

Severity of Coronary Artery Calcification by Electron Beam Computed Tomography Predicts Silent Myocardial Ischemia

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Background—Detection of subclinical coronary artery disease (CAD) before the development of life-threatening cardiac complications has great potential clinical relevance. Electron beam computed tomography (EBCT) is currently the only noninvasive test that can detect CAD in all stages of its development and thus has the potential to be an excellent screening technique for identifying asymptomatic subjects with underlying myocardial ischemia.

Methods and Results—Over 2.5 years, we prospectively studied 3895 generally asymptomatic subjects with EBCT, 411 of whom had stress myocardial perfusion tomography (SPECT) within a close (median, 17 days) time period. SPECT and exercise treadmill results were compared with the coronary artery calcium score (CACS) as assessed by EBCT. The total CACS identified a population at high risk for having myocardial ischemia by SPECT although only a minority of subjects (22%) with an abnormal EBCT had an abnormal SPECT. No subject with CACS <10 had an abnormal SPECT compared with 2.6% of those with scores from 11 to 100, 11.3% of those with scores from 101 to 399, and 46% of those with scores ≥ 400 ($P < 0.0001$). CACS predicted an abnormal SPECT regardless of subject age or sex.

Conclusions—CACS identifies a high-risk group of asymptomatic subjects who have clinically important silent myocardial ischemia. Our results support the role of EBCT as the initial screening tool for identifying individuals at various stages of CAD development for whom therapeutic decision making may differ considerably. (*Circulation*. 2000;101:244-251.)

Key Words: tomography ■ calcium ■ ischemia

The detection of subclinical coronary artery disease (CAD) before the development of life-threatening cardiac complications has great potential clinical relevance. However, currently available noninvasive techniques, such as exercise treadmill testing (ETT) and myocardial single photon emission computed tomography (SPECT), can identify only patients with advanced CAD who manifest myocardial ischemia.^{1,2} Although the presence and extent of left ventricular ischemia can accurately identify individuals at high risk for cardiac events,³⁻⁸ the low prevalence of a positive test result among asymptomatic subjects with cardiac risk factors mitigates against this approach.⁷⁻⁹

Electron beam computed tomography (EBCT) is a new noninvasive technique that can detect coronary atherosclerosis even at its earliest stages on the basis of the presence and severity of coronary artery calcification.¹⁰ Although calcification severity predicts the presence of significant anatomic CAD,^{11,12} there is little information as to whether the coronary artery calcium score (CACS) can identify asymptomatic individuals at high risk for having myocardial ischemia among a larger, asymptomatic, heterogeneous population

with cardiac risk factors.¹² This is clinically important because the presence and extent of left ventricular ischemia predict outcome beyond that provided by coronary angiographic findings alone.^{4,5,13}

Accordingly, the purpose of this study was to determine whether EBCT could identify subjects with scintigraphic ischemia on the basis of CACS severity and thereby define its role as a primary screening technique for identifying subjects with a broad spectrum of CAD.

Methods

Study Population

From December 1995 to May 1998, 3895 subjects had EBCT at our imaging center; 411 also had stress SPECT within a close temporal period (median, 17 days) to detect myocardial ischemia (Table 1). Individuals who had an abnormal EBCT were encouraged to have SPECT; however, we did not seek to identify subjects who had SPECT at institutions other than our own. Most of the 411 subjects (87%) were entirely asymptomatic although 54 (13%) had various nonanginal chest pain symptoms. All subjects had risk factors known to promote the development of CAD (Table 1). The baseline

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TABLE 1. Demographic and EBCT Results

