Myocardial Viability in Patients With Chronic Coronary Artery Disease

Comparison of $^{99m}$Tc-Sestamibi With Thallium Reinjection and $[^{18}F]$Fluorodeoxyglucose

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**Background** $^{99m}$Tc-sestamibi and thallium imaging have similar accuracy when used for diagnostic purposes, but whether sestamibi provides accurate information regarding myocardial viability in patients with chronic coronary artery disease has not been established. Since there is minimal redistribution of sestamibi over time, it may overestimate nonviable myocardium in patients with left ventricular dysfunction, in whom blood flow may be reduced at rest.

**Methods and Results** We studied 54 patients with chronic coronary artery disease with a mean ejection fraction of 34±14%. Patients underwent stress/redistribution/reinjection thallium tomography and, within a mean of 5 days, same-day rest/stress sestamibi imaging using the same exercise protocol and with patients achieving the same exercise duration. Of the 111 reversible thallium defects on either the redistribution or reinjection study, 40 (36%) were determined to be irreversible on the rest/stress sestamibi study, whereas only 3 of 63 irreversible thallium defects despite reinjection (5%) were classified to be reversible by sestamibi imaging. The concordance regarding reversibility of myocardial defects between thallium stress/redistribution/reinjection and same day rest/stress sestamibi studies was 75%. A subgroup of 25 patients also underwent positron emission tomography (PET) studies with $^{18}$O-labeled water and $[^{18}F]$fluorodeoxyglucose (FDG) at rest after an oral glucose load. As in the overall group of 54 patients, there was concordance between thallium and sestamibi imaging regarding defect reversibility in 51 of 73 regions (70%). In the remaining 22 discordant regions (30%), 18 (82%) appeared irreversible by sestamibi imaging but were reversible by thallium imaging. Myocardial viability was confirmed in 17 of 18 regions, as evidenced by normal FDG uptake (10 regions) or FDG/blood flow mismatch (7 regions) on PET. These regions were present in 16 of the 25 patients studied (64%). We then explored methods to improve the sestamibi results. First, when the 18 discordant regions with irreversible sestamibi defects were further analyzed according to the severity of defects, 14 (78%) demonstrated only mild-to-moderate reduction in sestamibi activity (51% to 85% of normal activity), suggestive of predominantly viable myocardium, and the overall concordance between thallium and sestamibi studies increased to 93%. Second, when an additional 4-hour redistribution image was acquired in 18 patients after the injection of sestamibi at rest, 6 of 16 discordant irreversible regions (38%) on the rest/stress sestamibi study became reversible, thereby increasing the concordance between thallium and sestamibi studies to 82%.

**Conclusions** These data indicate that same-day rest/stress sestamibi imaging will incorrectly identify 36% of myocardial regions as being irreversibly impaired and nonviable compared with both thallium redistribution/reinjection and PET. However, the identification of reversible and viable myocardium can be greatly enhanced with sestamibi if an additional redistribution image is acquired after the rest sestamibi injection or if the severity of reduction in sestamibi activity within irreversible defects is considered. (Circulation. 1994;89:578-587.)

**Key Words** scintigraphy • tomography • coronary disease • myocardium • ischemia

The substance $^{99m}$Tc-sestamibi is a lipid-soluble, cationic perfusion tracer that is taken up in the myocardium in proportion to blood flow in a manner parallel to that observed with microspheres and thallium, although with a somewhat lower myocardial extraction fraction than thallium. Unlike thallium, sestamibi uptake is not dependent on active transport, and there is minimal myocardial redistribution of sestamibi over time. Therefore, the only information thought to be related purely to the level of myocardial blood flow, not to washout kinetics. Animal studies with sestamibi have demonstrated that the uptake and retention of sestamibi require intact cell membrane and mitochondrial processes. However, whether the uptake of sestamibi can be used as a clinical marker of myocardial viability has not been established.

From a theoretical standpoint, the minimal redistribution of sestamibi might result in underestimation of ischemic but viable myocardium, especially in patients with reduced regional perfusion at rest, in whom initial tracer delivery will be reduced. However, the performance of sestamibi compared with thallium for identifying viable myocardium has not been fully explored, especially in relation to clinical gold standards of myocardial viability, such as preserved glucose metabolism assessed by positron emission tomography (PET). In the present study, we determined whether alterations in

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membrane function (measured by serial thallium imaging) or the level of myocardial glucose metabolism (measured by PET) are better discriminators of viable myocardium than abnormalities in relative myocardial flow reserve (measured by sestamibi). In addition, we determined whether redistribution of sestamibi after injection at rest can be detected clinically in patients with chronic ischemic coronary artery disease and whether this provides additional insight into myocardial viability beyond that obtained by rest/stress sestamibi imaging.

