

# Exercise Testing and Electron Beam Computed Tomography in the Evaluation of Coronary Artery Disease

David M. Shavelle, MD,\* Matthew J. Budoff, MD, FACC,\* Daniel H. LaMont, MD,†  
Robert M. Shavelle, PhD,‡ John M. Kennedy, MD,\* Bruce H. Brundage, MD, FACC\*

Torrance, Long Beach and Riverside, California

<b>OBJECTIVES</b>	This study compared coronary artery calcium (CC) as detected by electron beam computed tomography (EBCT) with conventional stress testing in the evaluation of patients with symptoms suggestive of coronary artery disease (CAD).
<b>BACKGROUND</b>	Exercise electrocardiogram treadmill stress testing (treadmill-ECG) is limited by its requirement of a normal resting ECG and the ability of the patient to exercise adequately. The addition of myocardial imaging agents such as technetium improves the sensitivity and specificity but substantially increases the cost and prolongs the testing time. The use of EBCT provides a noninvasive and rapid method for identifying the presence and amount of CC, which has been shown to be related to atherosclerosis, and may provide additional information in combination with more traditional noninvasive testing methods.
<b>METHODS</b>	A total of 97 patients underwent technetium stress testing (technetium-stress), treadmill-ECG, and EBCT coronary scanning within three months of coronary angiography for the evaluation of chest pain.
<b>RESULTS</b>	The relative risk (RR) of obstructive angiographic CAD for an abnormal test was higher for EBCT (4.53) than either treadmill-ECG (1.72) or technetium-stress (1.96). The low specificity of EBCT (47%) was improved by the addition of treadmill-ECG (83%, $p < 0.05$ ).
<b>CONCLUSIONS</b>	Electron beam computed tomography has a higher diagnostic ability than either treadmill-ECG or technetium-stress for the detection of obstructive angiographic CAD. Electron beam computed tomography is an accurate and noninvasive alternative to traditional stress testing for the detection of obstructive CAD in symptomatic patients. (J Am Coll Cardiol 2000;36:32-8) © 2000 by the American College of Cardiology

Coronary artery disease (CAD) is the number-one cause of mortality in both men and women in the U.S. (1). Exercise electrocardiogram treadmill stress testing (treadmill-ECG) has been available to clinicians since the 1970s to evaluate patients with symptoms suggestive of CAD (2,3). Despite its wide acceptance and availability, it is limited by its requirement of a normal resting ECG and the ability of the patient to exercise adequately. In addition, approximately 10% to 20% of symptomatic patients with obstructive CAD by angiography have a negative electrocardiographic response to exercise (4-6). The addition of myocardial imaging agents such as technetium improves the sensitivity and specificity, but substantially increases the cost and prolongs the time required for testing (7-9).

Among newer imaging modalities, electron beam computed tomography (EBCT) provides a noninvasive and rapid method for identifying the presence and amount of coronary artery calcification (CC), which has been shown to be related to atherosclerosis (10-13). In prior studies the detection of CC by EBCT has provided useful information in the evaluation of symptomatic patients (14-18).

Many patients undergo multiple diagnostic tests for the evaluation of suspected CAD, and because of the recent introduction of EBCT, its utility in this evaluation has yet to be defined (19). The EBCT test provides anatomic information, which may be complementary to the functional information obtained from stress testing. The added diagnostic value of EBCT combined with traditional tests, such as treadmill-ECG, is unclear.

We undertook this study to compare EBCT with treadmill-ECG and nuclear stress imaging in the prediction of obstructive angiographic CAD. In addition, we evaluated whether the specificity of EBCT could be improved by the addition of treadmill-ECG.

