Sequential Dual-Isotope SPECT Imaging with Thallium-201 and Technetium-99m-Sestamibi

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This study examined the results of sequential SPECT dual-isotope imaging with ^{201}Tl and ^{99m}Tc-sestamibi in 148 patients, 114 of whom also had coronary angiography and 34 had <5% pretest probability for coronary artery disease (CAD). **Methods:** Stress thallium/rest sestamibi was used in 82 patients and rest thallium/stress sestamibi in 66 patients. Coronary angiography showed that 17 patients had no CAD, 27 patients had one-vessel CAD, 41 patients had two-vessel CAD and 29 patients had three-vessel CAD. The thallium study (3 mCi) was always done before the sestamibi study (20–25 mCi). The stress was either symptom-limited treadmill exercise testing or adenosine infusion at a rate of 140 μg/kg/min for 6 min. **Results:** The study was completed within 2 hr. The stress and rest images were normal in 11 of 17 patients (65%) with no CAD by angiography and in 33 of 34 patients with a low pretest probability of CAD (normalcy rate = 97%). The images were abnormal in 75 patients with CAD (77%). The perfusion pattern was compared to wall motion in 485 segments (97 patients) assessed by contrast ventriculography. There were no or reversible perfusion defects in 357 of 386 segments (92%) with no wall motion abnormality. **Conclusion:** Sequential dual-isotope imaging is feasible and can be completed in a short period of time and may therefore enhance laboratory throughput and patient convenience.

Key Words: thallium-201; technetium-99m-sestamibi; SPECT

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Exercise or pharmacologic myocardial perfusion imaging with ^{201}Tl have been widely used methods for the detection of coronary artery disease (CAD) (*1–5*). The results with ^{99m}Tc-labeled imaging agents have been similar to ^{201}Tl (*6–11*). A potential disadvantage of both methods is the length of the protocol used. Thus, with ^{201}Tl, 4-hr delayed images and with sestamibi, a second set of images are needed 4 hr after the initial study or on a separate day. This paper describes the feasibility and initial results of a shorter protocol using sequential dual-isotope imaging with ^{201}Tl and sestamibi.

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MATERIALS AND METHODS

Study Population

There were 328 patients who underwent sequential SPECT dual-isotope imaging with ^{201}Tl and ^{99m}Tc-sestamibi. Of those, 114 patients had coronary angiography within 6 mo of each other (91 patients within a 1-mo period), and 34 patients had a low pretest probability of CAD (<5%) on the basis of age, sex, and other risk factors (*12*). The remaining 180 patients were excluded due to history of coronary artery bypass graft surgery or lack of coronary angiographic data. Thus, the study population consisted of a total of 148 patients (89 males, 59 females) age 58 ± 10 yr. Coronary angiography was performed using standard techniques in multiple projections. The results of coronary angiograms were interpreted by two angiographers without knowledge of perfusion imaging results. The presence of CAD was defined as ≥50% diameter stenosis in one or more of the major coronary arteries or their major branches. Contrast left ventriculograms in the right anterior oblique projection were available in 97 patients. The wall motion was assessed in five segments per patient (anterobasal, anterolateral, apical, inferior and inferobasal) as normal, hypokinetic, akinetic or dyskinetic.

Protocol Design

Two different imaging sequences were employed (Fig. 1). In rest thallium/stress sestamibi studies, rest thallium images were initially obtained, and then immediately afterwards a stress study was performed (exercise or adenosine) using sestamibi. Stress images were obtained 30 min after sestamibi injection. The dose of thallium was 111 MBq (3 mCi), and the dose of sestamibi was 740 MBq (20 mCi).

In stress thallium/rest sestamibi studies, the stress study was performed initially (exercise or adenosine), with ^{201}Tl, and immediately after completion of imaging, sestamibi was injected while the patient was still on the imaging table. Imaging was performed within 10 min of thallium injection, and 60 min after sestamibi injection. The doses of thallium and sestamibi were similar to the above imaging sequence. Thallium imaging was performed using a 20% window centered on 69–83 keV mercury x-rays and a 15% window on the 167-keV photon. For ^{99m}Tc-sestamibi imaging, a 20% window centered on 140 keV was used.

