^{99m}Tc-Tetrofosmin SPECT for Prediction of Functional Recovery Defined by MRI in Patients with Severe Left Ventricular Dysfunction: Additional Value of Gated SPECT

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This study was designed to evaluate gated ^{99m}Tc-tetrofosmin SPECT for prediction of functional recovery proven by sequential MRI. ^{99m}Tc-labeled tetrofosmin is a recently introduced tracer for myocardial perfusion. However, its role for viability assessment is still under investigation. **Methods:** ^{99m}Tc-tetrofosmin uptake in 19 patients with coronary artery disease and severe left ventricular dysfunction was correlated to regional wall thickening before and 4.5 ± 0.8 mo after successful coronary artery bypass grafting, as derived from corresponding gated short-axis MRI. Preoperative wall thickening determined by gated SPECT was used as an additional parameter for prediction of functional outcome. Optimal threshold cutoffs to separate reversible from irreversible dysfunction were determined by receiver operator characteristic (ROC) analysis. **Results:** The sensitivity and specificity of regional ^{99m}Tc-tetrofosmin for prediction of functional recovery was 87% and 42%, respectively (cutoff: 50% of maximum tracer retention). The area under ROC curves for prediction of functional recovery measured 0.66 ± 0.01. Segments with ≥50% uptake and impaired but detectable wall thickening determined by gated SPECT had a significantly higher likelihood for functional improvement compared with segments with absent wall thickening ($P < 0.05$). There was no difference in segments with <50% tracer retention. There was good agreement for ejection fraction measurements by MRI and gated SPECT (mean ejection fraction 32 ± 12 versus 34 ± 11; $r = 0.71$, $P < 0.001$). **Conclusion:** Regional ^{99m}Tc-tetrofosmin uptake provided high sensitivity but limited specificity for prediction of functional recovery after revascularization, leading to fair overall accuracy. Wall thickening assessment derived from gated SPECT may improve the specificity of ^{99m}Tc-tetrofosmin uptake for prediction of functional recovery but not the sensitivity in low-flow areas. In addition to the assessment of global function, gated data acquisition can be helpful to improve the overall accuracy of ^{99m}Tc-tetrofosmin SPECT for prediction of functional recovery after bypass surgery.

Key Words: gated SPECT; ^{99m}Tc-tetrofosmin; left ventricular function; gated MRI

J Nucl Med 1999; 40:1824–1831

In patients with chronic myocardial infarction and impaired left ventricular function, the distinction between left ventricular dysfunction as a result of irreversible damaged scar tissue and akinetic but still viable myocardium has important clinical implications (*1*). Several imaging techniques that depict different variables of myocardial viability are used to detect viable myocardium in akinetic or dyskinetic myocardial regions (*2–6*).

^{99m}Tc-tetrofosmin has been recently introduced as a tracer for myocardial perfusion as an alternative to ^{99m}Tc-sestamibi or ^{201}Tl imaging (*7–10*). Similar to ^{99m}Tc-sestamibi, the tissue retention of ^{99m}Tc-tetrofosmin is primarily determined by myocardial blood flow. However, myocyte cell membrane integrity and, thus, myocardial viability are prerequisites for both sestamibi and ^{99m}Tc-tetrofosmin uptake (*7,11*). Recent studies showed comparable diagnostic accuracy for ^{99m}Tc-tetrofosmin uptake and ^{201}Tl imaging for detection of myocardial viability as defined by functional outcome (*12,13*). Most of these investigations used two-dimensional approaches for definition of functional recovery, such as multiple gated blood pool studies or echocardiography, which are not optimal for comparison with three-dimensional SPECT. Excellent sensitivity but limited specificity was reported, leading to fair overall accuracy for ^{99m}Tc-tetrofosmin retention (*12,13*). However, gated SPECT offers potential not only for evaluation of tracer retention, but also for assessment of global and regional left ventricular function. Regional systolic wall thickening (WT) is an important parameter of function because it potentially indicates viable myocardium (*14*). We hypothesized that regional myocardial WT derived from gated SPECT can be used as a parameter for prediction of functional outcome in addition to regional myocardial ^{99m}Tc-tetrofosmin uptake.

This study was undertaken to assess the predictive value of regional ^{99m}Tc-tetrofosmin retention for functional recovery in patients with advanced coronary artery disease and severe left ventricular dysfunction, using MRI as a gold standard, and to investigate whether preoperative WT as-

Received Oct. 13, 1998; revision accepted Apr. 9, 1999.

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sessment by gated SPECT can improve the sensitivity or specificity for prediction of functional outcome, in addition to the classic approach of measuring semiquantitative tracer retention on nongated images.

MATERIALS AND METHODS

Patients

Nineteen patients (18 men, 1 woman; age range 40–78 y, mean age 60 y) with known coronary artery disease and severely impaired left ventricular function were prospectively selected before bypass surgery. Of the 19 patients, 15 (79%) had a history of myocardial infarction (7 anterior, 1 inferior, 2 both anterior and inferior and 5 of unknown site). All patients underwent cardiac catheterization according to standard procedures, including ventriculography. All films were interpreted by experienced observers without knowledge of the other noninvasive modalities. Fifteen patients had three-vessel coronary artery disease and 4 patients had two-vessel disease. Inclusion criteria were angiographic left ventricular ejection fraction (EF) < 40% (mean 35% ± 7%, range 21%–43%) or severe wall motion abnormality. Three patients were included with severe regional wall motion abnormalities and EF values between 40% and 43%. Exclusion criteria included previous bypass grafting or angioplasty, significant arrhythmia (atrial fibrillation), a ventricular pacemaker, recent myocardial infarction (<8 wk), unstable angina, concomitant heart disease (valve disease, cardiomyopathy) and childbearing potential. Patients did not receive any cardiac medication 12 h before the study. Long-acting nitrates were discontinued for 24 h before the study. The study protocol was approved by the hospital ethics committee, and all patients gave written informed consent.

