

## Simultaneous assessment of Tc-99m-sestamibi and I-123-BMIPP myocardial distribution in patients with myocardial infarction: Evaluation of left ventricular function with ECG-gated myocardial SPECT

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<sup>123</sup>I-labeled 15-(p-iodophenyl)-3R,S-methyl pentadecanoic acid (BMIPP) is a branched-chain free fatty acid that is used to evaluate various cardiac diseases. The aim of the present study was to investigate the relationship between myocardial perfusion (<sup>99m</sup>Tc-sestamibi) and BMIPP uptake, and to correlate perfusion and metabolic alterations with regional left ventricular dysfunction in patients with myocardial infarction (MI). ECG-gated dual-isotope myocardial SPECT was performed on 130 patients with MI with sestamibi (555 MBq) and BMIPP (148 MBq). The patients were classified into 3 groups according to PTCA therapy and the interval between the onset of infarction and RI injection (OR time). Group A (n = 56) included patients whose OR time was less than one month and who had undergone successful PTCA, Group B (n = 36) had OR times of less than one month and had conservative medical therapy, and Group C (n = 38) had OR times of over one month. The severity scores of the dual-isotope images were calculated from the defect scores in 9 segments. From the ECG-gated SPECT data with sestamibi, the left ventricular ejection fraction (LVEF; %) and regional wall motion were determined automatically using the QGS program<sup>TM</sup>. LVEF obtained from gated SPECT correlated well with the severity scores for sestamibi and BMIPP (r = -0.68 and -0.76, respectively). The  $\Delta$  severity scores (BMIPP scores - sestamibi scores) of Group A were significantly higher than those of the other two groups ( $3.6 \pm 3.0$  vs.  $1.5 \pm 1.7$  and  $1.0 \pm 1.4$ ,  $p < 0.001$ ). The rate of dysfunctional segments with normal sestamibi distribution was significantly higher in Group A than in Group C (20.7% vs. 6.7%,  $p < 0.001$ ). ECG-gated dual-isotope SPECT is useful since myocardial perfusion, fatty acid metabolism and left ventricular function can be analyzed during a single examination, so that this procedure has the potential to provide comprehensive information when evaluating patients with ischemic heart disease.

**Key words:** <sup>99m</sup>Tc-sestamibi, <sup>123</sup>I-BMIPP, dual-isotope SPECT, gated SPECT, myocardial infarction

### INTRODUCTION

UNDER AEROBIC CONDITIONS 60–70% of the energy source of myocardial metabolism is dependent on the  $\beta$  oxidation

of fatty acids, but in ischemic myocardium, fatty acid oxidation is suppressed and glucose becomes the major substrate for the production of high energy phosphates.<sup>1,2</sup>

Several radioiodinated fatty acid analogues with which to probe myocardial metabolic imaging have been developed. <sup>123</sup>I-labeled 15-(p-iodophenyl)-3R,S-methyl pentadecanoic acid (BMIPP) is a branched-chain free fatty acid that is well suited to single-photon emission computed tomography (SPECT) because of its considerably long myocardial retention.<sup>3–6</sup> Several clinical studies have

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described regional perfusion and BMIPP uptake in patients with myocardial infarction and ischemia. A perfusion/metabolism mismatch, defined as lower BMIPP activity relative to perfusion, is more frequently observed in areas of acute myocardial infarction and in regions supplied by a revascularized vessel than in non-revascularized areas.<sup>7-9</sup> In addition, a discordant BMIPP decrease is frequent in areas with wall motion abnormalities and relatively preserved perfusion.<sup>8,10</sup>

The present study investigates the relationship between myocardial perfusion (<sup>99m</sup>Tc-methoxy isobutyl isonitrile; sestamibi) and BMIPP uptake, and correlates perfusion and metabolic alterations with regional left ventricular dysfunction in patients with myocardial infarction. In particular, myocardial distribution and left ventricular function were evaluated simultaneously by ECG-gated myocardial SPECT data acquisition.

