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Detection of stunned myocardium in post-reperfusion cases of acute myocardial infarction

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Objective: This study was designed to evaluate the correlation between improvements in serial images obtained by SPECT imaging with Tc-99m MIBI (MIBI) and I-123 BMIPP (BMIPP) and the recovery of cardiac function in acute myocardial infarction (AMI) patients after reperfusion therapy. ***Methods:*** Twenty five patients who were admitted to the emergency room within 24 hours after the onset of the first event of AMI were enrolled in this study. The culprit coronary arteries were identified by CAG and were treated with direct percutaneous transluminal coronary angiography (PTCA), followed by stent implantation. To determine risk areas, initial image at the onset was acquired by the freeze method, in which MIBI was injected before the treatment and the image was collected after the reperfusion therapy. After the reperfusion treatment was completed, MIBI SPECT images at rest were performed on days 7 and 60. Both early and late images, including gated SPECT images were acquired after 30–60 minutes and 6 hours post injection, respectively. In addition, BMIPP SPECT images at rest were obtained 30 minutes after injection of 148 MBq BMIPP on days 7 and 60 (BMIPP image). The obtained image was divided into 48 segments and percent uptake of each segment was calculated. The number of abnormal areas (NAA) was defined as the segment with a % uptake less than 60% of normal uptake, and the change of NAA over time was evaluated. ***Results:*** The NAA on the MIBI-early image significantly improved between the pre image and the day 7 image ($p < 0.001$), but no similar improvement was observed between day 7 and day 60. On the other hand, the NAA of the MIBI-delayed image did not significantly improve up to day 7, but a slight improvement was observed on days 7 and 60 ($p < 0.05$). A significant improvement in the NAA of the BMIPP image was observed between day 7 and day 60, as shown in the delayed image ($p < 0.05$). An excellent correlation on the NAA between the MIBI-delayed image and the BMIPP image was observed with $r = 0.983$ ($p < 0.001$) at day 7 and $r = 0.984$ ($p < 0.001$) at day 60 resulting in a consistent diagnosis. Analysis of the myocardial function by means of gated SPECT indicated that the wall motion significantly improved as the myocardial perfusion improved up to day 7 and thereafter a steady improvement was observed up to day 60. The improvement in the NAA in MIBI-delayed images in the subacute phase (day 7) and in the chronic phase (day 60) as well as BMIPP images showed excellent correlation with the improvement in RWM and RWT (MIBI-delayed image: $r = 0.550$ (RWM), $r = 0.647$ (RWT)), (BMIPP image: $r = 0.536$ (RWM), $r = 0.565$ (RWT)). ***Conclusion:*** We conclude that insufficient ATP production caused by mitochondrial dysfunction in stunned myocardium is closely related to MIBI delayed and BMIPP images. Furthermore, MIBI delayed imaging as well as BMIPP imaging will provide a clue to the state of stunned myocardium after reperfusion therapy in patients with AMI.

Key words: Tc-99m MIBI, reverse redistribution, reperfusion, stunned myocardium, risk area

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INTRODUCTION

DIRECT PTCA is a widely-established treatment for AMI aimed at the speedy restoration of infarcted myocardium and recognized for low invasiveness and high effectiveness. This, together with the recent development of stent and other new devices, has greatly helped in reducing the recurrence rate of restenosis. The purpose of such revascularization treatments is to re-establish blood flow so as to prevent myocardial necrosis and help the recovery of cardiac function. Nevertheless, there are known cases where delay is observed in the recovery of cardiac function, even after perfusion was restored successfully by revascularization.[1]

We performed a series of MIBI (early/delayed) and BMIPP SPECT imagings for AMI post-reperfusion-therapy patients by following up until and after they entered the chronic phase. This report is based on that study, discussing the correlation of the recovery process as revealed by the images with the observed pattern of improvement in cardiac function.

MATERIALS AND METHODS

Subjects

The study population consisted of 25 patients (20 men and 5 women, mean age: 66.2 ± 13.7 years) who were admitted to hospital emergency because of his/her first AMI event, and was followed up for a term of one year and six months. Exclusion criteria were cardiogenic shock or restenosis, old myocardial infarction (OMI) and those who were brought in after more than 24 hours from the occurrence. Peak CPK was 1795 ± 1069 IU/*l*. The culprit coronary arteries were 11 left anterior descending branches (LAD), 4 left circumflexes (LCX), and 10 right coronary arteries (RCA). The time needed for disobliteration averaged 6 h 24 min ± 5 h 3 min. According to the IRB, informed consent was obtained from all patients before the examination, based on sufficient information including the predicted exposed dose. During the course of study sessions, patients were also informed and given an explanation of the test results as appropriate.

