One-year prognosis of patients with normal planar or single-photon emission computed tomographic technetium 99m–labeled sestamibi exercise imaging

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Background. **The favorable prognostic significance of normal ^{201}Tl stress perfusion images, even in the presence of known coronary artery disease, has been well documented. Relatively few data are available with regard to the prognostic significance of normal planar and single-photon emission computed tomographic (SPECT) stress ^{99m}Tc-labeled sestamibi (^{99m}Tc-sestamibi) images.**

Methods and Results. **The prognostic significance of normal exercise ^{99m}Tc-sestamibi myocardial perfusion imaging was evaluated in 208 consecutive patients. All patients were referred for evaluation of chest pain syndrome. One hundred eight patients (52%) underwent SPECT imaging, 79 patients (38%) underwent planar imaging, and 21 patients (10%) underwent both planar and SPECT imaging. One hundred seventy-five patients (84%) had a normal or nondiagnostic exercise electrocardiogram, and 33 patients (16%) had a positive exercise electrocardiogram. Follow-up was 13.5 ± 2 months and was complete in 99.5% of patients. No patient died of cardiac causes during follow-up. One patient (0.5%) had a nonfatal myocardial infarction and four patients (2%) had unstable angina necessitating revascularization. There was no difference in rate of cardiac events between men and women or whether SPECT or planar imaging was used. However, 33 patients with normal ^{99m}Tc-sestamibi imaging and a positive exercise electrocardiogram had a significantly higher cardiac event rate than had patients with negative exercise electrocardiograms (9% vs 1%, $p < 0.025$).**

Conclusion: **Patients with normal ^{99m}Tc-sestamibi exercise SPECT or planar imaging results and a normal or nondiagnostic exercise electrocardiogram have a favorable 1-year prognosis. Patients with normal ^{99m}Tc-sestamibi images and a positive stress electrocardiogram have a less favorable outcome. (J Nucl Cardiol 1994;1:449-56.)**

Key words: technetium 99m–labeled sestamibi · single-photon emission computed tomography · planar · prognosis · pretest likelihood · exercise

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Several studies have shown that patients with normal exercise ^{201}Tl myocardial perfusion images have excellent short- and long-term prognoses.[1-7] ^{99m}Tc-labeled sestamibi (^{99m}Tc-sestamibi), a relatively new myocardial perfusion imaging agent, has generally been shown to be comparable to ^{201}Tl for the detection of coronary artery disease by either planar or single-photon emission computed tomographic (SPECT) stress imaging.[8-25] Because of differences in tracer kinetics, in particular the lower myocardial extraction[26] fraction of sestamibi compared with that of ^{201}Tl, there has been concern that this agent may underestimate the presence of coronary artery disease under certain conditions. Therefore it remains to be shown that the well-established prognostic value of normal and abnormal ^{201}Tl stress images also applies to ^{99m}Tc-sestamibi exercise imaging. Unlike earlier investigations with ^{201}Tl,[27-30] the evaluation of the prognostic value of abnormal ^{99m}Tc-sestamibi images is presently confounded by a more aggressive interventional approach toward patients with abnormal findings. Decisions regarding cardiac catheterization and coronary revascularization are often guided by the results of stress myocardial perfusion imaging.

In this report we evaluated the prognostic significance of normal planar and SPECT ^{99m}Tc-sestamibi images during 1 year in patients referred for evaluation of chest pain.

PATIENTS AND METHODS

Patients. The study population consisted of 208 consecutive patients referred during a 1-year period (January to October 1991) to the Cardiovascular Nuclear Imaging Laboratory at Yale University for evaluation of chest pain syndromes, all of whom had normal results of ^{99m}Tc-sestamibi stress perfusion imaging. During this same period, 230 patients had abnormal results of ^{99m}Tc-sestamibi imaging. Patients were included in this study if the clinical report sent to the referring physician indicated a normal test result. All studies were interpreted by one of three experienced readers by quantitative analysis with visual overread. There were 108 men and 100 women. Patient age ranged from 31 to 90 years (mean age 59 ± 10.8 years) [± SD]).

