 132 (31%) had insignificant disease, and 184 (44%) were luminally normal. As shown in Fig 4, CT-detected calcification was not invariably present in vessels with $\geq 50\%$ stenosis. The absence of calcification in 30% of significantly diseased vessels was approximately similar to the rate of false-negative CT studies (25%) in patients having single-vessel disease.

The distribution of calcium scores as a function of the angiographic extent of disease is depicted in Fig 5. Individual scores have been plotted on a logarithmic scale to encompass the wide range of scores we observed within various angiographic subgroups. The average calcium score increased as the angiographic extent of disease increased (normal, $0-5$; $<50\%$ stenosis, $17\pm 31$; one-vessel disease, $78\pm 143$; two-vessel disease, $126\pm 161$; three-vessel disease, $285\pm 345$). Although the average calcium score increased with the extent of disease, there was considerable overlap between angiographic subgroups.

**Interobserver Variability**

There was agreement in categorization of patients as to the presence or absence of significant angiographic disease in 97% of the studies (Table 3). On a vessel-by-vessel basis, there was agreement in categorization of normal and insignificant and significant disease in 80% of the vessels reviewed (317 of 398). Most of the variability in categorization by vessel involved the distinction between luminal irregularities and smooth, luminally normal arteries.
All 106 fast CT studies were reviewed by two independent observers. There was agreement regarding the presence or absence of coronary calcification in 103 of the 106 studies (97%, Table 4). On an individual vessel basis, there was agreement as to the presence or absence of calcification in 391 of 424 vessels (92%). Total calcium scores showed more interobserver variability. Calcium scores agreed by ≤1 in 68 of the 106 scans (64%). The regression relation for scores between observers was $y = 1.05x + 7.83$, $r^2 = .87$. The average difference in scores between observers was 16%. Most of the variability in interpretation arose from uncertainty as to whether significant calcifications were within or outside the expected position of the vessel. This most frequently occurred in the distal segments of the right and circumflex arteries, which were variably delineated by low-density epicardial fat. Intraobserver variability was determined in 29 scans (3 of which had no calcification). The mean difference in calcium scores was 8%.

**Discussion**

There are several new findings in our study. First, although fast CT showed a very high sensitivity to detect the presence of angiographically significant multivessel disease, a significant number of patients with single-vessel CAD failed to have detectable calcification (25%). This was similar to the frequency with which CT calcification was absent in individual arteries with angiographically significant stenoses (30%). Although the specificity was better than that demonstrated in studies of older populations, it continued to be relatively low.

**Methodological Limitations**

Our investigation retrospectively enrolled patients who had angiography for routine clinical indications. Although our study group is clearly not representative of the general population in this age group, it should be representative of younger patients referred for the diagnostic evaluation of suspected CAD who would most likely benefit from this noninvasive test. A second potential limitation is that we restricted our fast CT scans to the basal 6 cm of the coronary arteries. Although this reduced radiation exposure and simplified the conduct of the scans by allowing them to be performed in a single breath hold, we would not have detected calcification in more distal segments. Nevertheless, pathological studies have shown that calcification isolated to the distal coronary arteries is relatively infrequent. When the additional yield of use of 40 contiguous 3-mm tomograms was assessed in a previous study, only 1 of 58 patients had calcification restricted to the lower 20 levels of the scan. Extrapolating from these results suggests that this limitation could have accounted for no more than 2 of the 9 patients with disease and a negative scan in our study.

**Findings in the Present Study**

We found that the sensitivity of fast CT to detect angiographically significant disease was lower than that previously reported in populations that included patients >50 years old. This was largely because of its relative inability to detect patients with single-vessel disease, in whom the sensitivity was only 75%. A similar limitation in the correlation between calcification and angiographic disease was found when we examined the prevalence of calcification in individual arteries. Only 70% of significantly diseased vessels had detectable calcification by fast CT. The prevalence of calcification fell to 44% in vessels with <50% stenosis and to 15% in luminal normal arteries. These findings are consistent with the notion that the prevalence of calcification varies as a function of the anatomic severity of disease. This is similar to the conclusion reached in studies examining this issue with cardiac fluoroscopy. Similar findings have also been noted in several preliminary reports that show increases in CT calcium scores with increasing angiographic extent of disease. Unfortunately, in young patients, the wide scatter in quantitative estimates observed within each angiographic subgroup does not support the notion that a cutoff calcium score can separate these groups with any degree of certainty (Fig 5).
The specificity of fast CT-detected calcification in patients without significant disease was only moderately improved in this study by restriction of its use to younger patients. The high prevalence of calcification in patients with luminal irregularities but stenoses <50% could have accounted for some of the false-positives in our study. Nevertheless, even when any degree of luminal disease was considered an “abnormal” angiographic study, the specificity improved only to 52%. The low specificity could be related to image noise or could reflect the ability of fast CT to detect atherosclerotic disease at a stage when there is no luminal narrowing. Previous studies have demonstrated an excellent prognosis for patients with smooth, luminally normal angiograms as opposed to those with insignificant CAD.10-21 Margolis and colleagues6 showed that fluoroscopic calcification was an independent predictor of increased mortality in patients with significant disease, but they did not separate patients without disease into those with and without luminal irregularities. Thus, the prognostic significance of coronary calcification in patients with insignificantly diseased arteries remains undefined.

