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Limitations of spontaneous reperfusion and conventional medical therapy to afford myocardial protection through antecedent angina pectoris in acute myocardial infarction

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Despite the cardioprotective effect of rapid coronary reperfusion, the effects of spontaneous recanalization on myocardial viability and metabolism are unknown. We studied whether preinfarction angina affords cardioprotection when spontaneous coronary reperfusion occurred in acute infarct patients. Myocardial tomographies with thallium and I-123-labeled-β-methyl-p-iodophenyl penta-decanoic acid (BMIPP) were performed in 27 acute myocardial infarct patients treated medically: 15 patients had preexisting angina before infarction (group A) and 12 did not (group B). Thallium and BMIPP abnormalities and regional function were quantified by a polar map and contrast ventriculography, respectively. There was no significant difference between thallium and BMIPP in the severity index in groups A and B (89 ± 97 vs. 85 ± 68, 97 ± 28 vs. 95 ± 27, respectively), and no significant difference between the groups in the thallium or BMIPP severity index. The ratio of the thallium severity index to that of BMIPP and the regional wall-motion abnormality index were identical in groups A and B. Both patient groups were divided into 2 subgroups based on the presence or absence of spontaneous coronary reperfusion: subgroups A1 and A2, and subgroups B1 and B2, respectively. There were no significant differences among the 4 subgroups in severity indexes for both tracers, the thallium/BMIPP ratio, or the asynergy score. The BMIPP severity index correlated significantly with that of thallium in all subgroups, but no significant difference between the regression lines was found. It is therefore unlikely that spontaneous coronary recanalization affords beneficial effects through preservation of myocardial viability in an ischemia-related zone, suggesting that the cardioprotective effect of preinfarction angina is a limited phenomenon in patients undergoing rapid coronary reperfusion.

Key words: fatty acid metabolism, pre-infarction angina, cardioprotection, spontaneous coronary recanalization

INTRODUCTION

AS DEMONSTRATED in animal models,[1–4] brief ischemia prior to more prolonged ischemia may have cardioprotective effects in humans. Such cardioprotective effects are suppression of infarct size, arrhythmias, and cardiac dysfunction, as well as augmentation of ischemic tolerance,[5–15] but controversy still remains as to whether preexisting angina before acute myocardial infarction has an "ischemic preconditioning effect" in clinical settings. We recently demonstrated the cardioprotective effects of preinfarction angina in patients with acute myocardial infarction undergoing primary percutaneous transluminal coronary angioplasty by quantitatively assessing myocardial perfusion, fatty acid metabolism, and regional cardiac function.[15] The results also suggested that complete reperfusion is very important for the manifestation of cardioprotection afforded by preinfarction angina in

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Table 1 Clinical backgrounds of 27 acute infarct patients in groups A and B

	Group A pre-MI angina	Group B no pre-MI angina	Significance (p-value)
No. of patient	15	12	
Age (years)	58 ± 9	63 ± 18	ns
Gender (% male)	93	83	ns
Location of infarction (anterior/inferior)	5/10	8/4	ns (0.182)
Q-wave infarction (%)	73	75	ns
Killip class ≧II, III (%)	20	20	ns
Peak serum creatine kinase level (IU/*l*)	2828 ± 1582	3876 ± 3734	ns (0.334)
Single vessel disease (%)	87	100	ns
Onset to study interval (days)			
Thallium scan	11 ± 10	15 ± 7	ns
BMIPP scan	15 ± 11	14 ± 7	ns
Contrast left ventriculography	18 ± 11	19 ± 10	ns
Medications after the onset of MI (%)			
Calcium channel antagonists	73	50	ns
Beta-blockers	13	17	ns
ACE inhibitors	7	17	ns
Nitrates	100	83	ns
Anti-platelet/coagulant	80	100	ns
Coronary risk factors (%)			
Hypertension	40	33	ns
Diabetes Mellitus	27	33	ns
Hyperlipidemia	47	25	ns
Smoking	80	67	ns
Family history	0	8	ns

Values are shown as mean ± S.D. ACE, angiotensin converting enzyme; BMIPP, beta-methyliodophenyl-pentadecanoic acid; LVEF, left ventricular ejection fraction; MI, myocardial infarction; ns, not significant.

clinical settings as well as in animal models. Another type of coronary reperfusion—spontaneous coronary reperfusion—has also been observed.[17–21] It is, however, not clear whether preexisting ischemia affords beneficial effects in medically treated patients in this case. Little is also known about the effect of spontaneous coronary reperfusion and preinfarction angina on myocardial perfusion and fatty acid metabolism, postischemic cardiac function, and their correlates. Our previous studies[15,22–24] and other clinical investigations[25–30] have demonstrated that derangement of myocardial fatty acid metabolism reflects ischemia-related injury in viable and non-viable myocardium better than myocardial perfusion abnormality. Dysfunctioning but viable myocardium in an ischemia-related zone can therefore be precisely evaluated by correlating myocardial perfusion with fatty acid metabolism by means of quantitative tomographic imaging. This technique is useful for identifying the extent of salvaged myocardium as well as infarcted myocardium in an infarct-related risk area.[15]

We studied patients who experienced spontaneous reperfusion after their first myocardial infarction to determine if preinfarction angina affected myocardial perfusion, ischemia-related metabolic impairment, or functional abnormality.

