CLINICAL STUDIES

USEFULNESS OF THALLIUM-201 RE-INJECTION METHOD FOR THE EVALUATION OF MYOCARDIAL VIABILITY

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Areas of the heart which are supposedly absent of myocardial viability due to persistent thallium defect in exercise thallium myocardial scintigraphy sometimes recover ventricular wall motion through coronary revascularization. To avoid such underestimation of myocardial viability, a "re-injection method" was developed. At the peak of supine ergometer exercise in 51 patients with coronary artery disease, 111 MBq thallium was injected. Conventional exercise and 3 h-delay images were then obtained using single photon emission computed tomography. Subsequently, 55 MBq thallium was injected and a re-injection image was obtained 1 h later. Each image was divided into 12 segments and compared by left ventriculography and coronary angiography. Redistribution was found in 36 patients (71%) on the delayed images and in 44 patients (86%) on either the delayed or the re-injection images (p<0.05). There were 127 redistribution segments (38%) on the delayed images and 163 (49%) on the re-injection images out of 336 defects on the exercise images (p<0.001). In normokinetic segments with significant coronary stenosis and in hypokinetic segments, redistribution was found in 42% and 45% of the defects, respectively, on the delayed images, and in 65% and 62% of the defects, respectively, on the re-injection images (p<0.01). However, no significant differences were observed between the delayed and either the delayed or re-injection images in the akinetic segments. These results suggest that the re-injection method is useful for avoiding underestimation of myocardial viability.

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Exercise thallium myocardial scintigraphy is a widely used technique for the diagnosis of coronary artery disease. In this method, thallium is injected at the end of multistage exercise, and an exercise image is taken immediately following the exercise. After 3 to 4 h, a delayed image is obtained. Myocardial tissue which contains only a transient defect is subject to myocardial ischemia, and myocardial viability will be present in that area. On the other hand, myocardial tissue which contains a persistent defect is considered a region of myocardial infarct in which myocardial viability is absent!−3 Nevertheless, an area which is believed to be absent of myocardial viability based on the results of thallium scintigraphy sometimes recovers ventricular wall motion through coronary revascularization, e.g. by percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery4−6. To avoid such an underestimation of myocardial viability on the basis of conventional exercise and delayed thallium

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imaging, a "re-injection method" was developed. In this technique, exercise and delayed images are obtained as in current procedures. However, after the delayed image is obtained, another injection of thallium is administered while the patient is at rest, and a re-injection image is obtained 1 h later. The purpose of the present study was to assess the usefulness of this newly developed "re-injection method" for detecting myocardial viability in patients showing persistent defect based on conventional exercise and delayed thallium imaging.

METHODS

Subjects
The subjects consisted of 51 patients (47 males and 4 females) who had been diagnosed as having coronary artery disease by coronary angiography. All of the subjects had one or more segments with a perfusion defect on exercise thallium images. Forty-two of the patients had prior myocardial infarction and 9 had angina pectoris. Their average age was 56 ± 10 (mean ± SD) years.

Conventional Exercise Thallium Myocardial Scintigraphy
Exercise thallium myocardial scintigraphy was performed using a supine ergometer. A multistage exercise test was performed: exercise was started at 25 watts, and increased in increments of 25 watts every 3 min. During the exercise, standard 12-lead electrocardiography and blood pressure levels were monitored at 1 min intervals.

At the end point of the exercise test (appearance of chest pain, ST depression ≥ 0.2 mV, pressure rate product ≥ 23,000), 111 MBq (3 mCi) of thallium chloride was injected and an additional 1 min of exercise was performed, if possible. Immediately after exercise and 3 h later, exercise and delayed images, respectively, were taken. Myocardial images were obtained by single photon emission computed tomography (SPECT). The conditions of SPECT acquisition were as follows: a 180-degree semicircle, 30 sec per step, and a 32-step acquisition.

Re-injection Method
Immediately after taking the delayed image of the conventional method, 55 MBq (1.5 mCi) of thallium was injected while the patient was resting. One h later (i.e., about 4 h after the completion of exercise), a re-injection image was obtained by SPECT under the same acquisition conditions as above (Fig. 1).

Analysis of Thallium Myocardial Scintigraphy
The resulting images were filtered before reconstruction using a smoothing filter, a low cut filter (fc=0.2), and a Chesler's filter. Images were reconstructed with respect to the heart axes: vertical long axis, horizontal long axis, and short axis. For analysis, the reconstructed left ventricle was divided into 3 short-axis layers: basal, middle, and apical (Fig. 2). Furthermore, each layer was divided into 4 segments: anterior, septum, posterior, and lateral. Qualitative analysis was performed for each segment on the basis of defect, hypo-perfusion, or normal perfusion. Finally, the number of abnormal perfusion segments in each image was evaluated.

