Exercise-rest Tc-99m tetrofosmin SPECT in patients with chronic ischemic left ventricular dysfunction: Direct comparison with Tl-201 reinjection

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Background. **This study was designed to compare the results of exercise-rest technetium-99m tetrofosmin single photon emission computed tomography (SPECT) with those of thallium-201 reinjection at rest after exercise-redistribution imaging in the same patients with chronic ischemic left ventricular (LV) dysfunction.**

Methods. **Within 1 week, 33 patients with chronic myocardial infarction and LV dysfunction underwent exercise-rest tetrofosmin SPECT and Tl-201 reinjection at rest after exercise-redistribution imaging. In each patient, regional tetrofosmin and Tl-201 activity was quantitatively measured in 22 myocardial segments. Regional LV function was assessed in corresponding segments by echocardiography.**

Results. **Agreement in the evaluation of regional perfusion status between tetrofosmin and Tl-201 imaging was observed in 78% of the 726 total segments, with a κ value of 0.61. In segments with normal function at echocardiography (n = 436), no difference between Tl-201 and tetrofosmin uptake was observed. In hypokinetic segments (n = 138), exercise tetrofosmin uptake was lower ($P < .01$) as compared with exercise Tl-201 activity, whereas no difference was observed between tetrofosmin uptake at rest as compared with Tl-201 activity on redistribution and reinjection images. In segments with severe functional impairment (akinetic or dyskinetic, n = 152), tetrofosmin uptake on exercise images was reduced ($P < .01$) as compared with exercise Tl-201 activity; furthermore, tetrofosmin uptake at rest was lower ($P < .01$) as compared with Tl-201 activity on both redistribution and reinjection images. In these segments, concordance in the detection of myocardial viability between tetrofosmin and Tl-201 imaging was observed in 138 (91%) of the 152 segments, with a κ value of 0.77.**

Conclusions. **In patients with chronic coronary artery disease and LV dysfunction quantitative exercise-rest tetrofosmin and Tl-201 reinjection SPECT provide similar information in the assessment of perfusion status and in the detection of myocardial viability. (J Nucl Cardiol 1999;6:270-7.)**

Key Words: Myocardial perfusion, myocardial viability, myocardial infarction

Technetium-99m (Tc-99m)–labeled tetrofosmin has been introduced for myocardial perfusion imaging in patients with coronary artery disease.[1-3] Recent studies demonstrated that regional myocardial distribution of tetrofosmin is related to the severity of coronary artery stenosis[4] and that this tracer shows similar diagnostic accuracy in detecting coronary artery disease as compared with sestamibi and thallium-201 imaging.[5-8] Although it has been reported that exercise-redistribution Tl-201 scintigraphy shows more reversibility than exercise-rest tetrofosmin in areas related to previous myocardial infarction,[7] few data are available on the direct comparison between Tl-201 and tetrofosmin imaging in the same patients with chronic ischemic left ventricular (LV) dysfunction. In particular, it has been recently demonstrated that visual analysis of exercise-rest tetrofosmin single photon emission computed tomography (SPECT) may underestimate the detection of myocardial viability as compared with exercise-redistribution Tl-201 scintigraphy with rest reinjection.[9] On the other hand, quantitative analysis of tetrofosmin and Tl-201 uptake provided similar information in the identification of viable myocardium in patients with coronary artery disease.[9] However,

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Table 1. Demographic data and clinical characteristics in 33 patients

Age (yr)	52 ± 8
Sex (men/women)	31/2
Left ventricular ejection fraction (%)	41 ± 14
Coronary artery disease	
One-vessel	17 (52%)
Two-vessel	8 (24%)
Three-vessel	8 (24%)

no data are currently available on the direct comparison between exercise-rest tetrofosmin cardiac imaging and Tl-201 reinjection in chronically dysfunctional myocardium. Therefore this study was designed to compare directly the results of quantitative exercise-rest tetrofosmin SPECT with those of Tl-201 reinjection at rest after exercise-redistribution scintigraphy in patients with chronic myocardial infarction and LV dysfunction.