Methods

Patient Selection

This was a prospective study involving 54 patients with chronic coronary artery disease who were referred for exercise thallium scintigraphy. Patients were eligible for this study if they demonstrated at least one irreversible perfusion defect on standard stress/redistribution thallium imaging. The patients ranged in age from 36 to 79 years (mean, 63 years); there were 49 men and 5 women. All patients underwent a history and physical examination, chest radiograph, ECG, thallium and 99mTc-sestamibi single photon emission computed tomography (SPECT) imaging, and coronary arteriography. Thirty-three patients also underwent PET imaging to assess regional myocardial glucose utilization. Coronary artery disease was defined as a 50% reduction in luminal diameter of at least one major epicardial coronary artery as determined by coronary angiography. ECG Q waves were assigned to one of four myocardial regions as follows: leads II, III, and aVF representing the inferior region, V1 and V2 representing the septal region, V3 through V5 representing the anterior region, and I, aVL, V4, and V5 representing the lateral region. All cardiac medications were withdrawn before exercise studies in 31 of 54 patients (57%). In the remaining 43% of the patients, the severity of anginal symptoms precluded discontinuation of medical therapy. We studied only patients with chronic stable coronary artery disease; no patient with recent acute myocardial infarction or unstable angina was included in the study.

Thallium SPECT Imaging

All patients underwent exercise thallium SPECT as previously described. After an overnight fast, patients were exercised on a treadmill, and 2 mCi thallium was injected at peak exercise. SPECT thallium images were obtained with a wide-field-of-view rotating gamma camera equipped with a low-energy, medium-resolution, high-sensitivity, parallel-hole collimator (Apex 415, APC-3, Elscint Co, Boston, Mass) centered on the 68-keV photo peak with a 20% window. The camera was rotated over a 180° arc in an elliptical orbit about the patient's thorax at 6° increments for 30 seconds each. Redistribution images were acquired 3 to 4 hours after exercise. Immediately after redistribution, a 1-mCi additional thallium dose was administered at rest, and reinjection images were acquired 10 to 15 minutes thereafter.

99mTc Sestamibi Imaging

Within a mean of 5 days after the stress/redistribution thallium study, patients demonstrating persistent thallium defects after conventional redistribution images were asked to return for a same-day rest/stress sestamibi study using 10 mCi of sestamibi at rest and 30 mCi at peak exercise. SPECT sestamibi data were acquired 45 to 60 minutes after the dose administered at rest and 60 minutes after the stress dose. In the first 29 patients, all technical factors for acquiring the data, such as the camera, camera angle and window settings, collimator distance from the chest wall, as well as the collimator itself, were kept identical for both the thallium and sestamibi studies. However, when the data in the first 29 patients appeared to be clearly in favor of thallium for identifying reversible defects, the next 25 sestamibi patient studies were acquired with a high-resolution collimator (while the other parameters were maintained the same) to optimize the resolution of the sestamibi images with depth. An additional 4-hour redistribution study after injection of sestamibi at rest was acquired in 18 of the last 25 patients before the stress study was performed. The reconstructed short- and long-axis images of both thallium and sestamibi were read blindly, with each segment graded as either normal, reversible, or irreversible. Short-axis tomograms from the three sets of thallium images (stress, redistribution, reinjection) and three sets of sestamibi images (rest, redistribution, stress) were also analyzed objectively, by use of a semiautomatic quantitative circumferential profile, as previously described.

Qualitative SPECT Analysis

The distribution of thallium and sestamibi uptake was analyzed qualitatively in the three standard orthogonal tomographic imaging planes as follows: the septal, apical, and lateral regions in the horizontal long-axis view; the anterior, apical, and inferior regions in the vertical long-axis view; and the anterior, septal, inferior, and lateral regions in the short-axis view. Thallium stress, redistribution, and reinjection images and sestamibi rest, redistribution, and stress images were all normalized to the region with the maximal myocardial activity on the corresponding stress images. Four consecutive representative slices of each view were displayed simultaneously for interpretation. The images were graded by two experienced, blinded observers on a five-point scale from 0, markedly reduced/absent activity, to 2, definitely reduced, and 4, normal. Differences were resolved by consensus. The grade assigned to a given region was the lowest regional score from all tomographic slices and views. A region was determined to be irreversible if the assigned regional grade was abnormal and remained the same abnormal grade on subsequent images. Similarly, a region was determined to be reversible if the assigned abnormal regional grade increased or normalized on subsequent images. In regions in which both reversible and irreversible defects were observed in the same vascular territory, the region was assigned to be partially reversible. Since the presence of any reversibility implies myocardial ischemia and viability, partially reversible defects were therefore considered to be irreversible defects in this analysis. A thallium defect that reversed on 3- to 4-hour redistribution images was considered to represent ischemic and viable myocardium, independent of the changes in relative thallium activity that occurred after reinjection. Consequently, the determination of whether a myocardial region was viable required that an abnormal region identified on exercise images be reversible on either the 3- to 4-hour redistribution or the reinjection study.