Redistribution was defined as either of the following: (1) a change from defect to either hypo-perfusion or normal perfusion, or (2) a change from hypo-perfusion to normal perfusion.

Catheterization
Catheterization and exercise thallium myocardial scintigraphy were performed within 4 weeks of each other. Coronary angiography was performed according to Judkins' technique. At least 75% stenosis by
Fig.2. Analysis of thallium myocardial scintigraphy and left ventriculography. The myocardium is divided into 3 short-axis layers, and each layer is divided into 4 segments for analysis of thallium myocardial scintigraphy. The left ventricle is also divided into 12 segments for analysis of left ventriculography, and all segments are compared.

Fig.3. Change in patients. Fifty-one patients with perfusion defects on their exercise images were evaluated. The flowchart shows the changes in either the delayed images or the re-injection images (left). The redistribution rates in the 51 patients on the delayed, re-injection, and either the delayed or re-injection images, are also indicated (right). There was no difference between the redistribution rate in the delayed images and that in the re-injection images. However, the redistribution rate on either the delayed or re-injection images was significantly higher than that on the delayed images alone (p<0.05).

the American Heart Association's criteria was defined as significant stenosis.

Left ventriculography was performed in 30-degree right anterior oblique and 60-degree left anterior oblique projections simultaneously. Left ventricular wall motion was evaluated in 12 segments, as shown in Fig. 2. Motion abnormalities were classified as follows: normal, hypokinesis, akinesia, and dyskinesis. The degree of redistribution

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Fig. 4. Change in segments. Three hundred thirty six of the 612 segments in the 51 patients, had perfusion defects on the exercise images. The flowchart shows the changes in either the delayed images or the re-injection images (left). The redistribution rates in the 336 segments on the delayed, re-injection, and either the delayed or re-injection, images are also shown (right). The redistribution rate on the re-injection images was higher than that on the delayed images (p<0.001). Furthermore, the redistribution rate on either the delayed or the re-injection images was also significantly higher than that on the delayed images (p<0.001).

<table>
<thead>
<tr>
<th>Wall Motion</th>
<th>Total Number of Segments</th>
<th>Number of Segments with Defects on Exercise Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normokinesis</td>
<td>265</td>
<td></td>
</tr>
<tr>
<td>without CAD</td>
<td>127</td>
<td>52 (41%)</td>
</tr>
<tr>
<td>with CAD</td>
<td>133</td>
<td>93 (70%)</td>
</tr>
<tr>
<td>Hypokinesis</td>
<td>73</td>
<td>67 (92%)</td>
</tr>
<tr>
<td>Akinesis</td>
<td>14</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>Dyskinesis</td>
<td>Total 612</td>
<td></td>
</tr>
</tbody>
</table>

and severity of wall motion abnormality were compared in each patient.

Statistical Analysis

All data were expressed as percentages based on the number of patients and defect areas on the exercise images. The chi-square test was used to compare the percentage values.

RESULTS

Change in the number of patients with perfusion defects on exercise images

Of the 51 patients who had perfusion defects on their exercise images, 36 had one or more segments of redistribution on their delayed images. Of the 15 patients who had perfusion defects on their delayed images, revealed new redistribution on their re-injection images. Of the 36 patients who had redistribution on their delayed images, 2 showed reverse redistribution on their re-injection images (Fig. 3, left).

Redistribution on the delayed images was found in 70.5% of the patients who had perfusion defects on their exercise images, while redistribution on the re-injection images was noted in 82.4% of the patients. Furthermore, redistribution on either the delayed or re-injection images was found in 86.3% of the patients. Statistically, redistribution on the re-injection image alone was not significantly higher than that on the delayed image. However, the number of patients with redistribution on either the delayed image or the re-injection image was higher than that with redistribution on just the delayed image (Fig. 3, right).

Change of perfusion defects in myocardial segments

In total, 612 segments were studied in the 51 patients who had perfusion defects on their delayed images. On the exercise images, 276 segments did not show defects. Of the 336 segments which did show defects on the exercise images, 127 revealed redistribution and 209 had defects on the delayed
images. Of these 209 segments, 60 revealed redistribution and 149 still had defects on the re-injection images. However, of the 127 segments that had redistribution on the delayed images, 24 showed defects on the re-injection images (i.e., reverse redistribution) (Fig. 4, left).