MATERIAL AND METHODS

Patient Population

Thirty-three consecutive patients (31 men and 2 women, mean age 52 ± 8 years) with angiographically documented coronary artery disease, previous myocardial infarction, and echocardiographic evidence of regional, and global LV dysfunction (mean LV ejection fraction 41% ± 14%) were studied. Demographic data and clinical characteristics of the patient population are summarized in Table 1. Patients with unstable angina, severe congestive heart failure (New York Heart Association class III to IV) or recent myocardial infarction (<8 weeks) were excluded from the study. Radionuclide studies were performed after withdrawal of all antianginal medications. All patients gave informed consent as part of protocol approved by the Institutional Clinical Research Subpanel on Human Studies of our University.

Study Protocol

All patients underwent symptom-limited bicycle exercise testing with a standardized multistage protocol with continuous monitoring of heart rate and rhythm, blood pressure, and electrocardiography.[10] Criteria for interrupting the exercise test included age-predicted maximal heart rate, severe angina, development of marked ST-segment depression, appearance of frequent or complex ventricular arrhythmia, hypotension (decrease in systolic blood pressure > 20 mm Hg), and exercise-limiting dyspnea. For tetrofosmin study, 370 MBq was intravenously injected as a bolus at peak exercise. Patients continued exercise for an additional 60 to 90 seconds after the injection of the tracer. Four hours later, tetrofosmin 1100 MBq was intravenously injected with the patient at rest. SPECT was performed 30 to 45 minutes after tracer injection for both exercise and rest tetrofosmin study as described previously.[11] Within 1 week all patients underwent Tl-201 imaging. Thallium was intravenously injected (111 MBq) at peak exercise, and the test was continued at the same workload for an additional 60 to 90 seconds. Acquisition of tomographic images was performed within 5 minutes after Tl-201 injection as reported previously.[12] Four hours later redistribution images were obtained. Immediately after undergoing redistribution imaging, all patients received Tl-201 37 MBq at rest, and a third acquisition was started 60 minutes after the second dose was administered by use of the same imaging protocol.

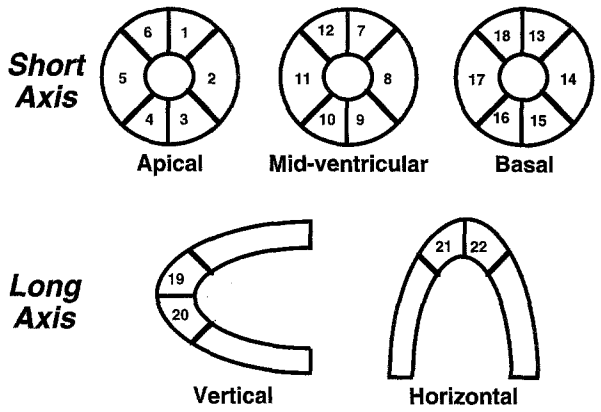

Figure 1. Diagram of standard segmentation scheme used for regional quantitative analysis of Tc-99m tetrofosmin and Tl-201 cardiac tomography.

Myocardial Tomography

SPECT was performed as described previously,[10] with a rotating large field of view gamma camera (Elscint SP4HR, Haifa, Israel) equipped with a low-energy, all-purpose, parallel-hole collimator and connected with a dedicated computer system. Thirty-two projections (30 sec/projection) were obtained over a semicircular 180-degree arc, which extended from the 30-degree right anterior oblique to the left posterior oblique position. For tetrofosmin study a 20% symmetric energy window centered on the 140 KeV peak was used. For Tl-201 imaging, a 15% symmetric energy window centered on the 70 to 80 KeV was used. Filtered back-projection was then performed with a low-resolution Butterworth filter with a cutoff frequency of 0.5 cycles/pixel, order 5.0. No attenuation or scatter correction was applied.