## METHODS

**Patient population.** This study involved 97 symptomatic patients who underwent coronary angiography and EBCT coronary scanning at Harbor-UCLA Medical Center and Long Beach Veterans Hospital between June 1996 and October 1997. All individuals met the following inclusion criteria: 1) EBCT studies done within three months of the coronary angiograms; 2) normal baseline ECGs, without left bundle branch blocks or resting ST segment or T-wave changes; 3) at least 85% of the maximum predicted heart rate achieved during treadmill-ECG; 4) technetium-stress testing (technetium-stress) performed at the same time as

From the \*Saint John's Cardiovascular Research Center, Division of Cardiology, Harbor-UCLA Research and Education Institute, Torrance; †Division of Cardiology, University of California, Irvine, Long Beach Veterans Hospital, Long Beach; and ‡Department of Statistics, University of California, Riverside, California.

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#### Abbreviations and Acronyms

CAD	= coronary artery disease
CC	= coronary artery calcification
EBCT	= electron beam computed tomography
HU	= Hounsfield unit
MIBI	= methoxyisobutylisonitrile
NPV	= negative predictive value
PPV	= positive predictive value
ROC	= receiver operating characteristic
technetium-stress	= technetium stress testing
treadmill-ECG	= exercise electrocardiogram treadmill stress testing

the treadmill-ECG, therefore ensuring that the same level of exertion was obtained on both tests; and 5) no history of cardiac valve replacement, coronary stenting procedures, or coronary artery bypass grafting prior to the completion of all testing methods (treadmill-ECG, technetium-stress, and EBCT). Approximately 90% of patients underwent noninvasive testing (treadmill-ECG and technetium-stress) prior to angiography. All EBCT studies were performed following angiography. All subjects signed a written consent form approved by the Institutional Review Board at Harbor-UCLA Medical Center.

**Exercise treadmill ECG testing.** Symptom-limited exercise treadmill-ECG testing with standard Bruce protocol was performed in all patients. Exercise was continued until one or more of the following end points was reached: 1) one or more ECG leads demonstrated  $>0.1$  mV of flat or downsloping ST-segment depression consistent with ischemia; 2) achievement of greater than 85% of maximum predicted heart rate; 3) inability of the patient to continue to exercise because of fatigue, dyspnea or chest pain; 4) failure of systolic blood pressure to increase  $\geq 120$  mm Hg or a sustained decrease in systolic blood pressure  $\geq 10$  mm Hg or a decrease to below the systolic blood pressure obtained prior to exercise; or 5) significant arrhythmias. A positive test was defined as  $>0.1$  mV of flat or downsloping ST-segment depression 0.08 s from the J point,  $>0.01$  mV ST-segment elevation in a non-Q-wave lead or the development of anginal chest pain. Two senior cardiologists reviewed the test results independently and were unaware of other clinical data and EBCT calcification scores.

**Technetium stress testing.** All patients were tested in the fasting state. Technetium-99m methoxyisobutylisonitrile (MIBI, 20 to 25 mCi) was injected at the peak level of exercise while the patient was on the treadmill. The patient was encouraged to maintain the peak level of exercise for an additional 30 to 60 s following the injection. Images were obtained 60 to 90 min later. A second injection of 20 mCi of MIBI was given one to two days after the stress studies for rest imaging. The MIBI acquisition protocol was identical for both stress and rest studies, and this has been described previously (20).

Briefly, MIBI acquisition was obtained with a rotating

gamma camera equipped with a parallel-hole collimator. A 180° rotation from 45° left posterior oblique to 45° right anterior oblique projection was accomplished in 6° steps. Postprocessing was performed with a dedicated computer by means of a filtered back projection reconstruction algorithm (Butterworth 6-16 filter). Transaxial slices were then reconstructed and realigned into frontal and sagittal sections. The post-stress and rest MIBI scans were interpreted using visual assessment of regional abnormalities. Reversible and nonreversible perfusion defects were evaluated by two nuclear medicine specialists, and disagreements were resolved by consensus with a third investigator. All investigators were blinded to the results of the EBCT and the coronary angiogram. An abnormal area in the initial images demonstrating complete or partial redistribution in the delayed images was considered to represent myocardial ischemia and was defined as a positive test. A perfusion defect that remained unchanged in the delayed images was considered to represent myocardial infarction and was defined as a negative test. In an attempt to identify all patients with CAD, a second analysis was performed. In this analysis, a positive test was defined if either myocardial ischemia (reversible defect) or myocardial infarction (nonreversible defect) was present.