Examination protocol

The patients were those who visited the hospital with chest pain within 24 hours of the onset of symptoms and were diagnosed with AMI by means of an electrocardiogram (ECG), echocardiographic evaluation of wall motion abnormalities, and emergency percutaneous coronary angiography with Ioversol. After identification of the culprit coronary artery, they were treated with direct percutaneous transluminal coronary angioplasty (PTCA), followed by stent implantation.

Initial images were acquired by the freeze method: 740 MBq of MIBI was injected intravenously before PTCA, and postoperative SPECT imaging was performed. These pre images (i.e., before-PTCA images), all obtained within 2 hours of MIBI injection, were used for the detection of risk areas.[2] Further MIBI SPECT imaging was performed in the subacute phase (on day 7) and in the chronic phase (on day 60) after PTCA, each providing both MIBI-early and MIBI-delayed images. MIBI-early images were obtained 30 to 60 min after injecting 740 MBq of MIBI at rest, and MIBI-delayed images 6 hours after injection. Each MIBI-early image was accompanied by ECG-gated SPECT imaging. As for BMIPP, SPECT images were acquired on 7 days and 60, 30 min after injecting 148 MBq of BMIPP at rest.

Data collection and analysis

A double-headed gamma camera was used to collect and analyze the image data. The MIBI imaging conditions were a low-energy high-resolution collimator, with a 141 keV ± 10% energy widow and 64 × 64 matrix. SPECT projections were collected at 4° increments over 360°, 8 sec per image. ECG-gated SPECT images were collected at 6° increments over 360°, 5 sec per image, and on RR interval divided into 8 frames. The BMIPP imaging conditions were: a low-energy all-purpose collimator, with a 160 keV ± 10% energy window and a 64 × 64 matrix. At 6° increments over 360°, 13 sec per image. Transverse images were reconstructed by the filtered backprojection method, with a Butterworth filter for preprocessing and a Ramp-Hanning filter for backprojecting. No scatter or absorption correction was performed. Instead, patients had chocolate and water to prevent scatter from other organs (especially the liver and biliary system).

Measured parameters and evaluation method

Polar maps of the obtained LV short-axis images were divided into a total of 48 segments each (16 radial sectors, 3 slices along the long axis from apex to base). Percent uptake was calculated for each segment, by rating the segment with the highest count value as having 100% uptake. A change in the number of segments with less than 60% uptake (number of abnormal areas: NAA) was observed over time.[3] (In this study, abnormal areas were obvious from visual evaluation alone, although standard deviation is a more commonly applied method.) A set of polar maps derived from one patient had an identical apex-base distance. Dedicated analysts took charge of the polar map evaluation. Germano et al's QGS program[4] was used in the ECG-gated SPECT analysis of cardiac function to determine stroke volume (Volume: m*l*), end diastolic volume (EDV: m*l*), end systolic volume (ESV: m*l*) and left ventricular ejection fraction (LVEF: %). Regional wall motion (RWM: mm) and regional wall thickening (RWT: %) were also measured to assess the change in regional wall motion and regional wall thickening in the risk area that was first identified by pre imaging. Furthermore, to estimate the improvement in the chronic

phase (60 days) compared to the subacute phase (7 days), we calculated the improvement in NAA, RWM and RWT. "NAA reduction" was defined as NAA (on day 7) minus NAA (on day 60). "RWM improvement" was defined as RWM (on day 60) minus RWM (on day 7). The definition of "RWT improvement" was the same as for RWM improvement.

Statistical assessment

All data were expressed as the average ± standard deviation. Change with time in NAA was evaluated by Wilcoxon matched pairs signed ranks test. Correlation was calculated with Spearman's correlation coefficient, regarding $p < 0.05$ as significant.

