Technetium-99m-Sestamibi Myocardial Perfusion Imaging in Detection of Coronary Artery Disease: Comparison Between Initial (1-Hour) and Delayed (3-Hour) Postexercise Images

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Technetium-99m-sestamibi, a new myocardial perfusion imaging agent, does not show significant or rapid myocardial redistribution following its intravenous injection at stress. The purpose of this study was to evaluate the myocardial clearance of ^{99m}Tc-sestamibi and ischemic/normal wall ratios at 1 hr and at 3 hr after injection at stress in patients with significant coronary artery disease. Twenty-five patients with ischemic defects on ^{201}Tl scans (n = 15) and/or significant disease on coronary angiogram (n = 18) were prospectively studied. Planar images were obtained at 65 and at 190 min after an injection at stress of 20–25 mCi of ^{99m}Tc-sestamibi. A rest study was performed 1–6 days later. Ischemic/normal wall ratios were 0.73 ± 0.10 and 0.83 ± 0.12 ($p < 0.05$) at 1 and 3 hr, respectively (0.98 ± 0.15 at rest). Myocardial washout was 26% ± 12% for normal walls and 15% ± 8% for ischemic walls ($p < 0.001$). Segmental analysis showed 48 and 46 ischemic segments at 1 and 3 hr, respectively. In conclusion, although only a few ischemic segments were missed at 3 hr, significantly lower ischemic/normal wall ratios were found at 1 hr. Faster myocardial washout from normal walls is responsible for the partial reduction of this ratio.

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Thallium-201 myocardial perfusion scintigraphy is recognized as a useful clinical procedure for the evaluation of patients with coronary artery disease (*1–4*). However, although its value as a diagnostic test has been well established, ^{201}Tl-chloride presents some disadvantages. Its physical and biologic characteristics are not ideal for imaging purposes. The development of a myocardial perfusion agent labeled with ^{99m}Tc is attractive because of the physical advantages of ^{99m}Tc over ^{201}Tl. The ^{99m}Tc-hexakisaliphatic isonitriles (*5*) have shown interesting properties as myocardial perfusion agents. At the present time, three isonitriles analogs have been the subject of more detailed evaluation in humans: ^{99m}Tc-TBI (t-butyl isonitrile) (*6*), ^{99m}Tc-CPI (carbomethoxy isopropyl isonitrile) (*7–8*) and ^{99m}Tc-sestamibi (methoxy isobutyl isonitrile) (*9–18*). Because of more favorable biologic characteristics, including rapid lung and liver clearance and slow myocardial washout, ^{99m}Tc-sestamibi is the most interesting of these agents.

Like ^{201}Tl, the myocardial distribution of ^{99m}Tc-sestamibi reflects the coronary blood flow (*19–25*). Besides advantages related to the physical characteristics of ^{99m}Tc, one interesting property of ^{99m}Tc-sestamibi is that there is no significant myocardial redistribution after its administration. This property gives a good scheduling flexibility for imaging which is particularly useful in the evaluation of acute conditions such as thrombolysis for acute myocardial infarction (*26*) or unstable angina (*27*). Patients can be stabilized before diagnostic imaging. Previous studies have reported a time interval between ^{99m}Tc-sestamibi injection and myocardial imaging varying from 30 min to 6 hr (*28–30*). However, there are few data available on the difference between early and late ^{99m}Tc-sestamibi imaging for detection of ischemic disease (*31*). The purpose of this study was to evaluate the myocardial clearance of both normal and abnormal walls and ischemic/normal wall ratios at 1 hr and 3 hr after ^{99m}Tc-sestamibi injection at stress in patients with coronary artery disease.

METHODS

Patient Population

Twenty-five patients (23 males, 2 females) with ischemic defects on ^{201}Tl myocardial perfusion imaging and/or significant coronary artery disease on coronary angiography were prospectively studied. The mean age was 57 yr (with a range from 36 to 75 yr). Since it is reported that ^{99m}Tc-sestamibi does not significantly redistribute, all patients were submitted to two separate injections, one at stress and one at rest a few days later. Written informed consent, approved by the ethics committee of our institution, was obtained from each patient. Patients with recent

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myocardial infarction (less than 4 wk), unstable angina, congestive heart failure or symptomatic known valvular heart disease were excluded from the study.