**Coronary angiography.** All patients underwent coronary angiography. The coronary angiograms were analyzed by an experienced reader blinded to the results of technetium-stress, treadmill-ECG, and the EBCT coronary scan. Each epicardial coronary vessel (left main, left anterior descending, circumflex, and right coronary artery) was assessed, and the visual estimation of the percent luminal reduction for each lesion was reported. Multiple projections were acquired to discern the maximal coronary artery luminal narrowing. Investigators recorded the maximum stenosis in each vessel. Angiographic abnormalities were considered significant if 50% or greater luminal diameter stenosis was found in any epicardial coronary vessel.

**Computed tomographic image acquisition.** The EBCT studies were performed with an Imatron C-150 XL ultrafast computed tomographic scanner (San Francisco, California), in the high resolution volume mode using a 100-ms exposure time. Electrocardiographic triggering was employed, so that each image was obtained at the same point in diastole, corresponding to 80% of the RR interval for standardized calcium scoring. Proximal coronary artery visualization was obtained without contrast medium injection, and 30 consecutive images were obtained at 3-mm intervals beginning 1 cm below the carina and progressing caudally to include the coronary arteries. Studies demonstrating incomplete coverage of the coronary anatomy at the conclusion of the study had three to five additional slices performed, a protocol methodology designed to decrease radiation exposure to participants. The entire course of all coronary arteries was visually in all patients using this protocol. Total radiation exposure using this technique was  $<1$  rad per patient. A computed tomographic threshold of 2 pixels and

130 Hounsfield units (Hu) was utilized for identification of a calcific lesion. Each focus exceeding the minimum criteria (1 mm<sup>2</sup>) was scored using the algorithm developed by Agatston *et al.* (21), calculated by multiplying the lesion area by a density factor derived from the maximal Hu within this area. The density factor was assigned in the following manner: 1, for lesions whose maximal density was 130 to 199 Hu; 2, for lesions 200 to 299 Hu; 3, for lesions 300 to 399 Hu; and 4, for lesions >400 Hu. A total calcium score was determined by summing individual lesion scores from each of four anatomic sites (left main, left anterior descending, circumflex, and right coronary arteries). A positive EBCT coronary scan was defined as a total CC score of greater than 0. The EBCT scoring was performed by a cardiologist blinded to the clinical, treadmill-ECG, technetium-stress, and angiographic information.

**Risk factor acquisition.** Cardiac risk factors were obtained by chart review of medical records combined with patient questionnaire. Hypertension was defined as systolic blood pressure greater than 140 mm Hg and/or diastolic blood pressure greater than 90 mm Hg or current use of antihypertensive medication. Diabetes mellitus was defined as a history of oral hypoglycemic or insulin use. Tobacco use was defined as currently smoking cigarettes. Family history of coronary disease was defined as CAD in a first-degree relative, in men under 55 years of age and women under 65 years of age. Hypercholesterolemia was defined as total cholesterol greater than 200 mg/dl. Fractionated lipid levels were not available in all patients, and therefore could not be used in the statistical analysis. Postmenopausal status was defined as a women over 50 years of age currently using hormone replacement therapy.

**Statistical analysis.** Data were analyzed using 2 × 2 contingency tables comparing obstructive CAD by angiography to an EBCT coronary scan, treadmill-ECG, technetium-stress, or the combination of treadmill-ECG and EBCT coronary scanning. Significance tests were two-tailed, with significance defined as *p* < 0.05. The ability of each method to predict obstructive angiographic CAD was evaluated by calculating the sensitivity, specificity, accuracy, relative risk (RR), positive predictive value (PPV), and negative predictive value (NPV). The RR of each testing method was determined as the ratio of the incidence of CAD for patients with a positive test to the incidence of CAD for patients with a negative test. To compare sensitivities and specificities for EBCT combined with treadmill-ECG to technetium-stress testing alone, the McNemar test was used separately for true positives and negatives, respectively. A receiver operating characteristic (ROC) curve was constructed for EBCT and for EBCT combined with treadmill-ECG. The ROC curves were constructed by calculating the sensitivity and specificity using different CC score threshold values (from 0 to 1290) and plotting sensitivity versus 1-specificity. The data points were smoothed to fit a curve secondary to the small sample size.