SUBJECTS AND METHODS

Patient population

Twenty-seven patients, 24 men and 3 women with a mean age of 61 years (range 22 to 86 years) and admitted within 2 days after the onset of acute myocardial infarction, were recruited according to the following criteria: 1) it was the first acute myocardial infarction for each patient, 2) the onset of infarction was determined by typical clinical symptoms, signs, and electrocardiographic changes, 3) both myocardial perfusion and fatty acid metabolism imaging were performed within a 3-day interval within 3 weeks after the onset of infarction, 4) the presence or absence of antecedent angina pectoris within 7 days before acute myocardial infarction was determined, and 5) informed consent was obtained for the present protocol. Patients could be excluded on the basis of the following criteria but none was: 1) successful percutaneous transluminal coronary angioplasty (PTCA) or bypass grafting following acute myocardial infarction, 2) evidence of previous myocardial infarction or coronary revascularization, 3) a critical condition, such as cardiogenic shock or uncontrollable heart failure during admission, 4) the presence of complicating cardiac conditions such as valvular heart disease or cardiomyopathy, and 5) the presence of hormonal disturbances, renal failure, or

Table 2 Coronary findings at pre-discharge examinations

		Group A pre-MI angina	Group B no pre-MI angina	Significance (p-value)
Luminal narrowing≧75% (%)		66	91	ns (0.277)
average (%)		77 ± 24	88 ± 17	ns (0.204)
TIMI grade (%)	0	27	60	
	1	7	0	
	2	13	0	
	3	53	40	
	average	1.93 ± 1.33	1.20 ± 1.55	ns (0.221)
collateral grade (%)	0	60	40	
	1	27	30	
	2	13	0	
	3	0	30	
	average	0.60 ± 0.74	1.20 ± 1.32	ns (0.158)

Values are shown as mean ± SD. ns, not significant.

malignancies. None of the patients had vasospasm-related angina or myocardial infarction documented during the clinical course observations.

Based on the presence or absence of preinfarction angina, the 27 patients were divided into 2 groups: 15 patients with preinfarction angina (group A) and 12 without (group B) (Table 1). The definition of preinfarction angina in the present study was chest pain suggestive of angina pectoris lasting less than 30 minutes and documented within the 7 days before the onset of acute myocardial infarction. When the following diagnostic findings were documented, the diagnosis of acute myocardial infarction was established[15,22,23]: severe chest pain lasting for 30 minutes or more, ST-segment increase of > 2 mm in 2 or more leads of the standard 12-lead electrocardiogram for more than 30 minutes, and a definite rise in serum creatine kinase levels in serial measurements during the first 2 days after the onset of infarction. In 4 patients in group A, coronary reperfusion with primary PTCA was tried but was not successful because of technical limitations due to complex lesions. Predischarge coronary angiography was performed in all patients to identify the infarct related coronary artery, its patency status, and other coronary lesions. Cardiac function analyses were performed by radionuclide ventriculography and contrast left ventriculography as pre-discharge tests. These study protocols conformed to the regulations of the hospital ethics committee.

Study protocol

Single-photon emission computed tomography (SPECT) with thallium and iodinated beta-methyl-p-iodophenyl pentadecanoic acid (BMIPP) was performed under resting and overnight fasting conditions at mean intervals of 11 to 15 days after the onset of infarction (Table 1). Thallium, 111 MBq, and iodine-123-labeled BMIPP, 111 MBq (Nihon MediPhysics, Osaka, Japan), were injected simultaneously. Thirty minutes later, tomographic data were acquired at 5-degree increments for 30 seconds per increment during a 180-degree rotation from the 45-degree left posterior oblique to the 45-degree right anterior oblique view by means of a gamma camera with a high-resolution collimator. Data were stored in a 64 × 64 word matrix nuclear medicine computer (Shimadzu SNC 5100R, Tokyo, or GE 4000XC/T, Milwaukee, Wisconsin). Based on the results of cardiac phantom experiments for dual-energy SPECT imaging in our nuclear medicine laboratory, a 159 keV photopeak of ^{123}I with a 20% window and a 75 keV photopeak of ^{201}Tl with a 20% window were selected.[15,22,23] After reconstruction with a back-projection algorithm and a Shepp & Logan or Hanning and Ramp filter, circumferential profile analysis was performed on short-axis slices to create a polar map display for quantification of thallium and BMIPP abnormalities.[15,23] Regional wall motion was quantified by contrast left ventriculography with mean onset-to-examination intervals of about 3 weeks (Table 1). No attenuation or cross-talk correction was performed.

Quantification of scintigraphic and cardiac function data

Reduced myocardial uptakes of thallium and BMIPP were quantified by means of a polar map method as a severity index with the following formula[15,23,31]:

Severity index = Δ count (normal count − abnormal count)/Total points[60x(number of slices)]*

The abnormality count (*) for thallium or BMIPP in 60 data points per short-axis slice was defined as that less than the mean count minus 2 standard deviations of normal files which were produced in 4 male and 4 female control subjects in our laboratory. The severity index therefore quantitatively indicates the extension and grade of thallium or BMIPP abnormality normalized to each heart size.

Global left ventricular function was assessed by radionuclide ventriculography with an intravenous injection of technetium-99m labeled human serum albumin (740 MBq) at rest to calculate the left ventricular ejection fraction.