Quantitative SPECT Analysis

For each patient, an operator-defined region of interest was drawn around the left ventricular activity of each of four consecutive, 10.3-mm-thick, short-axis slices on the thallium stress images and the corresponding thallium redistribution and reinjection tomograms and the sestamibi rest, redistribution, and stress tomograms. The myocardial activity was subdivided into eight sectors, each emanating from the center of the tomograms. All eight sectors were of equal arc and were constructed beginning at the 3 o'clock position (mid lateral wall) and proceeding counterclockwise. The sectors were then grouped into four myocardial regions: anterior, septal, inferior, and lateral. The apical myocardial activity was determined from the first, most apical tomogram. Assessment of regional thallium activity on the stress images was carried out with reference to mean thallium activity determined for groups of normal male and female subjects. Similarly, regional sestamibi activity on the stress images was assessed with reference to mean sestamibi activity determined for groups of normal male and female subjects.
normal male and female subjects. The myocardial region with the maximum mean counts per pixel on the thallium stress and sestamibi stress studies was normalized to the value for the corresponding region for normal subjects of the same sex, and this was used as a normal reference region for that patient. The same corresponding regions in the redistribution and reinjection thallium studies and rest and redistribution sestamibi studies were identified and used as the reference regions for those studies. The activity of thallium or sestamibi in all other myocardial regions was then expressed as a percent of the activity measured in that reference region for each of the thallium stress, redistribution, and reinjection and sestamibi rest, redistribution, and stress sestamibi image series. A myocardial region was considered abnormal in a patient with coronary artery disease if the thallium or sestamibi uptake on the stress image was greater than 2 SD below the mean observed in the same region for normal volunteers of the same sex. On the basis of previous reproducibility measurements in our laboratory, a region with reduced activity on the stress study was considered reversibly ischemic if the increase of normalized thallium or sestamibi activity exceeded 10% on the subsequent images for that region. Alternatively, a region with reduced activity on the stress study was considered irreversibly abnormal if the normalized thallium or sestamibi activity did not increase more than 10% on subsequent images for that region. These irreversible defects were then subcategorized on the basis of severity of reduction in tracer activity:1,14 mild to moderate (51% to 85% of peak activity) and severe (≤50% of peak) defects. Since there are no data in the literature that compare the severity of sestamibi defect to established markers of myocardial viability in patients with chronic ischemic left ventricular dysfunction, we arbitrarily chose to apply the same criteria of mild to moderate and severe reduction in tracer activity to the sestamibi studies.

**Positron Emission Tomography**

Thirty-three patients underwent PET studies within a mean of 10 days from the SPECT studies, of whom 25 had technically adequate $^{15}$O-labeled water ($[^{15}$O]H2O) and FDG data to assess regional myocardial perfusion and exogenous glucose utilization. Imaging was performed with a whole-body PET camera producing 21 contiguous tomograms spaced 5.1 mm apart with a slice thickness of 13 mm and an in-plane resolution of 6.5 mm. Images were obtained perpendicular to the long axis of the body to create a series of transaxial tomograms. All patients were pretreated with 50 g oral glucose 1 hour before the study after an overnight fast. After a 20-minute transmission scan to correct for attenuation, two separate bolus injections of 12 to 15 mCi of $[^{15}$O]H2O were administered intravenously 12 minutes apart. Like most PET scanners, our scanner is unable to accurately handle the bolus phase of an injection of more than 15 to 20 mCi when the heart is in the field of view. Each study was analyzed separately, and the flow values were averaged together. This resulted in average flow values with SDs comparable to those that would have been obtained from a single 30- to 40-mCi injection. The two separate bolus injections of $[^{15}$O]H2O were followed by the administration of 5 mCi of FDG 15 minutes later. Dynamic PET data were acquired continuously for 5 minutes after each $[^{15}$O]H2O injection and for 60 to 75 minutes after the FDG injection. The data acquired at 30 minutes after FDG injection, corresponding to the final 30 to 45 minutes of data acquisition, were reconstructed to create tomographic images of regional myocardial FDG uptake.

**Regional FDG Uptake**. To compare relative regional myocardial FDG uptake with thallium and sestamibi activities objectively, the acquired transaxial FDG images for each patient were reconstructed in the short-axis view with the same slice thickness as was used for the thallium studies (10.3 mm). For each patient, short-axis tomograms from the three sets of thallium images (stress, redistribution, reinjection) and the corresponding three sets of sestamibi images (rest, redistribution, stress) were visually aligned with the FDG tomograms for direct comparison. Myocardial regions of interest representing the apical, anterior, lateral, septal, and inferior myocardium were assessed by circumferential profile analysis on each of the thallium, sestamibi, and FDG short-axis tomograms. Thallium, sestamibi and FDG activities were then computed within each region. In each patient, the myocardial region with the maximum counts on the exercise study was used as the normal reference region for that patient. The myocardial region on the FDG series that corresponded to the normal reference region on the thallium stress image series was used as the normal reference region for relative FDG uptake. FDG uptake in all other myocardial regions was expressed as a percent of the activity in this reference region.