**Table 1.** Characteristics of Patient Population

	No. of Patients (%)
Total patients	97
Men	67 (69)
Women	30 (31)
Coronary risk factors	
Diabetes mellitus	25 (26)
Hypertension	68 (70)
Hypercholesterolemia	42 (43)
Family history of CAD	48 (49)
Tobacco use	60 (62)
Postmenopausal female	43 (44)
CC as detected by EBCT	83 (86)
Coronary anatomy	
No CAD	30 (31)
Single-vessel CAD	25 (26)
Multivessel CAD	42 (43)

CAD = coronary artery disease; CC = coronary calcification; EBCT = electron beam computed tomography.

## RESULTS

A total of 97 patients, 67 men and 30 women, were included in this study. The mean age of the patients was 54 ± 9 years, with a range of 30 to 73 years. The mean age of the men was 53 years, with a range of 30 to 73 years; for women, 58 years, with a range of 45 to 73 years. The distribution levels of coronary risk factors and CC scores are shown in Table 1. Coronary angiography was performed in all patients to determine the presence of obstructive lesions. Of the 97 patients, 67 (69%) had angiographically significant disease, which was defined as greater than 50% maximal luminal diameter stenosis in one or more major epicardial vessel. Additionally, 25 patients (26%) were found to have single-vessel CAD and 42 patients (43%) multivessel CAD.

Of the 97 patients, CC was found in 80 (83%), for an overall sensitivity of 96%. Patients with obstructive angiographic CAD had a higher mean CC score than did patients without obstructive angiographic CAD (485 vs. 166, *p* < 0.001). The PPV of CC was 80%. Of the 30 patients without obstructive angiographic CAD, 14 (47%) had no CC by EBCT, specificity of 47%, and NPV of 82% (Table 2). The RR of obstructive angiographic CAD for a positive EBCT test was 4.53. Increasing the CC score threshold decreased the sensitivity and improved specificity, as has been described in prior studies (22,23). The optimal CC threshold value depends on the application of EBCT, and because we were interested in achieving a high sensitivity, we choose a CC score threshold of >0 as a positive test. The sensitivity, specificity, PPV, NPV, and accuracy of EBCT with higher CC score threshold values are shown in Table 3. Increasing the CC score threshold for a positive EBCT scan to 80 increased the specificity to 63% and decreased the sensitivity to 78%.

Treadmill-ECG showed sensitivity of 76% and specificity of 60%, with accuracy of 71% and RR of 1.72 (Table 2). Technetium-stress had sensitivity of 78% and specificity of 67%, with accuracy of 74% and RR of 1.96 (Table 2). For

**Table 2.** Sensitivity, Specificity, Accuracy, Relative Risk, Positive Predictive Value, and Negative Predictive Value for Each Testing Method

Testing Method	Sensitivity (%)	Specificity (%)	Accuracy (%)	Relative Risk	Positive Predictive Value (%)	Negative Predictive Value (%)
Treadmill-ECG	76	60	71	1.72	81	53
Technetium-stress	78	67	74	1.96	83	57
CC as detected by EBCT	96	47	80	4.53	80	82
Treadmill-ECG combined with EBCT	72	83	75	2.10	91	57

CC = coronary calcification; EBCT = electron beam computed tomography; technetium-stress = technetium stress testing; treadmill-ECG = exercise electrocardiogram treadmill stress testing.

the second analysis of technetium-stress tests, a positive test was defined as the presence of either a reversible (ischemia) or a nonreversible (infarct) defect. For this analysis, the sensitivity was 75%, specificity 67%, accuracy 72% and RR 1.54.

