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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 (58 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

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between ^{123}I-BMIPP and ^{201}Tl 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 Tl defect (r = −0.60 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}Tl 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}Tl myocardial scintigraphy has been shown to be useful in achieving these goals.[1] Studies in the prereperfusion therapy era showed stress ^{201}Tl 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 ventricular 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}Tl 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}Tl 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)-methylpetadecanoic 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}Tl myocardial SPECT studies for AMI, the BMIPP defects have been shown to be larger than those obtained with ^{201}Tl after reperfusion therapy.[19–21] Furthermore, it has been reported that regions in which ^{123}I-BMIPP defect greater than that of ^{201}Tl represent ischemic but viable myocardium, the same as the discrepancy between myocardial blood flow and metabolism demonstrated by PET or redistribution on stress ^{201}Tl imaging.[22]

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

MATERIALS AND METHODS

Patient selection

Resting ^{123}I-BMIPP and ^{201}Tl 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 institutions 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}Tl 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}Tl myocardial SPECT

For myocardial perfusion imaging, 74–111 MBq of ^{201}Tl was intravenously injected in the resting state, and ^{201}Tl myocardial SPECT was performed 10 minutes later. The timing of ^{201}Tl myocardial SPECT was 7 ± 5 days after the

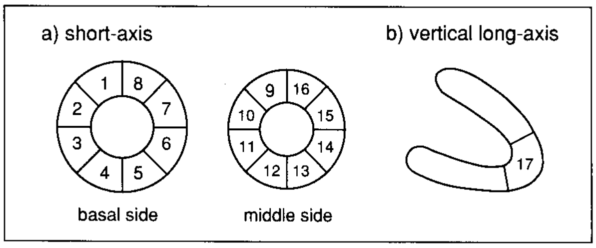

Fig. 1 Analysis of myocardial SPECT images. Basal and middle short-axis images are each divided into eight segments. The apical segment is one segment in the vertical long-axis image, making a total of 17 segments. The tracer uptake of each segments is scored visually using a four-point scoring method (0 = normal, 1 = mildly reduced, 2 = severely reduced and 3 = absent uptake).

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 timing of the ^{123}I-BMIPP myocardial SPECT was 8 ± 6 days after the onset. 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-(R,S)-methylpenta-decanoic acid dissolved in a solution containing ursodesoxycholic acid.

^{123}I-BMIPP and ^{201}Tl myocardial SPECT were performed again 31 days or more after the onset of symptoms in 58 of the 167 subjects (35%, Subgroup A). 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.[23]

SPECT analysis

The basal and midventricular segments on short axial views of the left ventricular myocardium were divided into 8 segments each, and 16 segments were taken. An apical region on the vertical long axial view was also 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 (^{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 passes). 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 infarct-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)[24] 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 (nonfatal reMI and angina pectoris). Cardiac events were diagnosed by an experienced physician-in-charge at each institution. Patients without symptoms who routinely underwent post-CAG reperfusion therapy were not included in analytical subjects for cardiac events. Resting chest pain and exertional angina were considered recurrent 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 Subgroup B (94 cases, 56%) and Subgroup C (76 cases, 46%), in which LVG had been performed at the time of discharge 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, hypertension, 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 circulation, 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.[25] 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 multivariate 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 stratified 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 radionuclide parameters both during the period from the subacute to chronic phase and during the chronic phase was investigated 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 coefficient 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 function. 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 determination. 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 analyses.[26,27] Continuous data are expressed as means ± standard deviation (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 summarized in Table 1. There were 167 subjects of the analysis, their mean age was 64 ± 10 years (38–83 years), and males (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*l* (59–10485, median: 2477 IU/m*l*), 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

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

*p < 0.05, **p < 0.01

Table 2 Angiographic and radionuclide parameters of the study patients

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

*p < 0.05, **p < 0.01.

tion 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).[28] 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 ^{123}I-BMIPP and ^{201}Tl 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 in at least one segment was observed in 159 cases (95%) in the subacute phase resting ^{201}Tl 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 Tl DS and Tl 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}Tl 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 Tl 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}Tl resting images or stress redistribution images and in 56 cases (97%) on the resting ^{123}I-BMIPP images, and both Tl DS (ES) and BMIPP DS (ES) significantly improved from the subacute to the chronic phase (Tl DS: 11 ± 8 to 8 ± 6; Tl 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).