**Regional Myocardial Blood Flow**. Absolute regional myocardial blood flow was computed from the dynamic $[^{15}$O]H2O data, as previously described.4 The FDG image series was reviewed for each patient to identify the appropriate tomographic levels in which the left ventricular cavity was well defined. An average of four such tomographic levels were identified per patient. Left ventricular cavity regions of interest were manually constructed on these FDG tomograms and were then applied directly to the corresponding tomographic $[^{15}$O]H2O data to derive a composite ventricular blood pool time-activity curve for the tracer. This time-activity curve was then used as the $[^{15}$O]H2O arterial input function. Previous studies have demonstrated that the blood pool time-activity curve computed in this manner accurately represents instantaneous arterial concentrations of $[^{15}$O]H2O.15,16 By use of the $[^{15}$O]H2O arterial input function, the myocardial $[^{15}$O]H2O time-activity curve, and an assumed partition coefficient for $[^{15}$O]H2O of 0.92, absolute regional myocardial blood flow was computed by a modification of the methods of lida et al17 and Herrero et al18 that automatically accounts for partial volume and spill-over effects. This water model also provides a partial volume correction factor that could in theory be used to provide partial volume correction for FDG. However, this correction factor also introduces additional statistical fluctuations in the FDG values. In addition, correction of the FDG data for partial volume effects would create difficulties in the comparison of the FDG data to the thallium and sestamibi data, which are also subject to partial volume effects. Thus, we elected not to correct the FDG data for partial volume. To the best of our knowledge, all previous viability studies using FDG have also not performed this correction.

**Regional FDG Uptake Relative to Blood Flow**. Regional FDG uptake was then interrelated to relative regional myocardial blood flow assessed by $[^{15}$O]H2O. Three groups of myocardial regions were identified: (1) normal (normal blood flow associated with normal FDG uptake), (2) mismatch (reduced myocardial blood flow with FDG:blood flow ratio ≥110% of that of the normal reference region), and (3) match (reduced FDG uptake and FDG:blood flow ratio <110% of that of the reference region). As previously described,19 a region could be defined as showing mismatch if FDG activity was normal, increased, or less than 10% as FDG activity was disproportionately increased relative to the reduced regional blood flow. The cutoff for the FDG:blood flow ratio of 110% was derived from previously published data obtained in normal volunteers in whom FDG:blood flow ratio values ranged from 1.02 to 1.12 mg/g per minute,20 which is similar to the 1.20 cutoff value used by Vanoverschelde et al.21 Although the ≥110% cutoff value has not been correlated with measures of functional recovery, we have previously shown, using the ≥110% cutoff value to define mismatch, that myocardial regions with FDG:blood flow mismatch have regional systolic wall thickening by gated magnetic resonance imaging that is similar to that of regions with normal FDG uptake and that is significantly greater than regions with FDG:blood flow match. This offers further support to the reliability of this objective
method to calculate FDG: blood flow mismatch for identifying viable myocardium.

**Radionuclide Angiography**

Gated blood pool cardiac scintigraphy was performed to assess left ventricular ejection fraction at rest, using red blood cells labeled in vivo with 20 to 25 mCi of $^{99m}$Tc-pertechnetate. Imaging was done within a mean of 13 days from the SPECT studies with a conventional Anger camera equipped with a high-sensitivity parallel-hole collimator, as previously described. The left ventricular ejection fraction was derived by computer analysis of the scintigraphic data, and regional wall motion was assessed qualitatively by two experienced observers from the images displayed in cineangiographic format. The lower limit of normal for resting ejection fraction by our technique is 45%.

**Coronary Arteriography**

Cardiac catheterization was performed with the percutaneous femoral technique. Coronary artery stenosis and graft patency were assessed by experienced cardiologists without knowledge of exercise thallium or sestamibi results. Twelve patients had marked narrowing of one vessel, 14 of two vessels, and 28 of three vessels. In patients with bypass grafts, a vessel was considered patent if there was no significant narrowing within the graft or in the native coronary artery distal to the graft anastomosis.

**Statistical Analysis**

Data are presented as mean±SD. Group comparisons between thallium stress/redistribution/reinjection and sestamibi rest/stress images and differences between thallium and sestamibi studies with respect to exercise duration, anginal symptoms, and ischemic ECG changes were performed by either $\chi^2$ analysis or paired t test. Differences between the entire group and the subgroup of patients who underwent PET studies with respect to exercise duration, rate-pressure product, symptoms of angina, left ventricular function, and wall motion abnormalities were analyzed by either two-tailed unpaired t test or $\chi^2$ analysis.

**Results**

**Characterization of Patients**

Among the 54 patients studied, there was no significant difference between the thallium and sestamibi studies with respect to exercise duration on treadmill testing (5.3±2.6 versus 5.6±2.5 minutes, $P=NS$), the percent of patients with anginal symptoms, or ischemic ECG changes. Furthermore, when the characteristics of the 25 patients who underwent PET studies were compared with the entire group of 54 patients, exercise duration on treadmill testing (5.6±2.5 versus 5.5±2.4 minutes, $P=NS$), rate-pressure product achieved during exercise (22±6×10$^3$ versus 21±6×10$^3$, $P=NS$), and the percent of patients with anginal symptoms were the same in both groups. There were also no differences between the two groups with respect to the left ventricular ejection fraction or wall motion abnormality at rest. Left ventricular ejection fraction in the 54 patients ranged from 8% to 66% (mean, 34±14%) and was below the normal range in 42 patients. In the subgroup of 25 patients who underwent PET studies, left ventricular ejection fraction ranged from 8% to 64% (mean, 30±12%) and was below the normal range in 23 patients.