## MATERIALS AND METHODS

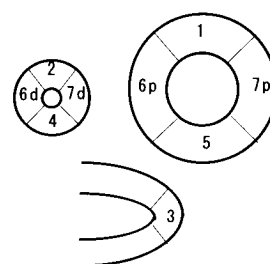
### Patient population

One-hundred and thirty consecutive patients with myocardial infarction (97 men and 33 women, ranging in age from 42 to 88 yr, mean 65 yr) were included in the study. A diagnosis of infarction was established according to clinical, enzymatic and ECG criteria. ECG showed Q-waves in 126 and non-Q waves in 4 patients. Patients were classified into 3 groups according to the therapy of direct percutaneous transluminal coronary angioplasty (PTCA) and the period between the onset of infarction and RI injection (OR time). Group A (n = 56) included patients whose OR time was less than one month and who had undergone successful PTCA therapy on the day of onset, Group B patients (n = 36) had OR times of less than one month and had had conservative medical therapy, and Group C patients (n = 38) had OR times of over one month. In Group C, patients who had received PTCA therapy within 2 months before the SPECT examination were excluded from the data base. The OR times were 7.6 ± 4.5 days (range: 2 to 22 days) in Group A, 9.3 ± 4.9 days (2 to 20 days) in Group B, and 86 ± 74 months (42 days to 20 yr) in Group C.

### ECG-gated myocardial SPECT data acquisition

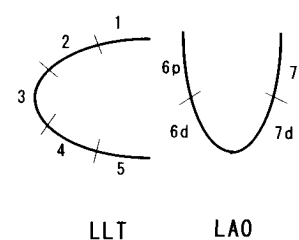
<sup>99m</sup>Tc-sestamibi (555 MBq) and <sup>123</sup>I-BMIPP (148 MBq) were injected simultaneously during rest after a fast of at least 6 hours. ECG-gated dual-isotope myocardial SPECT data acquisition was started 40 to 60 min after the injection with a three-head gamma camera (PRISM 3000, Marconi/Shimadzu), equipped with low-energy general purpose collimators. The ECG-gated myocardial SPECT data were acquired over 360° in 20 (×3) steps, each of which was 50 beats. Sixteen frames per R-R interval were acquired in a 64 × 64 matrix. To separate the distribution of the isotopes, <sup>99m</sup>Tc data were obtained in a symmetrical 140 keV with 10% width (133 to 147 keV), and <sup>123</sup>I were

### Dual-Isotope SPECT



Myocardial distribution

### ECG-gated SPECT



LLT LAO

Regional wall motion

**Fig. 1** Segmental division of the left ventricle for visual assessment of myocardial distribution and regional wall motion. LLT, left lateral image; LAO, left anterior oblique image.

**Table 1** Relationship between sestamibi and BMIPP defect scores in all myocardial segments

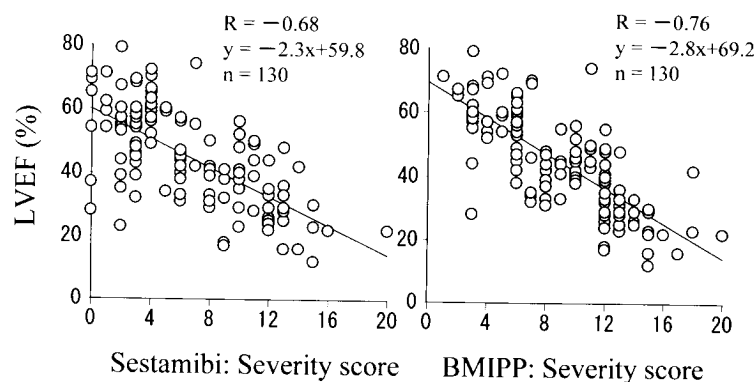
Sestamibi defect score	BMIPP defect score					Total
	0	1	2	3	4	
0	767	13	29	17	0	826
1	0	11	18	30	1	60
2	0	0	23	66	2	91
3	0	0	0	101	21	122
4	0	0	0	0	71	71
Total	767	24	70	214	95	1170

