Relationship Between Insufficient Redistribution in Exercise
Thallium-201 Myocardial Single-photon Emission Computed Tomography
and Reverse Redistribution at Rest

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It is widely accepted that perfusion defects in 3 to 4-h delayed images in exercise thallium-201 (\(^{201}\)TI) myocardial scintigraphy underestimate the viability of myocardium in the infarct region. In the present study, to examine the contribution of the condition of myocardium which demonstrates reverse redistribution in resting scintigraphy to the insufficiency of redistribution in the 4-h delayed image in exercise scintigraphy, we performed exercise and resting \(^{201}\)TI myocardial single-photon emission computed tomography in 58 patients with acute myocardial infarction and a single diseased coronary artery. Twenty eight patients demonstrated reverse redistribution (group RR) and 28 showed a fixed defect (group FD) in resting scintigraphy. Redistribution in the 4-h delayed image in exercise scintigraphy was significantly more insufficient in group RR than in group FD \((p<0.01)\), and the degree of the insufficiency of redistribution in exercise scintigraphy closely correlated with the degree of reverse redistribution in resting scintigraphy \((r=0.79, p<0.001)\). We conclude that in patients with acute myocardial infarction, the condition of myocardium which demonstrates reverse redistribution in resting myocardial scintigraphy is related to the insufficiency of redistribution in the delayed image in exercise scintigraphy.

\((Jpn\ Circ\ J\ 1995;\ 59:\ 23-32)\)

Pohost and coworkers have reported that perfusion defects in the image obtained immediately after exercise (initial image) may disappear, when another image is obtained several hours after exercise (delayed image) in thallium-201 (\(^{201}\)TI) myocardial scintigraphy. This phenomenon has been called “redistribution” and is considered to represent myocardial ischemia! The redistribution of \(^{201}\)TI can be used to differentiate ischemia from myocardial scar, and \(^{201}\)TI myocardial imaging has been used to select patients who may benefit from coronary artery revascularization by coronary angioplasty or coronary artery bypass grafting.

In many regions of viable myocardium, however, perfusion defects that are detected on the initial images persist, and appear to
be irreversible on delayed images obtained 3 to 4 h after exercise. Furthermore, patients with incomplete redistribution on 3 to 4-h post-exercise images have been shown to have a smaller defect, or even a normal scan, after successful coronary artery bypass grafting or coronary angioplasty. The defects are improved when an additional delayed image is obtained 8 to 72 h after $^{201}$Tl injection when the re-injection image is obtained after conventional 3 to 4-h delayed imaging or when the resting study is repeated using an additional injection of $^{201}$Tl. Thus, it has been widely accepted that a perfusion defect in the delayed image obtained 3 to 4 h after exercise underestimates the viability of myocardium in the infarct region. Thus, the redistribution in the delayed image obtained 3 to 4 h after exercise is insufficient.

Recently, perfusion defects that appear or become more evident in the delayed image in resting or stress $^{201}$Tl myocardial scans have been reported. This phenomenon has been called reverse redistribution. However, the significance and mechanism of this phenomenon remain controversial.

In this study, we investigated the contribution of the condition of myocardium which demonstrates reverse redistribution in resting $^{201}$Tl myocardial scintigraphy to the insufficiency of redistribution in 4-h delayed images in exercise $^{201}$Tl myocardial scintigraphy in patients with acute myocardial infarction.

METHODS

Study Population
We studied 58 patients with acute myocardial infarction (49 men and 9 women; mean age 57.6±10.7 (SD) years, range 37 to 75 years) who were admitted to our coronary care unit from October 1988 to December 1991. Acute myocardial infarction was defined by the presence of: 1) typical chest pain, 2) depression or elevation of ST segment on standard 12-lead electrocardiogram, and 3) elevation of serum creatine kinase and/or MB fraction more than 3 times the normal upper limit. All of the patients underwent exercise and resting $^{201}$Tl myocardial single-photon emission computed tomography and coronary arteriography within 2 months after the onset of myocardial infarction. None of the patients in this study had a history of previous myocardial infarction or coronary artery bypass grafting. Patients who had recurrent infarctions, who had undergone coronary angioplasty between $^{201}$Tl scintigraphy and coronary arteriography, or who had more than 50% stenosis in any coronary artery except the infarct-related coronary artery, were excluded from this study.