Exercise Testing

Symptom-limited exercise testing was performed on a treadmill using the Bruce protocol. Exercise was terminated if there was one or more of the following: angina of at least moderate degree, excessive fatigue, weakness, shortness of breath, ≥2 mm S-T segment depression or dizziness. The exercise electrocardiograms were interpreted as positive, negative or nondiagnostic as previously reported (*1,13*). At the end of exercise, thallium or sestamibi

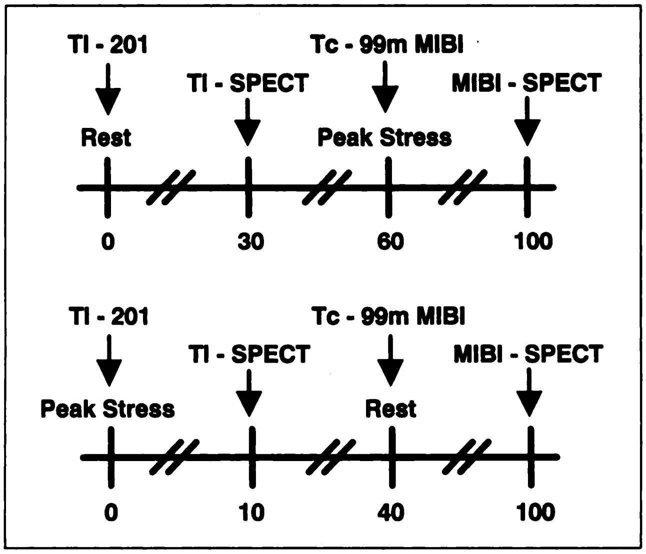

FIGURE 1. Imaging protocol: rest thallium/stress sestamibi (top panel) and stress thallium/rest sestamibi (bottom panel).

was injected and patients were exercised for one additional minute.

Adenosine Protocol

Intravenous infusion of adenosine was performed at a rate of 140 μg/kg/min for a total of 6 min. At the end of the third minute of the infusion, thallium or sestamibi was injected intravenously. The heart rate, blood pressure and electrocardiograms were constantly monitored and recorded at baseline and during each minute of infusion and for 5 min during recovery (*14*).

SPECT

Our method for tomographic imaging has previously been described (*4*). In short, images are obtained using a circular orbit over 180° anterior arc, starting at the 45° right anterior oblique projection and ending at the 45° left posterior oblique projection. For thallium, 32 projections are obtained using a 16-bit, 64 × 64 matrix for 40 sec per image. For ^{99m}Tc-sestamibi, 64 projections were obtained using 64 × 64 matrix for 20 sec per view. For tomographic reconstruction, a Ramp-Hanning filter (a cutoff frequency of 0.83 cycles/cm) was used for thallium and a Butterworth filter was used for sestamibi (a cutoff frequency of 0.5 cycles/cm and power of 5). After correction for nonuniformity of the field, a standard filtered backprojection technique was used to generate transaxial slices. No scatter or attenuation correction was applied. From these transaxial images, the long-axis of the left ventricle was identified and the oblique-angled images were generated creating the short-axis, vertical long-axis and horizontal long-axis slices. Tomographic images were interpreted by two experienced observers without prior knowledge of results of other studies.

