Predicting Recovery of Severe Regional Ventricular Dysfunction

Comparison of Resting Scintigraphy With 201Tl and 99mTc-Sestamibi

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Background Regional 201Tl activity after resting injection, imaged early and after redistribution, reflects viable myocardium and can predict improved isotope uptake as well as regional and global ventricular function after revascularization. 99mTc-sestamibi, a perfusion tracer with favorable imaging characteristics, has distinct kinetics compared with 201Tl, demonstrating minimal redistribution; this property may give 201Tl an advantage for detecting viable myocardium, particularly in segments with resting hypoperfusion. The purpose of this study was to compare regional activities of 201Tl and 99mTc-sestamibi after resting injections in patients with coronary artery disease and regional or global left ventricular dysfunction and to assess their comparative abilities for predicting recovery of severe regional ventricular dysfunction after revascularization.

Methods and Results Qualitative and quantitative comparisons of rest and redistribution 201Tl activity and sestamibi activity 1 hour after rest injection were performed in 31 patients with coronary artery disease and left ventricular dysfunction. Quantitative analysis of three short-axis tomograms per patient was performed by use of circumferential profiles that allowed analysis of 12 segments per patient. Two-dimensional echocardiography was used to assess wall motion and thickening in segments corresponding to the single photon emission computed tomography data. Concordance between regional 201Tl activity at redistribution imaging and regional sestamibi activity by semiquantitative visual analysis demonstrated concordant regional activity in 87% of segments; among discordant segments, no significant skew was seen, indicating enhanced uptake of one agent over the other. Quantitative analysis for all segments showed significant correlation (r=0.86, P<0.001) between quantitative regional 201Tl redistribution activity and 1-hour post–rest injection sestamibi activity in individual segments. Eighteen of these patients were revascularized, and echocardiography was repeated 20±16 days later; segments exhibiting significant regional ventricular dysfunction before revascularization were classified as having reversible or irreversible dysfunction on the basis of the change in wall motion and thickening. 201Tl and sestamibi regional activities were similar in those segments with reversible (72±11% [percent of peak activity] versus 75±9%, respectively, P=NS) as well as irreversible ventricular dysfunction (51±11% versus 50±8%, P=NS). Positive (75% versus 80% for 201Tl and sestamibi, respectively) and negative (92% versus 96%, respectively) predictive values for recovery of regional ventricular dysfunction after revascularization were similar for the two agents.

Conclusions In patients with coronary artery disease and left ventricular dysfunction, quantified sestamibi activity 1 hour after rest injection parallels redistribution 201Tl activity after a resting injection, suggesting that uptake and subsequent handling of sestamibi are more complex than can be explained by a pure flow tracer with no redistribution. Quantitative analysis of regional activities of both 201Tl and sestamibi after resting injections can differentiate viable from nonviable myocardium, and the two agents comparably predict reversibility of significant regional wall motion abnormalities after revascularization in such patients to a similar degree. (Circulation. 1994;89:2552-2561.)

Key Words • thallium • technetium • sestamibi • myocardium

In patients with known severe coronary artery disease and regional or global left ventricular dysfunction, the extent of myocardial viability and potential reversibility of regional ventricular dysfunction is an important factor in the decision to proceed with revascularization. Even among ventricular regions with severe contractile dysfunction, revascularization may result in a return to normal contractile function in myocardium that has not been irreversibly damaged. Many techniques have been used before revascularization in an attempt to accurately identify that subset of dysfunctional myocardium in which contractile function may be improved with revascularization, including invasive studies using postextrasystolic potentiation and intravenous nitroglycerin. More recently, noninvasive approaches using positron emission tomography (PET) and stress-redistribution thallium studies were found to provide such information before revascularization. The ability of 201Tl imaging to detect potential reversibility of severe regional ventricular dysfunction has been enhanced by the use of late redistribution imaging, thallium reinjection techniques, and quantitative analysis of thallium content within irreversible defects. In addition, 201Tl imaging at rest or with redis-
tribution after rest injection has also been found to provide data regarding potential reversibility of regional and global ventricular dysfunction. The technetium-based myocardial perfusion isotope sestamibi has imaging characteristics more favorable than those of $^{201}$Tl. Studies in isolated cardiac cells and in animal models have demonstrated that transmembrane uptake of sestamibi as well as its retention within myocardial cells is dependent on the presence of the transmembrane and mitochondrial membrane electrochemical gradients. This finding suggests that sestamibi activity in a myocardial region represents viable myocardial tissue. However, redistribution of sestamibi over time is markedly less than that of $^{201}$Tl.16,17; thus, isotope delivery into regions with severely compromised resting perfusion may be diminished. In these regions, the redistribution kinetics of $^{201}$Tl may provide an advantage in determining final tracer content and determination of cell membrane integrity. The purpose of this study was to compare quantitative assessment of regional activities of $^{201}$Tl and $^{99m}$Tc-sestamibi in a group of patients in whom the assessment of myocardial viability is of particular clinical importance, those with coronary artery disease and left ventricular dysfunction. In addition, we sought to assess the comparative efficacies of the two isotopes for accurate differentiation of reversible from irreversible severe regional ventricular dysfunction in patients undergoing revascularization.