Determination of infarct site was based on ST-T changes in electrocardiograms and the location of the perfusion defect in $^{201}$Tl images. Of the 58 patients, 36 had anterior infarctions and 22 had inferior infarctions. Eight patients had non-Q wave myocardial infarctions.

Exercise and Resting Thallium-201 Single-Photon Emission Computed Tomography

Exercise Study: Symptom-limited exercise studies were performed on a bicycle ergometer in the sitting position 15 to 56 days (mean 28.5±8.0) after the onset of myocardial infarction. Nitrates, beta-adrenergic blockers and calcium-channel blockers were withheld on the morning of the test. The workload was started at 25 or 50 watts and increased by 25 watts every 2 min until the endpoint of the exercise was reached. Twelve-lead electrocardiograms and blood pressure measurements were obtained at baseline and at every minute of exercise. Exercise endpoints were excessive fatigue, dyspnea, dizziness, moderate to severe angina, hypotension, diagnostic (>1.5 mm horizontal or downsloping, or >2.0 mm upsloping) ST segment depression, and significant arrhythmia. At peak exercise, a dose of 3 mCi (111 MBq) of $^{201}$Tl was injected intravenously and patients were encouraged to exercise for an additional minute. Initial images were obtained immediately after the termination of exercise and delayed images were obtained 4 h later.

Resting Study: Resting studies were performed 6 to 15 days before or after the exercise study (6 to 56 days after the onset of myocardial infarction, mean 26.7±12.4 days). Each patient received a dose of 3 mCi (111 MBq) of $^{201}$Tl injected intravenously at rest without withholding antianginal
deviations below the normal limit were considered abnormal. The severity score for the perfusion defect on each image was defined as follows:

\[
\text{Severity score} = \text{sum of the difference between the count of abnormal pixels and that of the corresponding normal pixels/total number of all pixels} (60 \times \text{the number of adopted slices}).
\]

Compared with the severity score in the initial image, a decrease or an increase in the severity score in the delayed image equal to or greater than 25\% was considered to be redistribution or reverse redistribution, respectively. If the severity score remained unchanged on the delayed image, it was considered to be a fixed defect.

On resting $^{201}$TI myocardial scintigraphy in patients with acute myocardial infarction, a defect which demonstrates reverse redistribution is expected, in time, to become a fixed defect, the size of which would be similar to that in the initial image. In addition, in patients who show reverse redistribution, the initial image more accurately reflects the viability of myocardium than does the delayed image.\(^{13}\) In the present study, we similarly assumed that the initial image in resting study reflected the viability of myocardium in patients who showed fixed defects or reverse redistribution in the resting study.

When there was an increase equal to or greater than 25\% in the severity score on the initial image in the exercise study, compared with that in the initial image on the resting study, the patient was considered to have myocardial ischemia induced by exercise.

**Calculation**: In the present study we defined the following scores and indexes. (Fig. 1)

Ischemia score and ischemia index, which represented the degree of ischemia induced by exercise, were calculated as follows:

\[
\text{Ischemia score} = \text{the severity score of in the initial image of in the exercise study (IEx)} - \text{the severity score in the initial image in the resting study (IR)}
\]

\[
\text{Ischemia Index} = \frac{\text{IEx}}{\text{IR}}
\]
Reverse redistribution score and reverse redistribution index, which represented the degree of reverse redistribution in the resting study, were calculated as follows:

Reverse redistribution score = the severity score of in the delayed image in the resting study (DR) - IR
Reverse redistribution index = DR/IR

Redistribution insufficiency score and redistribution insufficiency index, which represented the degree of underestimation of viability in the delayed image in the exercise study, were calculated as follows:

Redistribution insufficiency score = the severity score in the delayed image in the exercise study (DEx) - IR
Redistribution insufficiency index = DEx/IR