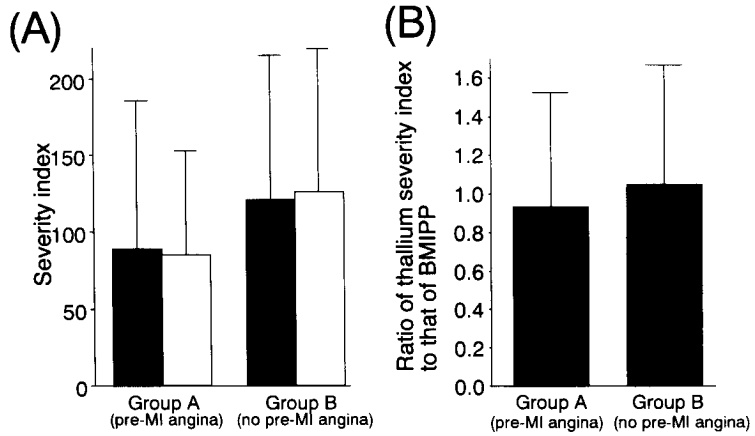

Fig. 1 (A) Comparisons of severity indexes of thallium (closed columns) and BMIPP (open columns) between groups A and B. Although there was a tendency for both severity indexes for thallium and BMIPP to be lower in group A, there were no significant differences. There was no significant difference in the severity index between thallium and BMIPP in either group. (B) Comparison of the ratio of thallium severity index to that of BMIPP between groups A and B shows no significant difference between them. MI, myocardial infarction.

The data were acquired in a multiple-gated mode of 500 cardiac cycles from a left anterior oblique view with a large-field-of-view gamma camera and a low energy, general-purpose parallel-hole collimator with a framing rate of 24 frames per cycle.[15,22,23] Regional wall motion of the left ventricle was assessed by quantitative contrast left ventriculography with a modified centerline method.[15,23] Briefly, cine-ventriculograms were from the right anterior oblique projection of 30 degrees on 35-mm cinefilm at 50 frames per second and end-diastolic and end-systolic silhouettes at sinus beats were manually traced by 2 experienced cardiologists blinded to clinical and scintigraphic data to superimpose the silhouettes by means of a modified centerline method assisted by a computer program (CAMAC 300, Goodman, Tokyo, Japan).[23] Regional wall-motion abnormality was quantified as the index (SD/chord) of ΣSD in areas showing an SD-chord below −1.5SD of a normal file derived from 50 control subjects in our laboratory.

Statistics

Statistical values are shown as the mean value ± SD. The difference between 2 groups in mean values was determined by an unpaired t-test. To compare the mean values for 4 subgroups, one-way analysis of variance (ANOVA) was used and when a significant difference was revealed, the Bonferroni approach was used for individual comparisons. The prevalence of clinical parameters (Table 1) was analyzed by means of 2×2 χ^2 tests. Correlations between the severity indexes of thallium and BMIPP were analyzed by linear regression analysis and the difference in regression lines was tested by analysis of covariance. A probability (p) value of less than 0.05 was considered significant.

RESULTS

Clinical characteristics and angiographic data

The clinical backgrounds and variables for the 27 patients in groups A and B are summarized in Table 1. There were no significant differences between the groups in age, gender, the prevalence of anterior infarction, intervals between the onset of infarction and examinations, medications or the incidence of coronary risk factors. There was no significant difference in peak serum creatine kinase levels or in the prevalence of anterior infarction, although higher enzyme levels and more frequent anterior infarction were more likely to occur in group B. Coronary angiography revealed no significant differences between groups A and B in coronary luminal narrowing in the infarct-related coronary arteries, the grade of TIMI coronary flow or the collateral grade (Table 2).

Perfusion and metabolic abnormalities and their correlations

Severity indexes for both thallium and BMIPP in group A showed a tendency to lower values than those in group B: thallium, 89 ± 97 vs. 126 ± 97 and BMIPP, 85 ± 68 vs. 130 ± 95, respectively (Fig. 1A), but the differences were not statistically significant. Furthermore, there was no significant difference between thallium and BMIPP in the severity index in the groups and there was no significant difference in the ratio of the thallium severity index to that of BMIPP (that is, perfusion-metabolism mismatch index) between groups A and B (0.91 ± 0.62 vs. 1.06 ± 0.66, respectively). Groups A and B were divided into 4 subgroups according to the presence or absence of spontaneous recanalization without a luminal narrowing of more than 90%: subgroups A1 and A2 and subgroups B1 and B2, respectively. The BMIPP severity index showed a

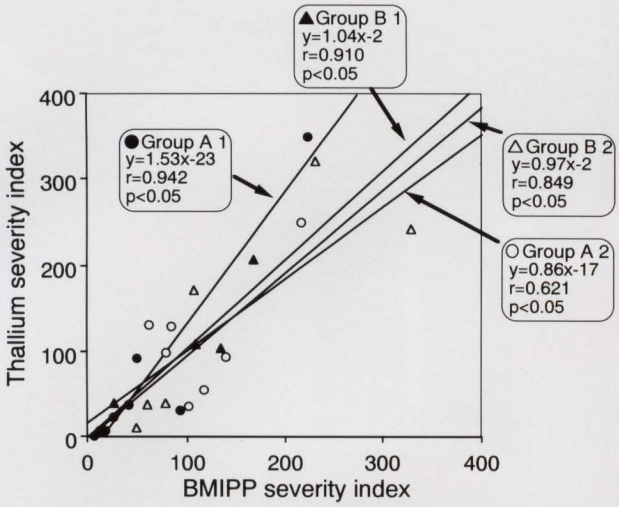

Fig. 2 Scatterplots of correlations between severity indexes of thallium and BMIPP in the 4 subgroups. There were significant positive correlations between the indexes in all groups but no significant difference was found in the regression lines among the 4 groups. Note that all regression lines are near the line of identity in Groups A2, B1, and B2, or show a slight upward shift which is probably due to thallium attenuation artifacts in inferior regions in Group A1, but no downward shift than this line, suggesting neither definite perfusion-metabolism mismatch nor significant difference in infarct-size limitation effect in any subgroups.