Defect score: 0, normal; 1, mildly reduced; 2, moderately reduced; 3 severely reduced; 4, defect.

obtained in an asymmetrical 159 keV (by using the upper half of the photopeak) with 10% width (159 to 175 keV).<sup>11-13</sup>

### Assessment of myocardial distribution with dual-isotope SPECT

Summed (non-gated) myocardial SPECT data for both radioisotopes were processed by filtered back projection (Butterworth filter, cutoff frequency at 0.28 cycles/pixel; order, 5; slice thickness, 3.9 mm). Sestamibi and BMIPP images were normalized to the maximal activity they contained and presented for analysis at a 20% threshold. The left ventricular myocardium was divided into 9 segments: apical, midventricular septal, anterior, lateral and inferior, basal septal, anterior, lateral and inferior (Fig. 1). For each segment, sestamibi and BMIPP uptake were graded in a five-point scoring system by two experienced observers after consultation to define normal uptake (defect score of 0), mildly reduced uptake (defect score of 1), moderately reduced uptake (defect score of 2), severely reduced uptake (defect score of 3), or defect (defect score of 4). Severity scores from both images of each patient were calculated by summing the defect scores of the 9 segments.



**Fig. 2** Correlation between severity scores on dual-isotope SPECT and left ventricular ejection fraction obtained from ECG-gated SPECT.

**Table 2** Myocardial distribution of sestamibi and BMIPP in segments with abnormal wall motion in three groups

	Reduced sestamibi Reduced BMIPP	Normal sestamibi Reduced BMIPP	Normal sestamibi Normal BMIPP	Total
Group A	134 (79.3%)	33 (19.5%)	2 (1.2%)	169 seg.
Group B	72 (85.7%)	9 (10.7%)	3 (3.6%)	84 seg.
Group C	126 (93.3%)	6 (4.4%)	3 (2.2%)	135 seg.
Total	332 (85.6%)	48 (12.4%)	8 (2.1%)	388 seg.

#### Assessment of left ventricular function with ECG-gated myocardial perfusion SPECT

The left ventricular ejection fraction (LVEF; %) was automatically calculated from the ECG-gated SPECT data with  $^{99m}\text{Tc}$ -sestamibi in an OdysseyFX<sup>TM</sup> processing computer and the function analysis software QGS program<sup>TM</sup> (Cedars-Sinai Medical Center).<sup>14-17</sup> With the QGS program, the left ventricular endocardial surface and volume were determined for all gating intervals in the cardiac cycle. Mobile images of the left anterior oblique (LAO) and left lateral (LLT) views for each patient were recorded on a videotape, and regional wall motion was qualitatively evaluated by two experienced observers. The left ventricle was divided into 9 segments (as shown in Fig. 1) to allow for comparison with the myocardial distribution data. For each segment, regional wall motion was graded on a five-point scoring system to define normokinesis (wall motion score of 0), mild hypokinesis (wall motion score of 1), moderate hypokinesis (wall motion score of 2), severe hypokinesis (wall motion score of 3), and akinesis or dyskinesis (wall motion score of 4).

