Prognostic Value of Normal Technetium-99m-Sestamibi Cardiac Imaging

Kenneth A. Brown, Eric Altland and Michaelanne Rowen

Cardiology Unit, Department of Medicine, University of Vermont College of Medicine, Burlington, Vermont

The purpose of this study was to describe the clinical outcome of patients with a normal ^{99m}Tc-sestamibi cardiac imaging study. **Methods:** One-day gated rest-stress planar dipyridamole (n = 112) and symptom-limited exercise (n = 122) ^{99m}Tc-sestamibi protocols were used. All patients (n = 234, mean age 55 ± 12 yr, 127 males and 107 females) had normal perfusion and wall motion on qualitative analysis. Patients were followed for 6–16 mo (mean 10 ± 2 mo). Cardiac events were defined as cardiac death or nonfatal myocardial infarction. **Results:** ST-segment depression or chest pain occurred in 8 (7%) and 29 (26%) patients in the dipyridamole group, respectively, and 20 (16%) and 28 (22%) patients in the exercise group. Cardiac events occurred in only one patient. The annualized event rate was 0.5% per year. In addition, only two patients underwent coronary revascularization during the follow-up period. **Conclusions:** Our data confirm the benign outcome of patients with normal ^{99m}Tc-sestamibi cardiac imaging, at least over an intermediate follow-up period.

Key Words: thallium-201; technetium-99m; cardiac imaging

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The prognostic value of ^{201}Tl myocardial perfusion imaging is well-established (*1*). A number of investigations have reported a very benign outcome in patients with normal ^{201}Tl imaging (*2–18*), with an overall cardiac death or myocardial infarction rate of <1% per year, as summarized in a recent review (*1*). Technetium-99m-sestamibi is a radiopharmaceutical recently released for myocardial perfusion imaging. Its shorter half-life allows administration of higher doses which, along with its higher intrinsic energy, can provide an image of superior quality to ^{201}Tl imaging. In addition, the higher count rates can allow image acquisition in a gated frame mode to provide analysis of regional and global ventricular function. While the diagnostic accuracy of ^{99m}Tc-sestamibi imaging for detecting coronary artery disease (CAD) has been shown to be comparable to ^{201}Tl (*19–24*), no data has yet been available regarding its prognostic implications. We therefore report the outcome of 234 patients with normal ^{99m}Tc-sestamibi cardiac imaging.

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For correspondence or reprints contact: Kenneth A. Brown, MD, Cardiology Unit, Medical Center Hospital of Vermont, Burlington, VT 05401.

METHODS

Patient Population

The study cohort consisted of 234 patients with known or suspected CAD referred for myocardial perfusion imaging between November 1, 1991 and June 1991 who had normal ^{99m}Tc-sestamibi cardiac imaging. Symptom-limited exercise ^{99m}Tc-sestamibi cardiac imaging was performed in 122 patients and dipyridamole-^{99m}Tc-sestamibi cardiac imaging was performed in 112 patients. Patient characteristics are listed in Table 1. Pre-test probability of CAD was determined from Bayesian analysis of age, sex, presenting symptoms and electrocardiographic response to stress (*25*).

Exercise Protocol

A baseline 12-lead electrocardiogram (ECG) was recorded. Patients then exercised on a treadmill according to a standard Bruce protocol until fatigue, dyspnea, chest pain or ventricular tachycardia. Heart rate, blood pressure and 12-lead ECG were recorded every 3 min. All patients achieving a heart rate ≥85% of their maximal predicted heart rate based on their age were considered to have undergone an adequate stress test. A positive, ischemic ECG response was defined as horizontal or downsloping ST-segment depression of 1 mm or greater.

Dipyridamole Protocol

A standard dipyridamole protocol using a 4-min infusion at 0.142 mg/kg/min was used (*26,27*). Heart rate and blood pressure were recorded before and every 2 min during the protocol.

Technetium-99m-Sestamibi Acquisition

Standard 1-day gated rest-stress planar ^{99m}Tc-sestamibi exercise and dipyridamole protocols were used. Rest planar static images were first obtained in the left anterior oblique, anterior and lateral projections 1 hr after injection of 7.5 mCi of ^{99m}Tc-sestamibi. The symptom-limited exercise or dipyridamole protocol was then performed and 22.5 mCi of ^{99m}Tc-sestamibi injected at peak exercise or 3 min after termination of the dipyridamole infusion, respectively. One hour later, sequential 16-frame gated planar images in the left anterior oblique, anterior and lateral projections were obtained.

