Prediction of functional recovery and prognosis in patients with acute myocardial infarction by $^{123}$I-BMIPP and $^{201}$Tl myocardial single photon emission computed tomography: A multicenter trial

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$^{123}$I-BMIPP [15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid] was developed for metabolic imaging with SPECT. A multicenter collaborative study was conducted on a large patient series to determine whether $^{123}$I-BMIPP and $^{201}$Tl myocardial SPECT are of use in predicting the prognosis and ventricular function after acute myocardial infarction (AMI). Patients with uncomplicated first AMI underwent resting $^{123}$I-BMIPP and $^{201}$Tl myocardial SPECT in the subacute phase after the onset of AMI. Of these, 167 patients who had been followed up for an average of 22 months were retrospectively reviewed to predict serious cardiac events and recurrent ischemia. In addition, the association between changes in radionuclide parameters and recurrent ischemia was investigated in Subgroup A (38 patients) who had repeated SPECT in the chronic phase. Furthermore, prediction of the ejection fraction (EF) was investigated in Subgroup B (94 patients) and Subgroup C (76 patients) in whom left ventriculography was performed at the time of discharge and 90 days or more after the onset, respectively. The prognosis was generally favorable, with 4 cases of cardiac death (2%), 3 of heart failure (2%), 4 of nonfatal reMI (2%), and 25 of recurrent ischemia (15%). The results of Cox multivariate regression analysis revealed a high probability of serious cardiac events in patients who were elderly (p = 0.04), who had 90% or more residual stenosis of the infarct-related artery (p = 0.09), and who had a high BMIPP defect score (p = 0.17). There was a high probability of recurrent ischemia in elderly patients (p = 0.10) who had multi-vessel disease (p = 0.03), but no association was found with radionuclide parameters in the subacute phase. In Subgroup A, however, the probability of recurrent ischemia tended to be high in patients with a large mismatch score.
between $^{123}$I-BMIPP and $^{201}$TI in the subacute to chronic phase. An important observation was that
the extent of BMIPP defect was more strongly correlated with EF at the time of discharge and 90 days
or more after the onset than the extent of TI defect ($r = -0.66$ vs. $r = -0.47$, and $r = -0.53$ vs.
$r = -0.43$, respectively). In addition, multiple regression analysis showed that parameters related to
the BMIPP defect were also better predictive factors of EF both at the time of discharge and 90 days
or more after the onset. In conclusion, resting $^{123}$I-BMIPP and $^{201}$TI myocardial SPECT performed
in the subacute phase of AMI were shown to be useful in predicting prognosis and ventricular
function for patient management.

Key words: $^{123}$I-BMIPP, single photon emission computed tomography, acute myocardial
infarction, ventricular function, prognosis

INTRODUCTION

RISK EVALUATION AND PROGNOSIS PREDICTION are indispensable to secondary prevention of myocardial infarction,
and stress $^{201}$TI myocardial scintigraphy has been shown to be useful in achieving these goals.1 Studies in the pre-
reperfusion therapy era showed stress $^{201}$TI myocardial scintigraphy to be an excellent method of predicting
prognosis in coronary artery disease.2-4

The greatest determinant of short-term prognosis in acute myocardial infarction (AMI) patients is left ven-
tricular function.5 This does not appear to have changed even in the reperfusion era.6,7 Furthermore, improved
prognosis in response to reperfusion therapy has been demonstrated even in patients with poor left ventricular
function.8

It seems that the prognosis of myocardial infarction has improved even more after entering the reperfusion era.9
Among the changes, the question of whether indices for predicting prognosis based on stress $^{201}$TI myocardial
scintigraphy are still valid has become an issue.10-12 On the other hand, according to the results of a study with
positron emission tomography (PET), the probability of occurrence of a cardiac event was higher in patients in
whom a discrepancy between myocardial blood flow and metabolism was present than in patients in whom no such
discrepancy was detected, and this appeared to be a more useful index than the redistribution phenomenon on stress
$^{201}$TI imaging.13-15 But, an in-house cyclotron is often required to perform PET studies, and they may therefore
only be possible at a limited number of institutions. In contrast, myocardial SPECT studies with $^{123}$I-BMIPP
[15-(p-iodophenyl)-3-(R,S)-methyl]petadecanoic acid], a myocardial fatty acid imaging agent,16,17 have become
available in Japan, with about more than 100,000 such examinations having been performed since 1993.18 In
$^{123}$I-BMIPP and $^{201}$TI myocardial SPECT studies for AMI, the BMIPP defects have been shown to be larger than those obtained with $^{201}$TI after reperfusion therapy.19-21 Furthermore, it has been reported that regions in
which $^{123}$I-BMIPP defect greater than that of $^{201}$TI represent ischemic but viable myocardium, the same as the
discrepancy between myocardial blood flow and metab-
OLISM demonstrated by PET or redistribution on stress
$^{201}$TI imaging.22

The present study was therefore designed to determine whether resting $^{123}$I-BMIPP and $^{201}$TI myocardial SPECT
performed in the subacute phase of AMI are of use in predicting cardiac events and improvement of left ven-
tricular function in a large patient series.

MATERIALS AND METHODS

Patient selection

Resting $^{123}$I-BMIPP and $^{201}$TI myocardial SPECT were both performed in the subacute phase in AMI patients
who first experienced symptoms between March, 1993 and April, 1995, and data were collected from 14 institu-
tions concerning 217 patients who were followed up for a minimum of 90 days after the onset of symptoms. The 167
(77%) cases that met the criteria below were adopted as subjects of the analysis.