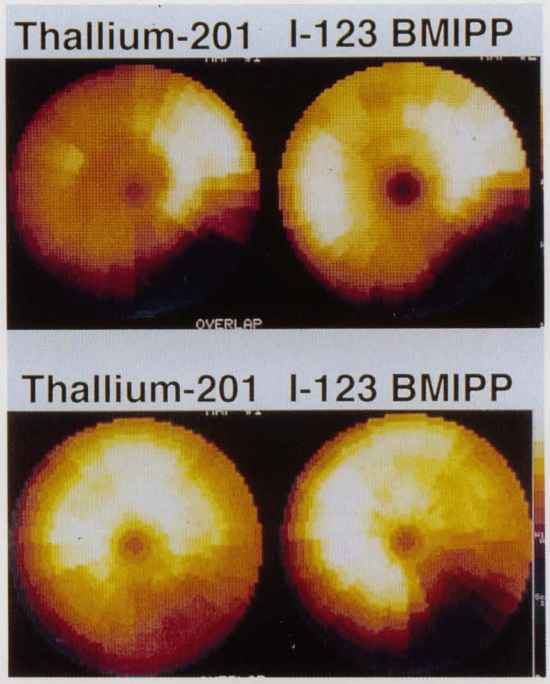

Fig. 3 Polar map displays of thallium and BMIPP tomographies from 2 patients with acute posterolateral infarction. (A) No dominant thallium-BMIPP mismatch is observed in a 66-year-old man with preinfarction angina and spontaneous coronary recanalization who was treated medically. (B) A typical perfusion-fatty acid metabolism mismatch derived from a 71-year-old man with preinfarction angina undergoing coronary reperfusion therapy.

significant positive correlation with that of thallium in all subgroups (Fig. 2). The regression lines in the 4 subgroups were comparable with the line of identity and there was no significant difference in the regression lines among the 4 groups, despite a slight upward shift in the line for subgroup A1.

Figure 3 shows 2 patients with acute posterolateral infarction and preinfarction angina. One patient (Fig. 3A) who was treated medically and had spontaneous recanalization of the infarct-related artery showed nearly comparable abnormalities of perfusion and fatty acid uptake, that is, there was no dominant mismatch. The other patient (Fig. 3B), who was treated with coronary reperfusion therapy, is presented as an example of less marked thallium perfusion abnormality relative to that of BMIPP, indicating a perfusion-metabolism mismatch.

Cardiac function at convalescence

There was no significant difference between groups A and B in left ventricular ejection fraction: 48 ± 9 vs. 51 ± 5%, respectively (Fig. 4A). Regional wall-motion abnormality was also comparable in groups A and B: 110 ± 42 to 140 ± 81 SD/Chord, respectively (Fig. 4B).

Effects of collaterals on perfusion, fatty acid metabolism, and cardiac function

The 27 patients in groups A and B were divided into 3 subgroups based on the Rentrop collateral grades: no visible collaterals, grade 0; definite but not sufficient collaterals, grades 1 and 2; rich collaterals, grade 3. No significant differences were found among the groups in the peak creatine kinase level, severity indexes of thallium and BMIPP, the ratio of severity indexes, or regional wall-motion abnormality (Table 3). When 13 patients without spontaneous recanalization (Groups A2 and B2) were divided into 2 subgroups, that is, 8 patients with poor collaterals (Rentrop grade 0/1) and 5 with relatively rich collaterals (Rentrop grade 2/3) based upon collateral development; there was no significant difference in the severity indexes of thallium and BMIPP and the ratio: 116 ± 120 vs. 128 ± 88, 115 ± 68 vs. 136 ± 94, and 1.0 ± 0.6 vs. 0.9 ± 0.5, respectively.

Effects of spontaneous recanalization on perfusion, fatty acid metabolism, and cardiac function

Table 4 compares collaterals, severity indexes of thallium and BMIPP, the ratio of severity indexes, and regional wall-motion abnormality among the 4 subgroups. Group B2 had a greater tendency to have rich collaterals and Group A1 had lower severity indexes for thallium and BMIPP, a lower ratio of indexes, and smaller regional wall-motion abnormality than those in the other 3 subgroups, but these values did not reach statistical significance.