Study Protocol

All patients underwent gated ^{99m}Tc-tetrofosmin SPECT and gated MRI within 1 wk before coronary artery bypass grafting. The follow-up MRI was performed 4.5 ± 0.8 mo (minimum of 3 mo) after surgical intervention. Bypass surgery was performed using standard techniques, with revascularization of all vessels with >70% stenosis if technically feasible. The surgeons were not aware of the MRI results or of the ^{99m}Tc-tetrofosmin imaging findings. Of 53 vessel territories, 36 (68%) were revascularized (17/19 left anterior descending artery [LAD], 11/17 right coronary artery [RCA] and 8/17 left circumflex artery [Lcx] territories).

^{99m}Tc-Tetrofosmin Imaging

Resting electrocardiographic-gated ^{99m}Tc-tetrofosmin (Myoview; Amersham International, Buckinghamshire, UK) SPECT was performed with a triple-head camera (Multispect 3; Siemens, Inc., Knoxville, TN). Imaging was started 30 min after injection of 280–370 MBq ^{99m}Tc-tetrofosmin. Acquisition parameters were as follows: matrix 64 × 64, three heads with clockwise rotation of 120° each (total 360°), 20 views per head and 40,000 ms per view, resulting in an acquisition time of 20 min. Gating was performed using 12 frames with 75% forward–backward framing. Three-head reconstruction (360°) was performed with a Butterworth filter, with a critical frequency of 0.45 cycle per pixel. The reconstruction time was 10 min. The resulting transverse images were reoriented into oblique tomograms (slice thickness of 1 pixel), as well as horizontal and vertical long-axis slices.

MRI

Resting MRI was performed within 24 h of the SPECT study with a 1.5-T ACS II (Philips Medical Systems, Best, The Netherlands) equipped with a standard whole-body coil. A fast gradient echo sequence was acquired using a multiphase, multislice technique with 10 planes (slice thickness of 8–10 mm) in a twofold reangulated short-axis orientation (echo time 9.4 ms, flow compensated; repetition time 800–1000 ms). ECG-gating was performed using 12 gates per cardiac cycle. The acquisition was also triggered by a breath signal. The acquisition matrix was 128 × 128 pixels in a field of view of 32.5 cm.

Left Ventricular Ejection Fraction

MRI EF was calculated on short-axis slices using manually drawn endocardial borders on end-diastolic (ED) and end-systolic (ES) images (*15,16*). SPECT EF was determined on left ventricular ES and ED horizontal and vertical long-axis slices with a computation algorithm developed by DePuey et al. (*17*), which was implemented in the Siemens software. Analysis was performed without algorithms enhancing the visual appearance of the myocardial contours in low-flow areas. The observer was free to alter brightness and contrast to gain as much information as possible concerning the location of the endocardial borders.

Image Analysis

Analysis of MRI and SPECT images was performed by different observers without knowledge of clinical data and patient identity. For analysis of regional WT and uptake, the myocardium was divided into 13 segments for both SPECT and MRI (1 apical, 6 distal and 6 basal). The 4 septal segments were excluded from analysis because of the effects of bypass surgery on septal wall motion (*18,19*). Thus, 171 regions were eligible for analysis. Functional recovery was assumed in segments showing more than 1 score point of improvement between presurgical and postsurgical MRI studies.

For analysis of ^{99m}Tc-tetrofosmin uptake, the frames of the raw projection data were summed and nongated tomograms were reconstructed. Tracer uptake on summed images was calculated with an automated circumferential profile analysis and expressed as a percentage of maximum uptake (*20*). Tracer uptake was assessed in the same 9 segments available for analysis.

SPECT wall thickening was defined as visual brightening (increase in counts during a cardiac cycle). Visual analysis of SPECT WT was performed on short-axis images with a semiquantitative five-point score (5 = absent thickening; 4 = severely reduced thickening; 3 = moderately reduced thickening; 2 = mildly reduced thickening; 1 = normal thickening). MRI WT before and after surgery was determined on corresponding cine short-axis images using the same scoring system. Potential for functional improvement was assumed in areas with impaired but still detectable SPECT WT (score of 2–4).

Statistical Analysis

The diagnostic accuracy of summed ^{99m}Tc-tetrofosmin uptake for prediction of functional recovery was investigated by receiver operating characteristic (ROC) analysis curves. ROC analysis was performed with Clabroc (University of Chicago, Chicago, IL) (*21*). Sensitivity, specificity and predictive values for functional recovery with and without consideration of additional SPECT WT data were calculated. Association between defect prevalence and EF was evaluated with Spearman rank correlation (Statview 4.5; Abacus Concepts Inc., Berkeley, CA). Differences between groups were evaluated with χ^2 analysis or the Fisher exact test when appropriate (HCstat 0.3 0.9; Apple Computer, Inc., Cupertino, CA).