Technetium-99m-Sestamibi Myocardial Study

Within a week, all patients had two ^{99m}Tc-sestamibi injections, the first with injection at stress and the second at rest. There was an interval of at least 24 hr between the two injections. Cardiovascular drugs were discontinued 24–48 hr prior to the injection. Patients were asked to fast after midnight. An intravenous line with NaCl 0.9% solution was started in an antecubital vein. Patients were exercised on a treadmill according to the Bruce protocol until they reached 85% of the age-predicted maximal heart rate or developed angina, shortness of breath, hypotension or arrhythmias. One minute before the end of the stress test, a dose of 20 mCi of ^{99m}Tc-sestamibi per 70 kg of body weight was injected. Patients drank two glasses of whole milk within 45 min after the ^{99m}Tc-sestamibi injection to accelerate hepatobiliary clearance.

The rest injection was performed after the patient rested for at least 15 min, with a dose of 25 mCi of ^{99m}Tc-sestamibi flushed with 10 cc of NaCl 0.9% solution.

Technetium-99m-Sestamibi Data Acquisition

Myocardial planar imaging was performed 1 and 3 hr after ^{99m}Tc-sestamibi stress injection with a small field of view scintillation camera using a low-energy, high-resolution parallel-hole collimator. The camera was interfaced to a medical data system (MDS) computer. The first image acquired was the best septal view (usually the 45° left anterior oblique view) followed by the anterior and left lateral view right decubitus. Ten-minute images were acquired for each view with the photopeak set at 140 keV with a 15% energy window. Digital images were recorded using 128 × 128 matrix. The same acquisition parameters were used for delayed (3-hr) imaging. Special care was taken to obtain exactly the same views and angles acquired for the 1-hr images. Imaging at rest was performed 90 min following ^{99m}Tc-sestamibi injection. The same gamma camera and acquisition parameters were used for the rest study. Again, the same views as the stress study were obtained.

Data Analysis

Qualitative Analysis. All myocardial ^{99m}Tc-sestamibi studies were analyzed by three experienced observers without prior knowledge of the patient's history, stress electrocardiogram, ^{201}Tl scan result or coronary anatomy. Disagreements in interpretation were resolved by consensus. Sets of rest-stress (1-hr) and rest-stress (3-hr) ^{99m}Tc-sestamibi images were interpreted separately. For the initial reading, observers did not know which images were performed at 1 or 3 hr following stress ^{99m}Tc-sestamibi injection. On the second reading, both stress studies (1 and 3 hr) were placed side by side for comparative analysis. The left ventricle was divided into three segments in each image. Segments were characterized as normal, ischemic or scar based on a normal myocardial distribution, transient defect or fixed defect, respectively. The observers also attempted to compare subjectively the diagnostic information of the 1-hr and the 3-hr stress images. This comparison takes into consideration only the subjective evaluation of normal-to-abnormal myocardial wall ratios and the diagnostic certainty of the images. The three sets of images (stress 1-hr, stress 3-hr, and rest study) were normalized to the maximal myocardial activity.

Quantitative Analysis. After visual analysis of ^{99m}Tc-sestamibi images and correlation with ^{201}Tl scan and/or coronary angiography results, ischemic/normal wall ratios were determined from the best view showing the ischemic defect. Regions of interest on normal and ischemic myocardial segments were drawn on the computer screen. The same regions (location and surface) and the same walls were chosen for each of the three studies (rest, stress 1-hr and stress 3-hr) in a given patient. A region of interest for the background was chosen over the left lung. Fixed myocardial defects were not included for analysis.

Segmental myocardial time-activity curves were obtained for both ischemic and normal walls and corrected for ^{99m}Tc physical decay. Myocardial washout between 1 and 3 hr was determined from these curves for both normal and abnormal walls.

Statistical Analysis

All data are presented as the mean ± 1 s.d. The Student's t-test for paired measures was used to assess differences between data.

RESULTS

Patient Population

Out of the 25 patients, 15 had a previous ^{201}Tl study with at least one ischemic segment and 18 had a coronary angiogram with significant coronary artery disease defined as a ≥70% reduction in the luminal diameter of one or more major coronary arteries. Eight patients had both ^{201}Tl testing and a coronary angiogram. The mean time interval between ^{99m}Tc-sestamibi scintigraphy and coronary angiogram was 12 days (with a range of 1–32 days) and the mean time interval between the ^{99m}Tc-sestamibi imaging and ^{201}Tl study was 14 days (with a range of 1–34 days). The mean time between both rest and stress ^{99m}Tc-sestamibi injection was 2.2 ± 1.6 days (with a range of 1–6 days).