Stress and rest images were displayed simultaneously at the same level of respective tomograms. By definition, a reversible abnormality was present when a perfusion abnormality was observed in the stress images, but not present or smaller in the corresponding rest images (Figs. 2 and 3). A fixed abnormality was present when there was no improvement in the perfusion abnormality from stress to rest images. From the short-axis and vertical long-axis images, segments that corresponded to the re-

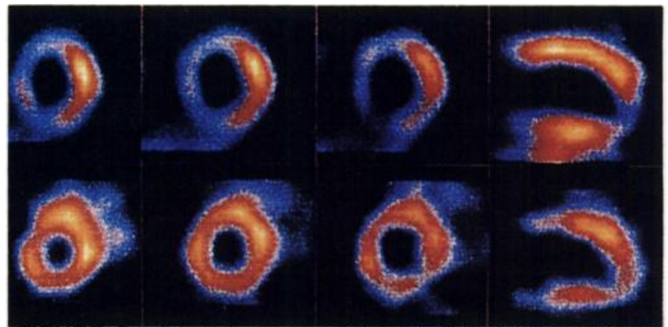

FIGURE 2. Adenosine sestamibi/rest thallium images. Adenosine sestamibi tomographic images (top row) demonstrate extensive perfusion abnormalities involving the anterior wall, septum, inferior wall, apex and part of the lateral wall. Three short-axis slices at apical, mid- and basal levels and one vertical long-axis slice at the mid-ventricular level are shown. Rest thallium images (bottom row) show considerable improvement in the perfusion pattern. The coronary angiogram of this 65-yr-old male showed three-vessel disease.

gions identified on the contrast left ventriculogram were selected to compare the perfusion pattern and wall motion.

Statistical Analysis

Data were presented as mean ± standard deviation when appropriate. For comparison, the chi-square analysis was used for discrete variables and the Student's t-test was used for continuous variables (*15*). A probability value of <0.05 was considered statistically significant.

RESULTS

Pertinent demographic data are listed in Table 1. Among the patients who had coronary angiography, there were 78 males and 36 females, age 61 ± 11 yr. Coronary angiography showed that 17 patients had no CAD, 27 patients had one-vessel CAD, 41 patients had two-vessel CAD and 29 patients had three-vessel CAD. The patients with a low pretest probability of CAD were 11 males and 23 females aged 48 ± 10 yr.

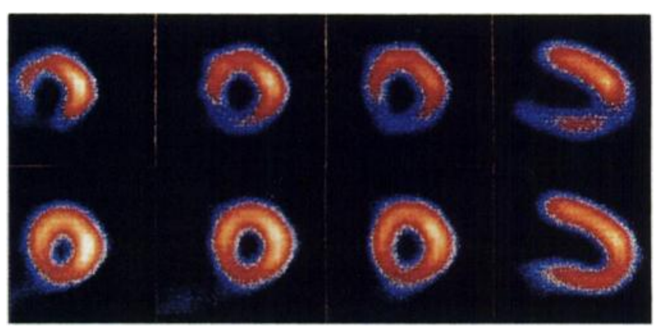

FIGURE 3. Exercise thallium/rest sestamibi images. Exercise thallium tomographic images (top row) demonstrate perfusion abnormalities involving the septum, inferior wall and apex (same format as in Fig. 2). Rest sestamibi images are within normal limits. This 57-yr-old male had 70% diameter stenosis involving the mid-left anterior descending artery and 90% stenosis of the proximal right coronary artery on his coronary angiogram.

TABLE 1
Pertinent Demographics*

Sex (M/F)	78/36
Age (years)	61 ± 11
Hypertension	57 (50%)
Diabetes mellitus	18 (16%)
Q-wave MI	37 (32%)
Nitrates	57 (50%)
Beta blockers	52 (46%)
Ca^{++}-blockers	74 (65%)

MI = myocardial infarction.

Hemodynamic Responses

The hemodynamic changes during exercise testing and adenosine infusion are listed in Table 2. During adenosine infusion, the heart rate increased, and the systolic blood pressure decreased slightly. S-T segment depression was present in 23% of exercise studies and 22% of adenosine studies.