The frequency of redistribution in segments which had defects on the exercise images was 37.8% on the delayed images. On the re-injection images, 48.5% of the segments had redistribution. Furthermore, redistribution on either the delayed and/or re-injection images was found in 55.7% of the segments. Statistically, redistribution on the re-injection images was significantly higher than that on the delayed images. Moreover, the number of segments which showed redistribution on either a delayed image or a re-injection image was higher than that which showed redistribution on just a delayed image (Fig. 4, right).

**Findings of contrast left ventriculography**

Left ventricular wall motion was evaluated by contrast left ventriculography. Among the 612 segments, normokinesis was found in 392, hypokinesis in 133, akinesis in 73, and dyskinesis in 14. Furthermore, of the 392 normokinetic segments, 127 were areas where the filling coronary artery was at least 75% stenotic (Table I).

**Redistribution on normokinetic segments with coronary stenosis**

On the exercise images, defects were observed in 52 of the 127 normokinetic segments with coronary stenosis. Redistribution was noted in 23 segments on the delayed images and in 34 segments on the re-injection images.

The redistribution rate was 42.3% on the delayed images, 65.4% on the re-injection images, and 69.2% on either the delayed or re-injection images. The redistribution rate on the re-injection images was significantly higher than that on the delayed images. Moreover, the number of segments which showed redistribution on either the delayed images or the re-injection images was higher than that which showed redistribution on just the delayed images (Fig. 5, left).

**Redistribution in hypokinetic segments**

Ninety-three of the 133 hypokinetic segments revealed defects on the exercise images. On the delayed images, redistribution appeared in 42 segments. Six of the 42 redis-
Before percutaneous transluminal coronary angioplasty

**Fig.6.** Coronary angiography and left ventriculography before percutaneous transluminal coronary angioplasty. Total occlusion in the right coronary artery and severe stenosis in the left circumflex branch were found on coronary arteriography. On left ventriculography, the inferior segments displayed akinesis.

Distributed segments on the delayed images showed defects on the re-injection images. Furthermore, newly developed redistribution was found in 22 segments on the re-injection images. Therefore, redistribution was noted in a total of 58 hypokinetic segments.

The redistribution rate was 45.2% on the delayed images, 62.4% on the re-injection images, and 68.8% on either the delayed or re-injection images. The redistribution on the re-injection images was significantly higher than that on the delayed images. Moreover, the number of segments which showed redistribution on either the delayed images or the re-injection images was higher than that which showed redistribution on just the delayed images (Fig. 5, center).

**Redistribution in akinetic segments**

Sixty-seven of the 73 akinetic segments revealed defects on the exercise images. On the delayed images, redistribution appeared in 12 segments. Three of the 12 redistributed segments on the delayed images showed defects on the re-injection images. Furthermore, newly developed redistribution was found in 8 segments on the re-injection images. Therefore, redistribution was noted in a total of 17 akinetic segments.

The redistribution rate was 17.9% on the delayed images, 25.4% on the re-injection images, and 29.8% on either the delayed or re-injection images. The redistribution on the re-injection images was higher than that on the delayed images. Moreover, the number of segments which showed redistribution on either the delayed images or the re-injection images was higher than that which...
showed redistribution on just the delayed images. There were no statistically significant differences (Fig. 5, right).

The data for the redistribution rates on the re-injection images are summarized in Fig. 5. Clearly, the redistribution rate in hypokinetic segments and in normokinetic segments with coronary stenosis was higher than that in akinetic segments.

CASE REPORT

The patient was a 56-year-old man. He had prior myocardial infarction (inferior, 4 years previously). He was recently admitted to our hospital because of unstable angina.

On coronary angiography, total occlusion was found in the proximal portion of the right coronary artery. Furthermore, 99% stenosis with filling delay was noted in the proximal left circumflex coronary artery. The periphery of the right coronary artery was filled with bridge collateral flow and collateral flow from the left circumflex artery. On contrast left ventriculography, the inferior wall showed akinesis (Fig. 6).

Exercise thallium myocardial scintigraphy was performed (Fig. 7: exercise, upper left panel; delayed, upper right panel; and re-injection, lower left panel). On the exercise image, a thallium perfusion defect was observed in the posterior and lateral segments. On the delayed image, a defect persisted in the same region. However, redistribution was observed on the re-injection image.

From these data, we considered that myocardial viability was still present in the posterior and lateral segments that showed akinesis on left ventriculography. Therefore, percutaneous transluminal coronary angioplasty was performed for left circumflex artery stenosis.