Methods

Study Population

The study population consisted of 31 patients with coronary artery disease documented by coronary angiography and impaired regional or global left ventricular function in whom a scintigraphic study of myocardial viability was indicated. There were 8 women and 23 men with a mean age of 67±11 years (SD) (range, 38 to 83 years). All 31 patients had a history of prior myocardial infarction. The ECG showed prior infarctions to be anterior in 13 patients, inferior in 14, non–Q wave in 1, and indeterminate (left bundle-branch block) in 3. No patient had enzymatic or ECG evidence of myocardial infarction while enrolled in the study. In 8 patients, the timing of remote infarction could not be determined; in these patients, the history of remote infarction was supported by the presence of pathological Q waves on the ECG in 7 patients, and 1 patient had chronic left bundle-branch block. Among the remaining patients, the timing of prior infarction ranged from 8 days to 22 years before study; the mean interval was 26 months. Two patients were studied scintigraphically 8 days after infarction; both of these patients had severe coronary stenoses and regional ventricular dysfunction in more than one vascular territory, suggesting at least one territory of chronic regional dysfunction. Twenty-six of the patients had angina as part of their symptom complex, with a mean Canadian Cardiovascular Society classification of 2. Sixteen of the patients had symptoms of heart failure; 10 of these had New York Heart Association functional class III and 6, functional class II symptomatology.

Coronary cineangiograms were reviewed, and percent stenosis of coronary lesions was visually assessed by two experienced angiographers blinded to the scintigraphic results. All patients had significant (≥70%) coronary artery disease in an average of 2.4±0.8 vessels per patient; 16 patients (52%) had three-vessel or left main coronary artery disease. On evaluation of left ventricular systolic performance (by left ventriculography, radionuclide ventriculography, or echocardiography), the left ventricular ejection fraction was 35±11%.

Eighteen patients were studied before and then again after a revascularization procedure: 12 patients underwent coronary artery bypass grafting, and 6 patients underwent percutaneous transluminal coronary angioplasty. There were 5 women and 13 men with a mean age of 67±10 years. In this subset of the study population undergoing revascularization, significant coronary artery disease was present in an average of 2.5±0.8 vessels per patient; 10 patients (56%) had three-vessel coronary artery disease. The mean left ventricular ejection fraction for the revascularization group was 34±10%. Referral to revascularization was made by the physicians caring for the patient, based on the clinical, angiographic, and scintigraphic data. The protocol for this study was approved by the Human Investigation Review Committee.

$^{201}$Tl and $^{99m}$Tc-Sestamibi Imaging Protocol

All patients were continued on their current cardiac medications without interruption. After an overnight fast, 2.5 mCi of $^{201}$Tl was injected at rest and flushed with 10 mL saline. Single photon emission computed tomographic (SPECT) image acquisition began 7 to 10 minutes later. Redistribution $^{201}$Tl images were acquired after a 3- to 4-hour delay. After completion of the $^{201}$Tl acquisitions, approximately 8.0 mCi of $^{99m}$Tc-sestamibi was injected at rest and flushed with 10 mL saline. Approximately 10 minutes after injection, patients were given 8 ounces of whole milk to increase hepatic clearance of the isotope. $^{99m}$Tc-sestamibi image acquisition began approximately 1 hour after the resting injection. No change in clinical status or medications occurred during or between acquisition of the three image sets. Scintigraphic studies were performed within 3±4 days of cardiac catheterization; among patients undergoing revascularization, the scintigraphic studies were performed an average of 3±3 days before the procedure. For the subset of patients undergoing revascularization, postrevascularization perfusion imaging was performed according to a 1-day rest-stress sestamibi protocol. These studies were performed an average of 20±16 days after the revascularization procedure.