#### Statistical analysis

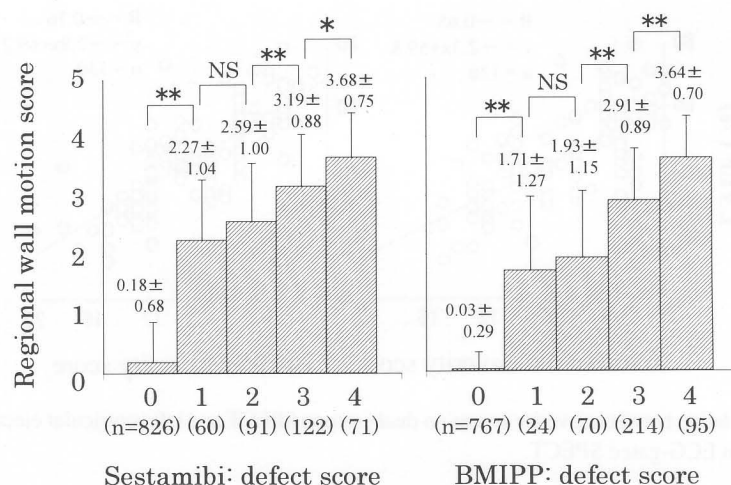
All data are expressed as the means  $\pm$  one standard deviation. Paired and unpaired Student's *t*-tests, as well as the Chi-squared analysis determined differences between proportions. Linear regression analysis determined correlations between severity scores and left ventricular ejection fractions. A *p* value of  $< 0.05$  was considered significant.

#### RESULTS

Of a total of 130 patients with myocardial infarction, the distribution of sestamibi and BMIPP in all segments was similar in 43 patients (concordant), whereas less BMIPP than sestamibi was taken up (discordant) in the remaining 87 patients in at least one myocardial segment. Table 1 shows the relationship between the scores for sestamibi and BMIPP in 1,170 segments (130 patients  $\times$  9 segments). In all patients with discordant BMIPP uptake the amount of regional BMIPP uptake was less than that of sestamibi. The rate of discordance was 87.5% (49/56) in Group A, 58.3% (21/36) in Group B, and 44.7% (17/38) in Group C. The rate was significantly higher in Group A than in the other groups (vs. Group B,  $p < 0.01$ ; vs. Group C,  $p < 0.0001$ ).

The severity scores of sestamibi and BMIPP were  $5.4 \pm 3.7$  and  $9.0 \pm 3.8$  in Group A,  $5.7 \pm 4.2$  and  $7.2 \pm 4.0$  in Group B, and  $10.1 \pm 4.0$  and  $11.1 \pm 4.0$  in Group C. The severity scores of BMIPP were significantly higher than those of sestamibi in all 3 groups ( $p < 0.001$ ). Delta severity scores ( $\Delta$  severity scores: BMIPP severity scores – sestamibi severity scores) were  $3.6 \pm 3.0$  in Group A,  $1.5 \pm 1.7$  in Group B, and  $1.0 \pm 1.4$  in Group C. The  $\Delta$  severity scores of Group A were significantly higher than those of the other two groups ( $p < 0.001$ ).

LVEF obtained from ECG-gated SPECT were  $45.0 \pm 13.8\%$  in Group A,  $50.5 \pm 15.2\%$  in Group B, and  $37.0 \pm 13.6\%$  in Group C. LVEF of group C was significantly lower than those of the other groups (vs. Group A,  $p <$



**Fig. 3** Comparison of regional wall motion scores grouped by defect scores in both isotopes. Defect score of sestamibi and BMIPP: 0, normal uptake; 1, mildly reduced uptake; 2, moderately reduced uptake; 3, severely reduced uptake; and 4, defect. \*,  $p < 0.001$ ; \*\*,  $p < 0.0001$ ; NS, not statistically significant.

0.01; vs. Group B,  $p < 0.001$ ). In all 130 patients, LVEF was significantly and negatively correlated with the severity scores of sestamibi (correlation coefficient,  $-0.68$ ;  $p < 0.0001$ ) and with the severity scores of BMIPP ( $r = -0.76$ ,  $p < 0.0001$ , Fig. 2).

