Reverse Redistribution Phenomenon on Rest $^{99m}$Tc-Tetrofosmin Myocardial Single Photon Emission Computed Tomography Involves Impaired Left Ventricular Contraction in Patients With Acute Myocardial Infarction

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The purpose of this study was to investigate the clinical significance of the reverse redistribution (RR) phenomenon on technetium-$^{99m}$ ($^{99m}$Tc)-tetrofosmin myocardial single photon emission computed tomography (SPECT) performed at rest. Twenty-five patients underwent myocardial SPECT 3 weeks after the onset of acute myocardial infarction. Myocardial images were acquired at 40 min (early) and 4 h (delayed) after the injection of 740 MBq of $^{99m}$Tc-tetrofosmin. The regional myocardial uptake of the tracer in 26 segments of the left ventricular (LV) wall was visually scored from 0 (no activity) to 3 (normal activity), and then the RR was defined as a decrease of more than 1 point in the activity score on the delayed image compared with that on the early image. Regions with an activity score of 3 on both the early and delayed images were defined as normal, and those with a score of 0 or 1 on the early image were considered to have a fixed defect. The regional myocardial $^{99m}$Tc-tetrofosmin uptake and washout rate were also quantitatively assessed in each region. In addition, exercise stress electrocardiograph-gated SPECT with $^{99m}$Tc-tetrofosmin was performed within 1 week of the rest study, and the percent count increase (%CI) during myocardial contraction in each corresponding region was studied. RR was observed in 18 of the 25 patients. The regional washout rate of $^{99m}$Tc-tetrofosmin was significantly higher in the RR regions (45.0±3.8%) than in either the normal regions (36.4±4.1%, p<0.001) or in those with a fixed defect (39.7±3.9%, p<0.001). However, no significant difference was found between the RR regions and those with a fixed defect (8.0±7.2%). In patients with acute myocardial infarction, the regions showing the RR phenomenon on $^{99m}$Tc-tetrofosmin SPECT have severely impaired LV wall contraction after exercise. (Circ J 2003; 67: 830–834)

Key Words: Acute myocardial infarction; Gated SPECT; Left ventricular contraction; Reverse redistribution; $^{99m}$Tc-tetrofosmin

Myocardial perfusion scintigraphy using thallium-201 ($^{201}$TI) as the flow tracer has been widely applied for the evaluation of myocardial ischemia and viability in patients with myocardial infarction! Simultaneous evaluation of left ventricular (LV) wall motion and LV myocardial perfusion provides more information for this purpose, but as $^{201}$TI is not suitable as the tracer for electrocardiograph (ECG)-gated single photon emission computed tomography (SPECT), which is used for elucidating LV wall motion, echocardiography and/or left ventriculography have been the alternative techniques. However, using a technetium (Tc)-labeled myocardial perfusion tracer, technetium-$^{99m}$ ($^{99m}$Tc)-tetrofosmin, as well as $^{99m}$Tc-sestamibi allows simultaneous assessment of myocardial perfusion and LV function by ECG-gated SPECT because once these tracers are taken up by the myocardium, then the clearance is relatively slow and redistribution does not occur for several hours.

Several investigators have reported that in patients with acute myocardial infarction (AMI) after reperfusion therapy, myocardial imaging with $^{99m}$Tc-tetrofosmin or $^{99m}$Tc-sestamibi shows a reverse redistribution (RR) phenomenon similar to that observed on $^{201}$TI scintigraphy in such patients. The clinical significance of the RR of $^{201}$TI has been vigorously investigated compared with that on $^{99m}$Tc-tetrofosmin scintigraphy, which has not been fully elucidated. Thus, we used ECG-gated myocardial SPECT to investigate this issue in patients with AMI from the viewpoint of LV wall thickening after exercise.