1) Patients who had experienced their first AMI (4 cases eliminated, 2%).
2) Patients with a history of coronary artery bypass surgery, and patients with congenital or valvular heart
diseases, or hypertrophic or dilated cardiomyopathy were excluded (1 case eliminated).
3) Patients who had been followed up for at least 90 days after the onset of the AMI, including those who had
cardiac events within 90 days after the onset (7 cases eliminated, 3%).
4) Patients in whom resting $^{123}$I-BMIPP and $^{201}$TI myocardial SPECT were both performed within a 7-day
examination interval within 21 days after the onset of the AMI (38 cases eliminated, 18%).

Experienced physicians-in-charge at each institution made the diagnosis of AMI on the basis of chest pain
lasting at least 30 minutes, ECG changes, and increase in serum myocardial enzyme activity.

$^{123}$I-BMIPP and $^{201}$TI myocardial SPECT

For myocardial perfusion imaging, 74-111 MBq of $^{201}$TI
was intravenously injected in the resting state, and $^{201}$TI
myocardial SPECT was performed 10 minutes later. The
timing of $^{201}$TI myocardial SPECT was 7 ± 5 days after the
onset. For myocardial fatty acid imaging, 111–148 MBq of $^{123}$I-BMIPP was intravenously injected in the resting state, and $^{123}$I-BMIPP myocardial SPECT was performed 20–30 minutes later. The interval between the $^{123}$I-BMIPP and $^{201}$Tl myocardial SPECT in the subacute phase was 2±2 days. The $^{123}$I-BMIPP agent used in this study was purchased from Nihon Medi-Physics Co., Ltd. (Hyogo, Japan). It contains iodine-123-labeled 15-(p-iodophenyl)-3,5,7-trimethyl-1-naphtyl-2-imidazoline (BMIPP) dissolved in a solution containing uroseosinylc acid.

$^{123}$I-BMIPP and $^{201}$Tl myocardial SPECT were performed again 31 days or more after the onset of symptoms in patients with MI. Resting images (42 cases, 72%) or stress redistribution images (16 cases, 28%) were obtained by $^{201}$Tl myocardial SPECT, and resting images were obtained by $^{123}$I-BMIPP myocardial SPECT.

$^{123}$I-BMIPP and $^{201}$Tl myocardial SPECT imaging procedures were based on the standard radionuclide imaging protocols recommended by the Medical and Pharmaceutical Committee of the Japan Radioisotope Association.

**SPECT analysis**

The basal and midventricular segments on short axis views of the left ventricular myocardium were divided into 8 segments each, and 16 segments were taken. An apical region on the vertical long axis view was taken, and a total of 17 segments were analyzed (Fig. 1). Evaluation of the imaging studies was blinded and images were read by eight experienced nuclear medicine physicians working in pairs who did not know the patients’ clinical history, coronary angiography findings, or ECG findings. Tracer accumulation in each of the segments was scored into one of four grades (scoring system: 0 = normal; 1 = mildly reduced uptake; 2 = severely reduced uptake; 3 = absent uptake, i.e., defect). The 4 parameters below were analyzed based on the $^{123}$I-BMIPP and $^{201}$Tl myocardial SPECT findings.

1. Tl and BMIPP defect score (Tl DS and BMIPP DS)
   The "total 17-segment score" was used as the DS.
2. Extent of the Tl and BMIPP defects (Tl extent score [ES] and BMIPP ES)
   The "number of segments of severely reduced uptake (score = 2) plus the number of segments of defect (score = 3)" was used as the ES.
3. Extent of mismatch
   "Extent of mismatch" is defined as the "number of mismatch segments, i.e., the number of segments in which the BMIPP score is higher than the Tl score in $^{123}$I-BMIPP accumulation is less than $^{201}$Tl accumulation."  
4. Mismatch score
   "The mismatch score" is defined as "the sum of the differences between the BMIPP scores and the Tl scores" on the mismatch segments.

Inter-observer variability was analyzed by having the $^{123}$I-BMIPP and $^{201}$Tl myocardial scintigrams of five patients randomly selected from the 167 subjects read independently, without consultation, by eight nuclear medicine physicians who did not know the patients’ findings. The rate of reading concordance was calculated as the mean of the concordance rates of the scores of the eight readers in 85 segments (17 segments × 5 cases) (It was calculated per total peer 8 readers, i.e., as the means of 28 cases). The reading concordance rate was 72% (60–86%) for the $^{201}$Tl myocardial scintigrams and 80% (71–88%) for the $^{123}$I-BMIPP myocardial scintigrams. When it was postulated that segments in which the reading score was up to 1 score different were reading matches, the reading match rate was 98% (94–100%) for $^{201}$Tl myocardial scintigrams and 96% (91–100%) for $^{123}$I-BMIPP myocardial scintigrams, and thus almost all of the segments in which the readings were discordant were differences of 1 score.

**Coronary angiography**

Selective coronary angiography (CAG) was performed in all of the patients immediately after being admitted. The infantar-related artery (IRA) was identified, and the degree of coronary stenosis and hemodynamics were evaluated. "Significant coronary vessel stenosis" was defined as a ≥75% stenosis of the lumen. The four parameters listed below were analyzed on the basis of the CAG findings at the onset of the AMI.

1. Multi-vessel disease
   Patients found to have significant coronary stenosis of at least two of the following vessels: the left anterior descending coronary artery (LAD), the left circumflex coronary artery and the right coronary artery. None of the patients had significant stenosis of the main trunk of the left coronary artery.
2. When the IRA was the LAD.
3. Good collateral circulation
   Patients in whom good collateral circulation (Rentrop classification grade II or III) was observed in the IRA at
the time of the onset of AMI but before reperfusion. 
4) IRA residual stenosis of 90% or more 
   Patients with 90% or more stenosis of the IRA after 
   reperfusion therapy/conservative therapy.