A visual assessment of regional wall motion with ECG-gated SPECT images revealed 388 dysfunctional segments (wall motion score  $\geq 1$ ; 33.2%) out of 1,170. The relationship between dysfunctional segments and myocardial uptake pattern is shown in Table 2. The rate of dysfunctional segments with normal sestamibi distribution in the three groups was 20.7% (35/169) in Group A, 14.3% (12/84) in Group B and 6.7% (9/135) in Group C. The rate was significantly higher in Group A than in Group C ( $p < 0.001$ ). The rate was also higher in Group A than in Group B, although the difference was not statistically significant. Figure 3 shows the relationship between the regional wall motion scores and defect scores in both isotopes. As shown in Figure 3, significant differences were found in the regional wall motion scores between each group with different defect scores except those with defect scores of 1 and 2. A comparison of the regional wall motion scores for the two groups with a defect score of 0 on sestamibi and BMIPP SPECT revealed a significant difference ( $0.18 \pm 0.68$  vs.  $0.03 \pm 0.29$ ,  $p < 0.0001$ ). A typical example illustrating sestamibi and BMIPP distribution with wall motion abnormality is given in Figure 4.

## DISCUSSION

BMIPP is an analogue of 15-(p-iodophenyl) pentadecanoic acid (IPPA),<sup>18,19</sup> in which a methyl-branch has been introduced into the  $\beta$  position of the carbon chain. The initial uptake of BMIPP is largely determined by regional myocardial blood flow. After transport into myocytes

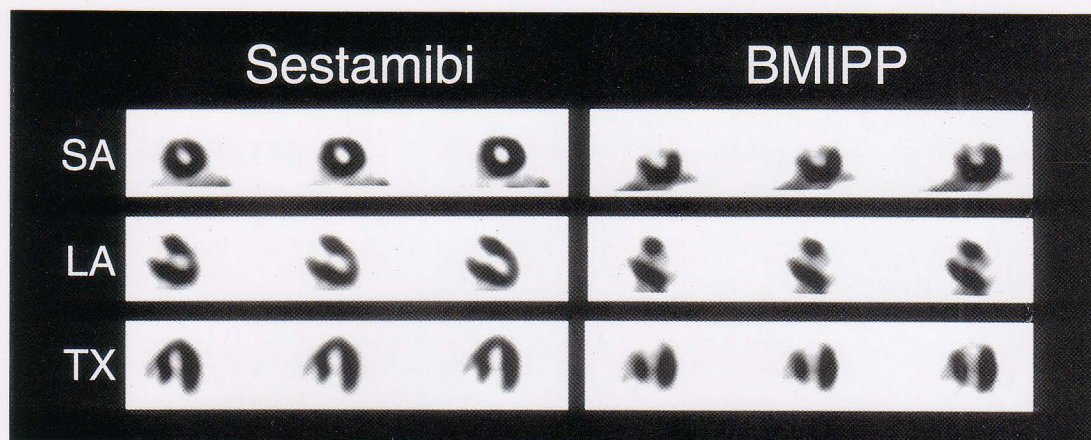
through a membrane fatty acid-binding protein, most BMIPP undergoes adenosine triphosphate (ATP)-dependent activation of the native long-chain fatty acids to acyl-coenzyme A.<sup>20</sup> The activated BMIPP is then esterified to triglyceride and incorporated into the endogenous lipid pool.<sup>6</sup> In ischemic myocardium, glucose metabolism plays an important role in residual oxidative metabolism, whereas oxidation of fatty acid is suppressed. BMIPP retention is affected by regional blood flow, a decreased triglyceride pool, and increased back diffusion due to reduced ATP content under ischemic conditions. BMIPP distribution may therefore provide comprehensive information about metabolic function in patients with ischemic heart disease.