	Total (n=3895)	SPECT (n=411)	No SPECT (n=3484)	P
Age, y (range)	53±8 (19–87)	58±10 (19–84)	52±10 (22–87)	<0.0001
Male sex, n (%)	2676 (69)	326 (79)	2350 (67)	<0.0001
Risk factors, n (%)				
Diabetes mellitus	216 (5.5)	28 (6.8)	188 (5.4)	NS
Family history	766 (19.7)	218 (53.0)	548 (15.7)	<0.0001
Smoking	1559 (40.0)	210 (51.1)	1349 (38.7)	<0.0001
Hyperlipidemia	2092 (53.7)	240 (58.4)	1852 (53.2)	<0.05
Hypertension	1523 (39.1)	191 (46.5)	1332 (38.2)	<0.0001
Mean risk factors, n	1.58±0.85	2.16±1.04	1.51±0.97	<0.0001
Chest pain, n (%)	597 (15.3)	54 (13.1)	543 (15.6)	NS
Agatston score, n (%)				
Normal	1529 (39.2)	37 (9.0)	1492 (42.8)	<0.0001
Mild	1215 (31.2)	60 (14.6)	1155 (33.2)	<0.0001
Moderate	651 (16.7)	155 (37.7)	496 (14.2)	<0.0001
Severe	500 (12.9)	159 (38.7)	341 (9.8)	<0.0001
Absolute CACS, n (%)				
0	1529 (39.2)	37 (9.0)	1492 (42.8)	<0.0001
1–10	606 (15.6)	19 (4.6)	587 (16.9)	<0.0001
11–100	805 (20.7)	76 (18.5)	729 (20.9)	NS
101–399	561 (14.4)	142 (34.5)	419 (12.0)	<0.0001
≥400	394 (10.1)	137 (33.4)	257 (7.4)	<0.0001

characteristics of subjects with and without a history of atypical chest pain were generally similar (Table 2).

EBCT Study

EBCT was performed on an Imatron C-150 ultrafast CT scanner with a 100-ms exposure time and 30-cm field size. With ECG gating, 32 consecutive images were obtained in diastole at 3-mm intervals. Coronary calcification was defined as a lesion of >130 Hounsfield units with an area >1.02 mm; lesions were manually planimeted by an experienced technologist and reviewed by a radiologist (T.D.H.). CACS was determined for the 4 main coronary arteries and then summed to generate a total score. The Agatston score was defined as normal, mild, moderate, or severe on the basis of total CACS and subject age and sex.¹⁴ We also performed analysis using a more recently proposed scoring system based on the total CACS: 0 (normal), 1 to 10 (minimal), 11 to 100 (mild), 101 to 399 (moderate), and ≥400 (severe).¹⁵

SPECT Study

Standard stress and rest SPECT were performed with ²⁰¹Tl (67%), ^{99m}Tc sestamibi (21%), or tetrofosmin (12%).^{2,16} Symptom-limited ETT by use of the Bruce protocol was performed in 352 subjects (86%), whereas 11% received adenosine¹⁷ and 3% received dobutamine¹⁸ with standard infusion protocols. ECG ischemia was defined as a ≥1-mm ST-segment depression occurring 80 ms after the J point. All exercise ECGs were interpreted by researchers who had no knowledge of EBCT or SPECT results. We excluded 10 subjects because of lack of stress ECG data (n=3), left ventricular hypertrophy (n=6), or left bundle-branch block (n=1). A standard Duke treadmill score was calculated in the remaining 342 subjects and defined as low (≥5), moderate (−10 to 4), or high (≤−11) risk.¹⁹

Stress and rest SPECT images were acquired by use of a large-field-of-view rotating gamma camera equipped with a high-resolution, parallel-hole collimator.^{2,16} Images were computer quantified and displayed as polar maps by an experienced investigator (J.J.M.) who had no knowledge of the EBCT or ETT results.^{2,5} Raw

data polar maps for each subject were statistically compared with those in a corresponding stressor and radiopharmaceutical specific normal data bank to determine total left ventricular perfusion defect size and the extent of scar and ischemia. Perfusion defects were localized to specific vascular territories, and a ≥3% focal defect was considered abnormal.² A ≥15% stress-induced perfusion defect defined high risk for cardiac events.^{3,4}

Statistical Analysis

Unpaired *t* tests were used to compare (1) clinical and EBCT variables in subjects who did or did not have SPECT (Table 1) and (2) EBCT, SPECT, and ETT variables in those who had all tests. Discrete data variables were examined by use of χ^2 analysis. Stepwise logistic regression (Minitab for Windows 95) identified variables independently associated with abnormalities on SPECT. Demographic, EBCT (Table 1), and ETT variables were considered potential factors for an abnormal SPECT. Variables entered and remained in the model if the value for an association was *P*<0.05. A value of *P*<0.05 was considered significant. All data are presented as mean±SD.