**Left ventriculography**

Left ventriculography (LVG) was performed, and the left 
ventricular ejection fraction (EF) was calculated at the 
time of discharge in 94 patients (56%, Subgroup B) and 90 
days or more after the onset of AMI in 76 patients (46%, 
Subgroup C). Specifically, LVG was performed at 23 ± 8 
days in Subgroup B and 169 ± 64 days in Subgroup C after 
the onset, respectively.

**Analysis of prognosis and prediction of ventricular function**

The patients' prognosis was observed for at least 90 days 
after the onset by reviewing the patient's chart or by 
telephone interview. Prognosis was analyzed by dividing 
into serious cardiac events (cardiac death and heart failure 
requiring hospitalization) and recurrent ischemia (nonfa-
tal reMI and angina pectoris). Cardiac events were diag-
nosed by an experienced physician-in-charge at each 
institution. Patients without symptoms who routinely 
underwent post-CAG reperfusion therapy were not in-
cluded in analytical subjects for cardiac events. Resting 
chest pain and exertional angina were considered recur-
rent angina.

Prognostic analysis was performed in all of the cases 
(167 cases) and in Subgroup A (58 cases, 35%). EF among 
the LVG findings was used as an index of ventricular function, 
and prediction of EF was investigated in Sub-

group B (94 cases, 56%) and Subgroup C (76 cases, 46%), 
in which LVG had been performed at the time of dis-
charge and 90 days or more after the onset of symptoms, 
respectively.

**Statistical analysis**

The parameters analyzed as predictive factors of cardiac 
events and ventricular function were clinical parameters 
(age, sex, coronary risk factors [hyperlipidemia, hyper-
tension, diabetes mellitus, obesity, smoking], peak CPK, 
surgical procedure [performance of PTCA], reperfusion 
within 3 hours), parameters related to CAG (multi-vessel 
disease, the IRA being the LAD, good collateral circula-
tion, 90% or more residual stenosis of the IRA), and 
parameters related to the radionuclide findings.

The relationship between the occurrence of cardiac 
events and predictive factors was investigated by the 
univariate Cox proportional hazard regression model for 
censored data. 

The relative risk (RR) ratio (hazard ratio) and 
the 95% confidence interval (CI) were defined as 
predictive factors when the results yielded a Wald chi-
square test p value of 0.2 or under. The stepwise multivari-
ate Cox proportional hazard model was used to identify 
the optimal combinations of predictive factors of cardiac 
events. A significance level of 0.20 was established for 
adopting predictive factors and eliminated cases. The 
predictive factors selected by Cox regression were strati-
"fied into a high- and a low-cardiac-risk group, and the 
event-free curves of the two groups obtained by the 
Kaplan-Meier method were log-rank tested.

Changes in radionuclide parameters from the subacute 
to chronic phase were investigated by the paired t-test. 
The association between recurrent ischemia and radionu-
clide parameters both during the period from the subacute 
to chronic phase and during the chronic phase was inves-
tigated by the unpaired t-test for continuous data and the 
chi-square test for discrete variant. The predictive factors 
shown to be related to recurrent ischemia were stratified 
into two groups, and the event-free rate was determined 
by the Kaplan-Meier method. The association between 
the subgroups and the eliminated cases was investigated 
by the unpaired t-test and the chi-square test.

The relationship between ventricular function (i.e., EF) 
and the predictive factors was investigated by correlation 
analysis, and Pearson's product-moment correlation co-
efficient and the p values were shown for predictive 
factors with a p value of 0.05 or less. Testing was also 
performed by the stepwise multiple regression method to 
identify the optimal predictive factors of ventricular func-
tion. A significance level of 0.05 was set for adoption of 
predictive factors and eliminated cases. The results are 
shown as the multivariate regression coefficients for the 
predictive factors selected, their p values and multiple 
regression equation, and their coefficients of determina-
tion. The associations between the subgroups and the 
eliminated cases were investigated by the unpaired t-test 
and the chi-square test.

SAS software was used for all of the statistical analy-
ses. 

Continuous data are expressed as means ± standard 
development (minimum value – maximum value) or 
medians (25% point – 75% point), whereas discrete 
variants are expressed as frequency and percentages.

**RESULTS**

**Patient characteristics**

The clinical parameters for patients evaluated are summa-
rized in Table 1. There were 167 subjects of the analysis, 
their mean age was 64 ± 10 years (38–83 years), and 
male (122, 73%) predominated. There were 122 patients who 
had one or more coronary risk factors, the most common 
of which were hypertension (64, 38%), followed by 
smoking (60, 36%), and diabetes mellitus (48, 29%). Peak 
CPK was 2955 ± 2458 IU/m (59–10485, median: 2477 
IU/m), and the values were widely distributed. In the 
acute phase percutaneous transluminal angioplasty (PTCA) 
was performed in 111 patients (66%) (direct PTCA in 68, rescue 
PTCA in 29, immediate PTCA in 11 and deferred PTCA in 3), 
intracoronary thrombolysis was performed in 37 patients (22%), 
spontaneous recanaliza-
Table 1  Clinical parameters of the study patients