When patients who were studied on cardiac medications were compared with those who were off medical therapy, as anticipated, there were differences in exercise duration (4.3±1.2 versus 6.2±2.8 minutes, $P<.002$) and rate-pressure product (19±6×10$^3$ versus 24±5×10$^3$, $P=.001$) between the two groups. However, the number of perfusion defects on stress images was the same in both groups (3±1 versus 3±1, $P=NS$).

**Qualitative Analysis of Thallium and Sestamibi Images**

During thallium stress testing, perfusion defects developed in 174 myocardial regions, of which 111 were reversible and 63 (36%) were irreversible on redistribution/reinjection images. Of the 111 reversible thallium defects, 40 (36%) were determined to be irreversible on the rest/stress sestamibi study. In contrast, only 3 of 63 irreversible thallium defects (5%) were classified as be reversible by sestamibi imaging (Fig 1). Hence, when regions were classified as reversible or irreversible, same-day rest/stress sestamibi and stress/redistribution/reinjection imaging provided concordant information regarding defect reversibility and myocardial viability in 131 regions (75%), with 71 (54%) identified as reversible and 60 (46%) identified as irreversible. However, sestamibi misidentified ischemic myocardium as nonviable in 40 of 174 abnormal regions (23%), representing 23 of the 54 patients (43%), compared with thallium.

When data from the patients in whom a high-resolution collimator was used for acquiring sestamibi images were compared with data obtained from a high-resolution collimator, the results for defect reversibility in the two patient groups were similar. Among the 29 patients in whom medium-resolution collimation was used, 19 of 57 regions (33%) that were identified to be reversible by thallium imaging were irreversible on rest/stress sestamibi images. Similarly, among the 25 patients studied with a high-resolution collimator, 21 of 54 regions (39%) identified to be reversible by thallium redistribution-reinjection imaging were irreversible by sestamibi imaging.

**Analysis of Perfusion Defects in Regions With ECG Q Waves and Wall Motion Abnormalities**

Of the 54 patients studied, a total of 100 asynergic myocardial regions were identified, of which 42 were in
the apical region and the remaining 58 were either in the anterior, septal, inferior, or lateral regions. Since there is no ECG correlate of the apical region, thallium and sestamibi perfusion defects in relation to presence or absence of ECG Q waves were assessed in the 58 asynergic regions. Twenty-one of the 58 asynergic regions were classified as hypokinetic and 37 as akinetic or dyskinetic.

**Hypokinetic Regions.** Among the 21 hypokinetic regions, 8 had associated Q waves and 13 did not. Of the 8 regions with Q waves, there was concordance of data between thallium and sestamibi regarding myocardial reversibility or irreversibility in 5 regions (63%). In the remaining 3 regions (37%) with discordant results, all 3 were reversible by thallium redistribution/reinjection studies but irreversible on the sestamibi rest/stress studies. Of the 13 non-Q-wave hypokinetic regions, there was concordance of data regarding myocardial reversibility or irreversibility in 12 regions (92%), and the remaining 1 region was reversible by thallium alone. Because hypokinetic regions indicate the presence of viable myocardium, it is in akinetic or dyskinetic regions that viability is a clinical concern. Thus, we directed our attention to the 37 regions that were judged to be akinetic or dyskinetic by radionuclide angiography.

**Akinetic or Dyskinetic Regions.** Among the 37 akinetic/dyskinetic regions, 24 had associated Q waves and 13 did not. Of the 24 regions with Q waves, there was concordance of data between thallium and sestamibi with respect to myocardial reversibility or irreversibility in 19 regions (79%). In the remaining 5 regions (21%) with discordant results, 4 were reversible by thallium and 1 by sestamibi studies. Of the 13 non-Q-wave akinetic/dyskinetic regions, there was concordance of data regarding myocardial reversibility or irreversibility in 10 regions (77%). In the remaining 3 regions (23%) with discordant results, all 3 were reversible by thallium redistribution/reinjection studies but irreversible on the sestamibi rest/stress studies.

**Comparison of Quantitative Thallium and Sestamibi Results With PET**

To investigate the apparent discordance between thallium and sestamibi imaging regarding myocardial viability, and also to verify the concordance of the two imaging protocols, regional blood flow and metabolic FDG data were analyzed in the subset of 25 patients. Among the 25 patients, 73 regions were identified to be abnormal on the stress thallium study. As in the findings obtained in the overall group of 54 patients, when the results of thallium and sestamibi images were compared, there was discordance of data regarding myocardial reversibility or irreversibility in the 22 regions (30%), with 18 regions (82%) identified as reversible by thallium redistribution/reinjection studies but irreversible on the sestamibi rest/stress studies. Myocardial viability was confirmed in 17 of 18 regions, as evidenced by normal FDG uptake (10 regions) or FDG:blood flow mismatch (7 regions) on PET. These regions were present in 16 of the 25 patients studied (64%).