RESULTS

All 19 patients completed the SPECT and MRI studies without complications and with good image quality. Figure 1 shows an example of a patient with improved ventricular function after bypass grafting to the LAD and RCA. Figure 2 shows an example of a patient without functional improvement.

Patient Analysis and ^{99m}Tc-Tetrofosmin Distribution

With a semiquantitative analysis of tracer uptake expressed as a percentage of the maximum, 42 of 171 (24%) segments had normal uptake (≥80%), 66/171 (39%) segments had mildly reduced uptake (60%–79%), 50 of 171 (29%) segments had moderately reduced tracer uptake (40%–59%) and 13 of 171 (8%) segments had severely reduced uptake (<40%). The latter group included 2 segments below 20% of maximum uptake. As expected, the likelihood for functional improvement in segments with impaired WT thickening increased with tracer uptake and the severity of presurgical functional impairment (Table 1).

The average defect size (number of segments with moderate or severe defects divided by 9) in an individual patient, judged by visual interpretation and quantitative measurements of uptake, was 21% ± 17% and 25% ± 15% of the whole left ventricle, respectively. There was an inverse relation of global function (EF) measured by MRI (visual uptake: $r = 0.44$, $P < 0.05$; quantitative uptake: $r = 0.51$, $P < 0.02$) and the number of segments with severely reduced uptake (<0%).

Effect of Revascularization on Regional Myocardial Wall Motion

Of 53 vessel territories, 36 (68%) were revascularized (17/19 LAD, 11/17 RCA and 8/17 Lcx). All 19 patients had at least 1 successfully revascularized vessel territory. Of a total of 131 asynergic segments (>mild reduction of WT) in 19 patients, 115 segments (88%) were revascularized. Of these, 63 segments (55%) in 17 patients showed an improvement in regional function, whereas 52 segments did not, despite vascular intervention. Of 131 segments, 16 (12%) in 6 patients were not revascularized, considering the presumable vessel territories. Three nonrevascularized segments in 3 patients showed regional improvement in function (1 score point).

Prediction of Regional Functional Recovery by ^{99m}Tc-Tetrofosmin SPECT

Sensitivity and specificity, as well as positive and negative predictive accuracy, for three different cutoffs are summarized in Table 2. The optimal threshold was considered to be 50% of maximum tracer retention. ROC curves for prediction of functional recovery after revascularization are presented in Figure 3. Including segments with more than moderately impaired baseline WT, the area under the ROC curve (AUC) for overall prediction of functional recovery measured 0.64 ± 0.05 (0.69 ± 0.07 for the segments with more than mildly impaired WT at baseline).

There was no significant difference between anterior and inferior segments in sensitivity (100% [31/31] versus 81% [21/26], respectively), specificity (6% [2/31] versus 35% [11/31], respectively) and positive predictive accuracy (52% [31/60] versus 51% [21/41], respectively). However, the negative predictive accuracy was significantly lower for inferior segments, considering a cutoff of 50% of maximum tracer uptake (100% [2/2] versus 68% [11/16]). There were five inferior segments showing functional improvement, despite a tracer uptake <50%. Considering a lower threshold of 45%, there were only two segments showing functional improvement below the cutoff (36% and 30% ^{99m}Tc-

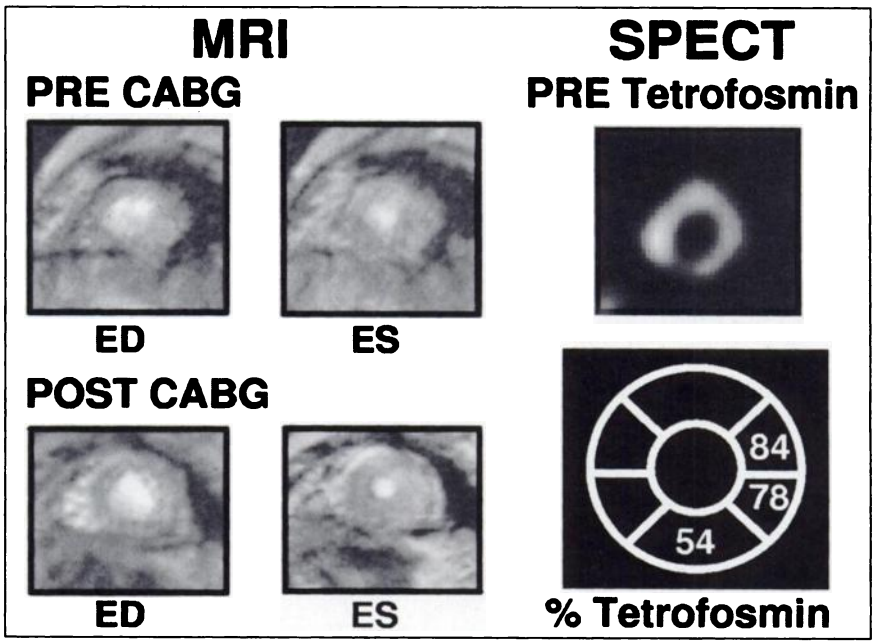

FIGURE 1. Corresponding MR and ^{99m}Tc-tetrofosmin SPECT short-axis images of patient with inferior infarction (top row). Corresponding MR images 3 mo after coronary artery bypass grafting (CABG) (bottom row). Small distal inferior perfusion abnormality at rest before surgery (54% of maximum uptake; see bull's-eye analysis, left bottom row) corresponds to some myocardial wall thinning on short-axis MR images. Regional wall thickening improved by one score 3 mo after CABG. Global EF improved from 32% to 47%. ED = end diastolic; ES = end systolic.