Results

EBCT Results

The 411 subjects studied with EBCT and SPECT had a mean CACS of 440±640 (range, 0 to 4611). Calcium was present in the left main artery in 98 subjects (24%) and in the left anterior descending, right, and circumflex arteries in 358 (87%), 294 (72%), and 244 (59%), respectively. Fifteen percent of subjects had calcium in 1 artery, 18% in 2, 40% in 3, and 18% in all 4 major coronary arteries.

By the Agatston scoring system, 37 subjects (9%) were normal and 60 (14.6%) had mild, 155 (37.7%) had moderate, and 159 (38.7%) had severe CACS. On the basis of absolute

TABLE 2. Demographic and EBCT Results in Subjects With and Without Chest Pain

	Chest Pain (n=54)	No Chest Pain (n=357)	P
Age, y	57±9	58±10	
Male sex, n (%)	38 (70)	288 (81)	NS
Risk factors, n (%)			
Diabetes mellitus	5 (9.2)	23 (6.4)	NS
Family history	29 (54)	189 (53)	NS
Smoking	23 (43)	187 (52)	NS
Hyperlipidemia	29 (54)	211 (59)	NS
Hypertension	27 (50)	164 (46)	NS
Mean risk factors, n	2.09±1.14	2.17±1.03	NS
Mean CACS	302±431	461±664	<0.05
Absolute CACS, n (%)			
0	10 (19)	27 (8)	<0.01
1–10	2 (4)	17 (5)	NS
11–100	9 (17)	67 (19)	NS
101–399	20 (37)	122 (34)	NS
≥400	13 (24)	124 (35)	NS

CACS, 37 subjects (9%) had no calcium and 19 (4.6%) had minimal (1 to 10), 76 (18.5%) had mild (11 to 100), 142 (34.5%) had moderate (101 to 399), and 137 (33.4%) had severe (≥400) calcium. CACS results for the 411 subjects who had SPECT and the 3484 who did not are shown in Table 1; 25% and 35% of all subjects with moderate (101 to 399) or severe (≥400) CACS had SPECT compared with 4.5% of subjects with CACS ≤100.

ETT Results

The mean exercise duration for all subjects was 10±5 minutes, and 17.5% had ECG ischemia. The Duke score was low in 273 subjects (80%), moderate in 65 (19%), and high in only 4 (1%).

SPECT Results

Of 411 subjects, 81 had an abnormal SPECT with perfusion defects in the left anterior descending (n=24), right (n=28), and circumflex (n=45) coronary artery vascular territories. The overall mean defect size was 3.8±8.0% (range, 0% to 48%) and 13.5±10.6% in those who had an abnormal SPECT. Large (≥15%) defects were observed in 23 of 411 subjects (5.6%).

Comparison of EBCT and SPECT

The mean CACS was significantly higher in subjects who had an abnormal (1065±983) compared with a normal (286±394, $P<0.00001$) SPECT. CACS was also significantly higher in coronary arteries that supplied abnormally (339±491) compared with normally (124±237, $P<0.0001$) perfused myocardium. On the basis of Agatston score, only 1 of 97 subjects (1%) with a normal or mildly abnormal EBCT had an abnormal SPECT compared with 16 (10%) and 64 (40%) of those with a moderate or severe score, respectively ($P<0.001$).