In the remaining 51 regions (70%) with concordant results between the thallium and sestamibi studies, 28 (55%) were identified as reversible and 23 (45%) identified as irreversible (Fig 2). Myocardial viability was confirmed in 26 of 28 regions (93%), as evidenced by normal FDG uptake (12 regions) or FDG:blood flow mismatch (14 regions) on PET. Of the 23 regions that were irreversible both by thallium and sestamibi, only 14 (61%) were confirmed to be nonviable by PET.

The apparent discordance between PET, thallium, and sestamibi imaging resulted when all irreversible defects were grouped together, without considering the severity of the reduction in tracer activity within the defect. We therefore determined whether a quantitative analysis in which the severity of the irreversible thallium and sestamibi defects was accounted for would improve the concordance between the PET, thallium, and sestamibi results.

**Quantitative Analysis of Sestamibi Activity in Irreversible Defects.** Of the 23 regions that were concordantly irreversible by both thallium stress/redistribution/reinjection and sestamibi rest/stress studies, 6 (26%) had mild-to-moderate reduction in sestamibi activity (68±14%) and 17 (74%) had severely reduced sestamibi activity (31±13%). Among the regions with mild-to-moderate irreversible sestamibi defects, thallium activity was also only moderately reduced in 5 regions (63±10%), and PET identified all 5 to be viable. In contrast, among the 17 regions with severe irreversible sestamibi defects, thallium activity was also severely reduced (35±7%), and only 4 of 17 regions (23%) had evidence for viability by PET.

Among the 22 regions in which the thallium and sestamibi studies were discordant (17 of which were viable by both PET and thallium), the majority (17, or 77%) had only mild-to-moderate reduction in sestamibi activity. The relative sestamibi activity within these mild-to-moderate discordant regions was 63±5%, which was similar to that observed in the mild-to-moderate concordant regions (68±14%, P=NS). Thus, the sever-
Thallium-201
Stress
Redistribution-Reinjection
Abnormal
Regions
Normalized or Improved
Irreversible

Tc-99m Sestamibi
Same Day Rest-Stress
Reversible
Irreversible

Rest-Redistribution-Stress
Reversible
Irreversible
Fig 3. Diagram showing enhanced detection of reversible defects by redistribution of sestamibi after injection of the tracer at rest. The prevalence of reversible and irreversible perfusion defects with and without sestamibi redistribution is compared with thallium stress/redistribution/reinjection studies in 18 patients.

ity of sestamibi activity within irreversible defects appears to provide valuable information regarding myocardial viability. When regions with irreversible sestamibi uptake were reclassified as viable if the magnitude of the reduction of sestamibi activity was only mild-to-moderate, sestamibi imaging underestimated viable myocardium in only 4 of 18 regions (22%) compared with thallium reinjection and FDG PET. This increased the overall concordance between thallium and sestamibi studies to 93% (Fig 2).

Rest/Redistribution/Stress Sestamibi Imaging. A subgroup of 18 patients had an additional 4-hour redistribution study acquired after the injection of sestamibi at rest. A total of 55 regions were abnormal on the stress thallium studies in these patients. As with the total group, when thallium stress/redistribution/reinjection and sestamibi rest/stress images were classified as reversible or irreversible, the two imaging methods provided concordant information regarding defect reversibility and myocardial viability in 39 of the 55 regions (71%), with discordance in 16 regions. All 16 discordant regions were identified to be reversible by thallium stress/redistribution/reinjection imaging but irreversible by rest/stress sestamibi imaging. However, this discordance rate was reduced by examining the sestamibi redistribution data. The 4-hour sestamibi redistribution images identified 6 of the 16 defects (38%) that were irreversible on the initial sestamibi rest study to be reversible and viable (Fig 3). Such redistribution was observed in 4 of 18 patients (22%). Two patient examples in whom irreversible sestamibi defects on rest/stress protocol were identified to be reversible on sestamibi redistribution images are shown in Figs 4 and 5. Thus, the inclusion of 4-hour redistribution data after the rest sestamibi injection increased the concordance between thallium and sestamibi in identifying reversibility of defects to 82%.

