

Quantitative Rest Technetium-99m Tetrofosmin Imaging in Predicting Functional Recovery After Revascularization: Comparison With Rest-Redistribution Thallium-201

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Objectives. This study was undertaken to 1) compare the regional myocardial tracer distributions between rest technetium (Tc)-99m tetrofosmin and rest-redistribution thallium (Tl)-201 images in patients with coronary artery disease and left ventricular dysfunction; and 2) assess the comparative values of these agents for predicting functional recovery after revascularization.

Background. Tc-99m tetrofosmin is a new myocardial perfusion imaging agent, but its role for detecting viable myocardium is still unclear.

Methods. Thirty-six patients with coronary artery disease and left ventricular dysfunction underwent rest Tc-99m tetrofosmin, rest-redistribution Tl-201 and gated blood pool scintigraphy. In 21 patients with successful revascularization confirmed by follow-up angiography, gated blood pool scintigraphy was repeated after revascularization. Optimal threshold cutoffs to separate reversible from irreversible dysfunction were determined by receiver operating characteristic analysis.

Results. Regional Tc-99m tetrofosmin activity highly correlated with redistribution Tl-201 activity ($r = 0.93$). The diagnostic performance for predicting functional recovery, as measured by the area under the receiver operating characteristic curves, measured 0.66 ± 0.07 (mean \pm SD) for Tc-99m tetrofosmin and 0.67 ± 0.07 for Tl-201 ($p = 0.60$, 96.7% power to detect difference in area of 0.10). The optimal threshold cutoffs for viability were considered to be 50% of peak activity for Tc-99m tetrofosmin and 55% of peak activity for Tl-201. The positive and negative predictive values for reversible dysfunction were, respectively, 69% and 82% for Tc-99m tetrofosmin and 69% ($p = 0.99$ vs. Tc-99m tetrofosmin) and 71% ($p = 0.66$ vs. Tc-99m tetrofosmin) by Tl-201.

Conclusions. The diagnostic performance of quantitative rest Tc-99m tetrofosmin imaging in predicting functional recovery after revascularization is comparable to that of rest-redistribution Tl-201.

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Technetium (Tc)-99m tetrofosmin is a new myocardial perfusion tracer that can be used as an alternative to thallium (Tl)-201 (1). This agent reportedly offers similar diagnostic accuracy in detecting coronary artery disease (CAD) comparable to Tl-201 (2-5). Compared with Tc-99m sestamibi, the most widely used Tc-99m-based myocardial perfusion imaging tracer, Tc-99m tetrofosmin does not require heating, but only a 15-min incubation at room temperature (1-5). Furthermore, its rapid accumulation in the myocardium and relatively rapid clearance from the background organs are more favorable for imaging at comparable time points (2,3). However, the utility of Tc-99m tetrofosmin for assessment of viability has not yet been fully demonstrated (5).

Rest-redistribution Tl-201 imaging is an established diag-

nostic protocol for detecting viable myocardium (6-8). This is especially true when defect severity is taken into account (i.e., the majority of mild to moderate irreversible defects are considered viable). Such a quantitative approach has also been used successfully with Tc-99m sestamibi (8,9), although the role of Tc-99m sestamibi in identifying viable myocardium is still an ongoing controversy (10). Recently, our preliminary results showed a highly significant correlation between regional rest Tc-99m tetrofosmin activity and reinjection Tl-201 activity (11), suggesting that such a quantitative approach could also be used for Tc-99m tetrofosmin. We hypothesized that quantitative rest Tc-99m tetrofosmin imaging would provide information on myocardial viability comparable to conventional rest-redistribution Tl-201 imaging.

The present study was undertaken to 1) compare the regional myocardial tracer distributions between rest Tc-99m tetrofosmin and rest-redistribution Tl-201 images; 2) assess the comparative values of these agents for predicting functional recovery after revascularization; and 3) determine the optimal threshold cutoff values for differentiating myocardial territories with reversible from those with irreversible dysfunc-

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Abbreviations and Acronyms

CABG	= coronary artery bypass surgery
CAD	= coronary artery disease
CAG	= coronary arteriography
GBP	= electrocardiographic gated blood pool scintigraphy
LV	= left ventricular
LVEF	= left ventricular ejection fraction
PTCA	= percutaneous transluminal coronary angioplasty
ROC	= receiver operating characteristic
ROI	= region of interest
SPECT	= single-photon emission computed tomographic

tion. To determine the optimal threshold cutoff values and to compare the diagnostic performance of Tc-99m tetrofosmin and Tl-201 imaging, receiver operating characteristic (ROC) analysis was performed because the use of ROC analysis provides more comprehensive information about the performance of a diagnostic test than a single sensitivity/specificity pair (12). In the subset of patients who underwent revascularization, we assessed only successfully revascularized territories that were confirmed by follow-up coronary arteriography (CAG) to optimize pre-revascularization viability predictive values.