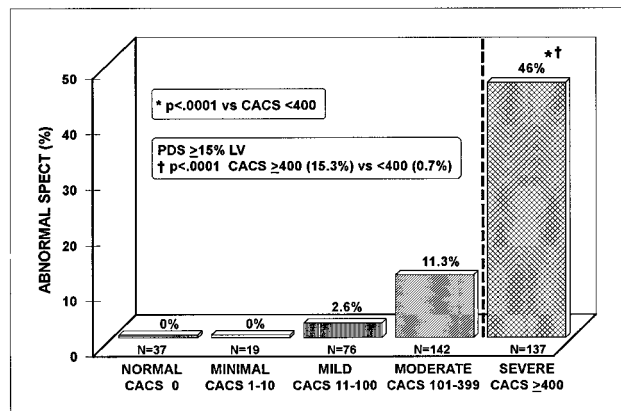


Figure 1. SPECT results based on total CACS. Few subjects with CACS <400 had abnormal SPECT (6.6%), and most (99.3%) had only small (<15%) perfusion defect size (PDS). LV indicates left ventricle.

Absolute CACS results are shown in Figure 1. No one with CACS ≤10 had an abnormal SPECT compared with 81 of 355 (23%) with higher scores. Only 2 of 76 subjects (2.6%) with mild CACS and 16 of 142 (11.3%) with a moderate score had an abnormal SPECT. All had ischemia localized to 1 vascular bed, and only 2 had a large (≥15%) stress-induced perfusion defect. Conversely, 63 of 137 subjects (46%) with severe CACS had an abnormal SPECT, which involved multiple vascular beds in 15 subjects (24%). Large (≥15%) perfusion defects were observed in a significantly greater number of subjects with severe (21 of 137, 15.3%) compared with moderate (1 of 142, 0.7%) CACS ($P<0.0001$).

In the subgroup of 357 entirely asymptomatic subjects, abnormal SPECT results were similar to those found in the total cohort: 1 of 111 (0.9%) with a score ≤100, 12 of 122 (9.8%) with a score of 101 to 399, and 59 of 124 (47.6%) with a score ≥400. Likewise, only 1 of 122 (0.8%) asymptomatic subjects with moderate CACS had a large (≥15%) perfusion defect compared with 19 of 124 (15.3%) of those with a severe score ($P<0.001$).

CACS predicted an abnormal SPECT regardless of subject age or sex although women with severe CACS were less likely to have an abnormal SPECT compared with men (16% versus 51%, $P=0.004$; Table 3). An abnormal SPECT was again observed predominantly in subjects with CACS ≥400. In the total population of 3895 subjects, only a minority (10%) had a score ≥400 (Table 1).

Exercise SPECT Versus EBCT

Most subjects who performed ETT had a normal SPECT and stress ECG (71%) and a low-risk Duke treadmill score (68%). However, 15% of 338 subjects with a low- or moderate-risk Duke score had an abnormal SPECT, and 16 (4.7%) had large (≥15%) perfusion defects. Few of the 342 subjects had an abnormal SPECT and concomitant ECG ischemia (4.4%) or a high-risk Duke score (1%).

Although a similar percentage of subjects had an abnormal SPECT (16.1%) or stress ECG (17.5%, $P=NS$), only the former was related to total CACS (Figure 2). No one with a score ≤100 had an abnormal SPECT compared with 40% of

TABLE 3. Abnormal SPECT Results Based on Age, Sex, and CACS

	CACS <400	CACS ≥400	P
Age, n/total (%)			
≤50 y (n=97)	2/82 (2.4)	5/15 (33)	<0.001
>50 y (n=314)	16/192 (8.3)	58/122 (48)	<0.001
Sex, n/total (%)			
Men (n=326)	17/208 (8.2)	60/118 (51)*	<0.001
Women (n=85)	1/66 (1.5)	3/19 (16)	<0.03

*P<0.01 vs women CACS ≥400.

those with scores ≥400; an abnormal exercise ECG was observed across a wide spectrum of CACS severity (Figure 2). The mean CACS was significantly lower in subjects with a normal compared with an abnormal SPECT regardless of the exercise ECG findings (Figure 3). The Duke treadmill score significantly decreased as CACS increased from ≤100 (9.05±4.5) to 101 to 399 (7.89±4.5) to ≥400 (6.48±6.25, P<0.007; Figure 4). Yet the vast majority of subjects had either a low- or moderate-risk Duke score that was evenly distributed across all CACS severities (Figure 4). A representative subject with severe CACS who had discordant SPECT and exercise ECG results is shown in Figure 5.