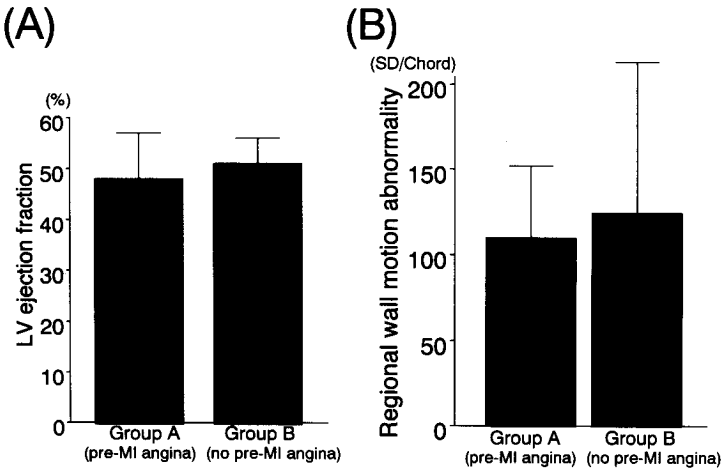

Fig. 4 Comparison of left ventricular (LV) ejection fraction (A) and regional wall-motion abnormality (B), indicating no significant differences in global or regional cardiac function between groups A and B. MI, myocardial infarction.

DISCUSSION

Correlations of myocardial perfusion, fatty acid metabolism, and left ventricular function quantitatively assessed in the present study demonstrated that preinfarction angina might have limitations in affording the cardioprotective effects (preserved myocardial viability relative to metabolic derangement and cardiac function) in acute myocardial infarct patients if rapid coronary recanalization was not achieved, even if the infarct-related coronary artery was recanalized spontaneously.

Preinfarction angina and coronary reperfusion for cardioprotection

In experimental settings, timely and complete coronary reperfusion is performed to induce ischemic preconditioning. This suggests that reperfusion after coronary occlusion is necessary to limit infarct size. We have recently demonstrated the beneficial effects of preinfarction angina on preserving myocardial viability and on functional recovery in patients undergoing primary coronary angioplasty.[15] Our previous study[15] showed significant correlations between severity indexes of thallium and BMIPP in 2 groups with and without preinfarction angina both of which underwent acute coronary reperfusion as seen in Figure 2, but what is more important in the analysis is that the slope of the regression line of the preinfarction angina group significantly ($p < 0.05$) shifted downwards compared to that in the non-preinfarction angina group, indicating less thallium abnormality relative to BMIPP abnormality (that is, more preserved myocardial viability relative to a metabolically damaged infarct-related zone).[15] On the other hand, myocardial perfusion-fatty acid metabolism correlation assessed by thallium and BMIPP tomographies did not demonstrate less thallium perfusion abnormality relative to metabolic derangement in the present study (Fig. 2, Table 4), that is, the perfusion-metabolism mismatch observed in patients undergoing rapid coronary reperfusion therapy[15] was not seen in patients who received medical treatment and had spontaneously recanalized infarct-related coronary artery (Figs. 2 and 3A). The present and our previous results[15] therefore strongly suggest that rapid reperfusion is essential but spontaneous reperfusion is not sufficient to afford cardioprotection in patients with preinfarction angina. The slight, but not significant, upward shift of the regression line between severity indexes of thallium and BMIPP in Group A1 (Fig. 2) may originate in thallium attenuation artifacts in inferior regions.[16]

Spontaneous recanalization, myocardial viability and cardiac function

The prevalence of spontaneous recanalization of infarct-related coronary arteries varies from 20% to 59%.[17–21] It occurs gradually over time from several hours to several months and, ultimately, spontaneous recanalization is observed in more than half of all patients, suggesting a delayed process of this phenomenon.[17] The timing and mechanism of spontaneous recanalization are not fully understood. There may be several factors involved for example, endogenous activities of thrombolysis and coagulability, such as platelet activity, fibrinogen, tissue plasminogen activator and its inhibitor 1,[33] atherosclerotic conditions, and coronary vasomotor tone in the coronary artery. The beneficial effects of a patent infarct-related coronary artery are better prognosis, better cardiac function and ventricular remodeling suppression. In our study, however, the patency status of the infarct-related vessel at the acute stage, the timing of spontaneous reperfusion, and the coronary flow grade soon after that were not fully determined. If autothrombolysis occurs immediately after the onset of infarction so that the

Table 3 Effect of collateral grades on cardiac function and the ratio of severity index of thallium to that of BMIPP in 27 patients of groups A and B

	Grade 0 (n = 15)	Grade 1, 2 (n = 7)	Grade 3 (n = 5)	
Peak serum creatine kinase level (IU/l)	3176 ± 3287	3316 ± 1376	3304 ± 1865	ns
Severity index Thallium	99 ± 103	111 ± 79	116 ± 120	ns
BMIPP	93 ± 83	125 ± 95	115 ± 68	ns
Ratio of severity indexes (Thallium/BMIPP)	1.01 ± 0.67	0.97 ± 0.68	0.89 ± 0.52	ns
Regional wall motion abnormality (ΔSD/Chord)	115 ± 55	121 ± 60	138 ± 78	ns
Coronary artery narrowing at follow-up (%)	65 ± 19	100 ± 0.4	100 ± 0.5	ns

Values are shown as mean ± SD. BMIPP, beta-methyl-p-iodophenyl pentadecanoic acid; ns, not significant.