Methods

Patients. This was a prospective study involving 36 patients with angiographically proved CAD and regional or global left ventricular (LV) dysfunction. The patients ranged in age from 43 to 82 years (mean 66); there were 26 men and 10 women. Twenty-five patients (69%) had a history of previous myocardial infarction (anterior wall infarction in 9, inferior wall infarction in 14, lateral wall infarction in 1, anterior and inferior infarction in 1). Patients with a recent myocardial infarction (<4 weeks before investigation) were not included in the study. Mean left ventricular ejection fraction (LVEF) by electrocardiographic (ECG) gated blood pool scintigraphy (GBP) was $41 \pm 9\%$ (mean \pm SD) (range 18% to 55%). CAD was defined as $\geq 50\%$ reduction in lumen diameter of at least one major epicardial coronary artery as determined by CAG, which was performed during the same period as the radionuclide studies. Sixteen patients had three-vessel disease; 10 had two-vessel disease; and 10 had one-vessel disease (mean 2.2 vessels/patient). Two patients had undergone previous percutaneous transluminal coronary angioplasty (PTCA), and two others had a history of coronary artery bypass graft surgery (CABG). All cardiac medications were continued during the study without interruption. All subjects signed an informed consent form based on the guidelines of the hospital's human clinical study committee before participation in the study.

Revascularization. Coronary revascularization was recommended by the patient's attending physician on the basis of clinical, angiographic and scintigraphic data. Of a total of 36 patients, 25 underwent coronary revascularization. Of these, 16

underwent CABG, and the remaining 9 had PTCA. Only myocardial regions without occluded bypass grafts after CABG or restenosis after PTCA, which was confirmed by follow-up CAG performed at 1 to 3 months after the intervention, were included in the follow-up wall motion analysis.

Tl-201 and Tc-99m tetrofosmin imaging. All patients underwent rest-redistribution Tl-201 and rest Tc-99m tetrofosmin single-photon emission computed tomographic (SPECT) imaging within 1 week. After an overnight fast, patients were given an injection of 3 mCi (111 MBq) of Tl-201 at rest, and images were obtained after 5 to 10 min and 3 to 4 h after injection. Rest Tc-99m tetrofosmin SPECT imaging was started at 45 to 60 min after injection of 14 to 19 mCi (500 to 700 MBq) of the tracer at rest.

Myocardial SPECT imaging was performed using a three-headed SPECT system with low energy high resolution parallel-hole collimators (GCA9300A/HG, Toshiba, Tokyo, Japan). The detector system was interfaced to a dedicated nuclear medicine computer (GMS5500A, Toshiba). A total of 60 projection images were obtained over 360° in 6° increments, with 30 s/view for rest Tl-201 and rest Tc-99m tetrofosmin SPECT and 40 s/view for redistribution Tl-201 SPECT. The energy discriminator was centered on 70 keV for Tl-201 and 140 keV for Tc-99m tetrofosmin with a 20% window. The data were recorded in 128×128 matrices on the magnetic disk. To reconstruct transaxial tomographic images from each of the acquisition data, Butterworth and Ramp filters were used. The parameter of the Butterworth filter was order 8, and the cutoff frequency was 0.15 to 0.17 cycles/pixel. Short-axis slices, 3.2 mm thick, were also generated. Then, four serial short-axis slices were added, resulting in a 12.8-mm slice thickness.

Data analysis. For quantitative analysis of regional tracer activities, three short-axis tomograms representing an apical, distal and basal left ventricle were chosen for each patient (8,9,13). After confirmation of optimal image registration, circumferential analysis was performed on an operator-defined region of interest (ROI) drawn around the LV activity of each tomogram. The center of each tomogram was determined, and the ROI was automatically subdivided into 128 sectors (13). The maximal pixel activity within each sector was normalized to the peak activity for each individual study, which was assigned as 100%. We separately determined the normal reference region for each of the rest and redistribution Tl-201 and rest Tc-99m tetrofosmin images because in clinical practice, either rest-redistribution Tl-201 or rest Tc-99m tetrofosmin alone, but not both, may be used for identifying viable myocardium. The activity in all other myocardial regions was expressed as a percent of this maximum. The sectors from distal and basal slices were then grouped into four myocardial segments corresponding to the septal, anterior, inferior and lateral walls, and segmental activity was defined as the average of the individual sector activities within that segment. The apical myocardial activity was determined from the first apical tomogram; the distal septal, anterior, inferior and lateral myocardial activities were determined from the distal LV tomogram; and the basal anterior, inferior and lateral myocar-

dial activities were determined from the basal LV tomogram. Thus, a total of 324 segments from 36 patients (9 segments/patient) were analyzed.

On the basis of regional Tl-201 activity, a segment was considered *normal* if the regional activity on the rest Tl-201 image was $\geq 80\%$ of peak activity and without significant ($\geq 10\%$) reverse redistribution on the corresponding redistribution image. A *reversible Tl-201 defect* was defined as $< 80\%$ of peak activity on the rest image and with a $\geq 10\%$ increase on the redistribution image. Our use of an 80% threshold for normal activity and a 10% change in Tl-201 activity for reversibility was based on a previous study by Udelson et al. (8). Because reverse redistribution on rest-redistribution Tl-201 imaging is reportedly not negligible (14), a segment was considered to have *reverse redistribution* if the regional activity decreased by $\geq 10\%$ from the rest to the redistribution image. Finally, an *irreversible Tl-201 defect* was defined as $< 80\%$ of peak activity on the rest image without a significant increase or decrease in activity on the redistribution image.