<table>
<thead>
<tr>
<th></th>
<th>All data (n = 167)</th>
<th>Subgroup A (n = 58)</th>
<th>Subgroup B (n = 94)</th>
<th>Subgroup C (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>64 ± 10</td>
<td>63 ± 10</td>
<td>63 ± 10</td>
<td>62 ± 10*</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>122 (73%)</td>
<td>43 (74%)</td>
<td>69 (73%)</td>
<td>50 (66%)</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>33 (20%)</td>
<td>15 (26%)</td>
<td>23 (24%)</td>
<td>26 (34%)**</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64 (38%)</td>
<td>21 (36%)</td>
<td>39 (41%)</td>
<td>36 (47%)*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>48 (29%)</td>
<td>23 (40%)*</td>
<td>32 (34%)</td>
<td>30 (39%)**</td>
</tr>
<tr>
<td>Obesity</td>
<td>17 (10%)</td>
<td>6 (10%)</td>
<td>11 (12%)</td>
<td>11 (14%)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>60 (36%)</td>
<td>27 (47%)*</td>
<td>40 (43%)</td>
<td>42 (55%)**</td>
</tr>
<tr>
<td>peak CKP (median)</td>
<td>2477</td>
<td>2637</td>
<td>2610</td>
<td>2374</td>
</tr>
<tr>
<td>Performance of PTCA</td>
<td>111 (66%)</td>
<td>34 (59%)</td>
<td>61 (65%)</td>
<td>45 (59%)</td>
</tr>
<tr>
<td>Reperfusion within 3 hrs</td>
<td>61 (37%)</td>
<td>29 (50%)*</td>
<td>37 (39%)</td>
<td>35 (46%)*</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01

Table 2  Angiographic and radionuclide parameters of the study patients

<table>
<thead>
<tr>
<th></th>
<th>All data (n = 167)</th>
<th>Subgroup A (n = 58)</th>
<th>Subgroup B (n = 94)</th>
<th>Subgroup C (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-vessel disease</td>
<td>61 (37%)</td>
<td>26 (45%)</td>
<td>37 (39%)</td>
<td>32 (42%)</td>
</tr>
<tr>
<td>the IRA being the LAD</td>
<td>109 (65%)</td>
<td>34 (59%)</td>
<td>64 (68%)</td>
<td>43 (57%)*</td>
</tr>
<tr>
<td>Good collateral circulation</td>
<td>21 (13%)</td>
<td>6 (10%)</td>
<td>13 (14%)</td>
<td>15 (20%)*</td>
</tr>
<tr>
<td>IRA residual stenosis (≥ 90%)</td>
<td>47 (28%)</td>
<td>23 (40%)*</td>
<td>31 (33%)</td>
<td>29 (38%)**</td>
</tr>
<tr>
<td>TI DS</td>
<td>11 ± 8</td>
<td>11 ± 8</td>
<td>12 ± 8</td>
<td>11 ± 8</td>
</tr>
<tr>
<td>BMIPP DS</td>
<td>17 ± 8</td>
<td>17 ± 7</td>
<td>18 ± 8</td>
<td>16 ± 8</td>
</tr>
<tr>
<td>TI ES</td>
<td>3.6 ± 3.0</td>
<td>3.9 ± 2.9</td>
<td>3.8 ± 3.2</td>
<td>3.6 ± 3.0</td>
</tr>
<tr>
<td>BMIPP ES</td>
<td>5.7 ± 3.0</td>
<td>5.6 ± 2.5</td>
<td>6.1 ± 2.9</td>
<td>5.5 ± 2.8</td>
</tr>
<tr>
<td>Extent of mismatch</td>
<td>4.7 ± 2.6</td>
<td>4.2 ± 2.4</td>
<td>4.8 ± 2.4</td>
<td>4.4 ± 2.6</td>
</tr>
<tr>
<td>Mismatch score</td>
<td>6.7 ± 4.5</td>
<td>6.1 ± 4.4</td>
<td>7.2 ± 4.7</td>
<td>6.2 ± 4.5</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01.

Reperfusion occurred in 8 (5%), and conservative therapy was performed in the other 11 patients (7%). Reperfusion therapy was successful in 146 of the 148 patients (99%) in whom PTCA/intracoronary thrombolysis therapy had been performed (TIMI classification grade 3 blood flow). Reperfusion was achieved within 3 hours after the onset of symptoms in 61 of the 154 patients in whom reperfusion was achieved in the acute phase. After acute phase reperfusion therapy/conservative therapy, the patients were treated with nitrates (98%), Ca antagonists (80%) or β-blockers (27%), etc., and they were discharged a median of 30 days (22–38 days) after the onset of symptoms of AMI.

Patients in Subgroup A (58 patients), in which 123I-BMIPP and 201TI myocardial SPECT were repeated in the chronic phase were more often diabetics (23, 40%), smokers (27, 47%) and patients who experienced early reperfusion (29, 50%) than among the patients as a whole. No significant differences in clinical parameters from the 73 eliminated cases were found in Subgroup B (94 cases), in which EF was calculated at the time of discharge. In Subgroup C, in which EF was calculated 90 days or more after the onset of symptoms, the patients were slightly younger (62 ± 10 years), there were more patients with risk factors (71, 93%), and more patients experienced early reperfusion (35, 46%).

CAG findings
The CAG parameters for the subjects of the analysis are shown in Table 2. The CAG findings at the time of the onset of the AMI before reperfusion were 1-vessel disease in 100 patients (60%), 2-vessel disease in 42 patients (25%), 3-vessel disease in 19 patients (11%) and no significant coronary stenosis in 6 patients (4%). The IRA was the LAD in 109 patients (65%), the left circumflex coronary artery in 13 patients (8%) and the right coronary artery in 45 patients (27%). There were 21 patients (13%) with grade II or more collateral circulation in the IRA according to the Rentrop classification. There were 47 patients (28%) with 90% or more residual stenosis in the IRA after acute phase reperfusion therapy/conservative therapy, and most of these patients had undergone intracoronary thrombolysis therapy; PTCA in 6 patients (13%), intracoronary thrombolysis therapy in 30 patients (64%), spontaneous recanalization in 4 (9%) and conservative therapy in 7 (15%). Since many of the patients in
Subgroup A and Subgroup C had undergone intracoronary thrombolysis (33% in Subgroup A and 34% in Subgroup C, as opposed to 22% of the total), there were more patients with severe residual stenosis of the IRA.