Table 4 Effects of spontaneous recanalization on thallium and BMIPP activities and regional wall motion abnormality in 4 subgroups

	Subgroup A1	Subgroup A2	Subgroup B1	Subgroup B2	significance
Spontaneous recanalization	present (n = 8)	absent (n = 7)	present (n = 6)	absent (n = 6)	
Location of infarction (anterior/inferior)	2/6	3/5	4/2	4/2	ns
collateral grade 0/1	8	5	6	3	
2/3	0	2	0	3	
average	1.0 ± 0.0	1.1 ± 0.7	1.0 ± 0.0	2.0 ± 1.1	ns
Severity index					
Thallium	68 ± 117	113 ± 70	113 ± 69	136 ± 128	ns
BMIPP	60 ± 72	115 ± 52	111 ± 60	144 ± 112	ns
Ratio of severity indexes (Thallium/BMIPP)	0.78 ± 0.63	1.06 ± 0.62	1.08 ± 0.26	0.82 ± 0.54	ns
Regional wall motion abnormality (ΔSD/Chord)	102 ± 47	121 ± 36	132 ± 83	147 ± 92	ns

Values are shown as mean ± SD. Spontaneous recanalization was defined when TIMI garde 3 coronary flow was observed at the infarct-related coronary artery without a residual stenosis of more than 90%. BMIPP, beta-methyl-p-iodophenyl pentadecanoic acid; ns, not significant.

myocardium in an infarct-related zone could be sufficiently reperfused in patients with preinfarction angina, spontaneous recanalization may have more beneficial effects. This possibility is suggested by the findings indicating that Group A1 who had preinfraction angina and spontaneous recanalization showed a lower tendency to a thallium-BMIPP severity index ratio compared to other groups (Table 4), and that rapid spontaneous coronary reperfusion has been demonstrated in some patients with acute myocardial infarction. Although it is well known that collaterals show cardioprotective effects when antegrade coronary flow is limited, a preconditioning phenomenon is observed not only in poor collateral animals, such as the rat and rabbit, but also in a rich collateral animal, the dog. In the present study, collateral development is unlikely to have any definite effect on the thallium-BMIPP correlation. Our previous results[15] and these findings suggest that collateral per se is not an influential factor in terms of preconditioning effect manifestation. It is still not clear whether preinfarction angina closer to the onset of infarction[32] is more effective, even if coronary reperfusion occurs in a delayed fashion caused by spontaneous reperfusion.

Rationale for myocardial fatty acid metabolism assessment

More extended and profound impairment of myocardial fatty acid metabolism relative to perfusion abnormality has been demonstrated by thallium and BMIPP imagings in patients with angina pectoris, vasospastic angina, or acute myocardial infarction.[15,22–30] Myocardium which survived acute myocardial infarction and coronary reperfusion has a larger perfusion-fatty acid metabolism mismatch, as shown in Figure 3B. Myocardial BMIPP uptake is impaired in damaged but viable myocardium when the intracellular ATP level is reduced,[34] as seen in infarcted myocardium. BMIPP uptake is therefore a sensitive indicator of ischemia-related myocardial injury in an ischemia-related coronary territory. Therefore, infarct size normalized to its risk (infarct-related) zone size can be assessed quantitatively by a perfusion-metabolism correlation with thallium and BMIPP imaging.[15,22,23] The

quantification of the infarct-risk ratio is essential for assessing the cardioprotective effect of any interventional therapy.[3,4,35,36] Except for the studies of Ottani[10] (who, however, used an angiogram from one direction for evaluating the area at risk) and of our group,[15,22,23] this kind of infarct sizing relative to the risk zone size has not been performed in other clinical investigations on preinfarction angina and cardioprotection.[9,11–14,32] SPECT imaging with thallium and BMIPP can also contribute to the precise quantifying of myocyte viability and metabolic derangement. The comparable values for thallium and BMIPP abnormalities did not indicate any definite mismatch between perfusion and metabolism, and myocardium survival is less likely in an infarct-related zone. As previously demonstrated,[15,22,23] the extent of perfusion metabolism mismatch relates positively to functional improvement in acute infarct patients treated with primary coronary angioplasty. Therefore, lack of a dominant perfusion-metabolism mismatch suggests lower probability of better preservation of viability and functional improvement in the ischemia-related area despite the spontaneous coronary reperfusion achieved.

STUDY LIMITATIONS

Variations in the spontaneous coronary reperfusion process,[17–21] the infarct-related risk size, location of infarction, residual coronary lesions and myocardial viability might affect the possible cardioprotective effects of preinfarction angina in clinical settings, indicating that the present results are inconclusive and thereby a large patient population is necessary. In particular, a clinical study of many patients with rapid to delayed processes of spontaneous coronary reperfusion documented angiographically can more clearly reveal the beneficial or limited effects of preinfraction angina in acute myocardial infraction. The present and our previous studies,[15] however, stressed the importance of precise identification of infarct size and risk zone size as well as difficulties in assessing the effect of preinfarction angina in clinical situations. In addition to metabolic (BMIPP) imaging, more precise clinical tools are desired to assess myocardial viability and ischemic zone size in clinical practice and to evaluate collateral flow grade more easily in an emergency situation. The present study aimed to evaluate the effect of antecedent angina, which is a clinically identifiable marker for transient ischemia, but not myocardial ischemia per se, as done in earlier studies.[9,11–14,32] It is still unclear whether transient silent ischemia prior to acute myocardial infarction is cardioprotective as well as antecedent angina, because it is clinically very difficult to identify a silent and brief episode of myocardial ischemia prior to the onset of acute myocardial infarction. A longer follow-up interval may be necessary for ultimate assessment of myocardial viability and functional status, as slow reperfusion may delay the manifestation of cardioprotective effects of preinfarction angina and spontaneous coronary reperfusion compared to rapid coronary reperfusion.