Predictors of an Abnormal SPECT

Total CACS was an important univariate predictor of an abnormal SPECT (Table 4). By logistic regression, CACS was the best single predictor of an abnormal SPECT (P<0.0001), followed by male sex (P<0.01) and diabetes mellitus (P<0.01). In those who performed ETT, total CACS was again the best predictor (P<0.0001), followed by male sex (P<0.05) and maximal exercise heart rate (P<0.05). Univariate and multivariate test results were similar in the 357 asymptomatic patients and in the entire 411 subject cohort.

Discussion

This study is the first to describe the relationship between severity of coronary artery calcification detected by EBCT and the presence of stress-induced myocardial ischemia in a large cohort of predominantly asymptomatic subjects with

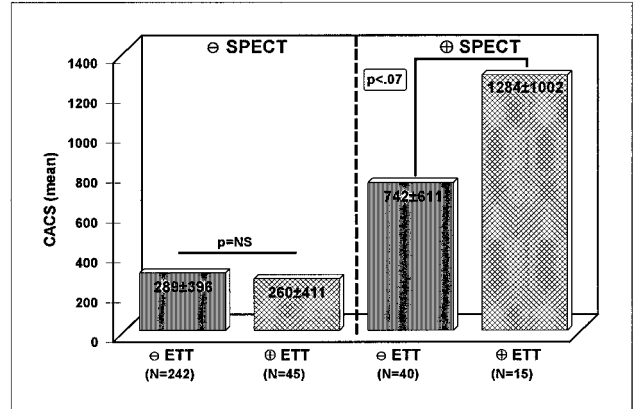


Figure 3. Mean±SD CACS based on exercise SPECT and ETT results. ⊖ indicates normal; ⊕, abnormal.

risk factors for CAD development. The presence and extent of stress-induced myocardial ischemia detected by SPECT are known to predict subsequent outcome.³⁻⁸ Our results indicate that most subjects with coronary calcium do not have inducible ischemia but that the likelihood of ischemia increases with total CACS, particularly with scores ≥400. In fact, total CACS ≥400 identified a group in whom a large percentage of subjects (46%) had demonstrable ischemia. Conversely, only 6.6% of those with scores <400 had an ischemic defect size by SPECT, and virtually all (99.3%) were small. These observations suggest that CACS ≥400 could be used to improve the selection and use of more definitive and expensive tests such as SPECT for identifying individuals at high risk for cardiac events within the next year.

In our study, the best predictor of an abnormal SPECT was CACS. This result is consistent with previous studies demonstrating that the angiographic extent and severity of CAD are directly related to CACS severity^{11,12} and that angiographic stenosis severity best predicts an abnormal SPECT.^{2,16} Our findings emphasize that EBCT is more sensitive than either ETT or SPECT for detecting subclinical CAD in which aggressive risk factor modification is war-

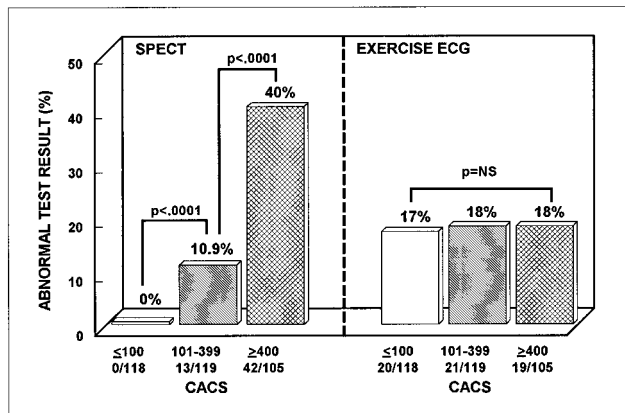


Figure 2. Exercise SPECT and ECG results based on total CACS.