ROC analysis. ROC analysis was performed to determine optimal threshold cutoffs to separate myocardial regions with reversible from those with irreversible regional dysfunction after revascularization. The ROC curves were generated using the program CLABROC developed by Metz (15). The determination of the optimal threshold of a diagnostic test is subjective rather than objective and should be based on the clinical impact of the decision. However, because no published reports of assessment of myocardial viability have focused on this issue, we surveyed studies that used a rest-redistribution Tl-201 protocol for detection of reversible dysfunction after revascularization and quantitative analysis of regional tracer activity as an index of viability. We found that the sensitivities for reversible dysfunction in previous reports were consistently kept high, ranging from 88% to 91%, whereas specificities were highly variable, ranging from 31% to 86% (7,8,10). On the basis of these observations, we arbitrarily defined an optimal threshold cutoff to obtain a sensitivity $> 88\%$ (the lowest sensitivity in reports surveyed) and to stay near the top left corner of the curve.

Radionuclide angiography. Analysis of regional wall motion was performed within 1 month (mean 17 days) before revascularization in all patients and was repeated at a mean of 64 days (range 24 to 135) after revascularization in patients with successful revascularization. Each patient underwent GBP to assess global and regional LV wall motion at rest using red blood cells labeled in vivo with 20 mCi (740 MBq) of Tc-99m. Images were acquired in the anterior, left anterior oblique and lateral views. LVEF was calculated by computer analysis of the scintigraphic data, and regional wall motion was assessed visually by two experienced observers (I.M., S.F.) who were unaware of the clinical and myocardial SPECT data from the images displayed in cine format. The apical and anterior walls were assessed from the anterior view, the septal and lateral walls from the left anterior oblique view and the inferior and posterior walls from the left lateral view. Regional wall motion was graded on a semiquantitative five-point scoring

system as follows (16): 3 = normal; 2 = mild hypokinesia; 1 = severe hypokinesia; 0 = akinesia; and -1 = dyskinesia. Disagreements in interpretation were resolved by consensus. A region was considered to have *improved wall motion* if the assigned abnormal wall motion (defined as ≤ 2 in score) normalized or increased by ≥ 1 in wall motion score after revascularization. In the study of patients who underwent CABG, the septal segment was excluded from the follow-up wall motion analysis because of frequent paradoxical motion after operation (16).

For comparison with coronary anatomy, apical, anterior and septal walls were considered to be supplied by the left anterior descending coronary artery, the lateral wall by the left circumflex coronary artery and the inferior and posterior walls by the right coronary artery.

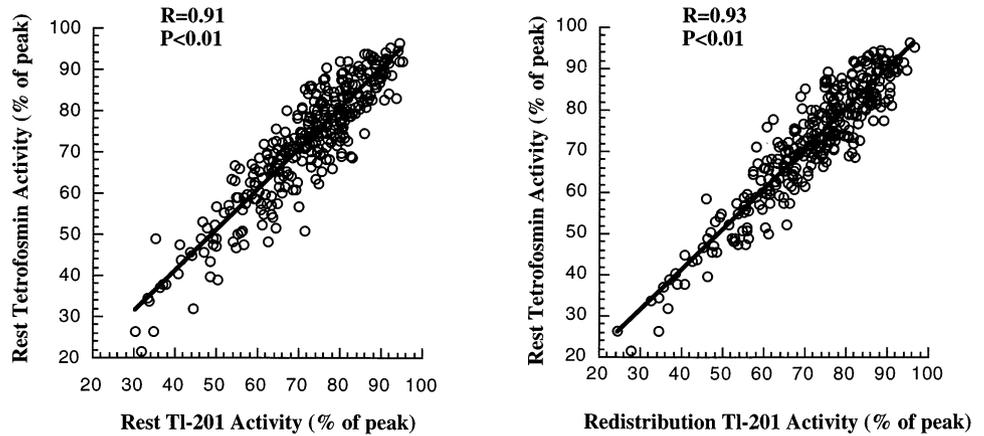
Statistical analysis. Results are reported as mean value \pm SD. Comparisons of two mean values were performed using a paired *t* test, nonpaired *t* test or Mann-Whitney rank sum test where appropriate. The initial rest, redistribution Tl-201 and rest Tc-99m tetrofosmin activities were compared using repeated measures analysis of variance and Bonferroni multiple comparisons test. Paired proportions were compared with the McNemar test. Nonpaired proportions were compared by chi-square or Fisher exact test where appropriate. Linear regression was performed by least-squares analysis. To compare the diagnostic performance of Tc-99m tetrofosmin and Tl-201 imaging, the areas under the ROC curves were compared by area test (12,15), and the power calculation was performed by ROC PWR (17). Statistical significance was defined as $p < 0.05$.

Results

Comparison of Tc-99m tetrofosmin and Tl-201 distribution. Quantitative regional activities for both Tc-99m tetrofosmin and Tl-201 images are shown for individual segments in Figure 1. There were highly significant correlations both between quantitative regional rest Tl-201 activity and rest Tc-99m tetrofosmin activity and between redistribution Tl-201 and rest Tc-99m tetrofosmin activity ($r = 0.91$, $p < 0.001$ and $r = 0.93$, $p < 0.001$, respectively).