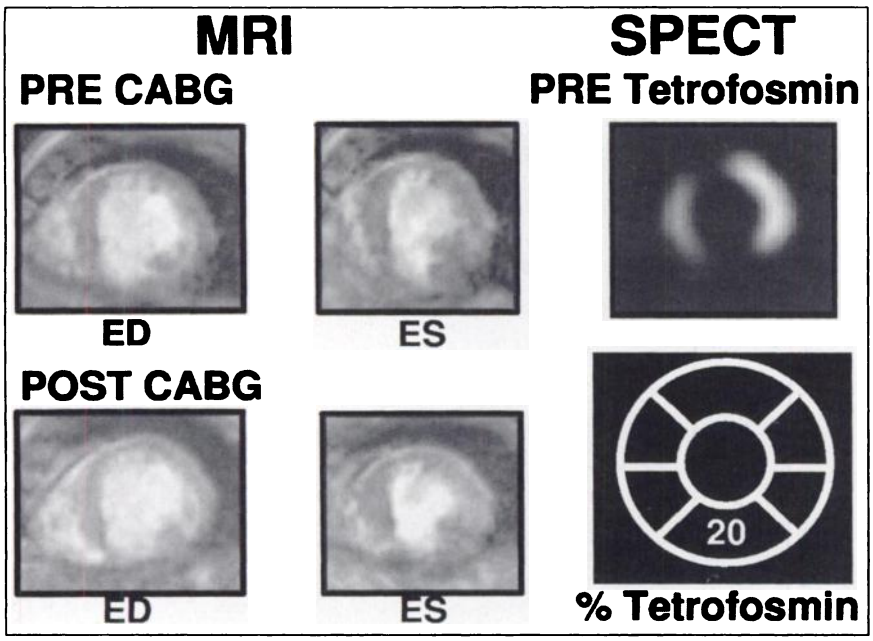

FIGURE 2. Corresponding MR and ^{99m}Tc-tetrofosmin SPECT short-axis images of patient with inferior and anterior infarction (top row). Corresponding MR images 3 mo after coronary artery bypass grafting (CABG) (bottom row). Both inferior and anterior perfusion abnormalities at rest before surgery (20% of maximum uptake in inferior segment; see bull's-eye analysis, left bottom row) correspond to obvious myocardial wall thinning on short-axis MR images. There was no improvement in regional or global function 3.5 mo after CABG (EF 19% before and 22% after surgery). ED = end diastolic; ES = end systolic.

tetrofosmin uptake), resulting in a negative predictive accuracy of 88% (sensitivity 92%). However, areas under ROC curves were not significantly different for inferior and anterior segments, indicating that the difference between these regions can be at least partially resolved by considering a lower uptake threshold for inferior segments (WT score > 2: 0.65 ± 0.07 inferior and 0.62 ± 0.05 anterior, $P = 0.45$; WT score > 3: 0.69 ± 0.07 inferior and 0.67 ± 0.09 anterior, $P = 0.60$).

Gated SPECT Wall Motion Analysis

Analysis was based on 18 patients (one data file was nongated). The prevalence of functional recovery, considering an additional WT assessment by preoperative gated SPECT, is summarized in Table 3. Segments with >50% maximum tracer retention and detectable but impaired SPECT WT (score of 2–4) had a higher chance for functional recovery compared with segments with absent WT (79% versus 44%, $P < 0.02$). However, there was no significant difference in segments with <50% tracer retention (25% versus 42%). Thus, it can be expected that the additional consideration of SPECT WT may lead to an increase in specificity and no improvement of sensitivity.

To calculate these values, the combination of >50% uptake and preserved SPECT WT was considered indicative of functional recovery and the combination of <50% uptake and absent WT was considered indicative of no functional change. The results are compared with those considering uptake alone and are shown in Table 4. As expected, there is higher specificity, positive predictive value and overall predictive accuracy for the combined approach using uptake and additional SPECT WT information. However, this approach did not show statistically significant differences (Fisher exact test). A potential reason may be that the segments considered for combined uptake and WT assessment are part of the group considering uptake alone, thereby reducing the differences compared with the approach shown in

TABLE 1
Relation Between Tracer Uptake and Likelihood for Functional Recovery in Segments with Impaired Wall Thickening

Finding	Tetrofosmin uptake (%) ≥80	60–79	40–59	<40	<20
Presurgery WTA Improved segments	55	47	45	18	0
No change	45	53	55	82	100
Presurgery WTA Improved segments	71	68	62	20	0
No change	29	32	38	80	100

WTA = wall thickening abnormality.

TABLE 2
Prediction of Regional Functional Recovery for Three Levels of Uptake Cutoff by ^{99m}Tc-Tetrofosmin SPECT

Index	Uptake cutoff (%) 40	50	60
Sensitivity	95 (36/38)	87 (33/38)	61 (23/38)
Specificity	33 (8/24)	42 (11/26)	61 (16/26)
PPV	67 (36/54)	69 (33/48)	70 (23/33)
NPV	80 (8/10)	69 (11/16)	52 (16/31)
PAC	69 (44/64)	69 (44/64)	61 (39/64)

PPV = positive predictive value; NPV = negative predictive value; PAC = predictive accuracy.