When treadmill-ECG was combined with EBCT, the specificity increased from 47% to 83%,  $p < 0.05$  (Table 2). For this approach, a positive test was defined as a mean CC threshold score  $>0$  and a positive treadmill-ECG. The results of treadmill-ECG testing combined with EBCT coronary scanning were comparable to technetium-stress alone (McNemar test,  $p = NS$ ).

An ROC curve was constructed to determine the predictive value of each testing method to diagnose obstructive angiographic CAD. The area under the ROC curve represents the ability of the testing method to detect patients with obstructive CAD, as defined by angiography. The area under the ROC curve for the EBCT was  $0.75 \pm 0.05$  (Fig. 1), and the combination of EBCT and treadmill-ECG increased the area to  $0.79 \pm 0.05$ ,  $p = NS$  (Fig. 2).

**DISCUSSION**

Various noninvasive testing methods are currently available to evaluate patients with symptoms suggestive of obstructive CAD. Standard exercise treadmill testing is limited by its requirement of a normal resting ECG and the ability of the patient to exercise adequately. Although the addition of nuclear imaging agents improves accuracy, both the cost and the testing time are substantially increased, and an IV injection is required. The relatively low cost for EBCT coronary calcium screening (approximately \$400), brief testing time (under 10 min) and no need for a physician during scanning makes it a reasonable alternative to tradi-

tional stress testing. Also, EBCT is able to identify accurately, rapidly, and noninvasively the presence of calcification of the coronary arteries, which is a marker for atherosclerosis.

**Limitations of EBCT coronary scanning.** Two factors have limited this tool from more widespread utilization in the evaluation of CAD. First, while multiple studies have demonstrated an EBCT sensitivity for obstructive angiographic CAD of 90% to 100%, test specificity has been relatively low and has ranged from 41% to 76% (24-27). This low specificity has limited the utility of this methodology to screen for obstructive angiographic CAD. Specificity can be increased by simply increasing the cutoff coronary calcium score (28). However, this would reduce test sensitivity, thus limiting its use as a screening test.

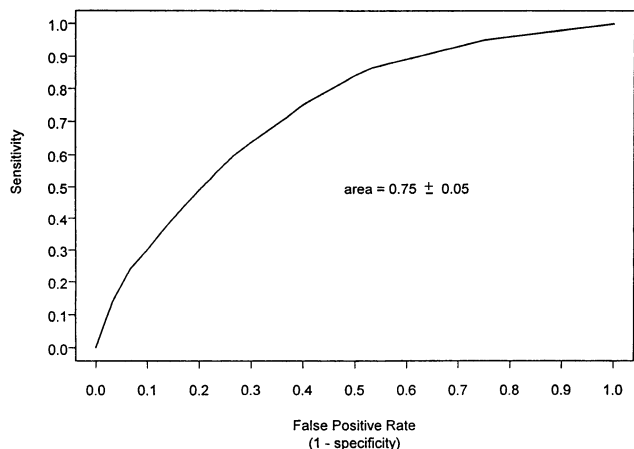
Second, there is a lack of functional information provided by EBCT coronary calcium screening. Although it is well established that the CC score correlates with the atherosclerotic burden, the severity of stenosis cannot be elucidated without administering IV contrast (29). In an effort to address both issues, we attempted to combine the high sensitivity of EBCT with the functional information of exercise treadmill testing. We tested the hypothesis that by first screening with EBCT (high sensitivity) and then using treadmill-ECG, an effective combination of tests could be obtained that would be at least as accurate as technetium-stress in diagnosing obstructive angiographic CAD. We also directly compared the diagnostic ability of treadmill-ECG, technetium-stress, and EBCT in a group of symptomatic patients.