**Radionuclide parameters**

The radionuclide parameters are shown in Table 2. A decrease in tracer uptake was observed in 159 cases (95%) in the subacute phase resting $^{201}$TI images and in 166 cases (99%) in the subacute phase resting $^{123}$I-BMIPP images, and the BMIPP DS and BMIPP ES were significantly higher than the TI DS and TI ES (17 ± 8 vs. 11 ± 8, and 5.7 ± 3.0 vs. 3.6 ± 3.0, respectively; both: p = 0.0001). There were 159 (95%) mismatch segments in which $^{123}$I-BMIPP accumulation was less than $^{201}$TI accumulation. The extent of mismatch (no. of mismatch segments) was 4.7 ± 2.6 segments, and the mismatch score (total of the differences between the BMIPP scores and the TI scores of mismatch segments) was 6.7 ± 4.5. No significant differences in radionuclide parameters were found among Subgroups A, B and C and their respective eliminated cases.

In Subgroup A, decrease in tracer uptake was observed in at least one segment in the chronic phase in 50 cases (86%) on the $^{201}$TI resting images or stress redistribution images and in 56 cases (97%) on the resting $^{123}$I-BMIPP images, and both TI DS (ES) and BMIPP DS (ES) significantly improved from the subacute to the chronic phase (TI DS: 11 ± 8 to 8 ± 6; TI ES: 3.9 ± 2.9 to 2.3 ± 2.5; BMIPP DS: 17 ± 7 to 13 ± 7; BMIPP ES: 5.6 ± 2.5 to 4.3 ± 2.7; all p = 0.0001), but, BMIPP DS and BMIPP ES were also significantly higher in the chronic phase (13 ± 7 vs. 8 ± 6, and 4.3 ± 2.7 vs. 2.3 ± 2.5; both p = 0.0001).

**Cardiac events**

During the 22 ± 8.8 month follow-up period (0.2–36 months), serious cardiac events occurred in 7 patients (4%) and ischemia occurred in 29 patients (17%) (Fig. 2). The serious cardiac events consisted of arrhythmia death in one case, sudden death in 3 cases, and heart failure in 3 cases (NYHA III in 1 case and IV in 2 cases). The time of occurrence of the serious cardiac events was within 30 days (1 case), 31–180 days (2 cases), 181–365 days (3 cases), and 366 days or more (1 case) after the onset of AMI. The recurrent ischemia consisted of nonfatal reMI in 4 cases and symptoms of angina pectoris in 25 cases. The recurrent ischemia was in the IRA in 26 of these patients and in another coronary artery in 3 of them. The time of the recurrence of ischemia was within 30 days (3 cases, 10%), 31–180 days (13 cases, 45%), 181–365 days (11 cases, 38%) and 366 days or more (2 cases, 7%) after the onset of AMI.

In Subgroup A there were 2 cases of serious cardiac events (3%) and 9 cases of recurrent ischemia (16%). The serious cardiac events consisted of sudden death 263 days after the onset in one case and heart failure (NYHA IV) 121 days after the onset in another case. The recurrent

![Cardiac death, Heart failure, Nonfatal reMI, Angina Pectoris](image)

**Fig. 2** Contents of adverse cardiac events in 167 patients.

| Table 3 | Estimated relative risk for univariate predictors of serious cardiac events and ischemic events in 167 patients by Cox regression analysis of clinical, angiographic and radionuclide data |
|-----------------|-------------------------------------------------|-----------------|-------------------------------------------------|-----------------|
| **Prediction of** | **Prediction of** | **RR (95% CI) p value** | **RR (95% CI) p value** |
| serious cardiac events (n = 7) | ischemic events (n = 29) |
| Clinical parameters | | | |
| Age | 1.11 (1.01 – 1.21) | 0.02 | 1.04 (1.00 – 1.08) | 0.08 |
| Smoking history | — | — | 0.47 (0.19 – 1.16) | 0.10 |
| Angiographic parameters | | | |
| Multi-vessel disease | — | — | 2.36 (1.13 – 4.90) | 0.02 |
| the IRA being the LAD | — | — | 0.60 (0.29 – 1.25) | 0.17 |
| IRA residual stenosis (≥ 90%) | 3.79 (0.85 – 16.9) | 0.08 | 1.79 (0.85 – 3.80) | 0.13 |
| Radionuclide parameters | | | |
| TI DS | 1.07 (0.98 – 1.17) | 0.14 | — | — |
| BMIPP DS | 1.09 (0.99 – 1.21) | 0.08 | — | — |
| BMIPP ES | 1.25 (0.96 – 1.63) | 0.09 | — | — |

Variables with p values of 0.2 or greater are not shown.

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ischemia consisted of nonfatal reMI in one case and symptoms of angina pectoris in 8 cases. It occurred in the IRA in 7 of these patients and in another coronary artery in 2 patients. The time of the recurrence of ischemia was 31–180 days (3 cases) and 181–365 days (6 cases) after the onset, and within 30 days (2 cases), 31–180 days (4 cases) and 181–365 days (3 cases) after 123I-BMIIP myocardial SPECT in the chronic phase.

Univariate prediction of cardiac events
The results of Cox univariate regression analysis of the 7 serious cardiac events, 29 recurrent ischemia cases, and 131 event-free cases are shown in Table 3. Because the rate of occurrence of serious cardiac events was very low, only 4%, predictive factors with a p value less than 0.2, are shown. The predictive factors for serious cardiac events were, among the clinical parameters, age (RR = 1.11, 95% CI = 1.01 to 1.21; p = 0.02), among the CAG parameters, 90% or more residual stenosis of the IRA (RR = 3.79, 95%

Fig. 3 Kaplan-Meier curves of serious cardiac event-free survival in 138 patients on the basis of BMIIP DS (upper left), BMIIP ES (upper right), age (lower left) and IRA residual stenosis (lower right).