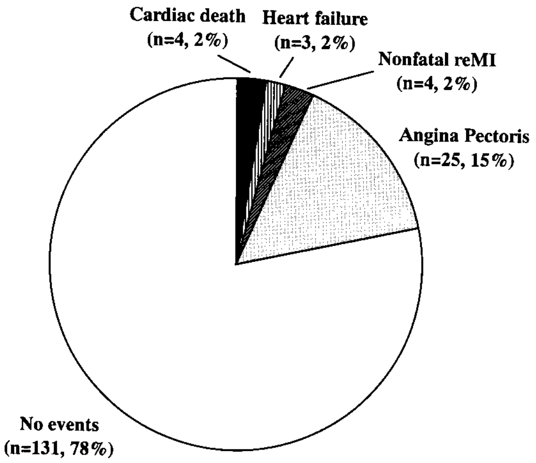

Fig. 2 Contents of adverse cardiac events in 167 patients.

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 recurred in 29 patients (17%) (Fig. 2). The serious cardiac events consisted of arrhythmic 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

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 serious cardiac events (n = 7)		Prediction of ischemic events (n = 29)	
	RR (95% CI)	p value	RR (95% CI)	p value
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				
Tl 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.

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 ^{123}I-BMIPP 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%

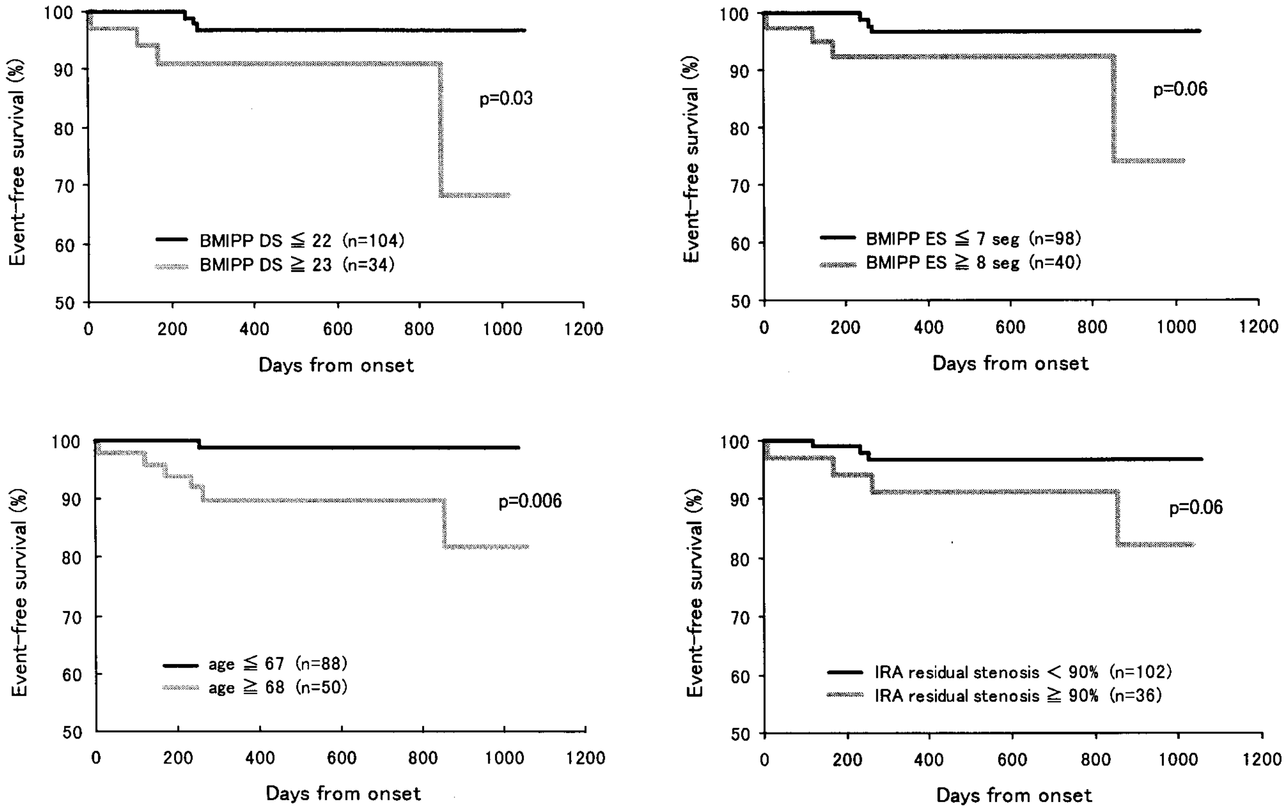

Fig. 3 Kaplan-Meier curves of serious cardiac event-free survival in 138 patients on the basis of BMIPP DS (upper left), BMIPP ES (upper right), age (lower left) and IRA residual stenosis (lower right).

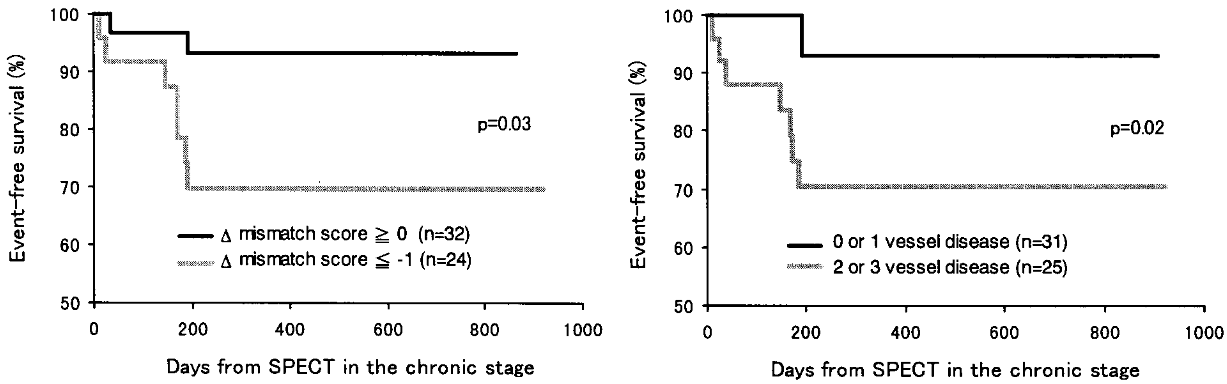

Fig. 4 Kaplan-Meier curves of ischemic event-free survival in the 56 patients on the basis of Δ mismatch score (left) and number of diseased vessels (right).