Echocardiography

Echocardiographic studies were performed by use of a wide-angle 2-dimensional phased-array sector scanner (Hewlett-Packard 77020AC, Andover, Mass.) equipped with a 2.5 MHz transducer. Two-dimensional images of the left ventricle were obtained by use of multiple imaging sections, including parasternal long and short axes and apical 2 and 4 chamber views with the patient at rest lying in the left lateral position. All

Table 2. Hemodynamic parameters recorded under control condition and at peak exercise in 33 patients

	Tc-99m tetrofosmin	Tl-201
Baseline		
Heart rate (beats/min)	78 ± 10	78 ± 11
Systolic blood pressure (mm Hg)	126 ± 15	126 ± 16
Diastolic blood pressure (mm Hg)	79 ± 10	78 ± 9
Rate-pressure product (beats/min × mm Hg)	9238 ± 3011	9816 ± 1886
Peak exercise		
Heart rate (beats/min)	138 ± 17*	135 ± 21*
Systolic blood pressure (mm Hg)	175 ± 22*	174 ± 28*
Diastolic blood pressure (mm Hg)	97 ± 11*	96 ± 14*
Rate-pressure product (beats/min × mm Hg)	22,707 ± 7189*	23,701 ± 5498*
ST depression ≥ 1.5 mm	11 (33%)	9 (27%)

*$P < .001$ versus baseline.

studies were videotaped on a ¾-inch videocassette recorder super video high scope. The video frame rate of the system was 60 frames per second.

Data Analysis

Radionuclide studies were evaluated by two observers unaware of clinical and angiographic data. A segmentation scheme with 22 myocardial regions (Figure 1) was used for quantitative analysis of tetrofosmin and Tl-201 activity.[10] Briefly, in each tomogram the myocardial region with the maximum counts was used as the normal reference region. Tracer uptake in all other myocardial segments was then expressed as a percentage of the activity measured in the reference region. Each myocardial segment was assigned to one of the major vascular territories.[4,10,11] Briefly, the left anterior descending artery territory included the anterior wall, septum, and apical wall. The posterior descending artery was assigned the inferior wall. The left circumflex artery was assigned the lateral wall. In each of these segments, perfusion data were directly compared with the functional data derived from the echocardiographic analysis as described below. Tracer uptake was considered abnormal when more than 2 SD less than the mean were observed in the same region for control subjects.[11,13] Segments with reduced activity on exercise images were considered reversible defects when tracer uptake increased more than 10% on redistribution or resting images. Alternatively, a segment with reduced activity on exercise images and no change on redistribution or resting images was considered irreversible. Irreversible defects were divided into moderate (tracer uptake ≥50% of peak activity) and severe (<50% of peak activity). Echocardiographic studies were analyzed independently by two experts unaware of clinical, radionuclide, and angiographic findings. A third investigator blindly reviewed the echocardiograms when the first two observers were not in agreement. Regional LV function was assessed in corresponding segments according to the recommendations of the American Society of Echocardiography.[14] Segmental LV wall motion and thickening were graded semiquantitatively by use of a scoring system where 1 indicated normal, 2 indicated hypokinesia (severely reduced wall thickening and inward motion), and 3 indicated akinesia (absence of wall motion and of systolic thickening) or dyskinesia. To compare directly the results of 2-dimensional echocardiography with those of tetrofosmin and Tl-201 SPECT, each ventricular segment was assigned to one of the major coronary vascular territories.[15] In particular, the anterior, anterolateral, proximal, and distal septal wall were assigned to the left anterior descending artery, the posterolateral wall to the left circumflex artery, and the posterior and inferior wall to the posterior descending artery. The assignment of the LV apex was variable and based on the presence of adjacent wall motion abnormalities. However, some error in the correlation between regional echocardiographic wall motion and regional quantitative perfusion resulting from misregistration could not be completely excluded. Reproducibility of echocardiographic measurements in our laboratory has been reported previously.[16] In particular, interobserver agreement was within 95% ($r = 0.96$, $P < .001$), and intraboserver agreement was within 98% ($r = 0.97$, $P < .001$). Dysfunctional myocardial segments at echocardiography were considered as showing evidence of tissue viability if they were normal, reversible defects or irreversible defects with a moderate reduction of tracer uptake on tetrofosmin or Tl-201 SPECT. A moderate reduction of tracer uptake was defined with two different thresholds: ≥50% and ≥60% of peak activity. Alternatively, segments with functional impairment were considered as nonviable if they were irreversible defects with a severe reduction of tracer uptake (<50% or 60% of peak activity).