Fig. 4 Kaplan-Meier curves of ischemic event-free survival in the 56 patients on the basis of Δ mismatch score (left) and number of diseased vessels (right).
CI = 0.85 to 16.9; p = 0.08) and among the radionuclide parameters, BMIIPP DS (RR = 1.09, 95% CI = 0.99 to 1.21; p = 0.08) and BMIIPP ES (RR = 1.25, 95% CI = 0.96 to 1.63; p = 0.09). When the serious cardiac events were analyzed by dividing them into cardiac death (n = 4) and heart failure (n = 3), residual stenosis of the IRA was found to be associated with cardiac death (RR = 8.33, 95% CI = 0.87 to 80.1; p = 0.07) and elderly age with heart failure (RR = 1.21, 95% CI = 1.00 to 1.45; p = 0.05).

These solitary cardiac event predictive factors were stratified into a high-risk group and a low-risk group, and event-free curves were plotted by the Kaplan-Meier method. The values with the lowest p values by the log-rank test were adopted as the risk distribution according to the results of $^{123}$I-BMIPP myocardial SPECT. The risk was higher in the patients with a BMIIPP DS greater than 23 segments (34 patients, 25%; p = 0.03) or with a BMIIPP ES greater than 8 segments (40 patients, 29%; p = 0.06) (Fig. 3, top). The risk was also higher in the elderly patients (68 years and over, 50 patients, 36%; p = 0.006) and patients with severe residual stenosis in the IRA (36 patients, 26%; p = 0.06) (Fig. 3, bottom).

Predictive factors of recurrent ischemia were, among clinical parameters, age (RR = 1.04, 95% CI = 1.00 to 1.08; p = 0.08) and smoking (RR = 0.47, 95% CI = 0.19 to 1.16; p = 0.10), among CAG parameters, multi-vessel disease (RR = 2.36, 95% CI = 1.13 to 4.90; p = 0.02) and the IRA being the LAD (RR = 0.60, 95% CI = 0.29 to 1.25; p = 0.17), and 90% or more residual stenosis of the IRA (RR = 1.79, 95% CI = 0.85 to 3.80; p = 0.13). Among the predictive factors selected there was a negative correlation between age and multi-vessel disease (r = -0.27, p = 0.0006) and between smoking and the IRA which was the LAD (r = -0.31, p = 0.0001). No associations were found between recurrence of ischemia and the radionuclide parameters.

We then investigated associations between recurrent ischemia and radionuclide parameters in Subgroup A. The results are shown in Table 4. There was no improvement in the $^{123}$I-BMIPP and $^{201}$Tl mismatches in the 9 patients with recurrent ischemia when compared with the 47 event-free patients (Δ mismatch extent [Δ extent in the chronic phase subtracted from the mismatch extent in the subacute phase] −1.0 ± 0.6 vs. 0.4 ± 3.1; p = 0.06, Δ mismatch score −1.4 ± 1.7 vs. 0.9 ± 5.2; p = 0.02). When the cases were then stratified into those in which the mismatch was small or unchanged (Δ mismatch score 0 or higher) and those in which the mismatch was large (Δ mismatch score < −1 or less) and cardiac-event-free curves were obtained by the Kaplan-Meier method, the risk of recurrent ischemia was found to be higher in the patients with the greater mismatch (24 patients, 43%; p = 0.03) (Fig. 4, left). The risk of recurrent ischemia was also higher in patients with multi-vessel disease (25 patients, 45%; p = 0.02) (Fig. 4, right).

**Multivariate prediction of cardiac events**

When Cox regression analysis was performed by the stepwise method for all of the predictive factors as explanatory variables in the 7 serious cardiac events and 131 event-free cases, age (RR = 1.10, 95% CI = 1.00 to 1.21; p = 0.04), 90% or more residual stenosis of the IRA (RR = 3.66, 95% CI = 0.81 to 16.6; p = 0.09) and BMIIPP DS (RR = 1.08, 95% CI = 0.97 to 1.21; p = 0.17), in that order, were selected as independent predictive factors (Table 5). The chi-square statistic of the likelihood ratio test, which indicated the closeness of fit of the model, increased stepwise from 5.9 for age alone (1 degree of freedom, p = 0.0151), to 9.5 for age plus 90% or more residual stenosis of the IRA (2 degrees of freedom, p = 0.0086), and to 11.6 for age plus 90% or more residual stenosis of the IRA plus BMIIPP DS (3 degrees of freedom, p = 0.0091). When the same analysis was performed for the 29 patients with recurrent ischemia and the 131 event-free patients, multi-vessel disease (p = 0.03) and age (p = 0.10), in that order, were selected as independent predictive factors, but no radionuclide parameters were selected.

**Prediction of ventricular function**

EF at the time of discharge (Subgroup B, n = 94) was 54 ± 15% (23–81%) and left ventricular function had decreased by 40% or below in 20 patients. Predictive factors highly correlated with EF at the time of discharge were the clinical parameter peak CPK (r = −0.46, p = 0.0001), the CAG parameter good collateral circulation (r = 0.27, p = 0.0082) and the radionuclide parameter BMIIPP ES (r = −0.60, p = 0.0001) (Table 6). Among the radionuclide parameters, BMIIPP DS and BMIIPP ES were more highly correlated with EF than TI DS or TI ES (r = −0.57 vs. −0.49, and r = −0.60 vs. −0.47, respectively). When multiple regression analysis was performed by the stepwise method for all of the predictive factors as explanatory variables, BMIIPP ES (multiple regression coefficient $\beta = -3.0 \pm 0.4$, p = 0.0001) and good collateral circulation ($\beta = 1.1 \pm 3.4$, p = 0.0018), in that order, were selected. The multiple regression equation was: $\text{EF} (%) = 71 - 3.0 \times \text{(BMIIPP ES)} + 11 \times \text{(good collateral circulation)}$ ($r^2 = 0.42$).