The hemodynamic parameters during the treadmill stress test with ^{99m}Tc-sestamibi injection were the following: maximal heart rate: 130 ± 22 bpm, maximal systolic blood pressure: 162 ± 28 mmHg, double product: 21,000 ± 6,100. Patients reached 79% ± 11% of the maximal predicted heart rate. Eight patients had a previous myocardial infarction. On coronary angiogram, 5 patients had single-vessel disease, 11 had double-vessel disease and 2 had triple-vessel disease.

The stress ^{99m}Tc-sestamibi images were obtained at 66 ± 10 min (initial imaging) and at 192 ± 12 min (delayed imaging) following the injection performed 60 sec before the end of exercise. Imaging was done at 90 ± 20 min after the ^{99m}Tc-sestamibi rest injection.

Qualitative Analysis

Two qualitative readings were performed by the three observers. The first blinded reading involved the segmental comparison between initial and delayed post-exercise images. The 1-hr postexercise imaging showed 48 ischemic, 12 scar and 165 normal segments, while the 3-hr post-exercise images detected 46 ischemic, 12 scar and 167 normal segments. There was no significant statistical difference between these values. Following the initial reading,

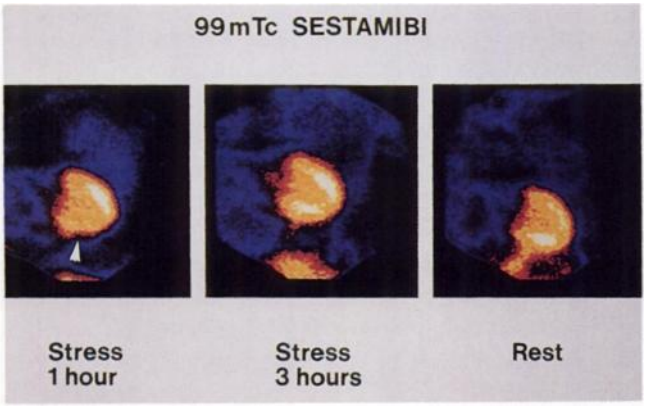

FIGURE 1. Three planar anterior views (stress 1-hr, stress 3-hr and at rest) obtained in a pateint with a 95% stenosis of the right coronary artery. Images were normalized to the maximal myocardial activity. One hour after the injection of ^{99m}Tc-sestamibi at stress, there is a defect involving the inferior wall (arrow). Two hr later (stress 3-hr image) there is a redistribution of ^{99m}Tc-sestamibi, the myocardial defect being almost completely corrected. The rest study shows a normal inferior wall radionuclide uptake.

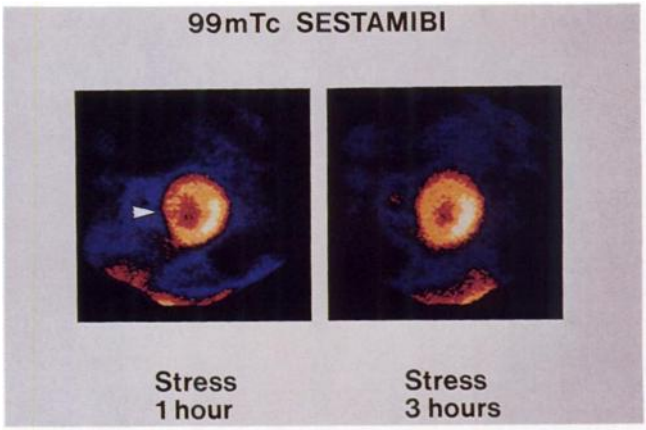

FIGURE 3. These two 45° left anterior oblique images were obtained in a patient with a 95% stenosis of the left anterior descending artery. The septal wall defect (arrow) clearly seen at 1 hr after ^{99m}Tc-sestamibi injection at stress shows a mild partial correction at 3 hr.

the 1 and 3-hr postexercise and rest images were placed side by side for subjective comparison on the diagnostic quality of the images. This comparison showed that the 1-hr postexercise images were superior to the 3-hr images in 15 patients, while they were judged to be similar in 10 patients (Figs. 1–3). In no cases were the 3-hr postexercise images judged to be better than the images obtained at 1 hr after the injection at stress.