CI = 0.85 to 16.9; p = 0.08) and among the radionuclide parameters, BMIPP DS (RR = 1.09, 95% CI = 0.99 to 1.21; p = 0.08) and BMIPP 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 BMIPP DS greater than 23 segments (34 patients, 25%; p = 0.03) or with a BMIPP 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 [= mismatch 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 BMIPP 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 BMIPP 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 BMIPP ES (r = −0.60, p = 0.0001) (Table 6). Among the radionuclide parameters, BMIPP DS and BMIPP ES were more highly correlated with EF than Tl DS or Tl 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, BMIPP ES (multiple regression coefficient β = −3.0 ± 0.4, p = 0.0001) and good collateral circulation (β = 11 ± 3.4, p = 0.0018), in that order, were selected. The multiple regression equation was: EF (%) at the time of discharge = 71 − 3.0*(BMIPP ES) + 11*(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, BMIPP DS and BMIPP ES were more strongly correlated with EF than Tl DS and Tl ES (r = −0.53 vs. −0.47, and r = −0.53 vs. −0.43), and BMIPP DS was selected first in the multiple regression analysis by the stepwise method. The multiple regression equation was: EF (%) 90 days or more after the onset = 74 − 0.57*(BMIPP DS) − 1.96*(peak CPK/10^3) (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