Discussion
In the past two decades, thallium scintigraphy has played an important role in detecting coronary artery disease and differentiating viable from infarcted myocardium. Since the uptake of thallium by myocardial cells is an active process, thallium scintigraphy has a unique potential for assessing regional blood flow and myocardial viability. Normal thallium uptake during stress and reversible thallium abnormalities on stress/3- to 4-hour redistribution images have been shown to be
accurate indicators of viable myocardium. However, a substantial number of severely ischemic but viable myocardial regions may appear irreversible on standard stress/3- to 4-hour redistribution thallium scintigraphy and thus mimic infarcted myocardium. Recent studies have shown that the identification of viable myocardium in such irreversible thallium defects may be enhanced by the reinjection of thallium at rest. Reinjection identifies viability in up to 50% of defects that appear irreversible at 3 to 4 hours and in 39% of defects that appear irreversible at 24 hours. That myocardial regions identified by thallium reinjection represent viable myocardium is supported by (1) improvement in both regional perfusion and regional wall motion after revascularization,11,13,14,24-34 and (2) preserved metabolic activity by PET.26,29 (3) preserved regional systolic wall thickening by gated nuclear magnetic resonance imaging,33,34 and (4) substantial regional augmentation of thallium (differential uptake >50%) after reinjection at rest.13

Despite the excellent physiological characteristics of thallium for imaging myocardial perfusion and viability, its low energy (68 to 80 keV) is suboptimal for scintillation camera imaging, since the radionuclide is readily scattered and attenuated. Its relatively long half-life (73 hours) limits the dose of thallium that may be administered, which further reduces image resolution. In contrast, the higher emission energy of 140 keV for Tc-99m (resulting in less attenuation) and significantly shorter half-life of 6 hours (permitting the administration of a much higher dose of the tracer) are more optimal for gamma camera imaging. Tc-99m-labeled sestamibi is a lipophilic perfusion tracer whose uptake by the myocardium is distinct from that of thallium. Unlike the transport of thallium, which (like potassium) requires predominantly active transport systems,36,37 the uptake of sestamibi is passive across mitochondrial membranes, but at equilibrium, sestamibi is retained within the mitochondria because of a large negative transmembrane potential.38

Transcapillary transport and myocardial retention of both sestamibi and thallium are affected by the perfusion rate, capillary permeability, and the binding characteristics within the myocardium.8,9 Despite the differences in kinetics between sestamibi and thallium, the initial regional myocardial uptake of the two tracers is similar. This fact is supported by recent published reports from several large trials in humans that have indicated that both agents have similar accuracy for detecting coronary artery disease.39-42 With respect to the assessment of myocardial viability, published reports to date have demonstrated an excellent correlation between rest sestamibi uptake and severity of coronary artery stenosis as well as a good general correlation between sestamibi uptake and viability as assessed by wall motion.5 Among regions with only moderate reduction (50% to 67% of peak activity) in sestamibi activity, 80% had improved sestamibi activity after coronary artery bypass surgery. In contrast, only 39% of regions with severe reduction (<50% of peak) in sestamibi activity showed improvement in regional perfusion postoperatively.5

In stunned but viable myocardium, in which coronary flow has been restored by reperfusion, sestamibi uptake should be an accurate marker of cellular viability, and this has been confirmed in several studies.5,10,43-48 In experimental models of stunned myocardium, the retention of sestamibi has been comparable to that of thallium.10,43 In contrast, in regions of necrotic myocardium, the retention of sestamibi is negligible and parallels indices of viability, such as deoxyglucose uptake and histochemical staining.10 Furthermore, after acute reperfusion in animal models, a close correlation between sestamibi autoradiograph images and pathological infarct size has been demonstrated,44,45 independent of regional blood flow.

In patients studied within the first week after thrombolytic therapy for acute myocardial infarction, sestamibi defect size correlates significantly with regional wall motion at the time of discharge,46 with late ejection fraction measurements,46 and with peak release of creatine kinase.47 These confirmatory clinical studies suggest that sestamibi may be useful as a viability marker in the setting of stunned myocardium after reperfusion therapy for acute myocardial infarction.

The available data regarding the use of sestamibi for identifying hibernating myocardium in patients with
chronic coronary artery disease and left ventricular dysfunction are conflicting.\textsuperscript{5,32,49-51} Using conventional planar imaging and qualitative analysis in a small group of coronary artery disease patients, Cuoco and co-workers\textsuperscript{32} reported that 29\% of reversible myocardial regions by thallium reinjection appeared irreversible when a 2-day stress/rest sestamibi protocol was performed. If the mechanism of the thallium reinjection effect is merely that the reinjected thallium dose provides a better assessment of resting myocardial perfusion than redistribution images, then thallium reinjection results should be equivalent to results obtained when sestamibi is injected at rest. It is likely that the period of thallium redistribution after exercise before the reinjected dose may be the key factor, with the images after reinjection incorporating the metabolic information inherent in the redistribution data. Thus, thallium reinjection images are not merely measures of resting blood flow.\textsuperscript{52} Uptake of thallium and sestamibi, like all other tracers, reflects both regional blood flow and myocardial extraction; these vary depending on the retention process involved for each individual tracer. However, despite the recognized metabolic or transmembrane trapping of these tracers, the relation between myocardial tracer uptake and blood flow is not significantly altered except during acute myocardial ischemia, during conditions of extremely low pH, or during hyperemic flow.