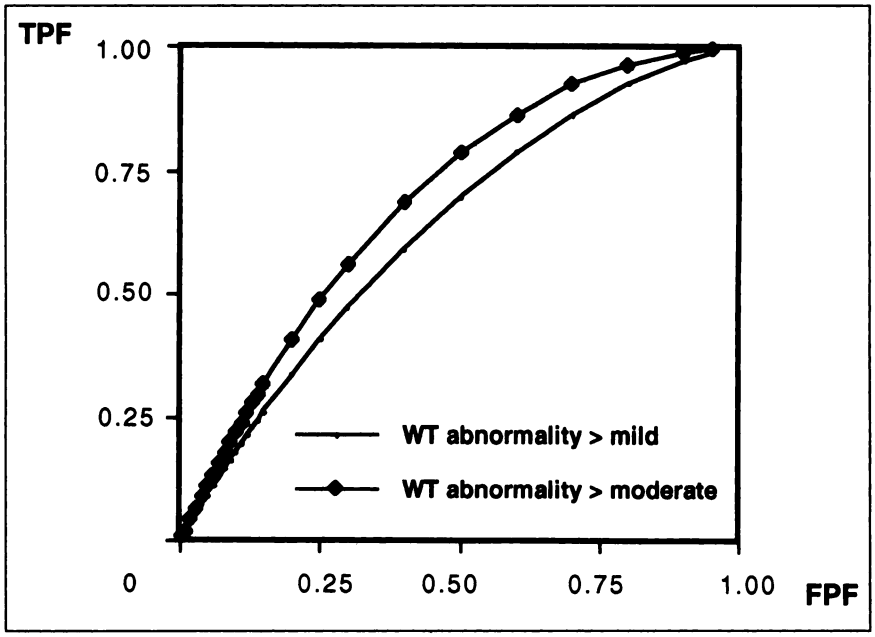

FIGURE 3. AUC of ROC (fitted) curves analyzing ^{99m}Tc-tetrofosmin for detection of reversible regional dysfunction in asynergic segments with more than mild and more than moderate baseline wall thickening (WT) reduction. Plots were generated by calculating sensitivity and specificity pairs for every 5% of peak activity retention. ● = more than mild baseline WT reduction; ■ = more than moderate baseline WT reduction; TPF = true-positive fraction (%); FPF = false-positive fraction (%).

Table 3. The small number of segments also contributes to the lack of statistical significance.

Average tracer uptake was lower in segments with absent WT compared with segments with detectable but impaired WT (≥50% uptake: 63% ± 10% versus 75% ± 11%; <50% uptake: 34% ± 8% versus 41% ± 10%). However, it has been previously shown that the accuracy of SPECT WT assessment is not independent of tracer retention and declines with defect severity (*22–24*).

Gated SPECT Ejection Fraction Analysis

SPECT EF was correlated with preoperative EF values measured by MRI in 18 patients. SPECT EF for all patients ranged from 17% to 48%. Overall correlation between EF determined by SPECT and MRI was 0.71 ($P < 0.001$). However, the relatively low value is not surprising because of the small range of EFs for this patient population (Fig. 4). Mean EF determined by SPECT and MRI was 34% ± 11% and 32% ± 11%, respectively (not significantly different). Mean significant difference in EF determined by SPECT and MRI was 1.5% ± 5.4% and considered insignificant. When considering >5% as a significant difference in EF between presurgical SPECT and MRI measurements, there were 4 patients with overestimation of EF by gated SPECT and 3 patients with underestimation.

Prediction of Global Functional Improvement by ^{99m}Tc-Tetrofosmin

EF before bypass surgery determined by MRI ranged from 11% to 58% (mean 32% ± 11%). Of 19 patients, 11

TABLE 3
Prediction of Regional Functional Recovery by ^{99m}Tc-Tetrofosmin SPECT Considering Preoperative SPECT Wall Thickening

SPECT finding	Percentage of segments with functional recovery	
	Uptake ≥ 50%	Uptake < 50%
Wall thickening		
Normal	75 (3/4)	0 (0/0)
Mildly reduced	66 (2/3)	0 (0/1)
Moderately reduced	71 (10/14)	50 (1/2)
Severely reduced	100 (8/8)	0 (0/1)
Preserved	79 (23/29)*	25 (1/4)†
Absent	44 (7/16)*	42 (5/12)†

*Not statistically significant.
†$P < 0.02$.
Fifty percent of maximum activity was used as a cutoff. Preoperative wall thickening scores were considered and summarized in segments with impaired but detectable (score: normal to severely reduced) as well as absent wall thickening categories.

TABLE 4
Prediction of Regional Functional Recovery by ^{99m}Tc-Tetrofosmin SPECT for Uptake Alone and Combined with Wall Thickening (WT)

Index	Percentage of segments with functional recovery	
	Uptake alone (cutoff 50%)	Combined uptake and WT assessment*
Sensitivity	87 (36/38)	82 (23/28)
Specificity	42 (11/26)†	54 (7/13)†
PPV	69 (33/48)†	79 (23/30)†
NPV	69 (11/16)	58 (7/12)
PAC	69 (44/64)†	73 (30/41)†

*Preserved or absent preoperative SPECT wall thickening.
†Not statistically significant.
The segments eligible were restricted to those with more than moderate reduction of baseline MRI wall thickening.

