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Significance of Exercise Labeled β-Methyl Lodophenyl Pentadecanoic Acid (BMIPP) and Resting Thallium-201 (TI) Delayed Single Photon Emission Computed Tomography (SPECT) Before and After Percutaneous Transluminal Coronary Angioplasty (PTCA)

Takao Mori¹, Masunori Hayakawa¹, Kaoru Hattori¹, Koujirou Awano¹, Jun Masuda¹, Tetuya Inatome¹, Hisashi Fukuzaki¹, and Kazumi Maeda²

To clarify the significance of exercise ¹²³I labeled β-methyl iodophenyl pentadecanoic acid (BMIPP) and resting thallium-201 (TI) delayed single photon emission computed tomography (SPECT), we studied maximal exercise loading BMIPP SPECT following rest-injected TI 3-hr SPECT in 7 patients with effort angina and 8 with old myocardial infarction before and one week after percutaneous transluminal coronary angioplasty (PTCA). Left ventricular wall on SPECT was divided into 9 segments. BMIPP and TI uptake were scored into four scale (0 = normal, 1 = reduced, 2 = severely reduced, 3 = absent). Discordance was defined when segments with reduced BMIPP uptake had better resting TI uptake. Left ventricular wall motion was assessed into normokinesis, hypokinesis, akinesis or dyskinesis on left ventriculogram. All patients with effort angina had reduced BMIPP uptake and normal TI uptake before PTCA. BMIPP uptake scores markedly improved after PTCA (6.3 ± 1.7 to 0.9 ± 1.2). Discordance scores were similar to BMIPP uptake scores. All patients with old myocardial infarction had reduced BMIPP uptake and TI uptake in infarcted regions. Discordance was observed in all infarcted regions. Not only hypokinetic segments but akinetic or dyskinetic segments frequently had discordant uptake. BMIPP uptake scores improved after PTCA (10.1 ± 2.6 to 6.9 ± 2.0). Discordance scores also improved after PTCA (6.0 ± 3.2 to 3.4 ± 2.3), but discordance was observed in all infarcted regions even after PTCA. Thus, discordant uptake on exercise BMIPP and resting TI delayed SPECT may be a useful marker of ischemia for effort angina and viability for old myocardial infarction. However, in almost patients with effort angina BMIPP uptake became to be normal, but in patients with old myocardial infarction reduced BMIPP uptake and discordance persisted even one week after PTCA.

Key Words
Exercise BMIPP SPECT
Resting TI delayed SPECT
Ischemia
Viability
PTCA
INTRODUCTION

Stress thallium-201 (Tl) myocardial single photon emission computed tomography (SPECT) has been widely used for not only detecting coronary artery disease but also assessing myocardial viability. It is well known, however, that some persistent defects without redistribution on stress Tl 4-hr delayed SPECT may improve in regional perfusion and function after revascularization (1). Even reinjection images and 24-hr delayed images espoused by some investigators were reported to underestimate myocardial viability (2-4). Though the rest injected Tl delayed scan is useful for assessing viability, this scan had disadvantage not to be able to detect ischemia (4-7).

Since fatty acids are a major energy source for the normal myocardium, a variety of iodinated fatty acid compounds have been introduced in order to probe the regional fatty acid metabolism in vivo (8,9). Among them, $^{123}$I labeled $\beta$-methyl iodophenyl pentadecanoic acid (BMIPP) is a suitable tracer for myocardial SPECT imaging, because it is metabolically trapped in the myocardium due to its methyl branching (10,11). Kropp et al (12) reported that BMIPP uptake reduced on exercise induced transient ischemia. Rest-injected Tl delayed scan gives us useful information for viability (4,6). In segments with persistent defects on resting Tl scan, however, it is difficult to distinguish viable regions from scars.

In this study, we attempted to clarify the utility of the exercise BMIPP following rest-injected Tl 3-hr delayed SPECT for detecting coronary artery disease and assessing viability.

Table 1. Standard of assessment of exercise BMIPP and resting Tl SPECT.

<table>
<thead>
<tr>
<th>Ex-BMIPP uptake</th>
<th>Rest Tl uptake</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>$\geq 1$</td>
<td>better than BMIPP</td>
<td>Discordance(+)</td>
</tr>
<tr>
<td>$\geq 1$</td>
<td>same as BMIPP (or more than)</td>
<td>Discordance(-)</td>
</tr>
</tbody>
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Discordance scores = Ex BMIPP uptake scores - Rest Tl uptake scores
in patients with effort angina pectoris and old myocardial infarction before and after percutaneous transluminal coronary angioplasty (PTCA).