Methods

Patients

We studied 25 consecutive patients (17 men, 8 women, age 48–80 years) with AMI who underwent $^{99m}$Tc-tetrofosmin myocardial SPECT at rest approximately 3 weeks after the onset of infarction. Patients who had a prior myocardial infarction and/or coronary artery bypass surgery were excluded from the study. All the study patients underwent exercise stress ECG-gated SPECT with $^{99m}$Tc-tetrofosmin within 1 week of the rest study, and then selective coronary angiography was carried out. In those patients who did not...
**Table 1 Patient Characteristics**

<table>
<thead>
<tr>
<th>n</th>
<th>25</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.4±8.5 (mean±SD)</td>
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<tr>
<td>M/F</td>
<td>17/8</td>
</tr>
<tr>
<td>Reperfusion therapy</td>
<td></td>
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<tr>
<td>Direct PTCA</td>
<td>12 (48.0%)</td>
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<tr>
<td>Emergency CABG</td>
<td>4 (1.6%)</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>5 (20.0%)</td>
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<tr>
<td>Not done</td>
<td>7 (28.0%)</td>
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**Infarction location**

<table>
<thead>
<tr>
<th>Location</th>
<th>Count (Percent)</th>
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<tbody>
<tr>
<td>Anterior</td>
<td>14 (56.0%)</td>
</tr>
<tr>
<td>Inferior</td>
<td>7 (28.0%)</td>
</tr>
<tr>
<td>Lateral</td>
<td>4 (16.0%)</td>
</tr>
</tbody>
</table>

**Peak of serum CK (IU/L)**

$3,232±2,270$ (mean±SD)

$616–9,981$ (range)

*CAβG,* coronary artery bypass grafting surgery; *CK,* creatine kinase; *PTCA,* percutaneous transluminal coronary angioplasty.

undergo a coronary intervention on admission, the culprit coronary lesion of the AMI was documented by the existence of residual coronary artery stenoses corresponding to the LV wall motion abnormality observed on left ventriculography with related ECG changes. Acute myocardial infarction was diagnosed on the basis of a combination of typical chest pain of at least 30 min duration, depression or elevation of the ST segment on the ST segment on the standard 12-lead ECG, and elevation of the MB fraction of serum creatine kinase. Within 12 h of the onset of infarction, 12 patients underwent direct percutaneous transluminal coronary angioplasty, 1 patient underwent emergency coronary artery bypass grafting surgery of the culprit artery, and 5 received thrombolytic therapy. No reperfusion therapy was performed in the remaining 7 patients because they had presented more than 12 h after the onset of symptoms. Patient characteristics are shown in Table 1. All patients provided written informed consent before participating in the study, which was performed according to the regulations proposed by The Ethical Guidelines Committee of the Nagoya City University Graduate School of Medical Sciences.

**Imaging Protocol**

Rest myocardial imaging was performed approximately 3 weeks ($21.5±2.1$ days) after the onset of the cardiac event. In each patient, $740 MBq$ of $99mTc$-tetrofosmin (Myoview, Nihon Medi-physics, Nishinomiya, Japan) was intravenously injected at rest, then data acquisition for SPECT imaging was performed twice: for early images at 40 min and for delayed images at 4 h after the injection of tracer, using a triple-headed rotating gamma camera equipped with low-energy high resolution parallel hole collimator (MULTISPECT-3, Siemens, Hoffman Estates, USA). Data were acquired with $64×64$ matrices from a total of 120 projections over a circular 360° orbit around the heart. The projection data sets were prefiltered with a 2-dimensional Butterworth filter (order 7, cutoff frequency of 0.45 cycle/cm) and reconstructed with filtered back projection (Ramp filter). The rest study was obtained without ECG gating. One week later, all patients underwent symptom-limited supine ergometer exercise stress $99mTc$-tetrofosmin gated SPECT at an initial work load of 25 W, which was increased by 25 W every 3 min. At near maximal exercise, $370 MBq$ of $99mTc$-tetrofosmin was injected intravenously and the patients continued to exercise for 2 additional minutes. Exercise myocardial imaging was performed 40 min after the injection of tracer, using an ECG-gated protocol. Each cardiac cycle was divided into 8 frames. The ECG R–R intervals and heart rate histogram were recorded with arrhythmia monitoring. An average R–R interval of ±15% was accepted for gating. The gated SPECT images were reconstructed using the same protocol as the rest non-gated study.