Results of SPECT Perfusion Imaging

The protocols used in these subjects were rest thallium/stress sestamibi in 66 patients and stress thallium/rest sestamibi in 82 patients. The stress was exercise in 74 patients and adenosine in 74 patients. The results of tomographic images with the dual-isotope technique in the 148 patients are listed in Table 3. The image quality was good to excellent in all studies. In the patients with a low pretest probability of CAD, stress/rest images were normal in 33 patients (normalcy rate = 97%). In the 17 patients with normal angiograms the images were normal in 11 patients (specificity = 65%).

In CAD patients, the perfusion images were abnormal in 75 (sensitivity = 77%). The sensitivity was 56% in 27 patients with one-vessel disease, 83% in 41 patients with two-vessel disease and 90% in 29 patients with three-vessel disease. The perfusion pattern was considered reversible in 44 patients, fixed in 14 patients and both fixed and reversible in 17 patients. There were no significant differences between the two imaging protocols in sensitivity or specificity. Most patients with CAD who had normal images had mild stenosis (50%–70%, n = 18), one-vessel (n = 12) or branch diseases.

TABLE 2
Hemodynamic Changes During Exercise and Adenosine Infusion

	Exercise (n = 74)	Adenosine (n = 74)
Rest heart rate (bpm)	75 ± 16	72 ± 12
Peak heart rate (bpm)	146 ± 23	87 ± 15
Rest SBP (mmHg)	125 ± 16	138 ± 18
Peak SBP (mmHg)	174 ± 25	131 ± 25
Exercise duration (min)	7.6 ± 2.9	
Exercise workload (METs)	8.3 ± 3.4	
Positive ECG changes	17 (23%)	16 (22%)
Chest pain during test	13 (18%)	32 (43%)

ECG = electrocardiogram and SBP = systolic blood pressure.

TABLE 3
SPECT Imaging Results

Sensitivity	Rest thallium/ stress MIBI	Stress thallium/ rest MIBI	Total
All CAD patients	31/42 (74%)	44/55 (80%)	75/97 (77%)
One-vessel disease	8/12 (67%)	7/15 (47%)	15/27 (56%)
Two-vessel disease	11/16 (69%)	23/25 (92%)	34/41 (83%)
Three-vessel disease	12/14 (86%)	14/15 (93%)	26/29 (90%)
Reversible defect	26/42 (62%)	35/55 (64%)	61/97 (63%)
Specificity	5/7 (71%)	6/10 (60%)	11/17 (65%)
Normalcy rate	17/17 (100%)	16/17 (94%)	33/34 (97%)

Correlation of Perfusion Pattern to Wall Motion

In 386 segments with no wall motion abnormality on contrast left ventriculography, 357 (92%) had normal perfusion pattern or reversible defects. In 73 segments with hypokinesis, 20 had fixed defects and of 26 segments with akinesis or dyskinesis, 19 had fixed defects. The agreement between wall motion and perfusion pattern was good ($p < 0.001$). The correlation between wall motion and perfusion pattern was not related to the imaging sequence.

DISCUSSION

Since its introduction into clinical use in 1973, ^{201}Tl myocardial perfusion imaging has been widely accepted as noninvasive diagnostic procedure for detection of CAD, risk stratification and myocardial viability assessment (*1–5*). In 1977, Pohost et al. introduced the method of 4-hr delayed imaging to characterize perfusion defects into reversible, fixed, or partially reversible (*16*). In 1990, Dilsizian et al. introduced the reinjection technique to enhance detection of viable myocardium (*17*).

Sestamibi Imaging

The advantages of ^{99m}Tc-sestamibi are: ideal photon energy (140 keV), a relatively short half-life of 6 hr and availability and suitability for gated acquisition and combined perfusion and functional assessment. The potential disadvantage is a lower extraction fraction. In a recent experimental study, the defect size was smaller with sestamibi than thallium in mild to moderate stenosis, but not in severe stenosis (*18*). There are also clinical data that have reached similar conclusions (*19*).