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

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

Prediction of serious cardiac events (n = 7)			Prediction of ischemic events (n = 29)		
Selected parameters	RR (95% CI)	p value	Selected parameters	RR (95% CI)	p value
Age	1.10 (1.00 – 1.21)	0.04	Multi-vessel disease	2.27 (1.09 – 4.73)	0.03
IRA residual stenosis (≥ 90%)	3.66 (0.81 – 16.6)	0.09	Age	1.03 (0.99 – 1.07)	0.10
BMIPP DS	1.08 (0.97 – 1.21)	0.17			

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

	EF at the time of discharge				EF at 90 days or more after the onset			
	correlation		multiple regression		correlation		multiple regression	
	r	p value	β ± SE	p value	r	p value	β ± SE	p value
Clinical parameters								
Hypertension	0.27	0.0094	—	—	—	—	—	—
peak CPK ($/10^3$)	−0.46	0.0001	—	—	−0.52	0.0001	−1.96 ± 0.61	0.0018
Angiographic parameters								
Good collateral circulation	0.27	0.0082	11 ± 3.4	0.0018	—	—	—	—
Radionuclide parameters								
Tl DS	−0.49	0.0001	—	—	−0.47	0.0001	—	—
BMIPP DS	−0.57	0.0001	—	—	−0.53	0.0001	−0.57 ± 0.17	0.0014
Tl ES	−0.47	0.0001	—	—	−0.43	0.0001	—	—
BMIPP ES	−0.60	0.0001	−3.0 ± 0.4	0.0001	−0.53	0.0001	—	—
Extent of mismatch	−0.22	0.0318	—	—	—	—	—	—

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 Tl ES ($p = 0.09$ vs. $p = 0.29$).

In animal studies, myocardial uptake of ^{123}I-BMIPP has been shown to reflect the myocardial intracellular ATP concentration, triglyceride content, and mitochondrial function.[16,17,29,30] In clinical research, ^{123}I-BMIPP findings were more closely correlated with ventricular function in the acute phase of AMI than ^{201}Tl findings.[19,20] In addition, comparisons between ^{99m}Tc-tetrofosmin and ^{99m}Tc-pyrophosphate have shown that the area of decreased ^{123}I-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 ^{123}I-BMIPP and ^{201}Tl 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 ^{123}I-BMIPP and ^{201}Tl increases.[34]

Stress redistribution images (28%) were included in chronic phase ^{201}Tl myocardial SPECT findings in Subgroup A, but, even when only the chronic phase resting ^{201}Tl 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 ± 30; $p = 0.10$, 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, ^{123}I-BMIPP may have the potential to diagnose stunned myocardium from the viewpoint of myocardial metabolism by using SPECT. In our study, BMIPP DS 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 ^{123}I-BMIPP better reflected post-AMI left ventricular function than ^{201}Tl myocardial blood flow did. This finding is consistent with reports[19–21,41] 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 ^{201}Tl and ^{123}I-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 radionuclide 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 differences in attenuation of ^{123}I-BMIPP and ^{201}Tl and the semiquantitative analysis of the SPECT images. We interpreted the ^{201}Tl accumulation in the septal and inferior segments very carefully in view of the photon attenuating effect. In addition, in order to reduce inter-reader differences 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 discarding 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 ^{123}I-BMIPP and ^{201}Tl 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 ^{123}I-BMIPP and ^{201}Tl myocardial SPECT in the chronic phase was useful in predicting recurrent ischemia. Although this study was retrospective, 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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