CONCLUSIONS

Perfusion-metabolism correlation assessed by thallium and BMIPP imagings shows neither a definite mismatched appearance nor better preservation of myocardial perfusion or function in medically treated patients with preinfarction angina even when the infarct-related coronary artery is spontaneously recanalized. Spontaneous coronary reperfusion due to autothrombolysis may be insufficient for manifesting the cardioprotective effects of preinfarction angina in acute myocardial infarction.

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REFERENCES

1. Kloner RA, Yellon DM. Does ischemic preconditioning occur in patients? *J Am Coll Cardiol* 24: 1133–1142, 1994.
2. Murry CE, Richard VJ, Reimer KA, Jennings RB. Ischemic preconditioning slows energy metabolism and delays ultrastructual damage during a sustained ischemic episode. *Circ Res* 66: 913–931, 1990.
3. Cohen MV, Downey JM. Myocardial stunning in dogs: Preconditioning effect and influence of coronary collateral flow. *Am Heart J* 120: 282–291, 1990.
4. Cohen MV, Liu GS, Downey JM. Preconditioning causes improved wall motion as well as smaller infarcts after transient coronary occlusion in rabbits. *Circulation* 84: 341–349, 1991.
5. Deutsch E, Berger M, Kussmaul WG, Hirshfeld JW, Herrmann HC, Laskey WL. Adaptation to ischemia during percutaneous transluminal coronary angioplasty: clinical, hemodynamic, and metabolic features. *Circulation* 82: 2044–2051, 1990.
6. Cribier A, Korsatz L, Koning R, Rath P, Gamra H, Stix G, et al. Improved myocardial ischemic response and enhanced collateral circulation with long repetitive coronary occlusion during angioplasty: a prospective study. *J Am Coll Cardiol* 20: 578–586, 1992.
7. Tomai F, Crea F, Gaspardone A, Versaci F, Esposito C, Chiariello L, et al. Mechanisms of cardiac pain during coronary angioplasty. *J Am Coll Cardiol* 22: 1892–1896, 1993.
8. Kerensky RA, Kutcher MA, Braden GA, Applegate RJ, Solis GA, Little WC. The effects of intracoronary adenosine on preconditioning during coronary angioplasty. *Clin Cardiol* 18: 91–96, 1995.
9. Kloner RA, Shook T, Przyklenk K, Davis VG, Junio L, Matthews RV, et al. Previous angina alters in-hospital