The lack of redistribution may be either an advantage or disadvantage. For example, in viability studies it may conceivably be a disadvantage because the resting coronary blood flow may be reduced in patients with severe coronary stenosis. Thus, a resting perfusion abnormality may reflect the reduction of flow rather than lack of viability. On the other hand, the advantage to a lack of redistribution is mainly due to uncoupling of injection and imaging, which is especially important in patients with acute coronary syndromes. Regardless of the protocol used with ^{201}Tl (stress-redistribution reinjection) and sestamibi (1-day or 2-day), results of the tests will not be available for at least 6 hr. In comparison, with ^{99m}Tc-teboroxime, rest and stress studies can be completed in 1 to 2 hr.

Dual-Isotope Imaging

Dual-isotope imaging is another method to expedite imaging. It can be done using either simultaneous or sequential imaging. Examples of this include use of ^{201}Tl and ^{111}In antimyosin antibody imaging or ^{201}Tl and sestamibi (or teboroxime) (*20–22*). Simultaneous imaging has the potential advantage of precise pixel registration, and artifacts, if present, are identical in both thallium and sestamibi modalities, and requires only one set of imaging. The disadvantage is the spillover of activity from the ^{99m}Tc to the ^{201}Tl window. This protocol awaits validation of methods to correct for spill-over. In phantom studies by Weinstein et al., images were obtained in three windows; 74 keV representing ^{201}Tl, 140 keV representing ^{99m}Tc and 95–105 keV representing spill-down (*23*). The spill-down images were then subtracted from the thallium window images. The resultant images looked very similar to uncontaminated thallium images. Thallium-201 spill-up correction was not needed because the single-isotope and dual-isotope ^{99m}Tc images were identical. It is not clear, however, whether this will be applicable in human studies because of variations in chest wall and attenuations.

The sequential protocol involves obtaining the thallium images first (before the injection of ^{99m}Tc), and hence, they are not contaminated by spillover from ^{99m}Tc. Although the technetium images are obtained in the presence of both ^{201}Tl and ^{99m}Tc, there is very little spillover from thallium to the ^{99m}Tc window. In preliminary studies by Cedars Sinai group investigators, there was only 2.7% spillover (*21,22*).

Because of differences in the energy levels of ^{201}Tl and ^{99m}Tc, there are differences in attenuation and scatter. These may affect the severity and reversibility but not necessarily the detection of perfusion defects with dual-isotope imaging. The lower sensitivity in this study is because many patients with mild coronary stenosis were included because indication for the imaging tests was to determine the hemodynamic significance of borderline lesions seen on angiography. Therefore, there was a clear selection bias. None of these patients with normal images subsequently had coronary revascularizations despite the presence of CAD by angiography.

In this study we compared the perfusion pattern to wall motion assessed by contrast left ventriculography. The results show that the preservation of wall motion was associated with normal or reversible perfusion abnormalities consistent with viable myocardium, whereas a wall motion abnormality was associated with a fixed defect. The protocol was well appreciated by both patients and referring physicians because management decisions were made in a fairly short time. Because the protocol was new, we randomly allocated patients to either rest thallium/stress sestamibi or stress thallium/rest sestamibi. We did not gate the sestamibi images or obtain first-pass radionuclide angiography in this study, though either or both is feasible and may provide further information.

Study Limitations

There was probably a selection bias in recruiting these patients; very obese patients were not recruited, most of our patients had normal perfusion pattern or reversible defects, and myocardial viability was not a clinically relevant issue. Presently, we still believe that if viability is the issue to be addressed, thallium imaging alone is the procedure of choice.

It is conceivable, however, that 24-hr delayed thallium imaging may be used to assess viability even with the dual-isotope technique. This requires further study. Defining the optimal imaging sequence (rest thallium/stress sestamibi versus stress thallium/rest sestamibi) requires a study in a larger group of patients, especially those with mild disease because of differences in tracer extraction at high coronary flow rates. Finally, the dual-isotope method needs to be compared to standard techniques using either thallium or sestamibi alone.

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