Exercise Testing. Patients exercised on a motor-driven treadmill by either Bruce, modified Bruce, or Naughton protocol. End points for exercise were either attainment of 85% of maximal age-predicted heart rate, severe chest pain, 3 mm or greater ST segment depression, dyspnea, systolic hypotension, ventricular arrhythmia, or extreme fatigue. Forty-two patients (20%) had submaximal exercise test results.

Exercise Electrocardiography. Flat or downsloping ST segment depression equal or greater than 0.20 mV at 0.08 second after the J point was considered a positive electrocardiographic exercise response. Sixty-six patients (32%) had a normal exercise electrocardiogram, 109 patients (52%) had a nondiagnostic exercise electrocardiogram because of baseline abnormalities and 33 patients (16%) had a positive exercise electrocardiogram.

^{99m}Tc-sestamibi Imaging. Patients underwent either a 2-day or a 1-day ^{99m}Tc-sestamibi imaging protocol depending on either patient convenience or laboratory logistics. The method of ^{99m}Tc-sestamibi imaging has been described previously.[8,9] According to the 2-day protocol, patients underwent rest imaging on the first day and stress imaging on the second day. For each of these imaging sessions, 25 mCi sestamibi was administered. According to the 1-day protocol, patients received 10 mCi sestamibi for the first imaging session (usually rest) and 25 mCi sestamibi for the second imaging session (usually stress), with a 4-hour interval between two injections.

^{99m}Tc-sestamibi was administered at peak exercise and the patient was encouraged to continue to exercise for another 1 to 2 minutes. Imaging was started 15 to 30 minutes after injection of ^{99m}Tc-sestamibi at peak exercise and 60 to 90 minutes after injection at rest. Of 208 patients, 108 (52%) underwent SPECT imaging, 79 (38%) underwent planar imaging, and 21 (10%) underwent both SPECT and planar imaging.

Planar Imaging. Planar imaging was performed by acquiring three views: left anterior oblique, anterior, and left lateral decubitus views with a single-crystal gamma camera equipped with a general all-purpose parallel-hole collimator. Images were acquired with a 20% energy window set symmetrically over the 140 keV photo peak of ^{99m}Tc-sestamibi. Each view was acquired for 5 minutes, accumulating approximately two million counts per view. Images were acquired in 128 × 128 matrix word mode with a Picker PCS 512 computer (Picker International, Bedford Heights, Ohio), and data were stored on floppy disks for processing and analysis.

The distribution of ^{99m}Tc-sestamibi on planar images was quantified according to previously described methods.[31,32] In brief, after modified interpolative background subtraction, circumferential count distribution profiles of the left ventricle were generated and displayed as mean count density in 36-segments. The count profile was displayed relative to the segment with the highest mean count density, which was assigned a value of 100%. The patient's circumferential profile was displayed simultaneously with a curve displaying the lower limit of normal (mean counts − 2 SD) ^{99m}Tc-sestamibi distribution, derived from a database of normal volunteers with less than a 3% likelihood of coronary artery disease.

Tomographic Imaging. Tomographic imaging was performed with a single-head or triple-head rotating gamma camera (SX-300 or PRISM; Picker International). The gamma camera was equipped with a high-resolution parallel-hole collimator. Thirty-two projection images were acquired from a 45-degree right anterior oblique to a 45-degree left posterior oblique position. Each stop was 25 seconds for a 25 mCi dose and 40 seconds for a 10 mCi dose of ^{99m}Tc-sestamibi. Images were acquired in 64 × 64 matrix word mode. Data were corrected for field uniformity and center-of-rotation offset.

Tomographic images were processed as follows: A two-dimensional Butterworth filter (order 4.0, 0.5 Nyquist cutoff) was applied before image reconstruction. Transverse slices of 1 pixel thickness (6 mm) were generated by ramp-filtered back-projection. No attenuation correction or scatter correction was used. Slices were reoriented according to the anatomic axis of the heart. Reconstructed slices were displayed as short-axis slices, vertical long-axis slices, and horizontal long-axis slices. The distribution of ^{99m}Tc-sestamibi on tomographic images was quantified by circumferential count distribution profiles with reference to a normal database. This method is a modification of the quantitative method described for planar imaging.[33] Briefly, circumferential count distribution profiles were generated from the short-axis slices and displayed as maximal pixel counts in 36 radial sectors relative to the segments with highest maximal pixel counts, which were assigned a value