Percent redistribution, which represented the percentage of myocardium which demonstrated redistribution in the delayed image in the exercise study in ischemic, but still viable, myocardium, was calculated as follows:
Percent redistribution = (IEx - DEx)/ ischemia score \times 100

Coronary Arteriography
Coronary arteriography was performed in multiple projections using standard techniques within 4 weeks of the exercise study (mean 27.8 ± 6.7 days after the onset of myocardial infarction). Coronary narrowing was estimated as the maximal percent narrowing of luminal area by cinevideodensitometry using a cineprojector and a coronary analyzer (Vanguard Instrument Corp., model XR-35 and XR-70, New York, U.S.A.).

Statistics
All variables are expressed as the mean ± standard deviation. Unpaired t-test, and chi-square test were used for continuous variables and discrete variables, respectively. Correlation coefficients were calculated by linear regression analysis. P values < 0.05 were considered significant.

RESULTS
Of the 58 patients, 28 showed fixed defects (group FD), 28 showed reverse redistribution (group RR), and 2 showed redistribution on resting scintigraphy. In the present study, we only investigated patients in group FD or group RR. Eighteen patients in group FD and all of the patients in group RR had exercise-induced ischemia.

Baseline Characteristics
The baseline characteristics in group FD and group RR are shown in Table I. These two groups did not differ significantly in age, non-Q wave infarction, interventional therapy before 201I scintigraphy and coronary arteriography, percent area stenosis of the infarct-related artery, or the presence of collateral flow to the infarct-related artery.
### TABLE II RESULTS OF EXERCISE AND RESTING SCINTIGRAPHY IN GROUP FD AND GROUP RR

<table>
<thead>
<tr>
<th>Group</th>
<th>FD</th>
<th>RR</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total workload (Watt-min)</td>
<td>319±137</td>
<td>392±177</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal SBP (mmHg)</td>
<td>155±23</td>
<td>164±20</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal HR (beats/min)</td>
<td>144±16</td>
<td>137±15</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal PRP (×10³)</td>
<td>22.5±4.4</td>
<td>22.5±3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise-induced angina (%)</td>
<td>1 (4)</td>
<td>3 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Positive ECG change (%)</td>
<td>4 (14)</td>
<td>8 (29)</td>
<td>NS</td>
</tr>
<tr>
<td>Severity score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>initial image</td>
<td>17.82±7.42</td>
<td>10.26±6.39</td>
<td>( p&lt;0.01 )</td>
</tr>
<tr>
<td>delayed image</td>
<td>14.42±6.91</td>
<td>6.92±4.35</td>
<td>( p&lt;0.01 )</td>
</tr>
<tr>
<td>Redistribution pattern (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>redistribution</td>
<td>11 (39)</td>
<td>17 (61)</td>
<td>NS</td>
</tr>
<tr>
<td>fixed defect</td>
<td>16 (57)</td>
<td>10 (35)</td>
<td></td>
</tr>
<tr>
<td>reverse redistribution</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td><strong>Resting study</strong></td>
<td></td>
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<tr>
<td>Severity score</td>
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<tr>
<td>initial image</td>
<td>12.36±7.14</td>
<td>3.12±3.48</td>
<td>( p&lt;0.01 )</td>
</tr>
<tr>
<td>delayed image</td>
<td>12.60±6.79</td>
<td>5.79±4.94</td>
<td>( p&lt;0.01 )</td>
</tr>
</tbody>
</table>

Values are mean±SD, NS, not significant; SBP, systolic blood pressure; HR, heart rate; PRP, pressure rate product; ECG, electrocardiogram.

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**Exercise and Resting Thallium-201 Single-photon Emission Computed Tomography**

There was no significant difference in the time of the exercise (29.3±7.5 days in group FD vs 27.4±8.4 days in group RR; NS) or resting (29.1±10.7 in group FD vs 28.0±11.7 days in group RR; NS) study after the onset of myocardial infarction. Results of the resting and exercise studies are shown in Table II. In the exercise study, there was no significant difference in the total workload, systolic blood pressure, heart rate or pressure rate product at the maximal exercise point, or in the redistribution pattern in \(^{201}\text{TI}\) imaging between the two groups. Severity scores in both the initial and delayed images in exercise and resting studies were significantly less in group RR than in group FD (all \( p<0.01 \)).