Technetium-99m-Sestamibi Cardiac Image Analysis

Myocardial perfusion imaging results were analyzed using the composite planar stress images resulting from summing the 16 gated frames for each projection, as well as the rest images. In each case, the study was interpreted qualitatively by two experienced observers as showing normal homogeneous uptake in each of the three projections. Regional and global wall motion were

TABLE 1
Patient Characteristics

	Exercise group (n = 122)	Dipyridamole group (n = 112)
Age (yr)	54 ± 12	62 ± 13
Gender (male/female)	61/61	66/46
Pretest probability of CAD (%)	52 ± 42	55 ± 40
Beta-blocker usage	41 (39%)	34 (30%)
Aspirin use	57 (47%)	54 (48%)
Stress testing response		
Baseline HR	77 ± 15	71 ± 13
Peak HR	143 ± 28	101 ± 21
Baseline BPs	129 ± 20	142 ± 25
Peak BPs	170 ± 27	127 ± 24
ST-segment depression	20 (16%)	8 (7%)
Chest pain	28 (22%)	29 (26%)

analyzed qualitatively using an endless-loop cine technique for each projection. Regional and global right and left ventricular wall motion was interpreted as normal in each case.

Cardiac Catheterization

Cardiac catheterization was performed at the discretion of each patient's treating physician, as clinically indicated. Coronary angiographic data was captured and recorded for this study. Significant angiographic coronary disease was defined as luminal diameter narrowing of ≥50% involving one of the three coronary arteries or a major branch.

Follow-up Data

Follow-up data were obtained from telephone interviews, hospital records and physician office notes and were 100% complete. The follow-up period ranged from 6 to 16 mo with a mean of 10 ± 2 mo. Primary cardiac events were defined as cardiac death or nonfatal myocardial infarction. In addition, coronary revascularization for any cause was recorded. Secondary cardiac events included patients who developed recurrent chest pain requiring coronary revascularization. All cardiac events were confirmed by hospital records and laboratory data, including serial ECGs and cardiac enzymes.

Statistical Analysis

Patients values are presented as mean ± s.d. Mean values were compared using an unpaired t-test. Frequency comparisons were made using chi-square analysis. Cardiac event confidence intervals were calculated based on a binomial distribution.

RESULTS

Hemodynamic responses to exercise and dipyridamole are recorded in Table 1. In addition, the frequency of ST-segment depression or chest pain during exercise and dipyridamole protocols are also displayed in Table 1.

Cardiac catheterization was performed in 50 patients; 18 in the dipyridamole group and 32 in the exercise group. In each patient, the myocardial perfusion imaging study was performed after cardiac catheterization. Coronary angiographic data is depicted in Table 2. All but three patients who underwent cardiac catheterization were found to have angiographically significant coronary disease, including 30 patients with multivessel coronary disease.

Primary cardiac events occurred in only one patient: a nonfatal myocardial infarction at 9 mo in a patient with a normal exercise ^{99m}Tc-sestamibi study. No angiographic data was available for this patient. The annualized cardiac event rate for the overall cohort was 0.5% (95% confidence interval = 0.0%–1.9%). Secondary cardiac events occurred in two patients who underwent coronary revascularization, each for recurrent chest pain. One patient underwent coronary angioplasty 10 mo after a normal dipyridamole ^{99m}Tc-sestamibi study. A second patient underwent multivessel coronary bypass surgery 8 mo after a normal exercise ^{99m}Tc-sestamibi study. No other patient underwent coronary revascularization. The overall annualized cardiac event rate was 1.5% (0.4%–3.7%).

Among the 47 patients with angiographically significant CAD but normal ^{99m}Tc-sestamibi myocardial perfusion imaging study (Table 2), no patient had a primary cardiac event and only two patients developed recurrent chest pain requiring coronary revascularization.