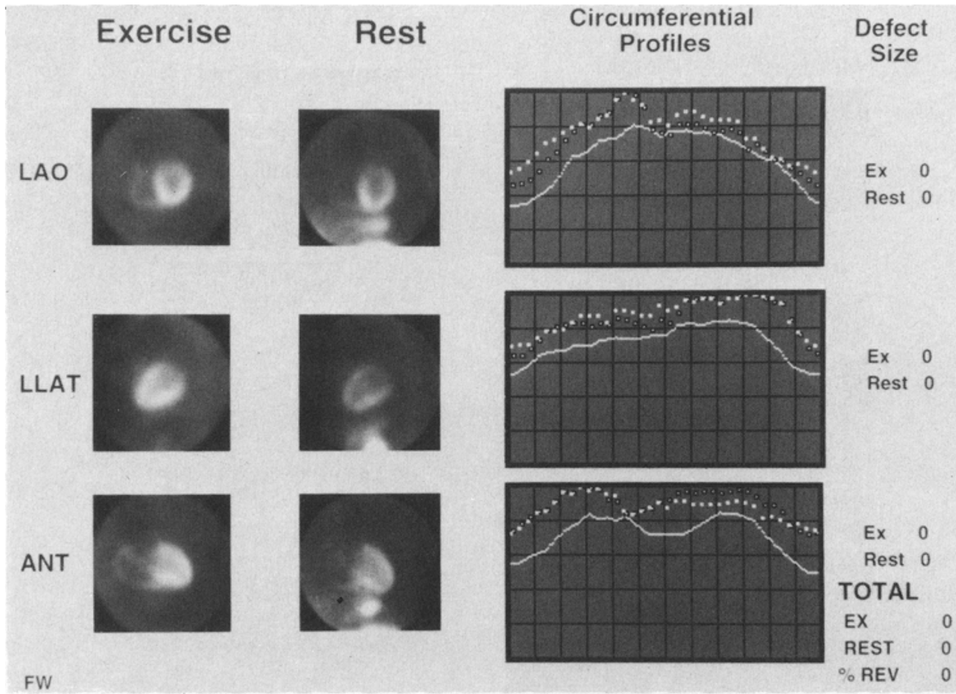

Figure 1. Example of quantitatively normal ^{99m}Tc-sestamibi planar images. *Left,* Unprocessed planar images in three views: anterior *(ANT),* left anterior oblique *(LAO),* and left lateral *(LLAT).* No myocardial perfusion defect is present by visual analysis. *Right,* Quantification of same planar images according to circumferential count distribution profiles. Continuous curve indicates lower limit of normal ^{99m}Tc-sestamibi distribution. Both exercise *(EX)* (□) and rest (⊡) profiles are above lower limit, indicating quantitatively normal planar images. *REV,* deflect reversibility.

of 100%. Patient profiles of all short-axis slices were displayed simultaneously with a curve describing the lower limit of normal (mean maximal counts − 2 SD) distribution, derived from a database of normal volunteers.

In a normal planar of SPECT ^{99m}Tc-sestamibi study, all data points of the circumferential profiles are above the curve delineating the lower limit of normal distribution (Figures 1 and 2).

Pretest Likelihood of Coronary Artery Disease. Pretest likelihood of coronary artery disease was determined with published tables based on patient age, sex, symptoms, and electrocardiographic ST segment response to exercise.[34] Patients were considered to have typical angina if they complained of substernal chest discomfort precipitated by physical exercise or emotional stress and relieved with rest or nitroglycerin. Patients were considered to have atypical angina if their discomfort was either not substernal, not precipitated by exercise, or not relieved by rest or nitroglycerin. If two or more of the three defining characteristics were absent, patients were considered to have nonanginal chest discomfort. Patients who denied any symptoms of chest discomfort were considered symptom free.

Patients with known coronary artery disease, either by coronary angiography or history of myocardial infarction, were assigned a pretest likelihood of coronary artery disease of 100%. A reduction of coronary luminal patency greater than 70% by visual analysis was considered significant coronary artery disease.