SPECT Image Acquisition

SPECT imaging was performed on a Siemens Orbiter camera. For each $^{201}$Tl SPECT acquisition, 32 projection images (30 seconds per projection) were obtained in a 180° circular orbit beginning from the 45° right anterior oblique to the 45° left posterior oblique projection. Projection images were obtained with a large-field-of-view scintillation camera equipped with 37 photomultiplier tubes and a sodium iodide crystal 0.375 inch (0.96 cm) thick coupled with a low-energy, high-resolution parallel-hole collimator. For $^{201}$Tl acquisition, a 20% energy window centered on the 68- to 80-keV peak with scatter suppression was used. Images were stored on a 64×64, 16-bit matrix. A Butterworth filter with a 0.4 cutoff and an order of 5.0 was used for processing the raw $^{201}$Tl data. For sestamibi acquisition, 64 projection images (20 seconds per projection) were acquired, and a 20% window centered on the 140-keV peak was used. The raw sestamibi data were processed with a Butterworth filter with a 0.4 cutoff and an order of 3.5.

From the rest and redistribution $^{201}$Tl data and the sestamibi data, short-axis tomograms were constructed from the three-dimensional voxel matrix; sagittal and coronal tomograms were constructed from the filtered short-axis tomograms by coordinate transformation. After image reconstruction, all images were checked and realigned if necessary for appropriate registration of the rest and redistribution $^{201}$Tl and sestamibi tomograms in each plane.

$^{201}$Tl and $^{99m}$Tc-Sestamibi Tomographic Image Analysis

Three contiguous two-pixel-thick midventricular short-axis tomograms representing a more apical, a midcavity, and a
more basal region of the ventricle were analyzed. After confirmation of optimal image registration, the rest and redistribution \(^{201}\text{TI}\) and the sestamibi images were coded and subsequently displayed and analyzed separately by two observers blinded as to patient identity, the type of study (rest \(^{201}\text{TI}\), redistribution \(^{201}\text{TI}\), or rest sestamibi), and findings of the other image sets. Semiquantitative visual analysis was performed by assigning regional tracer activities scores ranging from 0 to 3, with 0 representing severe reduction in activity and a score of 3 representing normal activity.

For quantitative assessment of regional tracer activities, circumferential profile analysis was performed on an operator-defined region of interest around the left ventricular activity of each tomogram. The center of each tomogram was identified, and the region of interest was automatically subdivided into 60 sectors, each subtending an arc of \(6^\circ\). The maximum pixel activity within each sector for the rest and redistribution \(^{201}\text{TI}\) and sestamibi images was standardized to the peak activity, which was assigned a value of 100\%, without correction or normalization relative to a normal database. The 60 sectors were then grouped into four myocardial segments corresponding to the septum and anterior, lateral, and inferior walls; segmental activity was the average of the individual sector activities within that segment, each of which had been normalized to a maximum activity within the same study.

**Analysis of Regional Wall Motion and Thickening**

Two-dimensional echocardiographic analysis of regional wall motion and thickening was performed with a Hewlett-Packard Sonus 1000 equipped with a 2.5-MHz transducer. Parasternal long-axis and short-axis and apical two-chamber, four-chamber, and long-axis views were analyzed by an experienced echocardiographer blinded to the clinical and graphic data and were used to assess regional wall motion and thickening of ventricular segments at the mitral valve, chordal, and mid-papillary muscle levels corresponding to the short-axis nuclear tomographic images. The echocardiographic images were divided into segments representing the septal, anterior, lateral, and inferior walls for comparison with the analogous SPECT segments. Regional wall motion was scored on a semiquantitative scale from 0 to 3, in increments of 1.0, with normal wall motion scored as 3 and dyssynergic wall motion scored as 0.

The subset of patients undergoing coronary artery bypass surgery or percutaneous transluminal coronary angioplasty was studied with two-dimensional echocardiography before and again after revascularization. The postrevascularization study was performed at a mean of 20±16 days after the procedure. Regional myocardial wall motion and thickening in individual segments was classified before revascularization as either preserved or with severe regional ventricular dysfunction: scores of 0 or 1 before revascularization. These latter segments were then subclassified according to the response to revascularization as having either reversible ventricular dysfunction, indicating an improvement in wall motion and thickening after revascularization (to a score of either 2 or 3), or irreversible ventricular dysfunction, indicating no improvement to this level after revascularization. For any individual segment to be included in the analysis of change after revascularization, it was required that at least two contiguous segments demonstrate the same change in wall motion/thickening after revascularization. Only segments that were successfully revascularized (by review of the operative and angioplasty reports) were included in the analysis.