DISCUSSION

The use of ^{201}Tl myocardial perfusion imaging for risk stratification of patients is now well established (*1*). Beyond making the diagnosis of CAD, ^{201}Tl myocardial perfusion imaging is now widely used to guide management decisions by identifying the highest risk group of patients and thus those patients most likely to benefit from the expense and risk of invasive intervention. The recent introduction of ^{99m}Tc-sestamibi has provided clinicians with an alternative agent for cardiac imaging that has superior imaging characteristics compared to ^{201}Tl, yielding studies with greater count densities, imaging quality and the ability to perform gated acquisitions to provide information regarding global and regional ventricular function. As a result, a growing number of nuclear cardiology laboratories are now using ^{99m}Tc-sestamibi rather than ^{201}Tl for their myocardial imaging studies. However, while the diagnostic accuracy of this agent has been demonstrated to be comparable to ^{201}Tl (*19–23*), no data has been available concerning its prognostic value, although it is likely that ^{99m}Tc-sestamibi imaging is being used for risk stratification. Such a use may be based on the assumption that the predictive value will be comparable to what has already been established for ^{201}Tl imaging. Nevertheless, it is important to

TABLE 2
Coronary Angiographic Data

	Patients classified by no. of coronary vessels diseases			
	0	1	2	3
Dipyridamole group (n = 18)	1	7	7	3
Exercise group (n = 32)	2	10	8	12
Total (n = 50)	3	17	15	15

determine the prognostic value of ^{99m}Tc-sestamibi imaging in its own right.

We found the outcome of patients with normal myocardial perfusion and contraction by ^{99m}Tc-sestamibi cardiac imaging in conjunction with either symptom-limited exercise or dipyridamole to be extremely benign, at least over an intermediate follow-up period. The overall annualized cardiac event rate was <1% per year, a rate very comparable to the rate described with ^{201}Tl myocardial perfusion imaging (*1–18*). Importantly, the natural history of the study cohort was relatively undisturbed by coronary revascularization, reflecting the benign outcome of the group as well as a probable post-test bias among physicians that revascularization was unlikely to benefit patients with a normal ^{99m}Tc-sestamibi cardiac imaging study, even when the patient was known to have CAD. Indeed, only 2 of 47 patients with angiographically significant coronary disease, including 30 with multivessel disease, underwent coronary revascularization.

The benign outcome observed in our study cohort does not appear to reflect a selection bias for a low-risk population of patients with normal coronary arteries. The average pre-test probability of CAD was moderate for the overall cohort (mean 53%). In addition, 47 (20%) were known to have angiographically significant coronary disease. The very high incidence of angiographic coronary disease among patients undergoing cardiac catheterization in our cohort (47/50, 94%) probably reflects the fact that in each patient, the sestamibi study was done after the cardiac catheterization. Although anatomic coronary disease had been documented, a functional assessment with myocardial perfusion imaging was requested by the treating physician. Thus, the vast majority of patients going on to sestamibi imaging following cardiac catheterization would have had significant angiographic disease. Very few with normal angiographic coronary disease would have subsequent myocardial perfusion imaging: only those in whom stress-induced coronary spasm or Syndrome X was being considered. The lack of patients in our cohort who had cardiac catheterization following a normal sestamibi study probably reflects the benign outcome of such patients as well as the determination by treating physicians that no further evaluation was necessary.

Since we did not evaluate patients with an abnormal perfusion imaging study, no meaningful conclusions can be drawn from our data regarding the sensitivity of ^{99m}Tc-sestamibi imaging for CAD. However, our data suggest that normal ^{99m}Tc-sestamibi cardiac imaging predicts a benign outcome even when angiographic coronary disease is present, consistent with prior observations for ^{201}Tl myocardial imaging (*18*).

Current Study Limitations

The principal limitation of the current study is the 10-mo follow-up period. It is possible that a longer follow-up would reveal different results, although prior studies have not reported a time-dependent rate of events. The relatively new release of the agent currently precludes a longer follow-up. However, because it is likely that ^{99m}Tc-sestamibi imaging is being used in clinical practice for risk stratification at this time, we feel it is important to provide at least preliminary data regarding the prognostic implications of ^{99m}Tc-sestamibi cardiac imaging.

CONCLUSIONS

Normal ^{99m}Tc-sestamibi cardiac imaging in conjunction with dipyridamole or symptom-limited exercise predicts a very low cardiac event rate over an intermediate follow-up period. Although our data suggest that the prognostic value of ^{99m}Tc-sestamibi myocardial perfusion imaging is likely to be comparable to ^{201}Tl imaging, studies with longer follow-up will be required to confirm this.

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