Quantitative Analysis

Figure 4 shows the ischemic/normal wall ratios obtained for the same myocardial regions of interest at 1 and 3 hr after stress ^{99m}Tc-sestamibi injection and at 90 min after injection at rest. Fixed defects were excluded from this analysis. The mean ratio at 1 hr and at 3 hr after stress injection was 0.73 ± 0.10 and 0.83 ± 0.12, respectively. This difference was statistically significant ($p < 0.05$). These two postexercise ischemic/normal wall ratios were also statistically different from the ischemic/normal wall ratio at rest which was 0.98 ± 0.15 ($p < 0.05$). The rate of clearance of ^{99m}Tc-sestamibi between the 1-hr and the 3-hr stress images was determined for both normal and ischemic myocardial walls. The net clearance was 26% ± 12% for myocardial walls with normal perfusion and 15% ± 8% for ischemic walls ($p < 0.001$).

DISCUSSION

For many years, the relatively rapid myocardial redistribution of ^{201}Tl has been considered to be an advantage since difference between ischemia and scar may be

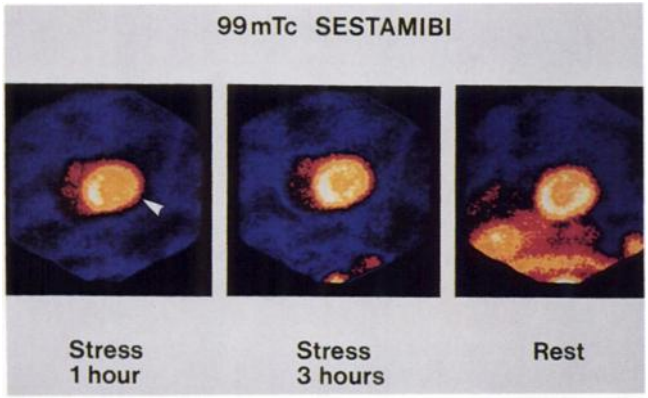

FIGURE 2. Patient with a 90% stenosis of the left circumflex artery. On the 45° left anterior oblique view, there is a significant perfusion defect of the lateral wall (arrow) 1 hr after the injection of ^{99m}Tc-sestamibi at stress. This defect is partially corrected 2 hr later (stress 3 hr). Normal myocardial uptake of ^{99m}Tc-sestamibi at rest.

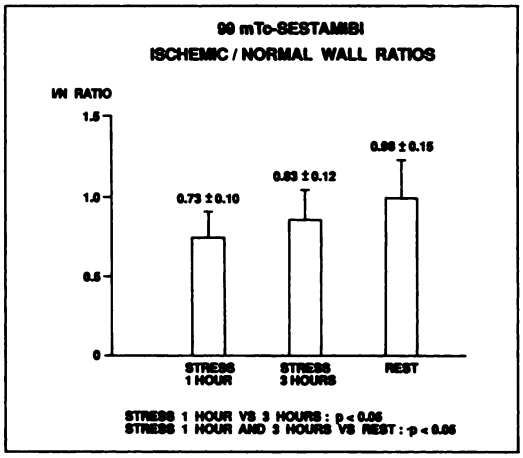

FIGURE 4. Ischemic/normal wall ratios obtained for the same myocardial regions of interest at 1 and 3 hr after injection of ^{99m}Tc-sestamibi at stress and at 90 min after injection at rest.

achieved with a single injection of the radionuclide. However, recent data showed that reinjection at rest or 24-hr delayed imaging is necessary in a significant number of patients in order to obtain better results in myocardial viability assessment (*32–35*). Although ^{201}Tl and ^{99m}Tc-sestamibi have a myocardial distribution which is proportional to coronary blood flow, all other biologic and physical characteristics are different. One of the most important differences in the pharmacokinetics of the two radiopharmaceuticals is the lack of significant or rapid myocardial redistribution of ^{99m}Tc-sestamibi following its intravenous injection at stress. This characteristic offers interesting advantages. Timing of imaging after the injection is not as critical as with ^{201}Tl. This property is particularly well suited for radionuclide imaging in the evaluation of acute conditions such as thrombolysis for acute myocardial infarction or unstable angina. Following ^{99m}Tc-sestamibi administration and usual medical therapy, imaging is performed when the patient's condition is stabilized. Furthermore, the absence of significant change in the myocardial activity during acquisition is preferable for optimal SPECT imaging.