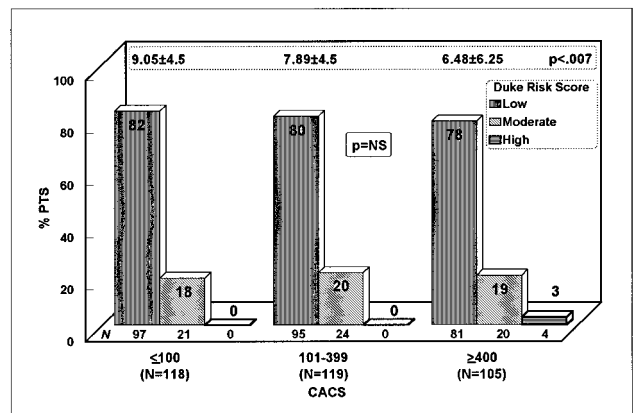


Figure 4. Duke score results based on total CACS. Mean±SD Duke scores for each CACS group are shown above bar graphs. PTS indicates patients.

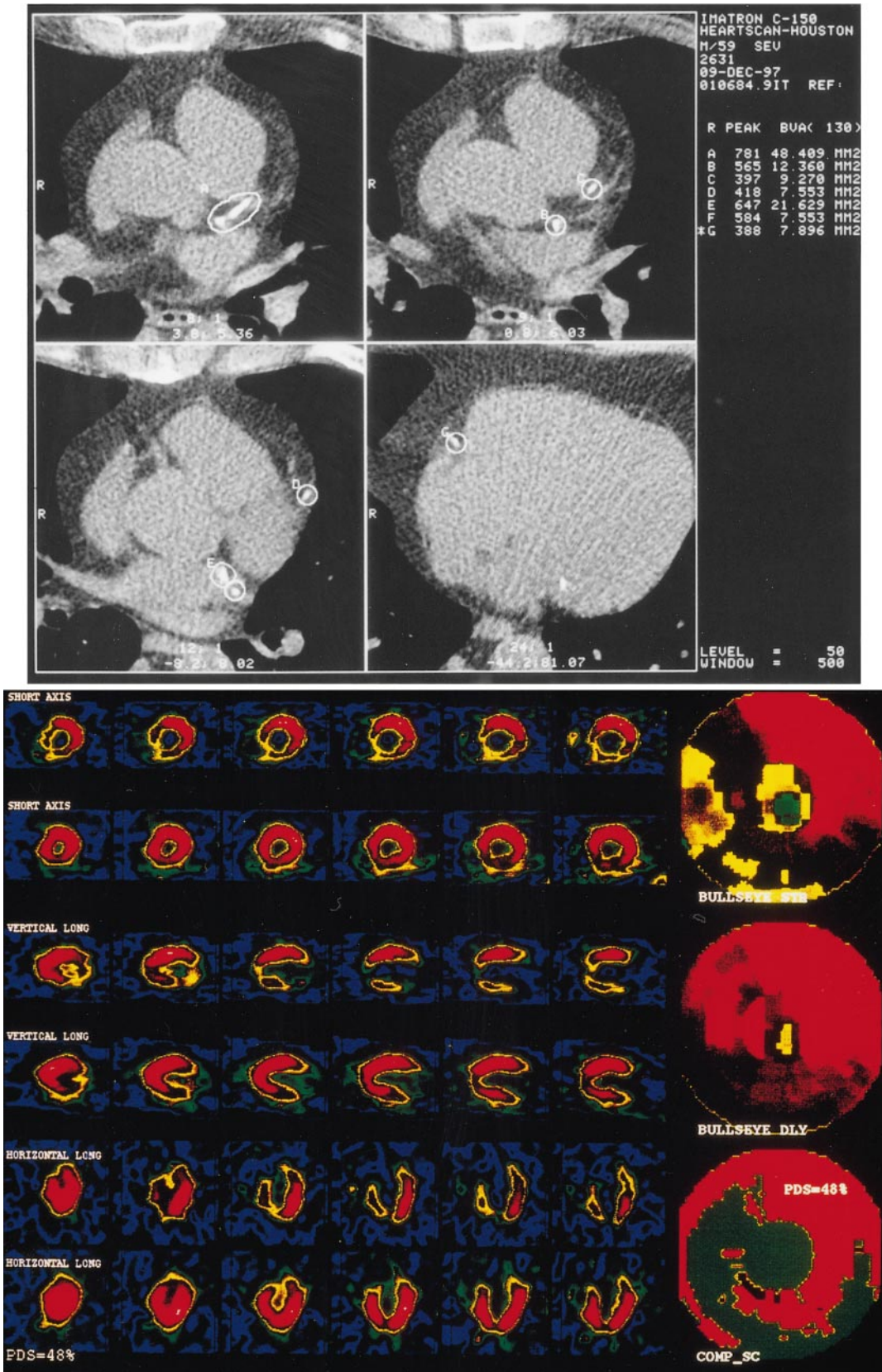


Figure 5. EBCT (top) and SPECT (bottom) images of asymptomatic subject who had high-risk CACS of 937. Circles define regions of coronary calcification. Upsloping (<1 mm) ST-segment depression occurred 9.0 minutes into ETT, which was terminated because of patient fatigue. Although Duke score was calculated as low risk (6.5), SPECT demonstrated large, reversible 48% perfusion defect (green) within distribution of all 3 major coronary arteries (COMP-SC) (bottom). This patient had severe 3-vessel disease on angiography and underwent CABG. PDS indicates perfusion defect size.

TABLE 4. Univariate Predictors of an Abnormal SPECT

Total Cohort (n=411)	Abnormal SPECT (n=81)	Normal SPECT (n=330)	P
Age, y	63±9	57±10	<0.0001
Male sex, n (%)	77 (95)	249 (75)	<0.0001
Diabetes mellitus, n (%)	13 (16)	15 (4.5)	<0.0001