### Myocardial perfusion/metabolism mismatch

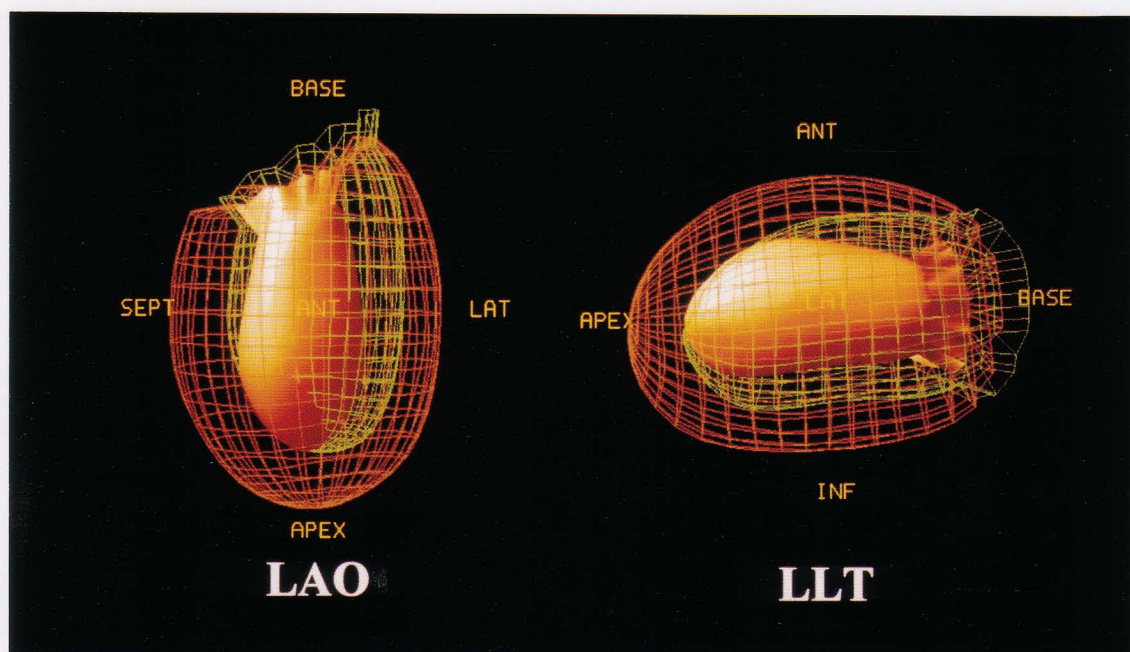
In the present study the distribution of sestamibi and BMIPP was frequently discordant in patients with acute myocardial infarction after successful revascularization (Group A) compared with those with no reperfusion (Group B) and chronic infarction (Group C). These results are similar to those found in previous studies.<sup>7-9</sup> Several clinical studies have suggested that regions with discordant distribution (less BMIPP uptake than flow tracers) are likely to correspond to metabolically jeopardized but viable myocardium.<sup>21,22</sup>

In the present dual-isotope protocol we used  $^{99m}\text{Tc}$ -sestamibi as a flow tracer. Since the photon energy of  $^{99m}\text{Tc}$  (140 keV) is close to that of  $^{123}\text{I}$  (159 keV), cross-contamination must be carefully taken into consideration. To separate the distribution of the two isotopes,  $^{99m}\text{Tc}$  data were obtained at a symmetrical 140 keV set with 10% width, and  $^{123}\text{I}$  data were taken at an asymmetrical 159 keV (by using the upper half of the photopeak) with 10% width, as described above. In a previous study of ours





A



B

**Fig. 4** ECG-gated dual isotope SPECT with sestamibi and BMIPP of a patient with acute (16 days) anterior wall myocardial infarction who received PTCA therapy on admission. (A) BMIPP uptake is severely reduced in the anteroapical region, while sestamibi uptake is almost normal (discordant). SA, short-axis; LA, vertical long-axis; TX, trans-axis image. (B) Left ventricular functional images using ECG-gated sestamibi data show severely hypokinetic wall motion in the anteroapical wall and distal septum. The inner wire cages and solid surfaces represent the endocardial surfaces at end-diastole and end-systole, respectively. LAO, left anterior oblique image; LLT, left lateral image.