**Statistics**

All values are expressed as the mean±SD. Significance of pairwise comparisons in multiple observations was determined by ANOVA with the Tukey studentized range test (SAS version 6.04 with the PROC GLM procedure). Comparisons of tracer uptake also used a paired two-tailed \(t\) test where appropriate. Tests for paired proportions were performed with \(\chi^2\) analysis, and agreement between visual analysis of the two tracers corrected for chance used the \(\kappa\) statistic. Linear regressions were performed by least-squares analysis.

**Results**

In the 31 patients, 372 myocardial segments (12 per patient) were evaluated. The mean values of regional quantitative tracer activity are plotted in Fig 1. Segments are grouped according to mean resting \(^{201}\text{TI}\) activity; corresponding mean activities for redistribution \(^{201}\text{TI}\) and sestamibi in those segments are displayed. Of these, 135 segments demonstrated \(\geq80\%\) of the maximal \(^{201}\text{TI}\) activity on rest imaging. In these segments, mean thallium activity at rest was 88±5\% (percent of peak activity) and on redistribution imaging, 87±8\% (P=NS). Mean normalized sestamibi activity in these segments was 86±8\% (percent of peak sestamibi activity), not significantly different from either rest or redistribution thallium uptake. An additional 122 segments had a mild reduction in resting thallium activity (65% to 79\% of peak activity), with mean regional activity of 72±4\%. \(^{201}\text{TI}\) activity on redistribution imaging in these segments was 74±8\% (P=NS compared with resting uptake), whereas sestamibi activity was 76±10\% (P<.05 compared with rest \(^{201}\text{TI}\) activity, P=NS compared with redistribution \(^{201}\text{TI}\) activity). A moderately severe reduction in resting \(^{201}\text{TI}\) activity (50\% to 64\% of peak activity) was noted in 59 segments. In these segments, redistribution \(^{201}\text{TI}\) activity was 62±9\%, significantly higher than the rest \(^{201}\text{TI}\) value of 58±4\% (P<.05). Sestamibi activity was 60±9\%, not significantly different from redistribution \(^{201}\text{TI}\). Fifty-six segments demonstrated more severely diminished resting \(^{201}\text{TI}\) activity (<50\% of peak activity). There was a significant increase in relative \(^{123}\text{I}\) uptake between rest and redistribution imaging, from 39±7\% to 45±11\% of peak (P<.05). Mean regional sestamibi uptake in these segments (49±14\%) was significantly greater than rest \(^{201}\text{TI}\) activity (P<.05) but was not significantly different from redistribution \(^{201}\text{TI}\) activity.
Fig 2. Graph showing concordance by segments between regional $^{201}$TI activity at redistribution imaging and 1-hour post-rest injection $^{99m}$Tc-sestamibi activity by semiquantitative visual analysis. Concordance in defect severity was seen in 87% of the segments ($\kappa=.76$; 95% confidence limits, 0.69 to 0.82).

To evaluate the concordance of regional $^{201}$TI and sestamibi activities, a 4 x 4 table was used to assess the agreement of tracer activities for individual segments (Fig 2), based on a semiquantitative visual analysis of regional tracer activity. In this analysis, $^{201}$TI activity is based on the redistribution acquisition. There was concordance in defect severity based on semiquantitative visual analysis in 87% of the 372 segments ($\kappa=.76$; 95% confidence limits, 0.69 to 0.82). By quantitative analysis for all segments, there was significant correlation ($r=.86$, $P<.001$) between quantitative regional $^{201}$TI redistribution activity and 1-hour post–rest injection sestamibi activity in individual segments (Fig 3).

Changes in Regional Ventricular Function After Revascularization

In the 18 patients, 216 myocardial segments (12 per patient) were analyzed. Among these segments, 166 (77%) had preserved regional wall motion and thickening before revascularization, whereas 50 segments (23%) demonstrated severe regional ventricular dysfunction. Forty-seven of these segments were in territories that subsequently were successfully revascularized. One segment was eliminated from analysis because it was isolated, without a contiguous segment demonstrating the same change after revascularization. Of the 46 analyzed segments with regional dysfunction, 17 (37%) were found to have significantly improved regional wall motion and thickening on the postrevascularization echocardiographic study, and 29 (63%) demonstrated no significant reversibility of regional dysfunction after revascularization.