**Analysis of the $99mTc$-Tetrofosmin SPECT Images**

The LV wall was divided into 26 segments: the basal, middle and apical regions in the short-axis view were each divided into 8 segments, and 2 apical regions on the vertical long-axis view made up the remaining segments (Fig 1). Regional $99mTc$-tetrofosmin activity was visually graded by the consensus of 2 experienced observers on the early and delayed rest images, using a 4-point scoring system: normal $99mTc$ activity = 3; mildly decreased activity = 2; severely decreased = 1; and no activity = 0. RR was considered to be present if the $99mTc$-tetrofosmin activity score had decreased by at least 1 point on the delayed image compared with the early image in each region that had an activity score of equal to or more than 2 on the early image. Regions with a $99mTc$-tetrofosmin activity score of 3 on both the early and delayed rest images were defined as normal. Regions with a score of 0 or 1 on the early rest image were considered to have a fixed defect.

Quantitative assessments of the myocardial $99mTc$-tetrofosmin washout rate on the early and delayed images and of the percent count increase during myocardial contraction were performed on the bull’s-eye polar maps. The washout rate between the early and delayed images was calculated in each of the 26 segments according to the formula:

$$\frac{(I–D)}{I}×100 \%,$$

where $I$ represents the initial myocardial $99mTc$-tetrofosmin uptake (counts per pixel) on the early image and $D$ represents the $99mTc$-tetrofosmin uptake (counts per pixel) in the same location on the delayed image. Using this calculation, a computer generated a circumferential profile of the washout rate from which the regional mean $99mTc$-tetrofosmin washout rates were obtained for the 26 regions in each patient. In this study, the natural decay of $99mTc$ was corrected according to the formula:

$$N=N_0\exp^{-\frac{t}{\tau}},$$

where $N$ is the $99mTc$-tetrofosmin counts in each region of interest on the delayed image, $N_0$ is those in the corresponding region of interest on the early image, $\Delta$ is a decay constant, $t$ is the time between the 2 image acquisition sessions. On the occasion of $99mTc$-labeled tracers being used, $\Delta$ can be obtained by dividing the decay constant 0.693 by the half-time of the physical decay of $99mTc$; that is, 6.02 h.
In all patients, polar map displays were figured for both the end-diastolic and end-systolic phases using short-axis slices on the ECG-gated SPECT images after correcting cardiac rotation. Thereafter, wall thickening was quantitatively evaluated by the percent increase in counts from diastole to systole; the percent count increase (%CI) in each segment was defined as:

\[
\text{\%CI} = \left( \frac{\text{ES} - \text{ED}}{\text{EDmax}} \right) \times 100 \%
\]

where ES represents the 99mTc-tetrofosmin uptake (counts per pixel) on the end-systolic image; ED represents the 99mTc-tetrofosmin uptake (counts per pixel) on the end-diastolic image. EDmax in this formula indicates the 99mTc-tetrofosmin uptake (counts per pixel) in the pixel that had maximal 99mTc-tetrofosmin uptake on the end-diastolic image. We used EDmax instead of ED to calculate the %CI accurately in the regions where severely decreased uptake of 99mTc-tetrofosmin was observed.16 Using this formula, the computer generated a %CI circumferential profile from which the regional mean %CI was obtained.

We defined the threshold value of percent 99mTc-tetrofosmin uptake, which distinguishes the regions having relatively better perfusion from those that are relatively worse on the early images, as mean minus 2SD in %uptake of 99mTc-tetrofosmin in the normal regions; that is, 70% in the present study.

In addition, the images from the exercise non-gated 99mTc-tetrofosmin myocardial SPECT were reconstructed from the exercise ECG-gated SPECT for evaluation of myocardial ischemia in comparison with the rest early images.

**Statistical Analysis**

Data are presented as mean±SD. Differences among 3 groups were evaluated using one-way ANOVA. Scheffe’s test was used for post hoc comparisons. A difference in incidence was compared using the chi-squared test. Probability levels less than 0.05 were considered statistically significant.