cardiac phantom examination was employed to determine an optimal window setting for simultaneous SPECT data acquisition with sestamibi and BMIPP.<sup>23</sup> The myocardial compartment of the phantom was filled with <sup>99m</sup>Tc (41.6 KBq/ml) and <sup>123</sup>I (50.0 KBq/ml), taking into account the dose of clinical administration (sestamibi 555 MBq, BMIPP 148 MBq) and the myocardial extraction fraction (sestamibi 1.2%, BMIPP 5.4%). Various window widths (8, 10 and 12%) and positions (centered and asymmetric to the photopeak) were examined, and the window setting

in the present protocol was determined for clinical use. In the phantom study with the determined window setting, contamination by <sup>123</sup>I to <sup>99m</sup>Tc was 9.6% and up-contamination by <sup>99m</sup>Tc to <sup>123</sup>I was 11.1%. Although clinical cases are different from the cardiac phantom study according to various factors (e.g., scatter from surrounding tissues), acquired SPECT data were adequate for clinical interpretation with the modified window setting in the present study. Conversely, in the dual-isotope SPECT with <sup>201</sup>TlCl and BMIPP, several types of attenuation in the body may

be of importance. Since the photon energy of  $^{201}\text{Tl}$  (60–80 keV) is considerably lower than that of  $^{123}\text{I}$ , the attenuation of  $^{201}\text{Tl}$  is emphasized in dual-isotope SPECT. Less  $^{201}\text{Tl}$  than  $^{123}\text{I}$  seemed to be distributed in the posterior and posteroseptal walls because of diaphragmatic attenuation and non-uniform gamma-ray attenuation. In addition, particularly in women, breast attenuation of  $^{201}\text{Tl}$  is also emphasized, and pseudo “reverse mismatch” may be produced in the anterior wall. Although cross-talk is a factor to be considered in dual-isotope SPECT with sestamibi and BMIPP, attenuation artifacts in the body are reduced.

#### *Simultaneous assessment of left ventricular function with ECG-gated SPECT*

With technetium-labeled myocardial perfusion tracers, left ventricular function and regional wall motion can be simultaneously determined by ECG-gated myocardial perfusion SPECT. Together with the QGS program<sup>TM</sup>, ECG-gated SPECT provides high quality data regarding LV function that are operator-independent and therefore reproducible.<sup>14,15</sup>

In an acute myocardial infarcted area after revascularization, reperfused viable myocardium often displays a prolonged wall motion abnormality, referred to as “stunned myocardium.” Clinical studies have suggested that an area-at-risk, showing a distribution mismatch between BMIPP and flow tracers, may reflect reversible conditions, such as myocardial stunning or hibernation.<sup>24,25</sup> The ECG-gated dual-isotope SPECT in the present study offers the advantage of simultaneous assessment of myocardial perfusion, fatty acid metabolism and regional wall motion. This technique therefore has the potential to provide useful information for evaluating myocardial conditions, such as stunning or hibernation. Table 2 shows that the rate of dysfunctional segments with normal sestamibi distribution was significantly higher in acute myocardial infarction after successful revascularization (Group A). An examination of the BMIPP distribution across the 388 dysfunctional segments in the present study showed that the rate of BMIPP decline was very high in all three groups (Group A, 98.8%; Group B, 96.4%; Group C, 97.8%), with no significant differences. These results support the notion that BMIPP distribution correlates closely with functional abnormality rather than with myocardial perfusion.<sup>26,27</sup> Nevertheless, further follow-up studies are required to address the relationship between the pattern of myocardial distribution and functional outcome so that recovery of impaired left ventricular function can be predicted.

#### CONCLUSION

Myocardial perfusion, fatty acid metabolism and left ventricular function were analyzed in a single examination by ECG-gated dual-isotope SPECT. This procedure

therefore has the potential to provide comprehensive information with which to evaluate patients with ischemic heart disease.

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