Statistical Analysis

Data are expressed as mean ± SD. Differences between mean values were assessed by Student's t test, with Bonferroni correction as appropriate. Differences between proportions were assessed by χ^2 testing. All P values < .05 were considered significant. The κ statistic and its standard error were used as a measure of agreement between tetrofosmin and Tl-201 studies. A value of 1 denotes perfect agreement, and 0 indicates no

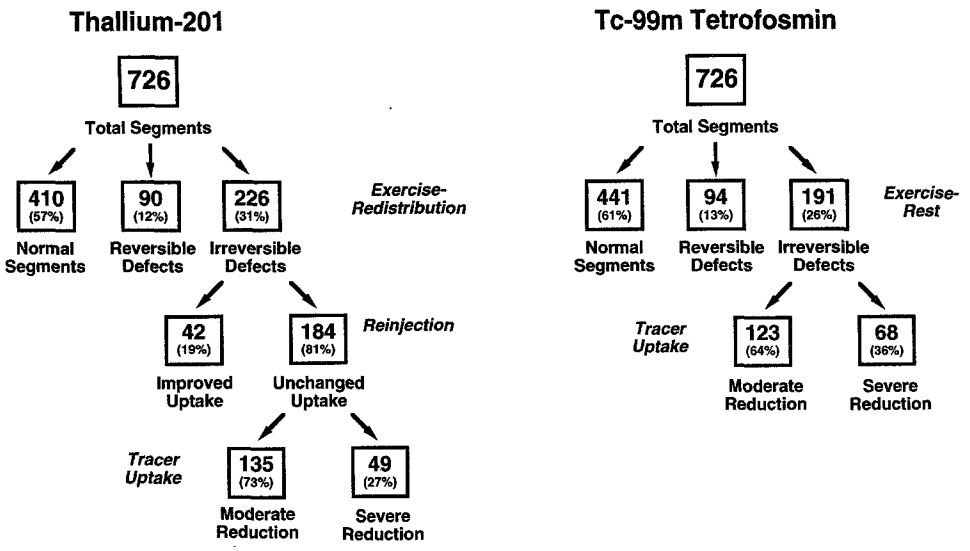

Figure 2. Nomogram of Tc-99m tetrofosmin and Tl-201 cardiac imaging findings in 726 myocardial segments analyzed.

agreement beyond change. In general, κ values of 0.6 or greater are considered indicative of good agreement.

RESULTS

Hemodynamic Parameters

Hemodynamic parameters recorded under control conditions and at peak exercise for tetrofosmin and Tl-201 studies are summarized in Table 2. No differences between the two exercise tests in heart rate, systolic and diastolic blood pressures, and rate-pressure product were observed.

Imaging Findings

The results of tetrofosmin and Tl-201 imaging are shown in Figure 2. Thirty-one (94%) of 33 patients with exercise-induced regional hypoperfusion on Tl-201 SPECT showed reversible defects on both redistribution and reinjection images. On tetrofosmin imaging, 28 (85%) of 33 patients with exercise-induced regional hypoperfusion had reversible defects on resting images (P = NS vs Tl). On regional analysis of the 316 segments with exercise-induced hypoperfusion on Tl-201 SPECT, 90 (28%) defects were reversible, and 226 (72%) were irreversible on redistribution images. Of these latter 226 segments, 42 (19%) showed improved Tl-201 uptake after reinjection, whereas 184 (81%) segments had unchanged tracer uptake. The occurrence of reversibility was significantly lower on redistribution images as compared with reinjection images ($P < .01$). Of the 285 segments with exercise-induced defects on tetrofosmin SPECT, 94 (33%) defects were reversible, and 191 (67%) irreversible on resting images (P = NS vs Tl-201 redistribution and $P < .05$ vs Tl-201 reinjection). Comparison of the diagnostic interpretation of the tetrofosmin and Tl-201 images performed on a segmental basis is shown in Figure 3. Agreement between exercise-rest tetrofosmin and exercise-redistribution Tl-201 imaging was observed in 78% of the 726 segments, with a κ value of 0.61. Similarly, exercise-rest tetrofosmin and Tl-201 reinjection imaging were concordant in 78% of the total segments with a κ value of 0.61. When the results were discordant, there was no systematic trend.