**Results**

The RR phenomenon of 99mTc-tetrofosmin was observed in 15 of 18 patients who had undergone reperfusion therapy and in 3 of 7 who had not. The incidence of the RR phenomenon was significantly higher in the former than in the latter (p<0.005). In patients showing the RR phenomenon, coronary angiography revealed that the infarct-related coronary arteries were patent in 17 of the 18 patients and in 1 patient, who had a closed anterior descending artery, a coronary artery bypass graft fed the infarct area. In 1 patient, the reperfusion therapy almost completely salvaged the acutely ischemic myocardium and the RR phenomenon was not observed. Fixed defect regions were observed in 14 patients and of these, 8 also had regions with the RR phenomenon around the fixed defect areas. The infarct-related coronary arteries in the regions with a fixed defect were closed in 5 patients and open in 9 patients. In the 6 patients who had fixed defect regions only, 5 of the infarct-related coronary arteries were closed and only 1 was open. Thus, the incidence of open infarct-related coronary arteries, including the bypass graft, was higher in the regions with the RR phenomenon than in those with a fixed defect but without adjacent areas showing the RR (100% vs 17%, p<0.001). In a total of 650 regions on a segmental basis, the RR phenomenon was observed in 56 regions (Fig 2), a fixed defect in 95, and there were 499 normal regions.

In the comparison of the exercise non-gated and early rest images, no difference in activity score (ie, no obviously visible myocardial ischemia) was observed in any of the RR phenomenon regions.

The mean %uptake of 99mTc-tetrofosmin on the early images in the regions with the RR phenomenon (74.0±8.8%) was significantly lower than that in the normal areas (82.8±6.4%, p<0.001), whereas it was significantly higher than that in the regions with a fixed defect (44.0±12.4%, p<0.001). The washout rate of 99mTc-tetrofosmin was significantly higher in the regions with the RR phenomenon (45.0±3.8%) than in the normal (36.4±4.1%, p<0.001) and also in the fixed defect regions (39.7±3.9%, p<0.001) as shown in Fig 3. The %CI after exercise was significantly less in the RR phenomenon regions (10.4±10.4%) than in the normal areas (23.5±10.1%, p<0.001); however, no significant difference was found between the RR phenomenon regions and those with a fixed defect (8.0±7.2%) (Fig 4). Even in 35 regions with the RR phenomenon and 99mTc-tetrofosmin regional %uptake more than 70% on the early images, the %CI (10.7±12.4%) was also significantly less than that in the normal areas (p<0.001), but was not significantly different from that in the RR phenomenon regions.
Diastole to systole because of the partial volume effect of
Percent Count Increase of 99mTc-Tetrofosmin as an Index of LV Wall Contraction
of 99mTc-tetrofosmin is observed in such regions on early images. Furthermore, this study indicates that patent coronary arteries in patients with AMI may cause the RR phenomenon of 99mTc-tetrofosmin imaging.

Discussion
The present study demonstrates that a relatively rapid clearance of 99mTc-tetrofosmin from the reperfused myocardium in patients with AMI is associated with impairment of the LV myocardial thickening after exercise assessed by ECG-gated SPECT. The presence of the RR phenomenon on 99mTc-tetrofosmin imaging is a sign of myocardial dysfunction, even though relatively better uptake of 99mTc-tetrofosmin is observed in such regions on early images. Furthermore, this study indicates that patent coronary arteries in patients with AMI may cause the RR phenomenon of 99mTc-tetrofosmin imaging.

Percent Count Increase of 99mTc-Tetrofosmin as an Index of LV Wall Contraction
A greater photon flux from the 99mTc-labeled myocardial perfusion tracers permits simultaneous assessment of myocardial perfusion and LV function by ECG-gated SPECT. In gated 99mTc-labeled flow tracer SPECT, regional LV wall thickening is sensitively measured by the %CI from diastole to systole because of the partial volume effect of the accumulated radioisotope in the myocardium. Shen et al \(^17,18\) studied regional LV wall thickening expressed as a %CI during the cardiac cycle on ECG-gated myocardial SPECT in normal subjects and in patients with prior myocardial infarction, demonstrating that a regional LV wall thickening abnormality could be reliably detected from the regional count density changes during the cardiac cycle. Everaert et al \(^18\) also reported that the severity of the regional myocardial dysfunction assessed by 99mTc-labeled flow tracers ECG-gated SPECT was closely correlated with the deterioration in LV wall motion evaluated by contrast left ventriculography. Furthermore, using ECG-gated SPECT, myocardial perfusion and myocardial contraction can be assessed in almost identical regions of interest. Thus, the evaluation of local LV myocardial contraction using %CI in the present study can be considered very dependable. If the formula (ES–ED)/EDmax is used for calculating %CI in the regions with severely deteriorated myocardial perfusion, the %CI can be overestimated and so to avoid this problem, we used an alternative formula [(ES–ED)/EDmax].\(^16\)