**Previous investigations.** To date there has been little information regarding the incremental value of EBCT scanning relative to exercise treadmill testing, and few

**Table 3.** Electron Beam Computed Tomographic Coronary Calcium Score Threshold Value: Increasing Threshold Value Lowers Sensitivity and Raises Specificity

EBCT CC Score Threshold	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
$\geq 0$	96	47	80	82	80
$\geq 20$	88	50	80	65	76
$\geq 40$	82	60	82	60	75
$\geq 80$	78	63	83	56	73

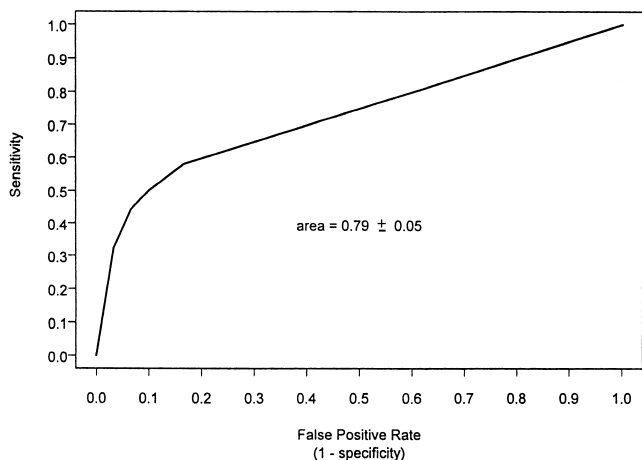
CC = coronary calcification; EBCT = electron beam computed tomography.



**Figure 1.** Receiver operating characteristic (ROC) curve for EBCT coronary scanning. The area under the curve is  $0.75 \pm 0.05$ , which represents the ability of EBCT to detect patients with obstructive CAD. CAD = coronary artery disease; EBCT = electron beam computed tomography.

studies have directly compared EBCT with traditional stress testing or stress nuclear imaging. Kajinami *et al.* (14) evaluated 251 symptomatic patients who underwent coronary angiography, ECG, and thallium exercise testing. The ECG and thallium exercise tests had overall sensitivity of 74% and 83%, and specificity of 73% and 60%, respectively. The sensitivity and specificity of EBCT was 77% and 86%, respectively. The prevalence of angiographically defined CAD was significantly different between men (59%) and women (37%), and also among groups of patients classified by age. Age and gender could therefore affect disease prevalence, and possibly the predictive values of the testing method.

Electron beam computed tomography was found to be most useful in middle-aged men (40 to 60 years old), older patients (>70 years old) and older women (>60 years old).



**Figure 2.** Receiver operating characteristic (ROC) curve for EBCT coronary scanning combined with treadmill-ECG. The area under the curve is  $0.79 \pm 0.05$ , which represents the ability of the combination of EBCT and treadmill-ECG to detect patients with obstructive CAD. CAD = coronary artery disease; EBCT = electron beam computed tomography; treadmill-ECG = exercise electrocardiogram treadmill stress testing.

The investigators concluded that the results of EBCT were at least as useful, and potentially more useful in some patient groups than those obtained with exercise thallium and treadmill testing. The combination of exercise treadmill testing and EBCT was not evaluated in that study.

In a related study by Spadaro *et al.* (15), 150 patients underwent thallium stress testing, EBCT, and coronary angiography. The RR of an abnormal thallium stress test was 3.5, compared to 14.9 for an elevated CC score as detected by EBCT. More recently, Yao *et al.* (16) compared technetium-99m single-photon emission tomography and EBCT in 51 patients with suspected CAD. Although differences were found between the two testing methods in patients with single-vessel CAD, the sensitivity, specificity, and accuracy were comparable in patients with multivessel CAD. LaMont *et al.* (18) found that the absence of CC by EBCT in symptomatic patients with a positive exercise treadmill test accurately identified those with a false-positive treadmill test. In a series of 118 patients, 18 were identified as having a false-positive treadmill test by EBCT coronary scanning (NPV 90%) and therefore could have avoided angiography.

The present study, in accordance with many previous ones on EBCT, has demonstrated an excellent sensitivity and a relatively low specificity for detecting the presence of obstructive CAD. We used a CC score threshold of >0 to maximize sensitivity for the combination of treadmill-ECG and EBCT. By raising the CC score threshold for a positive EBCT scan to 80, the specificity could be improved to 78%, with a sensitivity of 63%, thus achieving results similar to those of treadmill-ECG and technetium-stress alone.