Follow-up. Follow-up was obtained by mailed questionnaires to the patients' physicians and in some cases telephone interviews with either the patient, the patient's physician, or the patient's relatives. "Hard" cardiac events were defined as cardiac death, presumed cardiac-related death, or nonfatal myocardial infarction. Unstable angina (i.e., recurrent angina necessitating hospitalization), was considered a "soft" cardiact event. Cardiac catheterization, coronary angioplasty, and coronary artery disease bypass graft surgery, were recorded but not considered to be cardiac events.

Statistical Analysis. Noncardiac deaths were treated as patient "dropout" from follow-up. Data are presented as means ± SD. Differences in prevalence between two groups were analyzed by (two-tailed) unpaired *t* tests. A p value < 0.05 was considered statistically significant. The method of Kaplan-Meier was used to plot life-table rates.

RESULTS

Patient Characteristics and Pretest Likelihood of Coronary Artery Disease. Fifty-one patients (25%) had typical angina, 92 patients (44%)

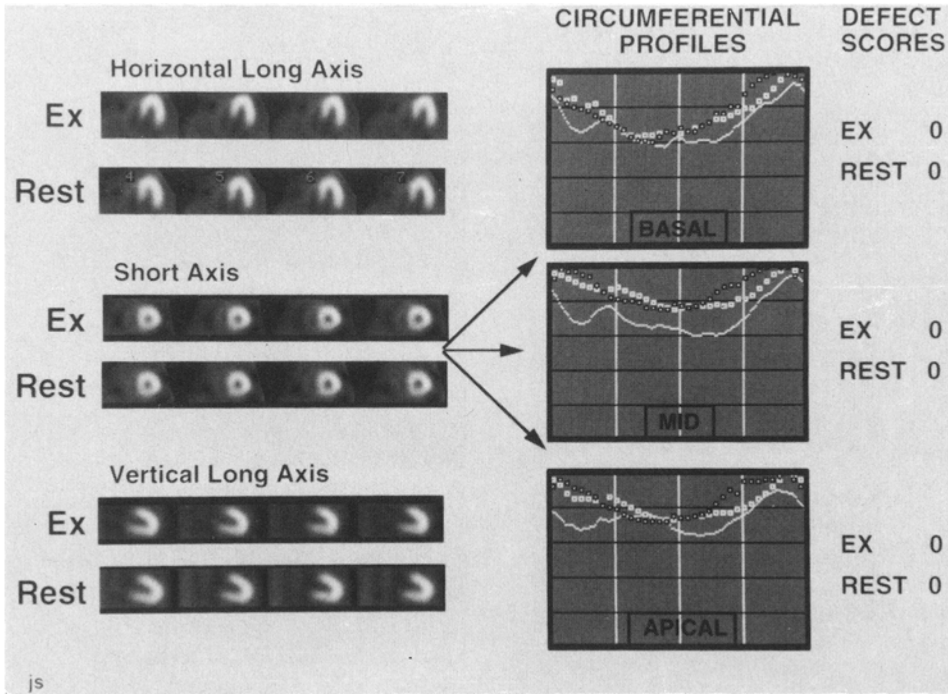

Figure 2. Example of quantitatively normal ^{99m}Tc-sestamibi SPECT images. *Left,* Reconstructed tomographic slices at exercise *(Ex)* and rest. *Top,* Vertical long-axis slices; *middle,* short-axis; *bottom,* horizontal long-axis slices. No myocardial perfusion defect is present by visual analysis. *Right,* Quantification of representative apical, midventricular, and basal sort-axis images according to circumferential count distribution profiles. Continuous curve indicates lower limit of normal ^{99m}Tc-sestamibi distribution. Both exercise (□) and rest (⊡) profiles are above lower limit, indicating quantitatively normal SPECT images.

Table 1. Reported yearly cardiac event rate in patients with normal ^{201}Tl stress perfusion images

Author	n	Cardiac death (%)	Nonfatal infarction (%)
Wackers et al.[1]	95	0	1.0
Pamelia et al.[2]	349	0.5	0.6
Wahl et al.[3]	455	0.2	0.6
Staniloff et al.[4]	372	0	0.5
Koss et al.[5]	309	0.3	1.2
Brown and Rowen[7]	75	0	0.7

had atypical angina, and 65 patients (31%) had atypical chest pain.