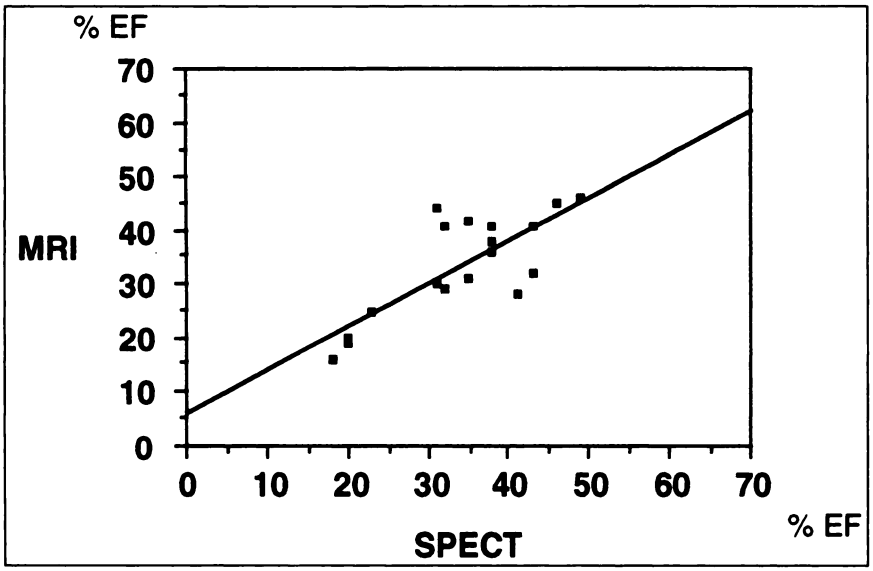

FIGURE 4. Correlation between ejection fraction (EF) measured by MRI and SPECT. Mean values were not significantly different (SPECT: 34% ± 11%; MRI: 32% ± 11%). $r = 0.71$, $P < 0.001$.

(58%) had an improvement in EF of >5%. Using an arbitrary 5% change criterion, 5 of 19 (26%) patients had no significant change in EF, whereas 3 of 19 (16%) patients had a worsening in EF. The overall EF improved significantly from 32% ± 11% to 39% ± 12% ($P < 0.02$) Eight of 10 (sensitivity 80%) patients with more than 6 segments with ≥50% uptake showed a significant (≥5%) increase in global left ventricular EF (positive predictive value 67%). Of 9 patients, 4 with less than 6 segments with ≥50% tracer retention also showed an increase of >5% in left ventricular EF (specificity 57%). The negative predictive value was 71%.

DISCUSSION

The first of two major findings in this study was that ^{99m}Tc-tetrofosmin has fair overall accuracy in predicting regional functional recovery in patients with severe left ventricular dysfunction using tracer uptake on nongated images. Second, additional preoperative WT assessment with a gated SPECT protocol may improve the specificity and, thus, overall diagnostic accuracy of the classic approach of analyzing tracer tissue retention.

^{99m}Tc-Tetrofosmin as a Marker for Functional Outcome

There are only a few studies focusing on the accuracy of ^{99m}Tc-tetrofosmin SPECT for prediction of functional recovery. A study by Matsunari et al. (*12*) found good agreement between the diagnostic accuracy of preoperative ^{201}Tl and ^{99m}Tc-tetrofosmin imaging using regional tracer retention. Preoperative and follow-up radionuclide angiography were used to define regional and global functional improvement in successfully revascularized myocardial territories in 21 patients (*12*). The overall accuracy expressed by the AUC was very similar to that in our study (0.66 ± 0.07 versus 0.64 ± 0.05).

ROC analysis is a graphic approach to determine the best cutoff level for making a decision that is based on a continuous measurement (*25*). Determination of the cutoff level requires assessment of clinical impact and cost-effectiveness associated with false-positive and false-negative results. Choosing a cutoff level of 50% results in a relatively high sensitivity (33/38 segments, 87%), which means selecting most of the patients who may benefit from bypass surgery. However, the 50% cutoff resulted in accepting a relatively high number of segments above the threshold without functional improvement, thereby overestimating potential functional recovery. As expected, considering a threshold of 60% of maximum activity would improve the specificity at the expense of lowered sensitivity and overall predictive accuracy (Table 2). The limited specificity for prediction of functional improvement has already been reported for both ^{201}Tl and ^{99m}Tc-tetrofosmin with similar cutoff levels (*12–13,26*).

Several potential factors could explain the limited specificity of tetrofosmin imaging. First, the follow-up period was relatively short in some patients. It is therefore possible that functional recovery may not have been completed in some segments within the follow-up period. Second, the limited resolution of the SPECT system, along with the moving heart, leads to partial volume effects. The measurement of tracer retention within a myocardial segment represents an average of transmural tracer distribution that may or may not be homogeneous. A mixture of subendocardial infarction and normal myocardium within a transmural section may thus lead to the same segmental uptake compared with a more homogeneous distribution of ischemically compromised myocardium. It is apparent that the last myocardial section has a much higher likelihood for functional recovery after restoration of blood flow compared with the first one. Another factor could be the potential for incomplete revascularization, leading to a low number of segments showing functional improvement. The importance of the success of revascularization has already been stressed in previous

reports (*12,26*). However, we believe that the relatively low number of segments with incomplete revascularization (16/131, 12%) is unlikely to contribute significantly to the low specificity of tetrofosmin imaging in our study. Lastly, the surgeons were unaware of the results of both MR and tetrofosmin imaging. It is therefore unlikely that selection of patients with higher uptake or better ventricles for revascularization caused the relatively low specificity.