As shown in Fig. 2, in 26 patients (93%) of group FD and 27 patients (96%) of group RR, the severity score in the delayed image in the exercise study was greater than that in the initial image in the resting study.

Ischemia score and ischemia index are shown in Fig. 3. Although there were no significant differences in ischemia scores between group RR and group FD (7.14±4.68
The redistribution insufficiency score was directly correlated with the reverse redistribution score ($r=0.51; p<0.001$) (Fig. 5), and the redistribution insufficiency index correlated directly with the reverse redistribution index ($r=0.79; p<0.001$) (Fig. 6).

All of the patients in group RR and 18 in group FD had exercise-induced ischemia. There was no significant difference in percent area stenosis of the infarct-related artery (87.0±23.6 vs 86.7±24.8%; NS) or ischemia score (7.14±4.68 vs 6.92±2.96; NS) between group RR and the 18 patients with exercise-induced ischemia in group FD. As shown in Fig. 7, among patients with exercise-induced ischemia, percent redistribution was significantly less in group RR than in group FD (38.0±38.0 vs 60.2±27.8%; $p<0.05$).

**DISCUSSION**

In the present study, redistribution in the 4-h delayed image in exercise $^{201}$Tl scintigraphy was obviously insufficient. This observation is consistent with previous reports. Moreover, we demonstrated that the redistribution in the 4-h delayed image in the exercise study was more insufficient in...
patients who demonstrated reverse redistribution than in patients who demonstrated a fixed defect on resting scintigraphy, and that the degree of the insufficiency of redistribution in the exercise study correlated closely with the degree of reverse redistribution in the resting study.

The time to completion of $^{201}$TI redistribution following stress appears to be related to the severity of stenosis in the coronary artery supplying the defect area\textsuperscript{14} and the degree of redistribution depends on the severity of the initial defect. Some investigators have reported that reverse redistribution correlates with the patency of coronary arteries\textsuperscript{15} while others have reported that this phenomenon indicates a stenosed coronary artery\textsuperscript{15} Still others have reported that this phenomenon does not correlate closely with either the degree of coronary artery disease, or with the location of the stenosis\textsuperscript{16}

In the present study there was no significant difference in the severity of the stenosis of the infarct-related coronary artery between group FD and group RR. Microcirculation in myocardium or factors other than myocardial regional blood flow (ie, uptake and washout rate of $^{201}$TI in the myocardium) may play a part in both insufficient redistribution in the exercise study and reverse redistribution in the resting study.

In this study, we did not investigate left ventricular function. However, we previously reported that reverse redistribution in resting $^{201}$TI scintigraphy in patients with acute myocardial infarction was observed in viable myocardium in infarct regions with severe systolic dysfunction\textsuperscript{13} Accordingly, myocardium which demonstrates insufficient redistribution in exercise scintigraphy and reverse redistribution in resting scintigraphy may be so-called "stunned myocardium", although it is unclear whether the condition of myocardium which demonstrates reverse redistribution in resting scintigraphy is directly related to the condition of stunned myocardium.

Weiss et al\textsuperscript{11} have reported that reverse redistribution in patients with acute myocardial infarction treated with streptokinase is caused by rapid washout of $^{201}$TI from the infarct region, and have proposed 3 mechanisms for reverse redistribution. The first
mechanism is higher-than-normal blood flow to the noninfarcted tissue in the reperfused myocardium. However, since there was no significant difference in percent area stenosis of the infarct-related artery between group FD and group RR in the present study, this mechanism can not explain the phenomenon observed here. The second mechanism is normal blood flow to the noninfarcted tissue in the reperfused zone with decreased blood flow in the infarcted portion of the reperfused zone associated with resting hypoperfusion in the contralateral myocardial region. However, since none of the patients in the present study had diseased coronary arteries other than the infarct-related artery, this mechanism can not explain the phenomenon observed here. The third mechanism is significant $^{201}$TI uptake by necrotic tissue or the interstitial component in the reperfused zone, and rapid washout of $^{201}$TI from this necrotic tissue or interstitial component. This mechanism can explain reverse redistribution but not our finding that insufficient redistribution in exercise scintigraphy is closely related to reverse redistribution in the resting study.