According to data obtained in a Phase II clinical trial with ^{99m}Tc-sestamibi (*18*), the best compromise between a high myocardial count rate and low background activity (decreased liver and lung uptake) is achieved between 1 and 2 hr following the injection of ^{99m}Tc-sestamibi at stress. Most of the clinical studies using this new radiopharmaceutical have reported a time interval with a range from 1 to 3 hr between injection and imaging, although some others have used an interval up to 6 hr (*28–30*). This has been particularly reported in the evaluation of thrombolysis or unstable angina where stabilization of the patient's condition is a critical factor.

The results of our study showed that although there was no significant statistical difference in the diagnostic accuracy between the 1- and 3-hr post-stress images, the ischemic/normal wall ratios were statistically higher at 3 hr (0.84) than at 1 hr (0.73). This may affect the diagnostic certainty and possibly the sensitivity of coronary artery disease detection in cases where the ischemic defect is slight or mild. This partial correction of the ischemic/normal wall ratio over time is related to a differential myocardial net clearance, the normally perfused walls showing a significantly faster clearance (26%) than the ischemic myocardial walls (15%) at 3 hr after the injection at stress. Although the time-activity myocardial curves obtained in this study represented a global myocardial washout over time, it was impossible to determine the presence or the relative role of a washin compartment. The net clearance is thus probably more appropriate than the term myocardial washout in this condition. In an animal model of myocardial ischemia, Okada et al. (*24*) reported a similar rate of ^{99m}Tc-sestamibi washout from both normal and ischemic areas. The ischemic/normal wall activity ratio was the same over a 4-hr period. Our results differ from that study probably because a permanent occlusion model has been used instead of a transient ischemia as seen in our patient population.

Franceschi et al. (*31*), reported similar findings in a group of nine patients studied with SPECT imaging at 20 min, 1, 2, 4 and 6 hr after injection of 25–30 mCi of ^{99m}Tc-sestamibi at stress. They have found significant differences between the clearance rates from normal and ischemic myocardium. The ^{99m}Tc-sestamibi washout from normal myocardium was 27% ± 8% at 6 hr after injection and 16% for ischemic myocardial defects. The ischemic/normal wall ratio increased with time for both mild and severe defects: 0.70 at 20 min, 0.80 at 4 hr and 0.84 at 6 hr. Reperfusion was more obvious at 4–6 hr. Their data, however, did not indicate if the sensitivity of coronary artery disease detection was decreased by late imaging. Their data were acquired on slices of the heart obtained with SPECT imaging, which provides better contrast resolution. Our study was performed with planar imaging. Because of the inherent limitations related to planar acquisition ("shine-through" and "overlapping" activity secondary to hyperemic response surrounding the ischemic defect), the effects of redistribution can possibly be more obvious than with SPECT imaging.

Based on the above-mentioned results, ^{99m}Tc-sestamibi imaging should be performed no later than 1–1.5 hr following the injection at stress in order to avoid the effect of myocardial redistribution on the diagnosis of coronary artery disease. This limitation does not represent a significant drawback in clinical practice for stress test imaging. However, the impact of ^{99m}Tc-sestamibi myocardial redistribution should be evaluated when this agent is used in the risk assessment and effect of thrombolytic therapy in patients with acute myocardial infarction. Some studies have reported a time interval of up to 6 hr between ^{99m}Tc-sestamibi injection and imaging in this acute condition, mainly for practical (injection performed during the night) and medical (patient's stabilization) considerations. Theoretically, in the presence of myocardial redistribution, such delay may cause an underestimation of the myocardium at risk (initial defect).

This study has used a time interval of 1 hr between ^{99m}Tc-sestamibi injection at stress and imaging as the reference. Although most of the clinical studies have reported a time interval varying from 1 to 2 hr (which offers the best compromise between good count rate and low background activity), it should be useful to evaluate the diagnostic impact and compare images performed at 15–30 min to images obtained later after the injection.

In conclusion, although only a few ischemic segments were missed at 3 hr, significantly lower ischemic/normal wall ratios were found at 1 hr. Faster myocardial washout from normal walls is responsible for the partial correction of this ratio. It is thus preferable to image earlier after ^{99m}Tc-sestamibi injection at stress in order to improve detection of coronary artery disease.

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