Relation to Regional LV Function

At echocardiography 436 (60%) of the total 726 myocardial segments showed normal function, 138 (19%) were hypokinetic, and the remaining 152 (21%) segments were akinetic or dyskinetic. Tetrofosmin and Tl uptake in normal, hypokinetic, and akinetic or dyskinetic segments is shown in Figure 4. In segments with normal function, no significant difference in uptake was observed. In hypokinetic segments exercise tetrofosmin uptake was significantly lower ($P < .01$) compared with exercise Tl-201 activity. No difference was observed between tetrofosmin uptake at rest and Tl-201 activity on redistribution and reinjection images. Most (n = 126, 91%) of the 138 hypokinetic segments were identified as showing evidence of myocardial viability on tetrofosmin and Tl-201 imaging. Only 2 segments (1%) were identified as necrotic on both tetrofosmin and Tl-201 SPECT.

In segments with severe functional impairment (akinetic or dyskinetic) tetrofosmin uptake on exercise images

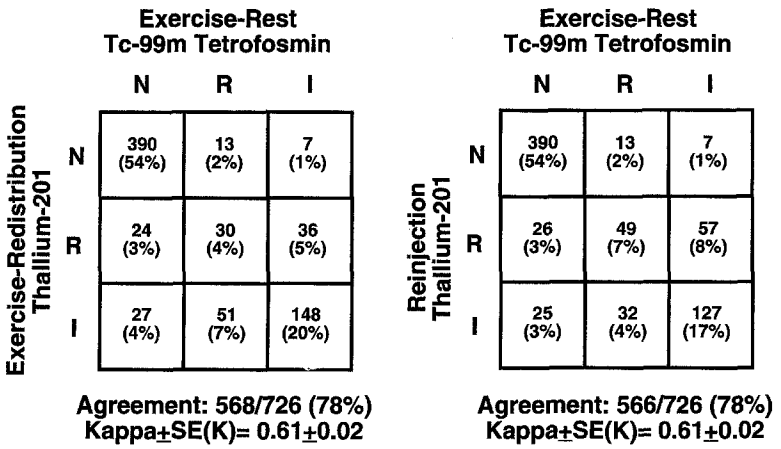

Figure 3. Concordance data of diagnostic classification of segments between exercise-rest Tc-99m tetrofosmin and exercise-redistribution Tl-201 (left panel) and between exercise-rest Tc-99m tetrofosmin and Tl-201 reinjection (right panel).

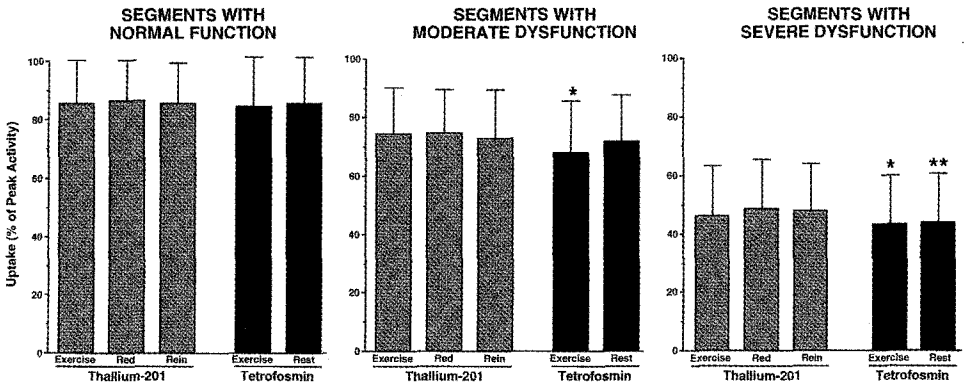

Figure 4. Thallium-201 uptake on exercise, redistribution *(Red)* and reinjection *(Rein)* images and Tc-99m tetrofosmin uptake on exercise and rest images in myocardial segments with normal function, moderate (hypokinetic) and severe (akinetic and dyskinetic) dysfunction. $^{*}P < .01$ versus Tl-201 exercise; $^{**}P < .01$ versus Tl-201 redistribution and reinjection.