Fifty-two patients (25%) had a pretest likelihood of coronary artery disease of 100% (Figure 3). In 42 patients coronary artery disease was shown by prior coronary angiography and 10 patients sustained prior documented myocardial infarction. Three patients had Q-wave infarcts, five patients had non-Q-wave infarcts, and in two patients the infarct type was unknown. Three patients received thrombolytic therapy.

No patients had a pretest likelihood of 80% to 99%. Twenty-eight patients (13%) had a pretest likelihood ranging from 10% to 79%. One hundred twenty-eight patients (62%) had a pretest likelihood of coronary artery disease of less than 10%.

Mean follow-up was 13.5 ± 1.7 months. One patient with a pretest likelihood of coronary artery disease of less than 10% was lost to follow-up. Follow-up was complete in 207 patients (99.5%) (Figure 4).

Cardiac Events

Cardiac death. No patient died of cardiac causes during follow-up.

Nonfatal myocardial infarction. One patient (0.5%) had a nonfatal myocardial infarction. This event occurred 8 months after the normal exercise ^{99m}Tc-sestamibi study. This patient underwent subsequent coronary bypass surgery.

Unstable angina. Four patients (2%) had unstable angina. These events occurred 9 to 16 months after the normal exercise ^{99m}Tc-sestamibi stress tests. All four patients underwent subsequent coronary revascularization; one patient underwent coronary bypass surgery and the other three patients underwent coronary angioplasty.

Cardiac catheterization. Three patients (1%) underwent cardiac catheterization and coronary angiography because of persistent complaints of chest pain. Two patients had mild and insignificant coronary artery lesions (< 40% stenosis), and one patient had entirely normal coronary arteries.

Noncardiac death. Three patients (1.4%) died of noncardiac causes. One patient died of renal failure, another patient died of lung cancer, and a third patient died of multisystem organ failure as a result of generalized atherosclerotic vascular disease.

Pretest likelihood and cardiac events. The one patient with nonfatal myocardial infarction during follow-up was known to have angiographic coronary artery disease and had undergone coronary angioplasty 6 months before ^{99m}Tc-sestamibi exercise testing. Of four patients who had unstable angina during follow-up, three had a pretest likelihood of 100% and one patient had a pretest likelihood of less than 10%. Characteristics of patients with cardiac events are shown in Figure 3 and Table 1.

Relationship of Cardiac Events to Exercise Effort, Sex, Imaging Technique, and Electrocardiographic Response to Exercise. Three patients with cardiac events achieved or exceeded 85% of age-predicted maximal heart rate during the exercise test. Two patients with cardiac events achieved only 59% and 70%, respectively, of age-predicted maximal heart rate. There was no significant difference in the frequency of cardiac events between patients who achieved maximal exercise end point and patients who had submaximal exercise performance (1.8% vs 4.7%; difference not significant).

Of five patients with hard or soft cardiac events, three were men and two were women. There was no significant difference in the frequency of cardiac events between men and women (2.8% vs 2%; difference not significant).

Of the patients with cardiac events, three underwent planar imaging and two underwent SPECT imaging. Again there was no significant difference in occurrence of events between the two groups (3% vs 1.5%; difference not significant).

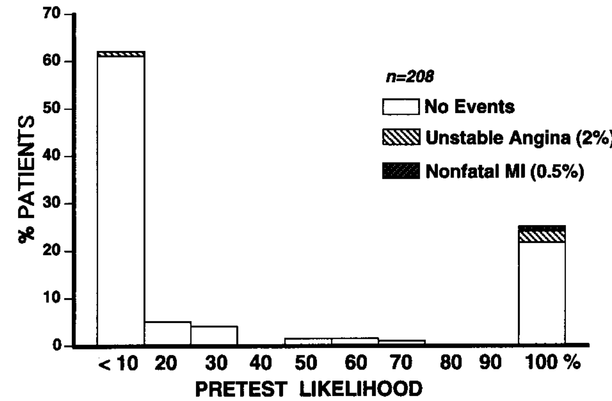

Figure 3. Distribution of pretest likelihood of coronary artery disease in 208 patients with quantitatively normal ^{99m}Tc-sestamibi exercise images. Occurrence of cardiac events during follow-up is indicated. *MI,* Myocardial infarction.