The mean values of regional tracer activity are plotted in Figure 2, in which segments are grouped according to Tl-201 findings. Of a total of 324 myocardial segments from 36 patients, 104 showed normal rest Tl-201 uptake ($\geq 80\%$ of peak activity) without significant reverse redistribution. In these segments, mean rest Tl-201, redistribution Tl-201 and rest Tc-99m tetrofosmin activities were $85 \pm 4\%$, $84 \pm 6\%$ and $85 \pm 7\%$ of peak activity, respectively. A rest Tl-201 defect with redistribution on the delayed image was observed in 23 segments. Mean rest Tl-201 activity in these segments was $65 \pm 11\%$, which increased to $78 \pm 11\%$ on the delayed image ($p < 0.01$). In these segments, mean Tc-99m tetrofosmin activity ($73 \pm 11\%$) was higher than rest Tl-201 activity ($p < 0.01$) but lower than redistribution Tl-201 activity ($p < 0.01$). Additionally, there were 16 segments with Tl-201 reverse redistribution. In contrast to the segments with Tl-201 redistribution, mean

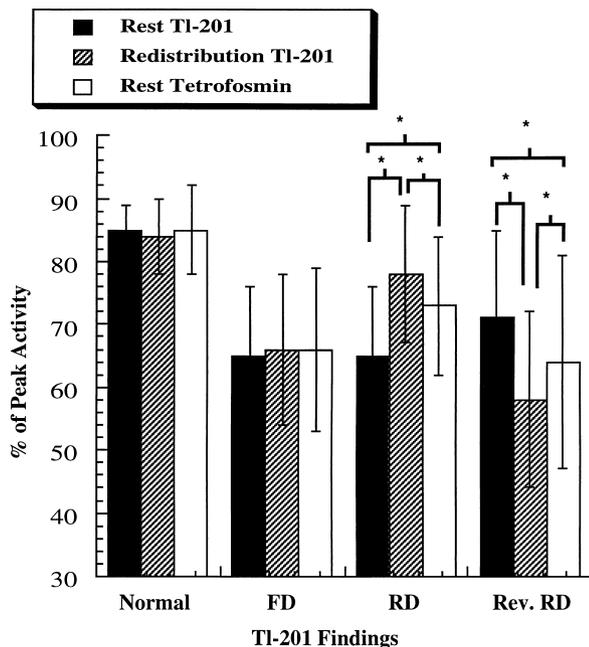
Figure 1. Scatterplots showing correlation of quantitative regional tracer activities between rest Tl-201 and rest Tc-99m tetrofosmin imaging (**left**) and between redistribution Tl-201 and rest Tc-99m tetrofosmin imaging (**right**).



Tc-99m tetrofosmin activity ($64 \pm 17\%$) was lower than rest Tl-201 activity ($71 \pm 14\%$, $p < 0.01$) but higher than redistribution Tl-201 activity ($58 \pm 14\%$, $p < 0.01$). In the remaining 181 segments with irreversible Tl-201 defects, there were no significant differences in mean regional activities among rest Tl-201, redistribution Tl-201 and Tc-99m tetrofosmin images ($65 \pm 11\%$, $66 \pm 12\%$ and $66 \pm 13\%$, respectively, $p = 0.326$). The wall motion scores in segments with normal Tl-201 uptake, reversible Tl-201 defects, reverse redistribution and irreversible defects were 2.4 ± 0.9 , 1.8 ± 1.2 , 1.6 ± 1.2 and 1.7 ± 1.2 , respectively.

A representative example comparing rest-redistribution

Figure 2. Bar graph showing quantitative analysis of rest Tl-201 activity, redistribution Tl-201 activity and rest Tc-99m tetrofosmin activity. Myocardial segments are grouped according to Tl-201 findings. Values are expressed as a percent peak activity. Error bars = 1 SD. * $p < 0.01$.



Tl-201 and rest Tc-99m tetrofosmin imaging is demonstrated in Figure 3.

Effect of revascularization on myocardial wall motion. Of 25 patients who had undergone coronary revascularization, 4 were excluded from further analysis (2 had restenosis after PTCA; 1 had cerebral stroke after intervention; 1 underwent a lung operation before follow-up study), leaving 21 who were included in the follow-up study. The clinical characteristics of patients with and without postrevascularization data are summarized in Table 1. The prevalence of angina, mean redistribution Tl-201 activity and mean Tc-99m tetrofosmin activity was higher in the group with revascularization.

Of a total of 86 asynergic segments in these 21 patients, 79 were considered to be successfully revascularized by the follow-up CAG. All 21 patients had at least one successfully revascularized vascular territory. Of these, 49 segments (62%) in 16 patients showed an improvement in function after revascularization. In contrast, 30 segments in 14 patients did not improve, even after the vascular intervention. Of the seven

Figure 3. Short-axis tomographic images from a 70-year old woman with three-vessel CAD. **Top**, Rest Tl-201 images show an anteroseptal defect. **Middle**, Redistribution Tl-201 images show partial redistribution of the anteroseptal wall. **Bottom**, Rest Tc-99m tetrofosmin images show a less severely reduced defect of that region than rest Tl-201 images.