**Study limitations.** The prevalence of angiographically significant CAD was 69% in our study population. This high prevalence could potentially raise sensitivity at the expense of specificity for all the testing methods evaluated.

In a recent meta-analysis of 44 trials (30), technetium-stress was found to have a mean sensitivity of 87% and mean specificity of 64%, similar to the results found in our study. The specificity of technetium-stress in clinical practice may be higher than this meta-analysis indicates. Using this as a reference, the relatively low specificity of 67% in our study may be related to several factors. First, a significant percentage (30%) of the defects were nonreversible and occurred in the inferior wall, suggesting the possibility of diaphragmatic attenuation. This study was performed before ECG-gated SPECT imaging was available at our institution, and therefore could not be used to evaluate for regional wall-motion abnormalities or wall thickening that may have aided in the distinction between myocardial infarction and diaphragmatic attenuation.

Second, a relatively large proportion of the patients in our study were women (31%), which may have resulted in an increased number of false-positive results secondary to breast attenuation. Several recent studies also suggest that technetium underestimates defect reversibility (ischemia) in patients with CAD, which can explain the lower sensitivity

in our study (31,32). Finally, we acquired images 60 to 90 min after injection of MIBI, which was standard practice at the time of the study. It has since been demonstrated that early acquisition of the images (30 min after stress) reduces redistribution and improves sensitivity and specificity of this modality (33).

In a meta-analysis of 147 trials evaluating treadmill stress testing (34), the mean sensitivity was found to be 68% and the mean specificity 77%. The sensitivity and specificity in our study of 97 symptomatic patients was 76% and 60%, respectively. The higher sensitivity and lower specificity may have been related to the recruitment process. The majority of patients underwent elective coronary angiography for the evaluation of chest pain in the outpatient setting. Approximately 90% had already undergone either technetium-stress, treadmill-ECG, or stress echocardiography prior to coronary angiography. The majority of patients were therefore referred for coronary angiography based on a positive noninvasive test. It is also likely that the majority of patients with a negative noninvasive test were not referred for coronary angiography, therefore creating a referral bias. This would result in an apparent increase in sensitivity and a decrease in specificity.

The effect of referral bias on sensitivity and specificity has been shown in studies with exercise radionuclide ventriculography (35) and exercise thallium imaging (36). By requiring that only optimal treadmill stress tests could be included in our study, a higher than usual number of "true-positive" tests would be selected out, and nondiagnostic treadmill stress tests would be excluded. This would again improve the sensitivity of treadmill stress testing and tend to underestimate the power of EBCT in comparison. Despite the discrepancies of the sensitivity and specificity of technetium-stress and treadmill-ECG compared to prior studies, our study was a direct comparison of each of the testing methods, with the results favoring EBCT.

**Conclusions.** The present study was performed to determine the usefulness of CC as detected by EBCT for the prediction of obstructive angiographic CAD compared with ECG and nuclear imaging exercise tests. We found significant and independent associations between the CC score and the presence of obstructive angiographic CAD in a symptomatic population. By considering the RR, we found that the strength of these associations proved more powerful for EBCT (4.53) than for either treadmill-ECG (1.72) or technetium-stress (1.96). The EBCT offers improved sensitivity and, in combination with a functional test (treadmill-ECG), offers specificity equal to that of a nuclear test (technetium-stress) in the identification of individuals with obstructive angiographic CAD. Although EBCT may be preferable due to reduced cost, rapid testing time, and improved diagnostic capability, other factors, including local expertise and availability of testing methods, will also influence the clinician's choice of noninvasive imaging in evaluating patients with symptoms suggestive of CAD.

**Reprint requests and correspondence:** Dr. David M. Shavelle, Division of Cardiology, Box 356422, University of Washington School of Medicine, Seattle, Washington 98195. E-mail: dshav@u.washington.edu.

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