Relation of the Present Study to Previous Studies

Our results differ from studies using fast CT in somewhat older patient populations, in which the presence of calcification was correlated with clinically and/or angiographically defined CAD. In a large series of patients evaluated with fast CT, Agatston et al14 found that the detection of calcification by fast CT had a sensitivity of 96% in patients with either a previous myocardial infarction or significant angiographic disease. In the subset of their 311 patients <50 years old, only 20 had documented CAD, and the prevalence of significant angiographic disease in their “normal” subjects was unknown. Sensitivity in patients <50 years old ranged from 88% to 100% (average, 90%), and specificity ranged from 61% to 75% (average, 66%). Although they found that the sensitivity of fast CT was higher in patients >50 years old (96% to 100%), the specificity fell to between 26% and 28%, making the test of questionable value in older populations because of the high prevalence of coronary calcification.

In a preliminary report of a large cohort of older patients (average age, 61±12 years), all of whom had angiography, the same group found that the sensitivity of fast CT was 95%, with a surprisingly high specificity of 76%.17 This study included an undefined number of patients who were enrolled from centers in Japan. The potential influences of ethnicity on calcification and atherosclerosis may have increased their specificity, since the age of onset of atherosclerosis in Japan may be later than that of the US population.

Breen et al15 correlated the presence of fast CT-detected calcification with angiography in 100 patients <60 years old (mean, 47±8 years). In contrast to the previously noted studies, as well as our own, their protocol used 40 contiguous 3-mm scan slices, as opposed to 20. In addition, they defined the minimum area required for a significant calcification as 2 adjacent voxels having a CT density ≥130 Hu. Using these criteria, they found sensitivity to be 100%, with a specificity of 47%. When we used 2 voxels to define a positive CT calcification in our study, the sensitivity improved only modestly to 88%, with a reduction in specificity to 36%. Differences in our population, including the lower mean age and the fact that we had more than twice as many women in our study, may have accounted for the reduction in sensitivity. The independent influence of including 20 additional caudal tomograms cannot be addressed, since Breen et al did not report the frequency of CT studies demonstrating only distal calcification. Based on the prevalence of isolated distal calcification in previous studies, this is unlikely to explain the difference between our studies. Finally, differences in the ages of patients with and without anatomic disease as well as the extent of CAD, which were not reported in their study, could have led to different results.

A recent postmortem study by Mautner et al22 demonstrated that histopathological calcium was present in 7% to 9% of coronary segments from patients with significant CAD who had all undergone coronary artery bypass graft surgery. Importantly, 21 of the 22 patients had histopathological evidence of one or more calcium deposits in the native coronary circulation. Although the correlation between histopathological calcification and fast CT-detected calcium remains unknown, a recent pathological study by Simons et al23 correlated cross-sectional area reduction in histological sections with fast CT-detected calcifications from 13 excised postmortem hearts. They used 1 voxel of CT density >130 Hu to define significant calcification and noted a 59% sensitivity and a 90% specificity for detecting any histopathological coronary artery (disease being defined as ≥75% area stenosis). This reinforces the notion that atherosclerotic disease is not invariably associated with calcification. They were also able to correlate the degree of “calcium burden” (voxels of CT density >130 Hu) with plaque area and luminal area stenosis. Although the spread of their data was large, the absence of calcium had a negative predictive value of 97.5% for the absence of significant pathological atherosclerotic disease. Although encouraging, the clinical applicability of a single high-density voxel in patients appears to be limited by the additional image noise caused by beam hardening and scatter encountered in vivo. In our study, the use of a 1-voxel threshold increased the sensitivity to 93%, but specificity fell to 17%.

Only one previous study has examined the ability of coronary calcification detected with cardiac fluoroscopy to predict disease in a patient population of similar age. Loeker et al11 compared the diagnostic use of cardiac fluoroscopy, exercise ECG, and 201TI scintigraphy in a largely asymptomatic male military population undergoing diagnostic evaluation for suspected CAD. Although their average age was similar to that in our own study (40.2±5.0 years), 13% of the population undergoing angiography was >50 years old. Since a positive noninvasive test was required before cardiac catheterization was performed, only approximate sensitivity and specificity for angiographically defined disease were available. Fluoroscopically detected calcification had a sensitivity for predicting significant disease (≥50% luminal diameter stenosis) of 66%, with a specificity of 77%, and was as accurate as 201TI scintigraphy in predicting the presence of significant CAD.

Clinical Implications

The clinical utility of detecting coronary calcification with fast CT in the noninvasive evaluation of CAD has
not been established. Unfortunately, a negative study does not reliably exclude anatomically significant CAD in patients <50 years old. Furthermore, the specificity is low and is only modestly improved by restricting its use to this age group. In screening populations with an even lower pretest likelihood of disease than those referred for angiography, the diagnostic accuracy of fast CT for predicting significant CAD would be expected to be even lower. Even though fast CT has the potential advantage of being quantified, further studies will be required to determine whether calcium scores can be used to provide any diagnostic or prognostic information over that provided by the presence or absence of calcification alone.

Scanning 20 levels and using 4 contiguous voxels >130 Hu in a single tomogram to define a positive CT study results in an overall sensitivity in detecting significant CAD that, although imperfect, appears to be comparable to noninvasive tests that assess physiological end points. Prospective studies directly comparing the efficacy and cost-effectiveness of CT in relation to other noninvasive tests and/or testing algorithms should be performed before its clinical use is recommended.

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References