Comparison of $^{201}$TI and Sestamibi Activities in Reversible and Irreversible Regional Dysfunction

Among segments demonstrating significant reversibility of regional dysfunction after revascularization, mean $^{201}$TI redistribution activity was $72\pm11\%$ (percent of peak activity). Quantified sestamibi activity 1 hour after rest injection in these segments was $75\pm9\%$ ($P=NS$ versus $^{201}$TI). Among segments with irreversible dysfunction after revascularization, $^{201}$TI redistribution activity was $51\pm11\%$, whereas sestamibi activity in these segments was $50\pm8\%$ ($P=NS$). Activities of both $^{201}$TI and sestamibi in regions with irreversible dysfunction were significantly higher than corresponding activities in those segments with irreversible dysfunction ($P<.001$ for both).

Quantitative regional activities for both $^{201}$TI redistribution images and sestamibi images 1 hour after rest injection in the 18 patients undergoing revascularization are shown for individual segments in Fig 3. Among all segments, there was a highly significant correlation between quantitative measures of the isotope activities ($r=.85$, $P<.001$). In Fig 4, only those segments with an important degree of regional dysfunction in these patients before revascularization are plotted; a significant correlation is seen between redistribution $^{201}$TI activity and sestamibi activity in these segments as well ($r=.78$, $P<.001$). Examination of the individual data points representing nonviable myocardial segments (that is, those with irreversible ventricular dysfunction after revascularization) compared with viable segments (those with either preserved wall motion before revascularization or reversible dysfunction after revascularization) suggests that an arbitrary cutoff point of 60% of peak activity may optimally separate myocardial terri-

![Graph showing correlation of quantitative regional activities of $^{201}$TI (at redistribution imaging) on the x axis and regional activities of $^{99m}$Tc-sestamibi on the y axis. Left, Data on individual segments are presented for all 31 patients, and there is a highly significant correlation. Right, Individual segmental regional activity data are presented for the 18 patients undergoing revascularization. The symbol □ represents those segments with either preserved wall motion before revascularization or improved regional dysfunction (reversible dysfunction) after revascularization; ●, segments with irreversible ventricular dysfunction.](http://circ.ahajournals.org/doi/abs/10.1161/01.CIR.88.1.2555?journalCode=circ)
The probability of a scintigraphic segment representing viable myocardium (either preserved wall motion before revascularization or improved wall motion after revascularization) was related to the quantified level of regional tracer activity for both $^{201}$Tl and sestamibi (Fig 5).

$^{201}$Tl Resting Uptake and Redistribution Patterns in Viable Myocardium

Recent studies using planar rest-redistribution $^{201}$Tl imaging in patients with coronary artery disease and left ventricular dysfunction undergoing revascularization have demonstrated that irreversible rest $^{201}$Tl defects of only mild-to-moderate severity (as assessed quantitatively) also represent viable myocardium,13,14 a concept analogous to that demonstrated for exercise-redistribution $^{201}$Tl imaging.6,10 Among the 98 segments with a resting $^{201}$Tl defect (defined as relative regional activity <80% of peak) and either preserved wall motion or reversible dysfunction in the 18 patients undergoing revascularization, 17 (17%) demonstrated a reversible rest $^{201}$Tl defect (defined as an increase of >10% in quantified regional tracer thallium activity at redistribution imaging), whereas 63 (64%) were irreversible defects of only mild-to-moderate severity (defined as a change in relative $^{201}$Tl activity <10% at redistribution imaging, with final $^{201}$Tl content >60% of peak); 18 segments demonstrated an irreversible defect of severe magnitude.

Comparative Tracer Activities in Segments With Reversible and Irreversible Resting Thallium Defects

The redistribution kinetics of $^{201}$Tl would theoretically allow an advantage to this agent in viable territories with resting hypoperfusion, in that tracer accumulation over time and delayed imaging would allow better identification of ultimate tracer uptake, manifested as a reversible resting $^{201}$Tl defect. To evaluate quantitative sestamibi activity in this setting, the 17 viable segments (that is, those segments with either preserved wall motion before revascularization or reversible dysfunc-

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Fig 4. Scatterplot showing correlation of quantitative regional activities of $^{201}$Tl (at redistribution imaging) on the x axis and regional activities of $^{99m}$Tc-sestamibi on the y axis among segments with significant regional dysfunction in patients undergoing revascularization. The symbol ○ represents those segments with improved regional dysfunction (reversible dysfunction) after revascularization; ●, segments with irreversible ventricular dysfunction.