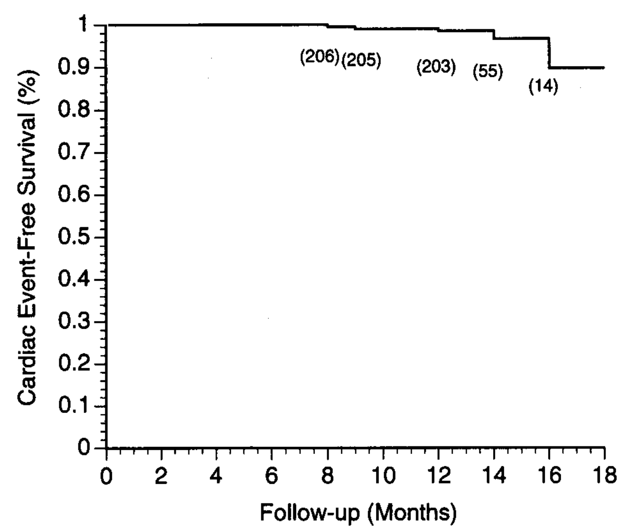

Figure 4. Kaplan-Meier survival curve in patients with quantitatively normal ^{99m}Tc-sestamibi exercise images. Number of patients still at risk during follow-up is indicated in parentheses.

The frequency of combined hard and soft cardiac events was significantly higher in patients with positive exercise electrocardiograms than in those with negative exercise electrocardiograms (3 [9%] of 33 vs 2 [1%] of 175; $p < 0.025$).

Retrospective Reanalysis of Sestamibi Images. To evaluate whether, in retrospect, the ^{99m}Tc-sestamibi images showed sestamibi missed on the initial reading, the images of the five patients with cardiac events were reanalyzed by two experienced reviewers. Even with knowledge of follow-up events, all study results were confirmed to be definitely normal according to quantitative criteria and normal reference database.

Table 2. Characteristics of patients with cardiac events

	Coronary artery disease (>70%)						
Patient	**LAD**	**LCX**	**RCA**	**CE**	**Procedure after CE**	**EX ECG**	**PTL (%)**
1	−	−	+	UA	PTCA	Pos	<10
2	+	−	+	MI	CABG	Pos	100
3	+	+	+	UA	CABG	LBBB	100
4	−	−	+	UA	PTCA	Neg	100
5	−	−	+	UA	PTCA	Pos	100

LAD, Left anterior descending coronary artery; *LCX*, left circumflex coronary artery; *RCA*, right coronary artery; *CE*, cardiac event; *Ex*, exercise; *ECG*, electrocardiogram; *PTL*, pretest likelihood; *UA*, *unstable angina*; *PTCA*, percutaneous transluminal coronary angioplasty; *Neg*, negative; *MI*, myocardial infarction; *CABG*, coronary bypass surgery; *POS*, positive; *LBBB*, left bundle branch block.

DISCUSSION

This study demonstrates that patients with quantitatively normal SPECT or planar ^{99m}Tc-sestamibi images have an excellent 1-year prognosis. The hard cardiac event rate was low (0.5%); there were no cardiac deaths and only one nonfatal myocardial infarction. Unstable angina, necessitating coronary revascularization, occurred in 2% of patients. These cardiac events did not occur shortly after radionuclide stress testing but 8 to 16 months later (Figure 4). These observations with ^{99m}Tc-sestamibi are comparable to those reported previously for normal stress ^{201}Tl imaging (Table 2) and identical to a recently published report by Brown et al.[35]

In our study there was no difference in favorable outcome between men and women, whether the SPECT or planar imaging technique was employed, or with maximal and submaximal exercise effort. However, patients with a positive exercise electrocardiogram, which occurred in only 16% of patients with normal ^{99m}Tc-sestamibi stress images, had a significantly higher incidence (9%) of cardiac events during follow-up than had patients with normal exercise electrocardiograms. The latter observation suggests that the prognostic value of myocardial perfusion imaging should be considered in the context of other exercise parameters. If ^{99m}Tc-sestamibi imaging is normal in conjunction with a normal or nondiagnostic exercise electrocardiogram, the cardiac event rate is extremely low (1%). It is particularly in the patients with nondiagnostic stress electrocardiograms, either because of baseline sestamibi or equivocal exercise changes, that normal stress ^{99m}Tc-sestamibi imaging provides unique prognostic information. From this study it should not be concluded that the exercise electrocardiogram has exceptional predictive value. It should be realized that this study was not designed to evaluate the prognostic value of normal or abnormal electrocardiograms but of normal exercise ^{99m}Tc-sestamibi images.