SUBJECTS AND METHODS

Subjects: The subjects were seven patients with effort angina pectoris, and eight patients with old myocardial infarction. Patients with effort angina had no episode of myocardial infarction and had 90% or more coronary artery stenosis on coronary arteriogram. Four were male and three were female. Their mean age were 61.7 ± 13.4 years old (range: 49-72). Coronary arteriogram showed one vessel disease in six cases, two vessel disease in one cases. Patients with old myocardial infarction had abnormal Q wave on electrocardiogram and the episode of myocardial infarction three months or more ago. No patients was treated with PTCA in both acute and chronic phase before myocardial scintigraphy. Six were male and two were female. Their mean age were 59.5 ± 7.9 years old (range: 46-71). Five had anterior infarction, two inferior infarction and one lateral infarction. One vessel disease was in five cases, two vessel disease in three cases.

Exercise BMIPP and resting Tl delayed SPECT: Subjects took the symptom-limited maximal exercise which was terminated by the occurrence of chest pain or leg fatigue, or significant ST depression. The 25 watt per 3-min incremental protocol by ergometer in the supine position was used, while monitoring electrocardiogram, heart rate and blood press-

| Table 2. Occurrence of chest pain and ST depression during exercise before and after PTCA. |

<table>
<thead>
<tr>
<th>Number Before PTCA</th>
<th>ST depression</th>
<th>After PTCA</th>
<th>Chest pain</th>
<th>ST depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effort angina</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4(57.1%)</td>
<td>0</td>
<td>5(71.4%)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarctin</td>
<td>8</td>
<td>5(62.5%)</td>
<td>6(75.0%)</td>
<td></td>
</tr>
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PTCA: Percutaneous transluminal coronary angioplasty

Table 3. Hemodynamics at rest and during exercise before and after PTCA.

<table>
<thead>
<tr>
<th>Heart rate</th>
<th>Systolic pressure</th>
<th>Double products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effort angina</td>
<td>Before PTCA</td>
<td>Rest 65.7±0.9 149±16 9842±2440</td>
</tr>
<tr>
<td></td>
<td>After PTCA</td>
<td>Rest 72.9±1.6 148±21 1077±2733</td>
</tr>
<tr>
<td>Myocardial infarctin</td>
<td>Before PTCA</td>
<td>Rest 71.5±0.3 143±23 10263±3296</td>
</tr>
<tr>
<td></td>
<td>After PTCA</td>
<td>Rest 70.1±0.8 135±24 9406±1583</td>
</tr>
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</table>

PTCA: Percutaneous transluminal coronary angioplasty

Figure 2. Exercise BMIPP uptake scores before and after PTCA in effort angina.
ure. Significant ST depression was defined as 1.0 mm or more at 0.08 seconds after J point with a horizontal or down-sloping configuration on any leads. One hundred and eleven MBq of BMIPP was injected intravenously at the maximal point, then subjects were encouraged to continue exercise for additional 1 min. Fifteen minutes after BMIPP injection, a BMIPP SPECT was taken. A three head gamma camera system (Toshiba 9300A/HG) was used for SPECT. Imaging data was acquired with 72 views throughout 360 degree at 5 degree intervals for 25 seconds a view. Energy peak for acquisition was 160 KeV and window was 20%. At resting state after data acquisition for

**Figure 3.** Resting TI uptake scores before and after PTCA in effort angina.

Table 4. Discordance and in BMIPP and TI Uptake before and after PTCA.

<table>
<thead>
<tr>
<th></th>
<th>Improved BMIPP uptake</th>
<th>Improved TI uptake</th>
<th>Discordance (+) before PTCA</th>
<th>Discordance (+) after PTCA</th>
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</thead>
<tbody>
<tr>
<td>Hypokinesis</td>
<td>14</td>
<td>2(14.3%)</td>
<td>12(85.7%)</td>
<td>9(64.3%)</td>
</tr>
<tr>
<td>Akinesis or Dyskinesis</td>
<td>15</td>
<td>6(40.0%)</td>
<td>3(20.0%)</td>
<td>11(73.3%)</td>
</tr>
</tbody>
</table>

PTCA: Percutaneous transluminal coronary angioplasty

**Figure 4.** Discordance scores before and after PTCA in effort angina.

**Figure 5.** Exercise BMIPP uptake scores before and after PTCA in old myocardial infarction.
Exercise BMIPP and resting TI delayed spect for ischemia and viability

BMIPP SPECT, 111 MBq of TI was injected intravenously. On 3 hr after TI injection imaging date for TI delayed ECT was acquired with 72 views throughout 360 degree at 5 degree intervals for 30 seconds a view. Energy peak was 71 KeV and window was 15%. Total 72 views for each SPECT were analyzed by the convolution method and Butter Worth filter without attenuation correction to 7 mm-slice vertical long axis and short axis myocardial images with 64 × 64 matrix. The left ventricular wall on central long axis and basal and apical short axis images was divided into 9

Figure 6. Resting TI uptake scores before and after PTCA in old myocardial infarction.