Although it is generally accepted that the main route by which TI enters cells is via the Na-K ATPase pump, which shows an approximately 10-fold higher affinity for TI than for K$^+$, there has been no study of Na-K ATPase activity in myocardium which demonstrates reverse redistribution on in $^{201}$TI myocardial scintigraphy. ATP stores are reportedly decreased in stunned myocardium$^{18,19}$ and reverse redistribution in resting scintigraphy in patients with acute myocardial infarction has been reported to be observed in viable myocardium in the infarct region with severe systolic dysfunction$^{13}$. Accordingly, Na-K ATPase activity may be reduced in viable myocardium in infarct regions in patients who show reverse redistribution. Recently, there has been doubt regarding whether Na-K ATPase is important for TI transport into cells, and a passive diffusion process has been proposed$^{20-23}$. Rauch and Kubler reported that while an almost complete inhibition of Na-K ATPase by ouabain caused only a small decrease in the initial uptake of TI by resting single heart muscle cells of rat, tetraethylammonia induced a marked reduction in TI uptake. They postulated that passive influx through membrane channels sensitive to tetraethylammonia played a major role in the initial TI uptake by resting single heart muscle cells of rat$^{20}$. Sessler et al. reported that TI passed through the cell membrane of Ehrlich mouse ascites tumor cells using three transport systems: ATPase, TI-Na-2Cl-cotransport, and a Ca-dependent ion channel. In the case of TI, the main route into the cells was thought to be the cotransport system$^{21}$. According to these findings, during myocardial $^{201}$TI scintigraphy, $^{201}$TI at high blood levels may enter viable heart muscle cells via passive pathways depending on the regional blood flow immediately after injection, while $^{201}$TI at low blood levels may enter via the Na-K ATPase pump 3 to 4 h after injection. The $^{201}$TI concentration in myocardium at 4 h after the injection depends on the balance between the loss through the membrane and active uptake by Na-K ATPase. Therefore, when Na-K ATPase activity is reduced in viable myocardium in infarct regions, the redistribution of $^{201}$TI ought to be insufficient in 4-h delayed images in an exercise study, and the washout of $^{201}$TI from the infarct region ought to be faster than that from noninfarct regions, resulting in reverse redistribution in a resting study. These speculations would help to explain our finding that redistribution in the 4-h delayed image in the exercise study was more insufficient in group RR than in group FD, and that the degree of insufficiency of redistribution in the exercise study correlated closely with the degree of reverse redistribution in the resting study.

Viability of myocardium is very important in determining whether a patient is a candidate for coronary revascularization. Considering the present findings and our previous report which suggested a relationship between reverse redistribution and stunned myocardium$^{13}$ exercise $^{201}$TI scintigraphy can be considered to frequently underestimate the viability of myocardium, especially stunned myocardium in the infarct region. To estimate the viability of myocardium with systolic dysfunction, resting $^{201}$TI scintigraphy or investigation metabolism of in the myocardium using positron-emission tomography are required.

In the present study, although we did not
investigate serial changes in exercise and resting scintigraphy, serial observation is necessary to gain further understanding of reverse redistribution in resting scintigraphy and insufficient redistribution in exercise study. Investigation of metabolism in the myocardium by basic methods and positron-emission tomography would also be helpful in understanding this phenomenon.

In conclusion, in patients with acute myocardial infarction, the condition of myocardium which demonstrated reverse redistribution in resting 201T1 myocardial scintigraphy was closely related to the insufficiency of redistribution in the delayed image in exercise scintigraphy.

Acknowledgment

We wish to thank Ms. Harumi Hamada and Ms. Manami Okamoto for their secretarial assistance.

REFERENCES