Gated SPECT Analysis

Gated SPECT using ^{99m}Tc-labeled flow markers is known to offer potential for simultaneous assessment of myocardial perfusion and of global and regional left ventricular function (*17,22,27*). Acceptable accuracy for assessment of regional WT and global EF by gated SPECT, even in patients with large perfusion defects, has been reported (*24*). However, our analysis was based on the assumption that segments with absent SPECT WT have a lower likelihood for functional recovery compared with segments with impaired but detectable WT. It was shown that segments with ≥50% tracer uptake and detectable residual SPECT WT had indeed a significantly higher likelihood for functional improvement compared with segments with absent WT. Thus, the rate of false-positive results would be lowered and specificity and overall predictive accuracy increased for prediction of functional recovery.

However, the differences with and without consideration of SPECT WT failed to be statistically significant (Fisher exact test). A potential reason may be that the segments considered for combined uptake and WT assessment are part of the subgroup considering uptake alone, thereby reducing the differences compared with the approach of Table 3. The low number of segments also contributes to the lack of statistical significance.

No improvement in sensitivity could be achieved using an additional WT criterion derived from preoperative gated SPECT analysis. However, in contrast to MRI, gated SPECT does not allow direct assessment of regional WT but relies on alleviated partial volume effects during systole, leading to a systolic increase in count recovery. It is also known that systolic count increase (ES count − ED count) and summed tracer uptake on nongated images are highly correlated (*24*). It is therefore most likely that summed uptake and count increase have similar limitations in low-flow areas because of partial volume effects and photon attenuation (*22–24*). However, simultaneous gating and attenuation correction for SPECT systems would be a promising approach. This protocol is the subject of current research; however, it is not yet available in routine clinical practice (*28*).

Regional Distribution of ^{99m}Tc-Tetrofosmin

All false-positive segments were in the inferior wall, which is consistent with nonattenuation-corrected data. The sensitivity could be improved by considering a lower threshold (≥45%) for inferior segments as indicative of viable myocardium; there were only two inferior segments showing functional improvement below this cutoff. However, looking at the overall diagnostic accuracy measured by the AUC, there was no significant difference between anterior and inferior segments, suggesting that the regional differences can be at least partially resolved by using a lower uptake threshold for inferior territories.

Limitations

The study has limitations. First, we did not perform quantitative analysis of short-axis MR images. Although quantitative analysis has recently been reported, visual interpretation of regional WT assessed by MRI is still the most widely used technique in a clinical setting (*29*). Second, the number of patients is limited, as is common in studies using functional outcome data, and the number of segments with <50% of maximum ^{99m}Tc-tetrofosmin retention is thus limited, raising the potential of type II error when analyzing subgroups in the low-uptake category. The relatively low number of segments may also contribute to the lack of statistical significance regarding the improvement in specificity and overall accuracy by adding SPECT WT measurements to regional tetrofosmin uptake on summed images. Finally, regional functional recovery after revascularization may not be an optimal endpoint. However, prospective evaluation of patients with severely impaired left ventricular function using long-term outcome, exercise capacity or quality of life as additional endpoints is still needed and requires long-term follow-up of large patient populations.

CONCLUSION

The data indicate that ^{99m}Tc-tetrofosmin retention has high sensitivity but limited specificity for prediction of functional recovery in patients with severely impaired left ventricular dysfunction, leading to fair overall accuracy. Most of the patients who potentially benefit from bypass surgery could be selected using a 50% cutoff for tracer retention on nongated images. However, fewer than half of the segments with >50% uptake improved in function, leading to limited specificity. WT assessment derived from gated SPECT may improve the limited specificity of ^{99m}Tc-tetrofosmin uptake for prediction of functional recovery. In addition to the assessment of global function, gated data acquisition can help improve the overall accuracy of ^{99m}Tc-tetrofosmin SPECT for the prediction of functional recovery after bypass surgery.

ACKNOWLEDGMENT

This study was supported by a grant from Amersham International, Buckinghamshire, UK.

REFERENCES

1. Gould KL. Myocardial viability: what does it mean and how to measure it? *Circulation.* 1991;83:333–335.
2. Baer FM, Voth E, Deutsch HJ, et al. Predictive value of low dose dobutamine transesophageal echocardiography and fluorine-18 fluorodeoxyglucose positron emission tomography for recovery of regional left ventricular function after successful revascularization. *J Am Coll Cardiol.* 1996;28:60–69.