Fig 5. Bar graph showing percentage of segments falling into quantitative quintiles of regional activity that represent viable myocardium (defined by either preserved wall motion or improved wall motion after revascularization) for either $^{201}$Tl or $^{99m}$Tc-sestamibi in 216 segments from 18 patients studied before and after revascularization. The probability of a scintigraphic segment representing viable myocardium is related to the magnitude of regional activity.
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Influence of Postrevascularization Perfusion on Recovery of Regional Dysfunction

Recent studies using planar rest-redistribution 201Tl imaging have demonstrated that the scintigraphic assessment of the likelihood of improvement in regional dysfunction is influenced by the postrevascularization perfusion status. In the present study, among the segments with regional dysfunction and preserved 201Tl uptake (that is, ≥60% of peak), postrevascularization perfusion studies with sestamibi revealed that those with reversible dysfunction had higher sestamibi uptake after revascularization (75±12% than those segments with preserved prerevascularization 201Tl uptake but irreversible dysfunction (60±7%, P=.01). Similar data were observed among segments with regional dysfunction and preserved sestamibi uptake before revascularization: those with reversible dysfunction had higher postrevascularization sestamibi uptake (74±12%) than those segments with irreversible dysfunction (61±9%, P≤.05).

Discussion

The present data indicate that quantitative analysis of regional activity of 201Tl after resting injection and redistribution imaging can distinguish reversible from irreversible abnormalities in regional ventricular function and that quantitative analysis of regional activity of the 99mTc-based tracer sestamibi provides comparable information after rest injection.

Several studies have demonstrated that reversibility of a stress-induced 201Tl defect, or redistribution, correlates with myocardial viability and with improvement in regional perfusion or function after revascularization. The absence of defect reversibility on standard redistribution imaging after stress injection of 201Tl, however, was found to be an unreliable indicator of irreversible ventricular dysfunction, since 30% to 50% of irreversible defects contain a significant degree of viable myocardium, as assessed by improved perfusion or function after revascularization or by PET imaging of metabolic activity. This limitation has been overcome by modified 201Tl imaging protocols incorporating late redistribution imaging or reinjection of a second dose of 201Tl after redistribution imaging to optimize the finding of defect reversibility and assessment of viable myocardium.

Among patients with known severe coronary artery disease, significant symptoms, and important degrees of regional or global ventricular dysfunction, delineation of the potential reversibility of regional or global ventricular dysfunction may be the primary issue for scintigraphic imaging. In such cases, imaging after rest injection alone may provide the clinically relevant data in formulating a decision to proceed with revascularization. Previous studies investigating 201Tl activity after rest injection with early postinjection and redistribution images have shown that 201Tl uptake in this setting can be used to predict improved regional perfusion after revascularization. In addition, in patients with left ventricular dysfunction, rest-redistribution 201Tl imaging may be used to identify that subset of patients more likely to demonstrate improvement in global left ventricular function as a result of revascularization.

Quantitative analysis of 201Tl content in rest-redistribution studies appears to enhance the ability to predict improvement in regional or global ventricular function. The present data demonstrating that irrevers-

Figure 6. Bar graphs showing quantitative analysis of 201Tl and 99mTc-sestamibi activity in regions demonstrating reversible (left) or irreversible (right) reductions in resting 201Tl activity. Isotope activity is expressed as a percentage of peak myocardial activity. Rest TL indicates mean normalized resting 201Tl activity; Redist TL, redistribution 201Tl activity; and MIBI, 1-hour post-rest injection sestamibi activity.
Fig 7. Facing page. Short-axis color tomographic images from a 61-year-old man with three-vessel coronary artery disease and depressed left ventricular function. Top, Resting $^{201}$TI images show extensive anterior, septal, and inferior defects. Center, Redistribution $^{201}$TI images show partial redistribution of the anterior and inferior defects. Bottom, Sestamibi images acquired 1 hour after rest injection demonstrate a moderately severe anteroseptal defect and a mildly severe inferior defect toward the apex (left), more closely resembling the redistribution $^{201}$TI images than the resting $^{201}$TI images.

Fig 8. Facing page. Short-axis color tomographic images from a patient with coronary disease and left ventricular dysfunction. Top, Rest $^{201}$TI images demonstrate anteroseptal and inferior defects. The $^{201}$TI redistribution images (middle) show reversibility of the anteroseptal defect and no change in the inferior defect. The $^{203}$Tc-sestamibi images acquired 1 hour after rest injection (bottom) show only mild reduction in counts in the anterior septum toward the apex and a severe inferior defect. This patient had septal and inferior wall motion abnormalities at rest; after revascularization, anteroseptal regional function improved, whereas inferior wall dysfunction was irreversible.