The selection of patients in this study was based on the reports sent out to the physician who requested the test. Thus this study reflects the reality of routine interpretation in our laboratory. Retrospective unblinded reinterpretation of the images of the patients who sustained cardiac events was identical to the initial interpretation. Because quantitative image analysis compared with a normal database was employed, the reproducibility of interpretation in our laboratory is excellent.

Numerous investigators have shown that ^{99m}Tc-sestamibi stress myocardial perfusion imaging, either by planar or SPECT techniques, is comparable to ^{201}Tl stress imaging for the detection of coronary artery disease.[8-25] Nevertheless, important differences in tracer kinetics and image patterns have been the cause of some concern. The relatively low extraction fraction of sestamibi[26] could conceivably affect the ability to visualize mild perfusion abnormalities. Increased lung uptake, an important unfavorable prognostic image pattern with ^{201}Tl,[36] is not observed with ^{99m}Tc-sestamibi. At the present time it is relatively difficult to evaluate the prognostic significance of abnormal ^{99m}Tc-sestamibi images, because patients with markedly abnormal images are likely to proceed to cardiac catheterization and undergo revascularization procedures when significant coronary artery disease is present. Stratman et al.[37] reported recently that abnormal stress ^{99m}Tc-sestamibi SPECT imaging provide significant independent prognostic information. This study evaluates the opposite end of the spectrum and indicates the favorable prognostic importance of normal ^{99m}Tc-sestamibi stress images.

The bimodal distribution of pretest likelihood in our patients is similar to that published previously in a subgroup of patients with normal scintigraphic studies but deserves a comment. This distribution is not representative of the entire population of patients referred to our laboratory for noninvasive evaluation of chest pain syndromes. The most appropriate and most cost-effective patient group to be studied by noninvasive testing for the detection of coronary artery disease are patients with an intermediate (40% to 70%) pretest likelihood of disease. In our laboratory the distribution of pretest likelihood in all patients referred is skewed toward mid and high likelihood of coronary artery disease.[1] Most of the latter patients have abnormal stress ^{99m}Tc-sestamibi images. When patients with abnormal ^{99m}Tc-sestamibi images are excluded, a bimodal distribution of our study population remains.

A most intriguing group of patients is that with a high likelihood of coronary artery disease and nevertheless normal ^{99m}Tc-sestamibi images. Many of these had known angiographic disease. Nevertheless, as shown in this study, their prognosis is relatively favorable. This is in agreement with the findings by Brown and Rowen,[7] who followed a selected group of patients with documented angiographic coronary artery disease and normal ^{201}Tl images. In this patient population the cardiac event rate was 0.5% per year. These data emphasize, once again, that myocardial perfusion imaging visualizes the functional significance of anatomic coronary artery disease. Four of five coronary events in our study occurred in patients with known coronary artery disease. It is conceivable that in these patients sudden plaque rupture occurred. This now well-appreciated dynamic aspect of coronary artery disease limits the ability of stress myocardial perfusion imaging to predict long-term prognosis. Only one of five patients with events had three-vessel coronary artery disease (Table 1).

Berman et al.[38] recently reported preliminary data concerning patients with normal ^{99m}Tc-sestamibi images. These investigators noted that prior coronary angioplasty was significantly associated with coronary events. Indeed, the one patient in our study who sustained nonfatal myocardial infarction had undergone prior coronary angioplasty.

Normal ^{99m}Tc-sestamibi stress images generally indicate an excellent prognosis even in patients with high likelihood or known coronary artery disease. This is true for male and female patients, regardless of which imaging technique, SPECT or planar, is employed. However, the relatively rare patients with normal ^{99m}Tc-sestamibi images and positive stress electrocardiograms have a higher prevalence of cardiac events than those with normal stress electrocardiograms. Although the latter patients are still at relatively low risk, it is probably advisable to follow these patients more closely than those in whom both test results are normal.

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