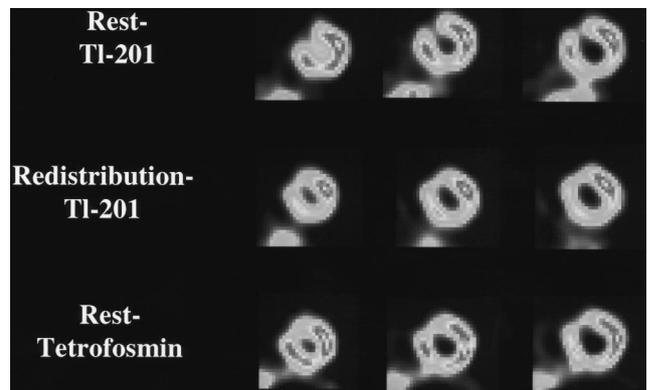


Table 1. Clinical Characteristics of Patients With and Without Revascularization

	Revascularization (n = 21)	No Revascularization (n = 15)	p Value
Age (yr)	67 ± 7	64 ± 12	0.33
M/F	14/7	12/3	0.47
Previous MI	12	13	0.08
Angina	21	8	0.001
NYHA functional class			
I/II	15/21	10/15	1.0
III/IV	6/21	5/15	
No. of diseased vessels	2.3 ± 0.7	2.0 ± 1.0	0.35
LVEF (%)	42 ± 8	39 ± 11	0.27
Redistribution Tl-201 activity in dysfunctional segments	69 ± 15	64 ± 15	0.04
Rest Tc-99m tetrofosmin activity in dysfunctional segments	69 ± 15	64 ± 15	0.03

Data presented are mean value ± SD or number of patients. LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association.

segments with incomplete revascularization, two showed functional recovery.

Mean global LVEF was 42 ± 8% before revascularization and increased to 46 ± 10% (p < 0.01) after revascularization. In 8 patients, global LVEF improved by at least 5% (from 41 ± 4% before to 51 ± 4% after revascularization) whereas it remained unchanged in the remaining 13 patients (from 43 ± 10% to 43 ± 11%).

Prediction of regional functional recovery by Tc-99m tetrofosmin and Tl-201. ROC curves for predicting reversible dysfunction after revascularization are presented in Figure 4. The optimal threshold cutoff values to identify viable myocardium were considered to be 50% of peak activity for Tc-99m tetrofosmin and 55% for Tl-201. The diagnostic performance of Tc-99m tetrofosmin, as measured by the area under maximum likelihood fitted ROC curves measured 0.66 ± 0.07, which was similar to that for Tl-201 (0.67 ± 0.07, p = 0.60). The power to detect a difference in ROC area of 0.10 was 96.7%. Sensitivity, specificity and positive and negative predictive accuracies are summarized in Table 2. There were no significant differences in these values between Tc-99m tetrofosmin and Tl-201. When only the patients who had prevascularization LVEF ≤ 40% (n = 10) were analyzed, the positive and negative predictive values for functional recovery were 61% and 80% for Tc-99m tetrofosmin and 60% (p = 0.96 vs. Tc-99m tetrofosmin) and 69% (p = 0.66 vs. Tc-99m tetrofosmin) for Tl-201, respectively.

In the segments without functional recovery, the mean baseline regional wall motion scores in the scintigraphically viable segments were significantly higher than those in the scintigraphically nonviable segments for both Tc-99m tetrofosmin (1.3 ± 0.8 vs. -0.2 ± 0.4, p < 0.001) and Tl-201 (1.4 ± 0.7 vs. -0.2 ± 0.4, p < 0.001).

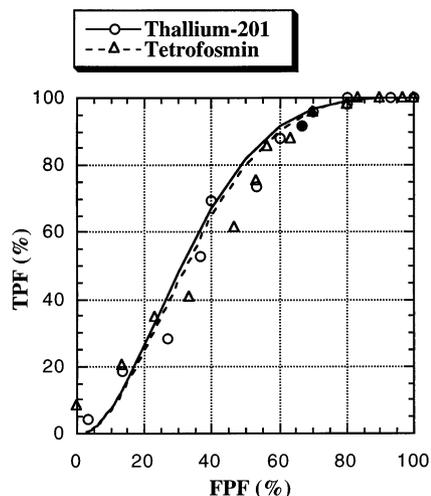


Figure 4. Fitted ROC curves (lines) and measured plots (symbols) comparing rest Tc-99m tetrofosmin and rest-redistribution Tl-201 imaging for detection of reversible dysfunction. The measured plots were calculated by generating sensitivity/specificity pairs for every 5% of peak activity. Circles = optimal threshold cutoff for Tl-201 (55% of peak activity); triangles = optimal threshold cutoff for Tc-99m tetrofosmin (50% of peak activity); FPF = 100-specificity (%); TPF = sensitivity (%).

Prediction of global LV functional improvement by Tc-99m tetrofosmin and Tl-201. Seven of 13 patients with three or more viable myocardial segments by Tc-99m tetrofosmin imaging showed an increase by ≥ 5% in global LVEF after revascularization (positive predictive value 54%), whereas only 1 of 8 patients with two or less viable segments showed ≥ 5% improvement in global LVEF (negative predictive value 88%). Tl-201 imaging showed positive (54%) and negative (88%) predictive values identical to those for Tc-99m tetrofosmin for improvement in global LV function.