Smoking, n (%)	47 (58)	163 (49)	NS
Hypertension, n (%)	44 (54)	147 (45)	NS
Family history, n (%)	45 (56)	173 (52)	NS
Hyperlipidemia, n (%)	45 (56)	195 (59)	NS
≥2 Risk factors, n (%)	62 (77)	234 (71)	NS
Chest pain, n (%)	9 (11.1)	45 (13.6)	NS
CACS	1065±983	286±394	<0.0001
CACS ≥400, n (%)	63 (78)	74 (22)	<0.0001
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Exercise SPECT (n=342)	Abnormal SPECT (n=55)	Normal SPECT (n=287)	P
Maximal heart rate, bpm	143±18	156±18	<0.0001
ECG ischemia, n (%)	15 (27)	45 (16)	0.04
Duke treadmill risk score	5.7±7.3	8.3±4.6	0.01
Low, n (%)	41 (75)	232 (81)	NS
Moderate, n (%)	10 (18)	55 (19)	NS
High, n (%)	4 (7)	0 (0)	NS
Exercise duration, min	10.0±2.8	10.0±2.8	NS
Maximal SBP, mm Hg	177±24	177±23	NS
Maximal DBP, mm Hg	84±12	86±14	NS
Target heart rate, %	95±10	92±14	NS

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

ranted and can further identify a subset of individuals at high risk for silent myocardial ischemia in whom additional diagnostic testing and treatment are advisable.