Discernible reductions of only mild-to-moderate severity in $^{201}$TI activity with rest-redistribution imaging also represent viable myocardium confirm these previous investigations $^{13,14}$ and extend these concepts to tomographic imaging. The concept that assessment of the $^{201}$TI content within an "irreversible" defect can provide important information regarding myocardial viability and the propensity for recovery of regional dysfunction, as well as the data presenting demonstrating that irreversible defects of only mild-to-moderate severity are a more common finding than reversible resting $^{201}$TI defects in viable myocardium, suggests that reversibility of a resting $^{201}$TI defect may not be a necessary sign of viability. Rather, it is possible that quantitative analysis of $^{201}$TI content in the redistribution image alone may provide the clinically relevant data regarding potential for recovery of regional dysfunction. $^{20}$

Information from quantitative analysis of rest-redistribution $^{201}$TI studies has been shown to be generally concordant with a stress-redistribution-reinjection $^{201}$TI protocol regarding myocardial viability, as identified by PET. $^{21}$

Based on the relative lack of redistribution with sestamibi compared with $^{201}$TI, it has been suggested that this agent may underestimate myocardial viability in myocardial territories associated with severe epicardial stenoses and poor collateral flow. $^{22,23}$ In these territories, with presumed resting hypoperfusion, the redistribution kinetics of $^{201}$TI may conceptually provide an advantage for detection of viability, in that $^{201}$TI will have a chance to accumulate over time in such a region on the basis of continuing arterial input, in contrast to sestamibi. The results of initial investigations in humans appear to support this concept: Rocco et al $^{23}$ demonstrated that after the resting injection of sestamibi, >50% of segments with markedly reduced sestamibi activity (by qualitative visual analysis of planar images) exhibited preserved wall motion. Among all territories with the most reduced sestamibi activity qualitatively, however, quantitative analysis could better separate segments with preserved compared with those with impaired wall motion. $^{23}$ Thus, in analogy to the concept that quantitative analysis of $^{201}$TI content within irreversible defects more accurately discriminates viable from nonviable myocardium, $^{6,10,13,14}$ quantitative analysis of sestamibi activity within a visually apparent defect may also contain such information.

In contrast to these initial human studies using sestamibi, data from relevant animal models of low-flow ischemia resulting in significant regional ventricular dysfunction have demonstrated that regional $^{201}$TI activity and sestamibi activity are comparable at multiple time points after resting injection. $^{24,25}$ The present data are consistent with these studies in animal models of low-flow ischemia. Studies comparing sestamibi activity in rest studies with PET assessment of metabolic activity $^{26,27}$ are also consistent with the present data.

Other studies have compared $^{201}$TI and sestamibi directly in patients with left ventricular dysfunction. Cuocolo and coworkers $^{28}$ found more stress defect reversibility using a stress-redistribution-reinjection $^{201}$TI protocol compared with a stress-rest sestamibi protocol. Conclusions from those data are constrained by the lack of quantitative scintigraphic analysis and the absence of a "gold standard" for determining which agent was supplying the more correct information regarding regional viability. In a study design similar to the present investigation, Marzullo and colleagues $^{29}$ performed quantitative analysis of planar rest-redistribution $^{201}$TI and rest sestamibi scans in patients also studied by echocardiography before and after revascularization. Quantitative regional activities of $^{201}$TI (at redistribution) and sestamibi were similar in segments with reversible ventricular dysfunction (67±9% versus 67±13%, respectively) as well as in segments with irreversible dysfunction (<46±6% versus 48±10%, respectively), which is analogous to the results of the present study. Although Marzullo et al $^{29}$ found that the sensitivity and specificity for preoperative identification of dysfunctional but viable myocardium were slightly higher with the redistribution $^{201}$TI data after rest injection compared with sestamibi, the confidence limits for these results were widely overlapping, suggesting no statistically significant difference between the two agents in this regard.

The exact mechanisms accounting for the comparability of the rest-redistribution $^{201}$TI data and the rest sestamibi data are uncertain, although there are several potential mechanisms that, alone or in combination, could have contributed to the findings. The behavior of diffusible tracers at low coronary flows is complex: at low flows, such tracers are overextracted; that is, they are not pure flow tracers in this range of flow. Data in animal models of low-flow ischemia demonstrate that sestamibi activity in such territories overestimates coronary flow, $^{25,30,32}$ suggesting that relative extraction rises at low flow rates. In addition, blood clearance of sestamibi early after rest injection is slower than that of $^{201}$TI. $^{33,34}$ These factors, together with the higher injected dose of sestamibi in this study, may allow higher early relative uptake of sestamibi compared with $^{201}$TI, particularly in territories with impaired perfusion at rest.