outcome in TIMI 4. A clinical correlate to preconditioning? *Circulation* 91: 37–47, 1995.
10. Ottani F, Galvani M, Ferrini D, Sorbello F, Limonetti P, Pantoli D, et al. Prodromal angina limits infarct size. A role for ischemic preconditioning. *Circulation* 91: 291–297, 1995.
11. Nakagawa Y, Ito H, Kitakaze M, Kusuoka H, Hori M, Kuzuya T, et al. Effect of angina pectoris on myocardial protection in patients with reperfused anterior wall myocardial infarction: Retrospective clinical evidence of "preconditioning." *J Am Coll Cardiol* 25: 1076–1083, 1995.
12. Anzai T, Yoshikawa T, Asakura Y, Abe S, Akaishi M, Mitamura H, et al. Preinfarction angina as a major predictor of left ventricular function and long-term prognosis after a first Q wave myocardial infarction. *J Am Coll Cardiol* 26: 319–327, 1995.
13. Williams DO, Bass TA, Gerwitz H, Most AS. Adaptation to the stress of tachycardia in patients with coronary artery disease: insight into the mechanism of the warm-up phenomenon. *Circulation* 71: 687–692, 1985.
14. Okazaki Y, Kodama K, Sato H, Kitakaze M, Hirayama A, Mishima M, et al. Attenuation of increased regional myocardial oxygen consumption during exercise as a major cause of warm-up phenomenon. *J Am Coll Cardiol* 21: 1597–1604, 1993.
15. Nakata T, Hashimoto A, Kobayashi H, Miyamoto K, Tsuchihashi K, Miura T, et al. Outcome significance of thallium-201 and iodine-123 BMIPP perfusion-metabolism mismatch in preinfarction angina. *J Nucl Med* 39: 1492–1499, 1998.
16. Nakata T, Hashimoto A, Miyamoto K, Fujimori K, Shogase T, Hirasawa K, et al. Clinical implications of mismatched uptakes of beta-methyl fatty acid analogue and thallium in infarcted myocardium: Correlations with coronary stenosis and regional wall motion abnormality. *KAKU IGAKU (Jpn J Nucl Med)* 32: 1061–1071, 1995.
17. Rentrop KP, Feit F, Sherman W, Thornton JC. Serial angiographic assessment of coronary artery obstruction and collateral flow in acute myocardial infarction. Report from the second Mount Sinai-New York University Reperfusion Trial. *Circulation* 80: 1166–1175, 1989.
18. Topol EJ, Califf RM, Vandormael M, Grines CL, George BS, Sanz ML, et al. A randomized trial of late reperfusion therapy for acute myocardial infarction. Thrombolysis and Angioplasty in Myocardial Infarction-6 Study Group. *Circulation* 85: 2090–2099, 1992.
19. Haq A, Morgan CD, Wilson RF, Daly PA, Baigrie RS, White CW, et al. Impact of tissue plasminogen activator and heparin versus heparin alone on quantitative coronary angiographic findings in myocardial infarction. The Toronto Tissue Plasminogen Activator Trial Study Group. *Am J Cardiol* 72: 379–383, 1993.
20. Kim S, Yamabe H, Yokoyama M. Impaired coronary circulation in acute myocardial infarction: a dipyridamole-thallium-201 study. *Eur J Nucl Med* 24: 210–214, 1997.
21. Akiyama H, Ishikawa K, Kanamasa K, Ogawa I, Koka H, Kamata N, et al. Increased coronary vasomotor tone in acute myocardial infarction patients with spontaneous coronary recanalization. *Jpn Circ J* 61: 503–509, 1997.
22. Hashimoto A, Nakata T, Nagao K, Kobayashi H, Hase M, Yoshioka N, et al. Prediction of left ventricular functional recovery in patients with acute myocardial infarction using SPECT with thallium and beta-methyliodophenyl pentadecanoic acid. *J Cardiol* 26: 35–44, 1995.
23. Hashimoto A, Nakata T, Tsuchihashi K, Tanaka S, Fujimori K, Iimura O. Postischemic functional recovery and BMIPP uptake after primary percutaneous transluminal coronary angioplasty in acute myocardial infarction. *Am J Cardiol* 77: 25–30, 1996.
24. Hase M, Nakata T, Yonekura S, Tsuchihashi K, Kobayashi H, Nagao K, et al. Correlation of regional wall motion and fatty acid metabolism in coronary artery disease, hypertension, and hypertrophic cardiomyopathy: Assessment by dual-isotope SPECT with thallium-201 and iodine-123 β-methyl fatty acid analogue. *KAKU IGAKU (Jpn J Nucl Med)* 30: 529–539, 1993.
25. Nishimura T, Uehara T, Strauss HW. Radionuclide assessment of stunned myocardium by alternations in perfusion, metabolic and function. *Jpn Circ J* 55: 913–918, 1991.
26. Tamaki N, Kawamoto M, Yonekura Y, Fujibayashi Y, Takahashi N, Konishi J, et al. Regional metabolic abnormality in relation to perfusion and wall motion in patients with myocardial infarction: Assessment with emission tomography using an iodinated branched fatty acid analog. *J Nucl Med* 33: 659–667, 1992.
27. Kawamoto M, Tamaki N, Yonekura Y, Tadamura E, Fujibayashi Y, Magata Y, et al. Combined study with I-123 fatty acid and thallium-201 to assess ischemic myocardium: Comparison with thallium redistribution and glucose metabolism. *Ann Nucl Med* 8: 47–54, 1994.
28. Takeishi Y, Sukekawa H, Saito H, Nishimura S, Shiba T, Sasaki Y, et al. Impaired myocardial fatty acid metabolism detected by ^{123}I-BMIPP in patients with unstable angina pectoris: Comparison with perfusion imaging by ^{99m}Tc-sestamibi. *Ann Nucl Med* 9: 125–130, 1995.
29. Nakajima K, Shimizu K, Taki J, Uetani Y, Konishi S, Tonami N, et al. Utility of iodine-123-BMIPP in the diagnosis and follow-up of vasospastic angina. *J Nucl Med* 36: 15934–15940, 1995.
30. Taki J, Nakajima K, Matsunari I, Bunko H, Tanaka S, Kawasuji M, et al. Assessment of improvement of myocardial fatty acid uptake and function after revascularization using iodine-123-BMIPP. *J Nucl Med* 38: 1503–1510, 1997.
31. Nakata T, Noto T, Uno K, Wada A, Hikita N, Tanaka S, et al. Quantification of area and percentage of infarcted myocardium by single photon emission computed tomography with thallium-201: A comparison with serial serum CK-MB measurements. *Ann Nucl Med* 3: 1–8, 1989.
32. Kloner RA, Shook T, Antman EA, Cannon CP, Przyklenk K, McCabe CH, et al. A prospective analysis on the potential preconditioning effect of preinfarct angina in TIMI 9. *Circulation* (Suppl) 94: I-611, 1996. (abstract)
33. Margaglione M, Grandone E, Di Minno G. Plasma predictors of ischemic complications of atherosclerosis: open issues. *Biomed Pharmacother* 47: 445–449, 1993.
34. Fujibayashi Y, Yonekura Y, Takemura Y, Wada K, Matsumoto K, Tamaki N, et al. Myocardial accumulation of iodinated beta-methyl-branched fatty acid analogue, iodine-125-15-(p-iodophenyl)-3(R,S)methylpentadecanoic acid (BMIPP), in relation to ATP concentration. *J Nucl Med* 31: 1818–1822, 1990.

35. Ovize M, Przyklenk K, Hale SL, Kloner RA. Preconditioning does not attenuate myocardial stunning. *Circulation* 85: 779–789, 1992.
36. Urabe K, Miura T, Iwamoto T, Ogawa T, Goto M, Sakamoto J, et al. Preconditioning enhances myocardial resistance to postischaemic myocardial stunning via adenosine receptor activation. *Cardiovasc Res* 27: 657–662, 1993.