3. Braunwald E, Rutherford JD. Reversible ischemic left ventricular dysfunction as evidence for "hibernating myocardium." *J Am Coll Cardiol.* 1986;8:1467–1470.
4. Brunken R, Tillisch J, Schwaiger M, et al. Regional perfusion, glucose metabolism and wall motion in patients with chronic electrocardiographic Q-wave infarction: evidence for persistence of viable tissue in some infarct regions by positron emission tomography. *Circulation.* 1986;73:951–961.
5. Tamaki N, Yonekura Y, Yamashita K, et al. Relation of left ventricular perfusion and wall motion with metabolic activity in persistent defects on thallium-201 tomography in healed myocardial infarction. *Am J Cardiol.* 1988;62:202–208.
6. Tillisch J, Brunken R, Marshall R, et al. Reversibility of cardiac wall motion abnormalities predicted by positron tomography. *N Engl J Med.* 1986;314:884–888.
7. 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;34:30–38.
8. Zaret BL, Rigo P, Wackers FJ, et al. Myocardial perfusion imaging with ^{99m}Tc tetrofosmin: comparison to ^{201}Tl imaging and coronary angiography in a phase III multicenter trial—Tetrofosmin International Trial Study Group. *Circulation.* 1995;91:313–319.
9. 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.
10. 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;77:350–354.
11. Beanlands R, Dawood F, Wen W, et al. Are the kinetics of technetium 99m-methoxyisobutyl isonitrile affected by cell metabolism and viability? *Circulation.* 1990;82:289–296.
12. 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;36:1961–1967.
13. Matsunari I, Fujino S, Taki S, et al. Quantitative rest technetium-99m tetrofosmin imaging in predicting functional recovery after revascularization: comparison with rest-redistribution thallium-201. *J Am Coll Cardiol.* 1997;29:1226–1233.
14. Perrone FP, Bacharach SL, Dilsizian V, Maurea S, Frank JA, Bonow RO. Regional left ventricular wall thickening: relation to regional uptake of ^{18}fluorodeoxyglucose and ^{201}Tl in patients with chronic coronary artery disease and left ventricular dysfunction. *Circulation.* 1992;86:1125–1137.
15. Pattynama PM, Lamb HJ, Van der Velde EA, Van der Geest RJ, Van der Wall EE, De Roos A. Reproducibility of MRI-derived measurements of right ventricular volumes and myocardial mass. *Magn Reson Imaging.* 1995;13:53–63.
16. Holman ER, Buller VG, De Roos A, et al. Detection and quantification of dysfunctional myocardium by magnetic resonance imaging: a new three-dimensional method for quantitative wall thickening analysis. *Circulation.* 1997;95:924–931.
17. DePuey GE, Nichols K, Dobrinsky C. Left ventricular ejection fraction assessed from gated technetium-99m-sestamibi SPECT. *J Nucl Med.* 1993;34:1871–1876.
18. Okada RD, Murphy JH, Boucher CA, et al. Relationship between septal perfusion, viability and motion before and after coronary artery bypass surgery. *Am Heart J.* 1992;124:1190–1195.
19. Vignola P, Boucher C, Curfman G. Abnormal interventricular septal motion following cardiac surgery: clinical, surgical, echocardiographic and radionuclide correlates. *Am Heart J.* 1979;97:27–34.
20. Nekolla SG, Miethaner C, Nguyen N, Ziegler SI, Schwaiger M. Reproducibility of polar map generation and assessment of defect severity and extent assessment in myocardial perfusion imaging using positron emission tomography. *Eur J Nucl Med.* 1998;25:1313–1321.
21. Metz CE, Wang P-L, Kronman HB. A new approach for testing the significance of differences between ROC curves measured from correlated data. In: Deconinck F, ed. *Information Processing in Medical Imaging.* The Hague, The Netherlands: Martinus Nijhoff; 1984:432–445.
22. Anagnostopoulos C, Gunning MG, Dudley JP, et al. Regional myocardial motion and thickening assessed at rest by ECG-gated ^{99m}Tc-MIBI emission tomography and by magnetic resonance imaging. *Eur J Nucl Med.* 1996;23:909–916.
23. Gunning MG, Anagnostolpoulos C, Davies G, Forbat SA, Ell PJ, Underwood R. Gated technetium-99m-tetrofosmin SPECT and cine MRI to assess left ventricular contraction. *J Nucl Med.* 1997;38:438–442.
24. Stollfuss J, Haas F, Matsunari I, et al. Regional myocardial wall thickening and global ejection fraction in patients with low angiographic ejection fraction assessed by visual and quantitative resting ECG-gated Tc-99m-tetrofosmin single-photon-emission tomography and magnetic resonance imaging. *Eur J Nucl Med.* 1997;25:522–530.
25. Metz C. Basic principles of ROC analysis. *Semin Nucl Med.* 1978;8:283–298.
26. Ragosta M, Beller GA, Watson DD, Kaul S, Gimple LW. Quantitative planar rest-redistribution Tl-201 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;87:1630–1641.
27. Chua T, Kiat H, Germano G, et al. Gated technetium-99m sestamibi for simultaneous assessment of stress myocardial perfusion, postexercise regional ventricular function and myocardial viability: correlation with echocardiography and rest thallium-201 scintigraphy. *J Am Coll Cardiol.* 1994;23:1107–1114.
28. Boening G, Ziegler S, Ficaro EP, Schwaiger M. Attenuation correction of gated SPECT: influence of length of transmission scan [abstract]. *J Nucl Med.* 1997;38(suppl):64P.
29. Lucignani G, Paolini G, Landoni C, et al. Presurgical identification of hibernating myocardium by combined use of technetium-99m hexakis 2-methoxyisobutylisonitrile single photon emission tomography and fluorine-18 fluoro-2-deoxy-D-glucose positron emission tomography in patients with coronary artery disease. *Eur J Nucl Med.* 1992;19:874–879.