Second, animal studies have demonstrated that after the initial distribution of sestamibi, there is a change over time in the ratio of ischemic to normal zone activity, or redistribution, although to a lesser degree than seen with the $^{201}$TI. $^{17,32}$ A recent study in a dog model of low coronary flow demonstrated that regional $^{201}$TI and sestamibi activities were similar after 3 hours.
of low-flow conditions, suggesting that redistribution of sestamibi may be clinically relevant. This finding has also been suggested in patients studied serially after stress sestamibi injection as well as after rest injection. Thus, both enhanced relative extraction of sestamibi at low flows and a degree of sestamibi redistribution may have resulted in the similarity of sestamibi and 123I activities at their respective imaging times in the present study.

Another factor that may have enhanced sestamibi activity relates to the concept of the recovery coefficient in tomographic imaging. Recovery of counts from objects below a certain thickness threshold is related to both object thickness and image resolution. Among the relatively thinned, poorly contractile, hibernating segments, sestamibi count recovery may have been more efficient than 123I recovery, based on the higher inherent resolution of the sestamibi images, related to the physical properties of the 99mTc label, as well as the image acquisition parameters (64 projections for sestamibi compared with 32 projections for 123I). Although this effect would be most pronounced for the dysfunctional segments, it may also come into play for normally contracting segments, since the resolution of SPECT imaging with single photon agents is such that all myocardial segments are subject to this effect. This concept would not come into play in planar imaging.

Finally, on the basis of the imaging protocol used in this study, it is possible that 123I counts that had redistributed into the region of a rest 123I defect may have “spilled” into the technetium window during the sestamibi acquisition, giving the appearance of increased tracer activity within what otherwise might have appeared to be a sestamibi defect. This is unlikely, since in preliminary studies using simultaneous dual isotope acquisition of 123I and sestamibi, “spill” of 123I into the technetium window has been relatively insignificant, with 123I activity accounting for <3% of the total counts within the technetium window.

Like previous studies of exercise-redistribution 123I imaging, Figs 3, 4, and 5 reinforce the concept that analysis of regional tracer content provides a spectrum of data regarding myocardial viability and the potential for recovery of regional dysfunction after revascularization, and it is unlikely that any specific cutoff point will clearly and absolutely differentiate viable from nonviable regions. Rather, within myocardial territories demonstrating severe contractile dysfunction, the probability of reversibility of regional dysfunction is related to the magnitude of isotope activity across a wide spectrum of activity. However, the 60% threshold cutoff point suggested by the present data is similar to that used in previous animal and phantom studies of sestamibi for differentiating “area at risk” in models of coronary occlusion as well as for determining the extent of myocardial salvage in serial sestamibi studies before and after thrombolytic therapy.

The present data also support the findings of Ragosta and coworkers regarding the influence of postrevascularization perfusion on the potential recovery of regional dysfunction and the predictive ability of pre-revascularization scintigraphy. Among the segments with regional dysfunction and preserved uptake of either 123I or sestamibi before revascularization, regions with reversible dysfunction had significantly higher postrevascularization tracer uptake than those segments with preserved uptake before revascularization but irreversible dysfunction. These data, like the findings of Ragosta et al., suggest that factors related to the adequacy of postrevascularization perfusion importantly influence the recovery of regional contractile function.

There are several limitations to the present analysis. It is not absolutely certain that myocardial segments defined by the SPECT studies correspond exactly to the echocardiographic segments. This limitation is present in all such studies comparing scintigraphic variables with functional parameters acquired by different techniques. The requirement that contiguous segments be abnormal and demonstrate the same change (or lack thereof) after revascularization would to some degree ensure that single small territories are not importantly influencing the analysis and also increase the likelihood that similar segments are being analyzed by scintigraphic and echocardiographic techniques as much as possible. No quantitative data are available on changes in global ventricular function after revascularization in this study; thus, segmental analysis alone is presented. How the present data impact on symptoms, quality of life, or changes in global left ventricular function after revascularization cannot be determined.

In conclusion, the present data indicate that after resting injections, regional activities of both 123I and sestamibi as assessed by quantitative analysis are similar in reversibly dysfunctional myocardium as well as in irreversibly dysfunctional myocardium and that both agents comparably predict recovery of severe regional wall motion abnormalities after revascularization.

References


Predicting recovery of severe regional ventricular dysfunction. Comparison of resting scintigraphy with 201Tl and 99mTc-sestamibi.

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