Reverse Redistribution Phenomenon of 99mTc-Tetrofosmin
Several experimental investigations have suggested that dysfunction of sarcolemmal and mitochondrial membranes may be related to the RR phenomenon of 99mTc-labeled flow tracers.\(^19–21\) In patients with AMI who underwent reperfusion therapy, the RR phenomenon has been demonstrated on 99mTc-labeled flow tracers myocardial scintigraphy and the myocardium that shows the RR phenomenon of 99mTc-labeled flow tracers is thought to be damaged, though contractile function is preserved to a certain extent.\(^16\) Sugihara et al \(^7\) reported that the impairment of the LV wall motion in the regions showing the 99mTc-tetrofosmin RR phenomenon, evaluated using contrast left ventriculography, ranged from akinesia/dyskinesia to normal, but was significantly better than that in the regions with a fixed defect. Takeishi et al \(^6\) had a comparable result for LV wall motion evaluated by contrast left ventriculography in the regions with the 99mTc-sestamibi RR phenomenon, and both those studies had findings that were similar to those observed in regions with RR on 201Tl scintigraphy.\(^19–15\) In contrast, in the present study, the mean %CI after exercise in the regions with the RR phenomenon was as bad as that in the regions with a fixed defect, indicating that myocardial contraction after exercise in such regions was severely weakened. Even in the regions with the RR phenomenon and relatively better initial %uptake of 99mTc-tetrofosmin (>70%), LV wall thickening was as poor as in the regions with a fixed defect. The areas in which myocardial perfusion and myocardial thickening were assessed were almost compatible in the present study, so LV wall contraction in the regions with the 99mTc-tetrofosmin RR phenomenon can be more precisely assessed compared with the previous studies that used contrast left ventriculography.

Although visible myocardial ischemia was not observed during exercise in the regions with the 99mTc-tetrofosmin RR phenomenon, exercise-induced myocardial ischemia cannot be ruled out as a cause of the severely deteriorated LV wall contraction?\(^22\) because the supine ergometer exercise test may not stress the myocardium as strongly as the seated ergometer exercise test. Åstrand et al reported that maximal oxygen consumption was approximately 15% less in the supine ergometer exercise?\(^23\)

Impaired myocardial glucose and oxidative metabolism (ie, inadequate energy production) may have caused the severely deteriorated myocardial contraction after exercise as it was observed in the regions with RR on 201Tl myocardial scintigraphy in patients with AMI who underwent reperfusion therapy.\(^14,15\) Tanaka and Nakamura \(^24\) detected deteriorated myocardial fatty acid metabolism in the regions with 99mTc-tetrofosmin RR phenomenon. Maintenance of oxidative metabolism is a critical determinant of the potential recovery of regional mechanical function in patients with a recent myocardial infarction.\(^25\) Exercise causes an increase in heart rate and systemic blood pressure, augmenting the myocardial workload and energy consumption. In the myocardium showing the 99mTc-tetrofosmin RR phenomenon, inadequate energy supply to the heart during exercise might affect LV wall contraction after exercise and further study is needed to clarify this.

Study Limitation
It may be necessary to clarify whether exercise caused...
the severely decreased %CI in the regions with RR by comparing the %CI between the rest and after exercise images of 99mTc-tetrofosmin. Although the present study did not provide such a pathophysiological interpretation, the finding that the mean %CI in regions with RR after exercise was as low as that observed in scarred areas adds to the findings of Sugihara et al elucidating the clinical significance of RR on 99mTc-tetrofosmin SPECT imaging.

Conclusions

The results of the present study suggest that the RR phenomenon of 99mTc-tetrofosmin SPECT imaging in patients with AMI is often observed in those who have undergone reperfusion therapy. In regions with the RR phenomenon, deteriorated myocardial contractile function is most obvious after exercise.

References