was significantly lower ($P < .01$) as compared with exercise Tl-201 activity (Figure 4). Furthermore, tetrofosmin uptake at rest was significantly lower ($P < .01$) as compared with Tl-201 activity on both redistribution and reinjection images (Figure 4). In these segments concordance in the detection of myocardial viability between tetrofosmin and Tl-201 imaging was observed in 138 (91%) of the 152 segments, with a κ value of 0.77 by use of a cutoff of 50% and in 126 (83%) of the 152 segments, with a κ value of 0.65 using a cutoff of 60% (Figure 5).

A separate analysis was performed to assess the occurrence of reversibility in segments with impaired LV function at echocardiography. Of the 290 dysfunctional segments, 221 had exercise-induced Tl-201 defects. Of these 221 segments, 130 (59%) defects were reversible and 91 (41%) were irreversible on Tl-201 reinjection images. Of the total 290 dysfunctional segments, 196 showed exercise-induced defects at tetrofosmin tomography. Of these 196 segments, 53 (27%) defects were reversible, and 143 (73%) were irreversible on resting tetrofosmin images ($P < .001$ vs Tl-201 reinjection).

DISCUSSION

In this study we directly compared the results of exercise-rest tetrofosmin cardiac SPECT with those of Tl-201 reinjection after exercise-redistribution imaging in patients with chronic coronary artery disease and LV dysfunction. Good overall concordance was found between Tl-201 reinjection and exercise-rest tetrofosmin tomography in the evaluation of regional perfusion status. These results are similar to those reported by Heo et al[17] demonstrating 83% concordance between exercise-rest tetrofosmin and exercise-reinjection Tl-201 SPECT in patients with coronary artery disease.

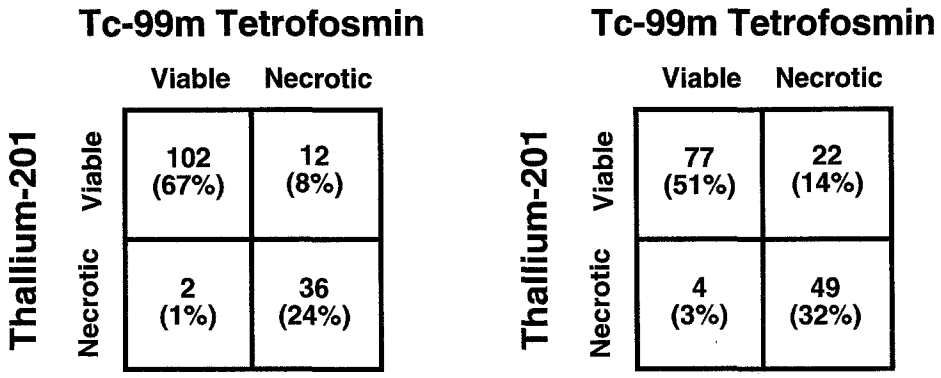

Figure 5. Concordance data of classification of segments as viable or necrotic between Tc-99m tetrofosmin and Tl-201 assuming a cutoff of 50% (left panel) and 60% (right panel) of peak activity.