EF 90 days or more after the onset (Subgroup C, n = 76) was 59 ± 12% (33–91%), and a mere 3 patients (4%) had decreased left ventricular function. The results for prediction of EF 90 days or more after the onset were almost the same as for prediction of EF at the time of discharge. Specifically, BMIIPP DS and BMIIPP ES were more strongly correlated with EF than TI DS and TI ES (r = −0.53 vs. −0.47, and r = −0.53 vs. −0.43), and BMIIPP DS was selected first in the multiple regression analysis by the stepwise method. The multiple regression equation was: $\text{EF} (%) = 90 \text{ days or more after the onset} = 74 - 0.57 \times \text{(BMIIPP DS)} - 1.96 \times \text{(peak CPK/10)}$ ($r^2 = 0.37$).
Table 4  Univariate analysis of clinical, angiographic and radionuclide data in 56 patients in whom $^{201}$Tl and $^{123}$I-BMIPP myocardial SPECT were performed again in the chronic stage

<table>
<thead>
<tr>
<th></th>
<th>No cardiac events (n = 47)</th>
<th>Ischemic events (n = 9)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiographic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-vessel disease</td>
<td>18 (38%)</td>
<td>7 (78%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Radionuclide parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tl DS in the chronic stage</td>
<td>8.1 ± 6.6</td>
<td>5.2 ± 4.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Δ mismatch extent</td>
<td>0.4 ± 3.1</td>
<td>-1.0 ± 1.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Δ mismatch score</td>
<td>0.9 ± 5.2</td>
<td>-1.4 ± 1.7</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Variables with p values higher than 0.15 are not shown.

Table 5  Parameters selected by multivariate Cox regression analysis of serious cardiac events and ischemic events in 167 patients based on clinical, angiographic and radionuclide data

<table>
<thead>
<tr>
<th>Prediction of serious cardiac events (n = 7)</th>
<th>Prediction of ischemic events (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selected parameters</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.10 (1.00 - 1.21)</td>
</tr>
<tr>
<td>IRA residual stenosis (≥ 90%)</td>
<td>3.66 (0.81 - 16.6)</td>
</tr>
<tr>
<td>BMIPP DS</td>
<td>1.08 (0.97 - 1.21)</td>
</tr>
<tr>
<td>Multi-vessel disease</td>
<td>2.27 (1.09 - 4.73)</td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (0.99 - 1.07)</td>
</tr>
</tbody>
</table>

Parameters are listed in the order of selection by stepwise regression method.

Table 6  Simple correlation and multiple regression analyses of ejection fraction at the time of discharge and 90 days or more after the onset by clinical, angiographic and radionuclide parameters

<table>
<thead>
<tr>
<th>EF at the time of discharge</th>
<th>EF at 90 days or more after the onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>correlation</td>
</tr>
<tr>
<td></td>
<td>r</td>
</tr>
<tr>
<td>Clinical parameters</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.27</td>
</tr>
<tr>
<td>peak CPK (/10³)</td>
<td>-0.46</td>
</tr>
<tr>
<td>Angiographic parameters</td>
<td></td>
</tr>
<tr>
<td>Good collateral circulation</td>
<td>0.27</td>
</tr>
<tr>
<td>Radionuclide parameters</td>
<td></td>
</tr>
<tr>
<td>Tl DS</td>
<td>-0.49</td>
</tr>
<tr>
<td>BMIPP DS</td>
<td>-0.57</td>
</tr>
<tr>
<td>Ti ES</td>
<td>-0.47</td>
</tr>
<tr>
<td>BMIPP ES</td>
<td>-0.60</td>
</tr>
<tr>
<td>Extent of mismatch</td>
<td>-0.22</td>
</tr>
</tbody>
</table>

Variables with p values higher than 0.05 are not shown. r = Pearson’s product-moment correlation coefficient, β = multiple regression coefficient; SE = standard error.

DISCUSSION

In the present study, the mean age of onset of AMI was 64 years, and the male-female ratio was 2.7. These are the mean age and male-female ratio for AMI patients in Japan, and patients who had one-vessel disease (60%) and whose IRA was the LAD (65%) formed the largest groups. The ratio of patients who underwent PTCA (66%) in the acute phase to those treated by intracoronary thrombolysis (22%) was 3 : 1, and slightly higher than the 2 : 1 ratio in a 1995 nationwide survey (62% vs. 31%). At a mean of 22 months of follow-up, there were 4 cardiac deaths (2%), 3 cases of heart failure (2%) and 4 cases of nonfatal reMI (2%). Based on these findings, the same as reported by Dakik et al.,12 the prognosis of AMI has been considerably improved by reperfusion therapy. Since our cohort was small in relation to the incidence of cardiac deaths, we conducted the analysis by using heart failure, nonfatal reMI and recurrent ischemia as endpoints.

Prediction of cardiac events
Serious cardiac events occurred in a mere 7 cases (4%),
but the probability of occurrence of cardiac events tended to increase with advancing age, residual stenosis of the IRA and larger BMIPP ES (Table 3, Table 5). Among these, advanced age was a factor for heart failure, and residual IRA stenosis was a factor for cardiac death. Examination of parameters related to radionuclide findings showed that BMIPP ES was a better predictive factor than TI ES (p = 0.09 vs. p = 0.29).