Coronary angiography and left ventriculography were performed again after 3 months (Fig. 8). The portion of the left circumflex artery which had undergone angioplasty was smooth, and the motion of the inferior wall had changed from akinesis to hypokinesis.
After percutaneous transluminal coronary angioplasty

Fig. 8. Coronary angiography and left ventriculography after percutaneous transluminal coronary angioplasty. On coronary angiography, the left circumflex branch stenosis was found to be completely revascularized. The wall motion in the inferior segment which was observed by left ventriculography showed recovery from akinesis to mild hypokinesis.

DISCUSSION

Myocardial viability is defined as a reversible impairment of the regional myocardial contractile function, involving “myocardial stunning” and “myocardial hibernation”. Generally, an area with normal wall motion is considered to be viable myocardium. However, areas with impaired wall motion are not necessarily considered non-viable because some cases recover wall motion after revascularization. Determination of myocardial viability, especially in myocardial infarcted areas, is tremendously important, since any recovery of the impaired function can affect the prognosis or quality of life of a patient with coronary artery disease. Assessment of the wall motion on postextrasystolic potentiation or dobutamine infusion, determination of myocardial metabolism by positron emission tomography (PET), and coronary perfusion by thallium imaging have all been used to evaluate viability.

Postextrasystolic potentiation has been used to detect myocardial viability in a catheterization laboratory, and the wall motion was evaluated by contrast left ventriculography during induction of extrasystole by electrical stimulation. Dobutamine infusion (5-10 μg/kg/min) stress tests were performed on either echocardiography or radionuclide pool scintigraphy. With these stimulations, the area of viable myocardium temporarily recovered its wall motion.

In viable myocardium, metabolism is maintained. With a lack of coronary perfu-

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sion, basic metabolism would involve an anaerobic process: glucose would be metabolized rather than fatty acid. In PET imaging, glucose metabolism is evaluated using Fluorine-18 fluorodeoxyglucose, and coronary perfusion is evaluated with either Nitrogen-13-Ammonia or Rubidium-82. Viable myocardium is defined as an area of decreased coronary perfusion and increased glucose metabolism using PET.\(^5\) Tamaki et al\(^11\) examined the correlation between PET viability and wall motion recovery after coronary revascularization employing bypass graft surgery. A good relationship was observed, and they concluded that PET imaging might represent the most suitable technique for detecting viable myocardium. However, although evaluation of viability by PET is useful, few institutions have positron generators and detectors.

Single photon scintigraphy is generally employed. To assess myocardial perfusion, the thallium-201 technique was developed. By combining either exercise or pharmacological stress testing, a diagnosis of either normal, myocardial ischemia or myocardial infarct can be obtained. In 1977, Pohost et al\(^1\) developed the single injection method, in which images are taken immediately after exercise and 3–4 h later, with a single injection administered during exercise. Before this technique was developed, rest and stress thallium images were obtained on different days. Since 1977, such exercise-delayed thallium scintigraphy has been widely used around the world for detecting myocardial ischemia or viability.\(^1–4,12–18\) Recently, however, some investigators have reported that the single injection method results in underestimation of myocardial ischemia or viability.\(^5,6,19\) In an attempt to avoid this underestimation, extremely delayed imaging (up to 18–72 h after injection during exercise)\(^20,21\) or very limited quantitative analysis have been applied.\(^22\)

Extremely delayed imaging was developed because redistribution in the viable area tended to appear more than 3–4 h after injection. To acquire a sufficiently high count for clinical diagnosis at 18–72 h after injection, the acquisition time must be increased to as much as 60–80 sec/step (total, 32–40 min). It is difficult for patients to remain in the same position for this length of time. Another difficulty with this method is that patients must be available for several days of imaging in order to make a proper evaluation. This is particularly difficult with outpatients. Using very limited quantitative analysis, we can also detect viable myocardium from minimum levels of redistribution. However, it is difficult to detect true ischemia with this method.

To evaluate myocardial perfusion while the patient is at rest, a resting thallium image would be useful for comparison with the redistribution thallium image taken 3–4 h after exercise. The thallium re-injection method was developed to enable us to obtain a rest-like image on the same day that we obtain exercise and delay images. In this method, a half dose of thallium is injected after conventional exercise thallium myocardial scintigraphy and a re-injection image is taken 15 or 60 min later.