Identifying High-Risk Individuals With Ischemia

The presence and extent of scintigraphic ischemia predict short-term risk for cardiac events.³⁻⁶ Patients who have a normal or minimally abnormal SPECT have a <1%/y risk of death or myocardial infarction compared with a 5- to 10-fold-higher event rate with larger defects (≥15%).³⁻⁶ In our study, total CACS ≥400 defined a population at high risk for having scintigraphic ischemia. In fact, 15% of subjects with CACS ≥400 had large (≥15%) perfusion defects compared with <1% of those with lower scores. Thus, most cardiac events should occur in the small subset of subjects with high CACS. Indeed, a recent large clinical trial reported that asymptomatic subjects with CACS <400 had an exceedingly low (<0.5%) 1- to 2-year cardiac event rate, with virtually all events occurring in individuals with higher scores.²⁰

EBCT for Detection of Subclinical CAD

We specifically chose to compare SPECT and EBCT because of the well-recognized accuracy of SPECT in detecting CAD.^{2,16-18} However, most of our subjects

(78%) with coronary calcium had a normal SPECT and would have been incorrectly labeled as not having coronary atherosclerosis. Likewise, only 4 (1.3%) with an abnormal EBCT had a high-risk Duke score. Our results support previous studies demonstrating that asymptomatic subjects with cardiac risk factors generally have normal ETT and perfusion scans.⁷⁻⁹ In the Lipid Research Clinics trial,⁹ only 8.3% of 3775 asymptomatic men with hyperlipidemia had exercise-induced ECG ischemia. In a study of middle-aged siblings of patients with premature CAD, the stress ECG was abnormal in only 10% and thallium imaging in 22%.⁷ In the Baltimore Longitudinal Study on Aging, few asymptomatic subjects had an abnormal stress ECG (16%) or thallium perfusion scan (14%).⁸ Although subjects who had abnormal results for both tests had a reduced event-free survival (52%), this was observed in only 5% of individuals screened; likewise, only 4.4% of our subjects had both abnormal ETT and perfusion imaging.

The low incidence of abnormal ETT or SPECT precludes their use as primary screening tests for early detection and treatment of CAD. The low incidence of ECG ischemia, particularly of a high-risk Duke score, in our study across a broad spectrum of CACS further emphasizes the poor diagnostic accuracy of ETT in iden-

tifying significant CAD in asymptomatic subjects.⁷⁻⁹ In fact, ETT and SPECT have both received a class III indication (ie, no justification for their use) for screening asymptomatic individuals.^{21,22} These tests, however, remain the cornerstone for evaluating risk in symptomatic patients with known or suspected CAD.^{1-6,19}

Detection of subclinical CAD seems desirable, particularly in view of recent primary prevention trials demonstrating that aggressive risk factor modification, including treatment of hyperlipidemia, reduces the incidence of subsequent cardiac events.^{9,23,24} Moreover, many asymptomatic individuals with subclinical CAD die suddenly²⁵ and would not have been identified with ETT or SPECT. In this regard, EBCT is appealing as a relatively low-cost, primary screening technique through which coronary atherosclerosis can be detected and potentially treated before the development of critical coronary artery stenosis and/or stress-induced myocardial ischemia.

Study Limitations

Subjects with CACS >100 were well represented in our study (29%), but <5% of those with lower scores had SPECT. It is unlikely, however, that studying a larger population with CACS ≤100 would have altered our results because these individuals generally have insignificant CAD by angiography.^{11,12,14} Another issue is whether our results vary with subject age. We observed similar correlations between SPECT and EBCT when individuals were dichotomized at 50 years of age; analysis by decade of life would require a larger sample size. Because of the small number of women who had SPECT, further study in this group is warranted.

Clinical Implications

In asymptomatic populations who have clinical characteristics similar to those of our cohort, 61 of every 100 individuals screened will have an abnormal EBCT, but only 10 will have CACS ≥400, warranting further evaluation with SPECT. Coronary angiography can then be appropriately reserved for the very few patients (1% to 2%) who have significant myocardial ischemia. Our study emphasizes the effectiveness of selectively combining SPECT with EBCT to identify individuals with silent myocardial ischemia who may require more intensive therapy with either anti-ischemic medications and/or coronary revascularization.

Conclusions

CACS severity measured by EBCT can identify a high-risk group with silent myocardial ischemia among an otherwise low-risk heterogeneous population with cardiac risk factors. Our results support the role of EBCT as a primary screening tool for identifying individuals with various degrees of subclinical CAD, particularly those at high risk for short-term events in whom aggressive diagnosis and therapy are advisable.

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