We have previously shown that thallium reinjection data provide a more accurate reflection of myocardial viability (as confirmed by FDG-blood flow mismatch by PET) than images obtained in the same patients immediately after a separate resting injection of thallium 1 week later.\textsuperscript{52} These observations imply that perfusion agents that measure coronary blood flow alone may not provide as complete or as accurate a measure of myocardial viability as an agent that redistributes, such as thallium. Since others have shown that sestamibi tracks with regional myocardial blood flow but does not redistribute appreciably compared with thallium, sestamibi may underestimate viable myocardium in regions with chronic reduction in blood flow. Our data with resting sestamibi images in the present paper support this concept. We identified a large number of myocardial regions that were classified as viable by the thallium stress/redistribution/reinjection protocol but nonviable on the sestamibi rest/stress protocol. Viability of these regions was confirmed by the PET data.

Our data also identify two approaches that may be used to maximize the ability of sestamibi to serve as a marker of viability. These surmount, in part, the limitations of sestamibi in relation to thallium for assessing viable myocardium. The first of these is the observation that sestamibi will redistribute after a resting injection in some patients with left ventricular dysfunction. Previous studies suggest that sestamibi does redistribute in certain situations.\textsuperscript{4,53-55} After injection of sestamibi at peak exercise, minimal but clinically relevant redistribution of the tracer has been reported in ischemic myocardium of patients with coronary artery disease.\textsuperscript{53} Recently, in a model of sustained low-flow ischemia, Sinusas et al.\textsuperscript{54,55} have reported that sestamibi may redistribute over 2.5 hours in a manner comparable to thallium. In the subgroup of our patients undergoing an additional redistribution sestamibi study 4 hours after the tracer is injected at rest, sestamibi redistribution occurred in 38\% of the regions with perfusion defects on the initial rest image that were identified as viable on the thallium and PET studies. Such redistribution was observed in 22\% of patients and increased the overall concordance between thallium and sestamibi imaging regarding defect reversibility to 82\%. Thus, our data indicate that 4-hour redistribution images (acquired after injection of sestamibi at rest) may provide additional insight into myocardial viability in patients with chronic coronary artery disease beyond that obtained by qualitative rest/stress sestamibi imaging. It is also important to note that, despite the acquisition of redistribution images, qualitative sestamibi imaging may still underestimate the presence of viable myocardium in 18\% of viable myocardial regions compared with thallium.

The second approach that may be beneficial to enhance the performance of \textsuperscript{99m}Tc-sestamibi for viability assessment is a quantitative analysis of regional sestamibi activity. Such quantitative methods have been useful in thallium imaging for identifying viable myocardium within apparently irreversible thallium defects.\textsuperscript{13,14,52} Among regions that were considered viable by thallium imaging and PET but possibly nonviable on the basis of an irreversible defect on rest/stress images, 78\% had sestamibi activity that was >50\% of the activity in normal territories. If such mild-to-moderate sestamibi defects are considered to represent viable myocardial tissue on the basis of sestamibi activity alone, and only severe reduction in activity (<50\% of normal) is considered evidence of nonviability, then the overall concordance between thallium and sestamibi studies increased to 93\%.

Limitations of the Study

The application of criteria for grading severity of thallium defects to the sestamibi studies was arbitrary, and it may not have been optimal for sestamibi. It is also important to point out that thallium and sestamibi quantitative data are not truly “quantitative,” for, unlike PET studies, attenuation correction cannot be performed on SPECT studies. Furthermore, since SPECT does not correct for soft-tissue attenuation, there is regional heterogeneity of lower limits of normal for both thallium and sestamibi that ranges from 70\% in the septum to 90\% in the lateral wall. Thus, although it is possible to demonstrate values that fall outside this normal range, i.e., “perfusion defect,” it is not possible to use these normal profiles to quantify severity of defect, since the magnitude of heterogeneity of measured tracer activity in normal subjects varies considerably among subjects. This is a limitation of SPECT imaging that may be overcome by PET. However, despite these limitations, the overall concordance between thallium and sestamibi studies for the presence or absence of viable myocardium by this quantitative approach is largely confirmed by PET.

Conclusions

In summary, \textsuperscript{99m}Tc-sestamibi has inherent limitations in the identification of viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction, in whom hibernating myocardium may remain viable despite chronic reduction in regional
blood flow. Rest/stress sestamibi imaging will incorrectly identify up to 36% of myocardial regions as being irreversibly impaired and nonviable compared with thallium redistribution/reinjection imaging and PET. Thus, if the clinical question to be addressed is one of the presence or absence of exercise-induced ischemia and viability, then thallium imaging and PET appear to be preferred techniques. However, two approaches can be used to improve the identification of reversible and viable myocardium with sestamibi. Despite a washout rate from normal myocardium that is substantially less than that of thallium, sestamibi does exhibit redistribution in some patients, and additional redistribution images acquired after rest sestamibi injection greatly enhance the identification of defect reversibility and viability. Alternatively, a quantitative analysis of regional sestamibi activity after resting injections also enhances the detection of viable myocardium. Thus, either of these approaches or a combination of them may be used to improve the performance of sestamibi for viability assessment.

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