In animal studies, myocardial uptake of 123I-BMIPP has been shown to reflect the myocardial intracellular ATP concentration, triglyceride content, and mitochondrial function.16,17,29,30 In clinical research, 123I-BMIPP findings were more closely correlated with ventricular function in the acute phase of AMI than 201Tl findings.19,20 In addition, comparisons between 99mTc-tetrofosmin and 99mTc-pyrophosphate have shown that the area of decreased 123I-BMIPP myocardial uptake reflects the area at risk of AMI. This suggests that patients with a large BMIPP ES in the subacute phase of AMI have an extensive risk area or fatty acid metabolism disturbance, and that their ventricular function in the acute phase is poorer and their condition is more serious.

Recurrence of ischemia appeared to be high in aged patients with multi-vessel disease (Table 3, Table 5). According to the results of univariate analysis, patients with a history of smoking and patients whose IRA is the LAD had a lower probability of recurrence of ischemia, but since the patients with a history of smoking were younger and fewer patients whose IRA was the LAD had multi-vessel disease, the results for these 2 parameters are assumed to be the results of an inner correlation.

The same as in many previous reports on subacute phase and chronic phase 123I-BMIPP and 201Tl myocardial SPECT findings, a discrepancy was found between myocardial blood flow and fatty acid metabolism in almost all of the patients (95% and 91%, respectively).31-33 Unfortunately, however, no relationship between this mismatch and recurrent ischemia could be detected based on the subacute phase findings. Because the current evaluation was a retrospective multicenter collaborative study, the length of time during which the radionuclide studies were performed, extending from the acute to subacute phase, i.e., a period of instability during the recovery process, may have been a factor. In Subgroup A patients in whom findings were obtained in the chronic phase, i.e., when the disease condition was stable, the probability of recurrent ischemia was higher in the patients with a large mismatch from the subacute to the chronic phase (Table 4, Fig. 4). Tamaki et al. have already reported that the probability of occurrence of cardiac events (nonfatal reMI, unstable angina pectoris, late reperfusion) rises in chronic myocardial infarct patients treated conservatively as the mismatch between 123I-BMIPP and 201Tl increases.24 Stress redistribution images (28%) were included in chronic phase 201Tl myocardial SPECT findings in Subgroup A, but, even when only the chronic phase resting 201Tl images were examined, the probability of recurrent ischemia was higher in patients who had larger mismatches (Δ mismatch extent –0.8 ± 1.5 vs. 0.5 ± 3.0; p = 0.10, Δ mismatch score –1.1 ± 1.6 vs. 0.8 ± 5.1, p = 0.07) (Table 4).

Prediction of cardiac function
Left ventricular function (i.e., EF) is the most important determinant of an AMI patient's prognosis.35 Recent advances in acute reperfusion therapy prevent extension of infarct and depression of ventricular function, but, the improvements in ventricular function after reperfusion therapy differ among patients. Therefore, it is still not certain how to correctly predict the ventricular function of these patients in the near future, in the subacute phase after AMI.36,37 It is well known that reversible myocardial damage may exist after reperfusion. This concept of stunned myocardium has demonstrated that myocardial function is depressed compared to myocardial blood flow.38 To predict ventricular function after AMI, it is necessary to evaluate such conditions as stunned myocardium noninvasively.39

It was demonstrated by PET studies that regional glucose metabolism is increased in patients after reperfusion therapy.40 On the other hand, 123I-BMIPP may have the potential to diagnose stunned myocardium from the viewpoint of myocardial metabolism by using SPECT. In our study, BMIPP ES and BMIPP ES were more highly correlated with EF at discharge, and EF 90 days or more after the onset by multiple regression analysis, so that 123I-BMIPP better reflected post-AMI left ventricular function than 201Tl myocardial blood flow did. This finding is consistent with reports19-21,41 that post-AMI impaired left ventricular function is more closely associated with fatty acid metabolism disturbances due to decreased blood flow.

Limitations of the present study
A prospective study on methods of examination to use in making a prognosis in AMI is needed. In Japan, however, there is great variation in reperfusion therapy, discharge days and days on which examinations with a SPECT camera can be performed, etc., and for that reason we had to conduct the study retrospectively. We therefore had to make the time during which the 201Tl and 123I-BMIPP studies were conducted in the subacute phase of AMI rather lengthy. Nevertheless, the present retrospective study provided information on the usefulness of metabolic SPECT imaging.

Cardiac deaths occurred in only 2% of the patients during the 22-month follow-up period. The reasons for this are thought to have been that the subjects of the study were AMI patients who had low-to-moderate risk because of a bias in patient selection, and that AMI patients in Japan generally have a good prognosis. Some of the biases in patient selection included the following: fatal cases up
to the subacute phase had been eliminated because radio-
nuclide examinations were required in the subacute phase;
89% of the subjects had received reperfusion therapy in the
acute phase; and at that point the aged and severely ill
had been eliminated. Other latent limitations are differ-
ences in attenuation of 123I-BMIPP and 201Tl and the
semi quantitative analysis of the SPECT images. We
interpreted the 201Tl accumulation in the septal and inferior
segments very carefully in view of the photon attenuating
effect. In addition, in order to reduce inter-reader differ-
ences in the visual score graded on a 4-point scale,
whenever there was uncertainty between score A and
score B, we made the decision by averaging the two and
counting the value when it was 0.5 and over and discard-
ing it when it was 0.4 or less. But, the difference between
the readers' scores was frequently 1, suggesting that
quantitative analysis is needed.

CONCLUSION

Resting 123I-BMIPP and 201Tl myocardial SPECT findings
in the subacute phase of AMI were useful in predicting
cardiac function in the chronic phase and in making a
prognosis in relation to serious cardiac events. In addition,
re-evaluation of resting 123I-BMIPP and 201Tl myocardial
SPECT in the chronic phase was useful in predicting
recurrent ischemia. Although this study was retrospec-
tive, this is the first report of a study demonstrating the
usefulness of myocardial metabolic SPECT imaging in
making a prognosis of AMI in a large patient series.

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