Several similar small dose re-injection studies have been reported.\(^23–29\) Therefore, we compared these studies with our own. Concerning the re-injection dose, all of the studies, including the present study, used 37 to 55 MBq (1.0 to 1.5 mCi) of thallium. No remarkable differences were noted between the results a each dose. Concerning the timing of the images, in all of the studies, except our present study, images were taken 15 min after re-injection. We obtained our images 1 h after re-injection, since more than 30 min is required to ensure equalization of the thallium distribution when thallium is injected during rest.\(^9\) We believed that if images were obtained 10 to 15 min after injection, then some patients with severe coronary stenosis in viable myocardium would show a perfusion defect at rest because of hypoperfusion. Because the purpose of this re-injection method is to detect viable myocardium that cannot be detected by conventional exercise thallium myocardial scintigraphy, more than 30 min should elapse between the re-injection and acquisition of the re-injection images. Similarly, Kayden et al suggested that a wait of more than 30 to 45 min after re-injection as part of a 24 h re-injection method would enable a researcher to distinguish severe ischemia from myocardial scar.\(^30\) Based on our results, redistribution on the re-injection images occurred in

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29% of the persistent defects on conventional exercise 3-hour-delay thallium myocardial scintigraphy, which suggests the viability of these areas.

Rozanski et al\textsuperscript{4} reported that 50% of a hypokinetic area had recovered its wall motion after coronary artery bypass graft surgery, as determined by radionuclide ventriculography. In a hypokinetic area in the present study, we observed redistribution in 51% of post-exercise initial defects on the re-injection images, as compared with only 34% on the delayed images. The redistribution rate on the re-injection images was significantly higher than that on the delayed images. A similar analysis was performed for the ischemic area, in which there was significant stenosis in the filling coronary artery, but no wall motion abnormality. The redistribution rate on the re-injection images (44%) was significantly higher than that on the delayed images (33%). These findings suggest that the re-injection method is a useful technique for detecting ischemia and for detecting severe ischemic regions which were not detected by conventional exercise thallium myocardial scintigraphy. In the conventional single injection exercise-delayed method, there was less blood flow and minimum thallium uptake by the myocardium even after the 3 h delay.

Although the re-injection method represents a useful means for detecting myocardial viability, some unresolved problems exist.

The first problem is that of reverse redistribution, in which redistribution on the delayed image disappears on the re-injection image. The mechanism behind this phenomenon remains unclear. We believe that the following factors may contribute to the re-injection images: (1) spontaneous or mechanical revascularization of the respective coronary artery, (2) collateral flow, (3) the time from re-injection to imaging, and (4) differential washin following re-injection, among others\textsuperscript{31}

We must consider that if viability of myocardium is evaluated by exercise and re-injection images, without using delayed images, the reverse redistribution phenomenon may contribute to an underestimation of myocardial viability. For example, an area which contained a defect on the exercise image, redistribution on the delayed image, and defect again on the re-injection image would be diagnosed as viable if we considered the exercise and delayed images. However, if we based our evaluation on the exercise and re-injection images, and did not consider the delayed image, the area would be diagnosed as non-viable. Therefore, the exercise, delayed and re-injection images are all required to evaluate the viability of myocardium. If redistribution is present on either the delayed or re-injection image, then viability of the myocardium will be present. Clinically, this does not present a serious problem, but the mechanism behind this phenomenon should be investigated further.

The second problem is the issue of quantitative analysis. A re-injection image may not be suitable for quantitative analysis involving, for example, the washout rate between the exercise and delayed images, because of the complexity of the calculation of the distribution of thallium and evaluation of the re-injected thallium dose, especially in practical cases.

Finally, there is the problem of the burden on the patient. This entire re-injection procedure, including acquisition of the re-injection image, requires about 5 h. However, this does not present as much of a problem for patients as do the procedures in which images are taken after 24 h.

The re-injection method was developed in order to determine the viability of the myocardium in selecting candidates for coronary revascularization, e.g. by percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery. In the present study, we examined the redistribution rate in myocardium that had been evaluated as being viable or nonviable based on an analysis of wall motion using left ventriculography. We confirmed that the re-injection method can be used to detect viability of myocardium which cannot be detected by conventional exercise thallium myocardial scintigraphy. Since viability is defined as the recovery of wall motion following restoration of coronary flow, it is necessary to assess the recovery of wall motion after coronary revascularization in an area which shows redistribution. Therefore,
we are in the process of evaluating the wall motion before and after revascularization. Additional information regarding the suitability of the re-injection method for the evaluation of viability should be obtained. Recently, Dilsizian et al reported on the relationship between wall motion recovery after coronary revascularization and a diagnosis of viability based on the re-injection method in thallium scintigraphy. According to their article, the accuracy of the diagnosis regarding viability obtained using the re-injection method was superior to the diagnosis regarding viability which was not obtained using that method.

Based on our data regarding redistribution, in cases where evidence of myocardial viability is not demonstrated by conventional exercise thallium myocardial scintigraphy, the re-injection method should be used to prevent underestimation of the viability.

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