Discussion

The major findings of this study were that 1) regional Tc-99m tetrofosmin activity showed a highly significant correlation with

Table 2. Sensitivity, Specificity and Predictive Values for Tc-99m Tetrofosmin and Tl-201 Imaging in Predicting Functional Recovery After Revascularization

	Tc-99m Tetrofosmin	Tl-201	p Value
Optimal cutoff	50%	55%	
Sens (seg)	96% (47/49)	92% (45/49)	0.16
Spec (seg)	30% (9/30)	33% (10/30)	0.32
PPV (seg)	69% (47/68)	69% (45/65)	0.99
NPV (seg)	82% (9/11)	71% (10/14)	0.66
PAC (seg)	71% (56/79)	70% (55/79)	0.56
ROC area	0.66 ± 0.07	0.67 ± 0.07	0.60

NPV = negative predictive value; Optimal cutoff = optimal cutoff for viability expressed as percent of peak activity; PAC = predictive accuracy; PPV = positive predictive value; ROC area = area under the receiver operating characteristic curve (mean ± SD); (seg) = number of segments; Sens = sensitivity; Spec = specificity.

redistribution Tl-201 activity; and 2) rest Tc-99m tetrofosmin imaging had a diagnostic performance in predicting functional improvement after revascularization comparable to rest-redistribution Tl-201.

Tc-99m tetrofosmin as a marker of myocardial viability. Having demonstrated that the diagnostic performance of Tc-99m tetrofosmin in detecting viable myocardium is comparable to that of Tl-201, there are several advantages of the use of Tc-99m tetrofosmin rather than Tl-201: 1) The favorable emitting energy of Tc-99m (140 keV) reduces the photon attenuation compared with that of Tl-201. 2) The effective dose equivalent for an administration of 500 to 700 MBq of Tc-99m tetrofosmin is reportedly <50% of that of a typical Tl-201 study (111 MBq) and even lower than that of Tc-99m sestamibi (1), indicating the favorable radiation dosimetry of this agent. 3) It is convenient for patients that the entire imaging procedure be completed within 1.0 to 1.5 h with Tc-99m tetrofosmin, whereas rest-redistribution Tl-201 protocol usually requires at least 3 to 4 h.

According to recent experimental studies (18), the uptake and retention of Tc-99m tetrofosmin into myocytes is a process that may be inhibited by gross metabolic blockade, suggesting that the uptake of this agent may reflect cellular viability.

Regional distribution of Tc-99m tetrofosmin and Tl-201. Our present data showed that regional Tc-99m tetrofosmin activity at rest closely correlated with initial and redistribution Tl-201 activity ($r = 0.91$ and $r = 0.93$, respectively). This finding is consistent with our previous reports that regional reinjection Tl-201 activity is highly correlated with resting Tc-99m tetrofosmin activity (11) and that defect size on reinjection Tl-201 images is similar to that on rest Tc-99m tetrofosmin images (19).

Notably, regional Tc-99m tetrofosmin activity in the areas of Tl-201 redistribution was higher than that of initial Tl-201 activity but slightly lower than that for redistribution Tl-201. Similar findings are reported for Tc-99m sestamibi (8), which may suggest that Tc-99m tetrofosmin activity tracks myocardial viability, not just blood flow in hypoperfused but viable myocardium. In a canine study by Sinusas et al. (20), Tc-99m tetrofosmin was overextracted at low flow ranges, which may also contribute to our observation. Conversely, Tc-99m tetrofosmin uptake in the segments with Tl-201 reverse redistribution was lower than initial Tl-201 uptake but higher than redistribution Tl-201 uptake. In patients with chronic CAD, reverse redistribution of Tl-201 at rest was reported by Pace et al. (14). In their study, the myocardial regions with rest Tl-201 reverse redistribution showed reduced Tc-99m sestamibi uptake compared with initial Tl-201 uptake. Although it is not clear whether their observation with Tc-99m sestamibi directly relates to our findings with Tc-99m tetrofosmin, it can be argued that the reduced Tc-99m tetrofosmin uptake compared with the initial Tl-201 uptake in areas of Tl-201 reverse redistribution was due to impaired cellular viability despite maintained blood flow.

One may speculate that Tc-99m tetrofosmin redistribution over time may have contributed to our observation. Several

studies have shown (9,21) that Tc-99m sestamibi may redistribute to some degree and that the presence of Tc-99m sestamibi redistribution may be useful for assessing viability. However, unlike Tc-99m sestamibi, Tc-99m tetrofosmin appears to have minimal, if any, ability to redistribute over time as demonstrated by Sridhara et al. (2) and by our previous report (11). Furthermore, a recent experimental study (22) also indicated that Tc-99m tetrofosmin redistribution was negligible compared with Tl-201 and even Tc-99m sestamibi. Thus, it is not likely that Tc-99m tetrofosmin redistribution occurred to a relevant degree in the present study.