Figure 7. Discordance scores before and after PTCA in old myocardial infarction.

Figure 8. Exercise BMIPP and resting TI delayed SPECT of a case. A 58-yr-old woman with prior myocardial infarction.

Figure 9. Coronary arteriogram and left ventriculogram of the case of figure 8.
segments, based on angiographic ventricular segmentation recommendations of the American Heart Association superscript (Figure 1). Counts per pixel ranged from 119 to 250 (mean: 169 ± 36) on BMIPP SPECT and from 163 to 466 (mean: 261 ± 80) on TI SPECT. BMIPP and TI uptake on each segment were scored into four scale by two experienced observers who did not know findings of cardiac catheterization (0 = normal, 1 = reduced, 2 = severely reduced, 3 = absent). The exercise BMIPP and resting TI delayed SPECT were performed before and one week after successful PTCA.

Assessment of SPECT findings (Table 1): Subjects with normal (Score = 0) uptake on exercise BMIPP were assessed to be normal. All subjects with normal BMIPP uptake had normal resting TI uptake. The uptake abnormality was determined when the BMIPP uptake score was one or more. Discordance was defined when BMIPP uptake scores were one or more greater than TI uptake scores. Discordance scores were calculated as difference between BMIPP uptake and TI uptake scores.

Coronary angiography, left ventriculography and PTCA: All patients were studied with coronary angiography and left ventriculography within two weeks after radionuclide examination. The severity of a coronary artery stenosis was expressed as a percentage based on the classification of the American Heart Association. The left ventricular wall motion on left ventriculography was evaluated subjectively by four experienced observers. Left ventricular wall was divided into 9 segments (Figure 1). The wall motion was assessed to four grades; normokinesis, hypokinesis, akinesis and dyskinesis. PTCA was performed on another day after coronary arteriogram. Patients with unsuccessful PTCA were not included. Statistical analysis: Mean values and standard deviations were calculated for each variable. The paired t test was used to compare date in the same variable of a group. The non-paired t test was used to compare data between groups. The chi-square test was used to determine the significance of differences in rates of occurrence. A probability value of less than 0.05 was considered to be significant.

RESULTS

Clinical findings and hemodynamics during exercise (Table 2 and 3): Table 2 shows prevalence of chest pain and ST depression during exercise test before after PTCA. In both patients with effort angina and old myocardial infarction the prevalence of ST depression were high. After
PTCA chest pain disappeared, but ST depression during exercise frequently observed. Hemodynamics at rest and during exercise were shown in table 3. Heart rate, systolic pressure and rate pressure products were not different between effort angina and old myocardial infarction before and after PTCA.

SPECT findings in effort angina (Figure 2, 3 and 4): Figure 2 shows change in exercise BMIPP uptake before and after PTCA. BMIPP uptake reduction was observed in all patients with effort angina before PTCA. BMIPP uptake scores markedly improved after PTCA (6.3 ± 1.7 to 0.9 ± 1.2; p < 0.001). Three patients had mild BMIPP uptake reduction after PTCA. On the other hand, resting Tl uptake was normal before and after PTCA (Figure 3). Discordance scores was same as BMIPP uptake scores (Figure 4).

SPECT findings in regions with infarct-related artery and wall motion abnormality (Table 5 and Figure 5, 6 and 7): All infarcted regions had reduced BMIPP and TI uptake and discordance. Table 5 shows relationship between severity of wall motion abnormality and frequency of discordance. Before PTCA discordance was frequently observed in not only hypokinetic segments but akinetic or dyskinetic segments. Even after PTCA several segments had discordant uptake. Figure 5 revealed BMIPP uptake scores before and after PTCA. In all regions BMIPP uptake scores improved after PTCA (10.1 ± 2.6 to 6.9 ± 2.0; p < 0.01). Resting TI uptake slightly improved after PTCA (4.1 ± 1.3 to 3.5 ± 1.4; p < 0.05). Discordance scores improved after PTCA (6.0 ± 3.2 to 3.4 ± 2.1; p < 0.05), but all infarcted region had discordant uptake segments even after PTCA. Case presentation (Figure 8, 9 and 10): A 58-yr-old woman who suffered from acute myocardial infarction on October, 1993 came to our hospital for cardiac examination in February, 1994. She did not complain of chest pain after her acute infarction. Electrocardiogram revealed abnormal Q wave on leads V1, V2 and V3. Exercise BMIPP and resting TI delayed SPECT revealed BMIPP uptake reduction and discordant BMIPP and Tl uptake on anteroseptal and apical segments (Figure 8). Exercise provoked significant ST depression on leads V4, V5 and V6, although she did not complain of chest pain. Coronary arteriography revealed 99% stenosis of left anterior descending artery. Left ventriculography showed akinesis on anteroseptal and apical segments (Figure 9). After PTCA improvement of exercise BMIPP uptake was slight (Figure 10).