Assessment of Reversibility

Our data demonstrate that exercise-rest tetrofosmin imaging shows lower reversibility as compared with Tl-201 reinjection. In particular 59% of dysfunctional segments with exercise-induced regional hypoperfusion were reversible on Tl-201 reinjection, whereas only 27% were reversible on tetrofosmin imaging at rest. These results are in agreement with those of previous studies.[7-9] Rigo et al,[7] using planar imaging, reported that Tl-201 redistribution shows higher reversibility as compared with rest tetrofosmin in areas related to myocardial infarction. In particular, four of the 26 patients with previous myocardial infarction had reversible or partially reversible defects at tetrofosmin imaging.[7] Results with Tl-201 were similar, although defects were seen as reversible or partially reversible in 8 patients.[7] Tamaki et al[8] demonstrated that exercise-rest tetrofosmin and exercise-redistribution Tl-201 tomography showed similar accuracy in the detection of coronary artery disease and in the assessment of defect reversibility. In our study 31 patients showed reversible defects on both redistribution and reinjection images and 28 patients had reversible defects on tetrofosmin images. Matsunari et al[9] reported a lower reversibility of exercise-rest tetrofosmin as compared with exercise-redistribution with rest reinjection Tl-201 imaging in patients with chronic coronary artery disease. A possible explanation for the underestimation of defect reversibility by exercise-rest tetrofosmin may be related to the different mechanisms of uptake between the two tracers on the resting images: redistribution for thallium and uptake related to coronary blood flow for tetrofosmin.[18] However, in the interpretation of the results of this study and of previous reports, several factors such as different acquisition protocols (1-day or 2-day protocols, planar or tomographic imaging) and different data analysis approaches (qualitative or quantitative evaluation) should be also considered.

Assessment of Myocardial Viability

Matsunari et al[9] demonstrated that visual analysis of exercise-rest tetrofosmin imaging may underestimate the detection of myocardial viability as compared with Tl-201 reinjection. On the other hand, quantitative analysis of Tl-201 and tetrofosmin uptake within irreversible defects provided similar information in the identification of viable myocardium.[9] However, no functional data were reported in that study, and comparison between Tl-201 reinjection and exercise-rest tetrofosmin imaging in relation to regional LV function remain to be addressed.

The results of this study show that Tl-201 and tetrofosmin activity is comparable in normokinetic and hypokinetic myocardium. However, in segments with severe LV dysfunction, tetrofosmin myocardial uptake at rest was lower as compared with both redistribution and Tl-201 activity. These data are in agreement with those of Koplan et al[19] demonstrating in a low-flow canine experimental model with severe LV dysfunction that myocardial uptake of rest-injected tetrofosmin was significantly lower as compared with 2-hour Tl-201 redistribution activity. In myocardial segments with severe functional impairment, where myocardial viability is in question, our data suggest that quantitative analysis of Tl-201 reinjection and tetrofosmin give comparable results in the assessment of tissue viability. Similar results were recently reported by Galassi et al[20] and Matsunari et al[21] comparing rest-redistribution Tl-201 and rest tetrofosmin quantitative SPECT.

The results of this study suggest that exercise-rest tetrofosmin and Tl-201 reinjection imaging give comparable information relevant to exercise-induced perfusion defects and myocardial viability in dysfunctional hypoperfused regions. These findings are concordant with those reported in a previous study with resting Tc-99m–labeled sestamibi.[22] Experimental evidence suggests that the mechanism of uptake of tetrofosmin into myocardial cells is similar to that of sestamibi along an electronegative mitochondrial membrane potential and is a metabolism-dependent process.[23-25]

Study Limitations

In this study we directly compared the results of Tl-201 reinjection with those of exercise-rest tetrofosmin on SPECT in patients with chronic coronary artery disease and mild LV dysfunction. However, there are no data on functional recovery after revascularization or viability assessment by positron emission tomography in these patients.

Although several studies have demonstrated the usefulness of Tl-201 reinjection imaging to detect myocardial viability,[26-29] definitive statement regarding the use of exercise-rest tetrofosmin to address this issue is not possible with these data, and further studies are required. In addition, the fundamental mechanism of tetrofosmin myocardial uptake have not been fully clarified, and other studies are needed to determine transmembrane uptake and tetrofosmin retention in myocardial cells.

Conclusions

The results of this study suggest that in patients with chronic myocardial infarction and LV dysfunction quantitative exercise-rest tetrofosmin SPECT and Tl-201 reinjection at rest after exercise-redistribution scintigraphy provide similar information in the assessment of perfusion status and in the detection of myocardial viability. However, in segments with severe dysfunction tetrofosmin tomography may underestimate myocardial viability as compared with Tl-201 reinjection imaging.

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