Optimal threshold value for predicting functional recovery with Tc-99m tetrofosmin and Tl-201. ROC analysis is a graphic approach to determining the best threshold cutoff level for making a decision based on a continuous measurement (12). Determination of the cutoff levels requires assessment of clinical impact (not only financial cost) associated with false positive and negative results. In the present study, the optimal threshold was chosen to maintain a high sensitivity >88%, which was derived from the previous viability studies using Tl-201 (7,8,10), resulting in accepting a relatively high false positive fraction. However, our results are not inconsistent with previous reports. In particular, Ragosta et al. (7) reported that 27 of 87 segments with no functional improvement were correctly identified as nonviable by rest-redistribution Tl-201 imaging, indicating that the specificity in their study was only 31%.

The optimal threshold cutoff of Tc-99m tetrofosmin (50% of peak) appeared to be slightly lower than that of Tl-201 (55% of peak). Although the precise mechanisms are not clear, there are several possible explanations that may contribute to our results: 1) Although tracer distribution of Tc-99m tetrofosmin is very similar to that of redistribution Tl-201, it is not identical, as demonstrated in the present report (e.g., in areas of Tl-201 redistribution, Tc-99m tetrofosmin activity was slightly lower than Tl-201 activity). 2) Because Tc-99m offers better resolution than Tl-201, reduced regional activity in small areas could be better recognized with Tc-99m tetrofosmin and thus revealed more reduced activity than with Tl-201.

Tetrofosmin and Tl-201 imaging in predicting functional recovery. Our data indicate that the diagnostic performance of Tc-99m tetrofosmin in predicting functional recovery after revascularization is similar to that of Tl-201, which is supported by nearly superimposable ROC curves between Tc-99m tetrofosmin and Tl-201 images. This finding is explained by the highly significant correlation of regional tracer activities between rest Tc-99m tetrofosmin and redistribution Tl-201 images.

As described earlier, the specificities were not satisfactory with both tracers. Only segments with successful revascularization, confirmed by follow-up CAG, were analyzed in this study and is based on previous studies (7,8) that have stressed the importance of the success of revascularization in optimizing pre-revascularization viability predictive values. Although some functional improvement may occur even in the territories of incomplete revascularization, probably due to temporary restoration of flow as reported in the present study (two of

seven segments), including such territories in the analysis would cause discordance between preoperative assessment and postoperative recovery.

There are at least two potential factors to explain the relatively low specificities in the present study: 1) The follow-up period after revascularization was relatively short in some patients. It is therefore possible that functional recovery may not have been completed in some segments within the observation period. 2) The scintigraphic data were not blinded to the attending clinicians because TI-201 imaging is an accepted diagnostic technique for assessing viability in the clinical setting. As one would expect, the patients with successful revascularization had a slightly higher mean regional tracer uptake within dysfunctional areas on both TI-201 and Tc-99m tetrofosmin images than those without revascularization (Table 1), suggesting that the scintigraphic results may have been used in determining which patients would undergo revascularization. This selection may also have contributed to the relatively low specificities observed in our study.

However, our data also indicate that viable myocardium by scintigraphic methods without functional recovery had better baseline regional contractile function than the scintigraphically nonviable segments, suggesting that a large part of such segments are apparently viable but may not be ischemically compromised. Because disease progression in such myocardium could cause worsening of contractile function if not revascularized, revascularization of such myocardial segments may have potential benefit to prevent worsening of LV function.

Because global LV function is clinically more important than regional function, we assessed the diagnostic value of Tc-99m tetrofosmin and TI-201 for improvement of global LV function. As expected from the results of regional wall motion analysis, both protocols equally predicted functional recovery after revascularization. The absence of scintigraphically viable myocardium was a strong negative predictor of global functional recovery, whereas the presence of three or more viable segments was a fair predictor of improvement in global function.

Study limitations. There are several limitations of the study:

1. We assessed regional and global LV wall motion by planar GBP. Because planar GBP provides only two-dimensional information, the comparison with three-dimensional images, such as those obtained with SPECT, is not ideal.

2. Apical activity was determined from the set of short-axis tomograms in this study. Therefore, it could be argued that whether the apical slice was truly representative of apical activity may be uncertain. However, this technique has also been used in previous reports (9,13). In addition, great care was taken to select the most apical slice to avoid potential geometric errors.

3. Because the number of patients with functional outcome data in this study was limited as is common in such viability studies, we cannot completely rule out the fact that either rest-redistribution TI-201 or rest Tc-99m tetrofosmin has a slightly better diagnostic performance in predicting functional recovery. However, given the high correlation of regional

tracer activities and nearly superimposable ROC curves between the two agents observed in this study, we believe that the diagnostic performance of both protocols for detecting viable myocardium and predicting functional recovery is similar.

Conclusions. Our data indicate that quantitative rest Tc-99m tetrofosmin SPECT provides information on myocardial viability comparable to the conventional rest-redistribution TI-201 protocol. When the lower radiation dosimetry and shorter imaging time period are considered, rest Tc-99m tetrofosmin imaging can be one of the practical diagnostic protocols in patients with CAD and LV dysfunction who are being considered for revascularization.