DISCUSSION

Metabolic myocardial imaging by using positron emission tomography (PET) techniques are costly and will probably continue to be limited to only a few institutes, alternative substrates were developed to transfer this concept to the more widely used SPECT techniques. Mismatch of increase in fluorine-18-deoxy-glucose (FDG) uptake compared to perfusion tracer uptake such as $^{15}$NH$_3$ are considered to be golden standard for viable myocardium in PET study, though loading condition on FDG administra
tion is not defined (13,14). The methyl-branched fatty acid tracer, BMIPP has been developed to be promising agent for SPECT imaging (8-11). The myocardial uptake of BMIPP is dependent on regional myocardial blood flow, and it is incorporated into the endogenous lipid pool as the acyl-CoA. Under aerobic condition, oxidative metabolism of free fatty acids provides principle energy source used by the myocardium (15, 16). Vuusse et al (17) reported in dog myocardium under ischemic condition that free fatty acid level in the myocardium increased but that incorporation into ischemic myocardium decreased. Kropp et al (12) reported in human subjects that BMIPP uptake reduced in transient ischemic myocardium and reinjection at rest was necessary for assessing ischemia and viability because of few frequency of redistribution. Intracellular accumulation of TI is caused by a transport mechanism by the transmembrane electropotential gradient (18). TI redistribution is a marker of ischemia and viability. Kawamoto et al (19) observed that most of the segments with discordant BMIPP uptake compared to TI at rest had preserved metabolic activity on FDG PET. We investigated the significance of discordance between exercise BMIPP uptake and resting TI delayed uptake in patients with effort angina pectoris and old myocardial infarction before and after PTCA.

Discordance in angina pectoris: All patients with effort angina had reduced exercise BMIPP uptake and normal TI uptake before PTCA. Reduced exercise BMIPP uptake on transient ischemia was considered to be due to two factors which were decreased coronary blood flow and reduced incorporation of free fatty acid into myocardium. In PET study segments with discordance between BMIPP and TI uptake was investigated to have increased FDG uptake (19). After PTCA almost all patients had normal exercise BMIPP uptake. Only three patients had mildly reduced BMIPP uptake. Accordingly discordance in angina pectoris is considered to reflect stress induced ischemia.

Discordance in old myocardial infarctcon: In our study, all patients with asynergy and episode of myocardial infarction had reduced exercise BMIPP uptake. Asynergic regions includes stunned myocardium, hibernating myocardium and scar (20, 21). Free fatty acid metabolism may be disturbed in not only regions with scar but also stunning or hibernation at rest. Accordingly, chronic asynergic region can have reduced BMIPP uptake on resting BMIPP SPECT. Exercise BMIPP SPECT in patients with old myocardial infarction can reveal uptake reduction on regions with not only transient ischemia but scar, stunning and hibernation. Frequency of resting discordant BMIPP and TI uptake on infarcted region was not often at more than 4 weeks from the onset (22). Our chronic infarcted regions had frequently discordant uptake between exercise BMIPP and resting TI SPECT. Rest injected TI delayed scan give us useful information for viability, but was not appropriate for detecting ischemia (4,5). The comparison between exercise BMIPP and resting TI delayed SPECT can resolve the dis-
advantage of resting Tl scan. Frequent discordant uptake may be due to following reasons; one is that segments with exercise BMIPP uptake reduction included not only transient ischemic myocardium but stunning, hibernating myocardium and scar (19,22,23). Another is that Tl uptake on resting Tl delayed SPECT was almost in all under equilibrium state because of scan after resting Tl 3-hr redistribution, supported by that no defect was observed on resting Tl delayed SPECT in patients with angina pectoris. In stunning or hibernating myocardium, myocardial asynergy may not be accompanied by diminished Tl uptake (24-26). After PTCA, BMIPP uptake in infarcted regions improved but reduced BMIPP uptake persisted and discordance was observed in all infarcted regions. This indicated that discordance in infarcted regions was a marker of viability and that recovery of exercise BMIPP uptake was not prompt. Mechanism of persistent discordance in infarcted regions is unknown. Because of myocardial perfusion can recover after PTCA, myocardial stunning might be associated with disturbed myocardial incorporation of BMIPP. The further studies to investigate recovery of myocardial perfusion, metabolism and function are necessary.

Limitation: First, compton scatter of 1-123 emission make effects on counts within Tl window. Tl counts within $71 \pm 15\%$ on dual SPECT can be higher than those on Tl single tracer SPECT. However, compton scatter of 1-123 emission can make Tl defect to be underestimated, because in many patients relative BMIPP uptake reduction was severer than relative Tl uptake reduction. Second, reliable quantitative analysis was difficult because Tl scan was performed as dual SPECT. The correction using triple window method developing by Toshiba company may make quantitative to be reliable.

REFERENCES

T. Mori et al.