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References

- Higley B, Smith FW, Smith T, et al. Technetium-99m-1, 2-bis[bis(2-ethoxyethyl) phosphino]ethane: human biodistribution, dosimetry and safety of a new myocardial perfusion imaging agent. *J Nucl Med* 1993;34:30-8.
- Sridhara BS, Braat S, Rigo P, Itti R, Cload P, Lahiri A. Comparison of myocardial perfusion imaging with technetium-99m tetrofosmin versus thallium-201 in coronary artery disease. *Am J Cardiol* 1993;72:1015-19.
- Nakajima K, Taki J, Shuke N, Bunko H, Takata S, Hisada K. Myocardial perfusion imaging and dynamic analysis with technetium-99m tetrofosmin. *J Nucl Med* 1993;34:1478-84.
- Tamaki N, Takahashi N, Kawamoto M, et al. Myocardial tomography using technetium-99m-tetrofosmin to evaluate coronary artery disease. *J Nucl Med* 1994;35:594-600.
- Zaret BL, Rigo P, Wackers FJT, et al. Myocardial perfusion imaging with ^{99m}Tc tetrofosmin: comparison to ²⁰¹Tl imaging and coronary angiography in a phase III multicenter trial. *Circulation* 1995;91:313-9.
- Dilsizian V, Bonow RO. Current diagnostic techniques of assessing myocardial viability in patients with hibernating and stunned myocardium. *Circulation* 1993;87:1-20.
- Ragosta M, Beller GA, Watson DD, Kaul S, Gimple LW. Quantitative planar rest-redistribution ²⁰¹Tl imaging in detection of myocardial viability and prediction of improvement in left ventricular function after coronary bypass surgery in patients with severely depressed left ventricular function. *Circulation* 1993;87:1630-41.
- Udelson JE, Coleman PS, Metherall J, et al. Predicting recovery of severe regional ventricular dysfunction: comparison of resting scintigraphy with ²⁰¹Tl and ^{99m}Tc-sestamibi. *Circulation* 1994;89:2552-61.
- Dilsizian V, Arrighi JA, Diodati JG, et al. Myocardial viability in patients with chronic coronary artery disease: comparison of ^{99m}Tc-sestamibi with thallium reinjection and [¹⁸F]fluorodeoxyglucose. *Circulation* 1994;89:578-87.
- Marzullo P, Sambucetti G, Parodi O, et al. Regional concordance and discordance between rest thallium 201 and sestamibi imaging for assessing tissue viability: comparison with postrevascularization functional recovery. *J Nucl Cardiol* 1995;2:309-16.
- Matsunari I, Fujino S, Taki J, et al. Myocardial viability assessment with technetium-99m-tetrofosmin and thallium-201 reinjection in coronary artery disease. *J Nucl Med* 1995;36:1961-7.
- Metz CE. Basic principles of ROC analysis. *Semin Nucl Med* 1978;8:283-98.
- Matsunari I, Tanishima Y, Taki J, et al. Early and delayed technetium-99m-tetrofosmin myocardial SPECT compared in normal volunteers. *J Nucl Med* 1996;37:1622-6.
- Pace L, Cuocolo A, Maurea S, et al. Reverse redistribution in resting thallium-201 myocardial scintigraphy in patients with coronary artery disease: relation to coronary anatomy and ventricular function. *J Nucl Med* 1993;34:1688-92.

15. Vera DR, Stadalnik RC, Metz CE, Pimstone NR. Diagnostic performance of a receptor-binding radiopharmacokinetic model. *J Nucl Med* 1996;37:160-4.
16. vom Dahl J, Eitzman DT, Al-Aouar ZR, et al. Relation of regional function, perfusion and metabolism in patients with advanced coronary artery disease undergoing surgical revascularization. *Circulation* 1994;90:2356-66.
17. Metz CE, Wang PL, Kronman HB. A new approach for testing the significance of differences between ROC curves measured from correlated data. In: Deconinck F, editor. *Information Processing in Medical Imaging*. The Hague: Nijhoff, 1984:432-45.
18. Platts EA, North TL, Pickett RD, Kelly JD. Mechanism of uptake of technetium-tetrofosmin. I: uptake into isolated adult rat ventricular myocytes and subcellular localization. *J Nucl Cardiol* 1995;2:317-26.
19. Matsunari I, Fujino S, Taki J, et al. Comparison of defect size between thallium-201 and technetium-99m tetrofosmin myocardial single-photon emission computed tomography in patients with single-vessel coronary artery disease. *Am J Cardiol* 1996;77:350-4.
20. Sinusas AJ, Shi Q-X, Saltzberg MT, et al. Technetium-99m-tetrofosmin to assess myocardial blood flow: experimental validation in an intact canine model of ischemia. *J Nucl Med* 1994;35:664-71.
21. Sinusas AJ, Bergin JD, Edwards NC, et al. Redistribution of ^{99m}Tc -sestamibi and ^{201}Tl in the presence of a severe coronary artery disease. *Circulation* 1994;89:2332-41.
22. Takahashi N, Reinhardt CP, Marcel R, Leppo JA. Myocardial uptake of ^{99m}Tc -tetrofosmin, sestamibi, and ^{201}Tl in a model of acute coronary reperfusion. *Circulation* 1996;94:2605-13.