RESULTS

Change in NAA over time on MIBI-early, -delayed and BMIPP images

Table 1 shows the change in mean NAA observed over time in MIBI-early, MIBI-delayed, and BMIPP images. NAA values in the MIBI-early image at pre, 7 days, and 60 days were 15.5, 4.4 and 2.2, respectively, suggesting a remarkable and significant improvement from pre to 7 day images ($p < 0.001$), followed by gradual improvement from 7 days to 60 days, but never on a significant scale. Mean NAA values in the MIBI-delayed image at 7 days and 60 days were 12.1, and 10.2, respectively, showing a significant improvement from 7 days through 60 days ($p < 0.05$). Nevertheless, the MIBI-delayed image improvement pattern had quite different characteristics from that of the MIBI-early image, including reverse redistribution as well as persistently high values. The difference between MIBI-delayed and MIBI-early images was significant ($p < 0.001$). BMIPP images at 7 days and 60 days had a mean NAA of 12.4, and 10.0, respectively, indicative of a significant recovery between 7 days and 60 days ($p < 0.05$). With BMIPP, NAA change over time followed an almost identical course to that in the MIBI-delayed image.

Comparison of NAA: MIBI-delayed image and BMIPP image

Both showed mild but significant reduction in NAA between 7 days and 60 days ($p < 0.05$). No significant difference was observed between MIBI-delayed and BMIPP (ns).

Figure 1 shows the correlation between MIBI-delayed images and BMIPP images at each time point. The regression equation and correlation coefficient were: $y = 0.934x + 0.517$ ($r = 0.983$, $p < 0.001$) at 7 days, $y = 0.952x + 0.512$ ($r = 0.984$, $p < 0.001$) at 60 days, with a high degree of concordance at each time point.

Table 1 Change of NAA

	Pre	7d	60d
early-image	15.5 ± 12.0	4.4 ± 6.4*	2.2 ± 3.1**
delay-image		12.1 ± 10.9	10.2 ± 9.5†
BMIPP-image		12.4 ± 11.5	10.0 ± 10.0‡

Values are mean ± SD. *: $p < 0.001$ vs. pre image, **: ns vs. 7d early image, †: $p < 0.05$ vs. 7d delay image. ‡: $p < 0.05$ vs. 7d BMIPP image.

Table 2 Change of the index of cardiac functions

	7d	60d
Volume (m*l*)	39.3 ± 12.4	38.6 ± 11.7*
EDV (m*l*)	85.5 ± 24.8	78.2 ± 26.2†
ESV (m*l*)	47.3 ± 17.5	39.6 ± 18.8‡
LVEF (%)	45.8 ± 9.4	51.1 ± 11.4§
RWM (mm)	3.3 ± 1.9	4.0 ± 2.3 ‖
RWT (%)	18.0 ± 9.0	23.1 ± 11.4¶

Values are mean ± SD. Volume: stroke volume, EDV: end diastolic volume, ESV: end systolic volume, LVEF: left ventricular ejection fraction, RWM: regional wall motion, RWT: regional wall thickening. *: ns vs. 7d volume, †: $p < 0.05$ vs. 7d EDV, ‡: $p < 0.001$ vs. 7d ESV, §: $p < 0.01$ vs. 7d LVEF, ‖ : $p < 0.05$ vs. 7d RWM, ¶: $p < 0.01$ vs. 7d RWT

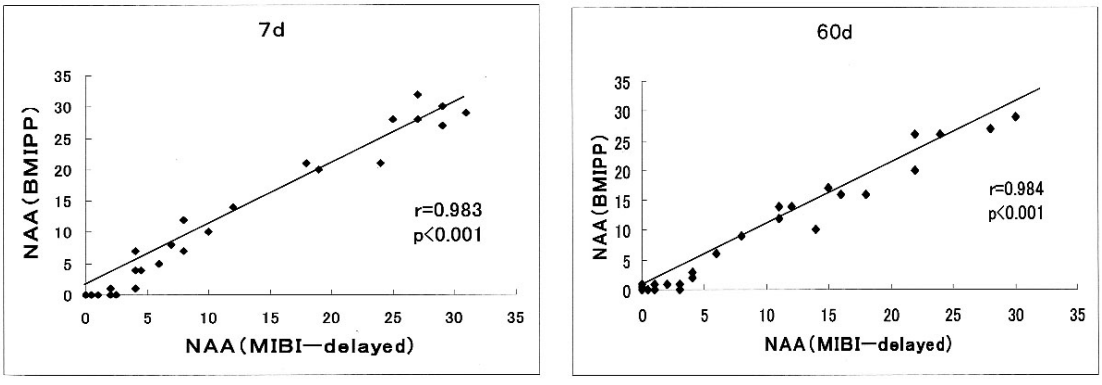

Fig. 1 Change over time in correlation between MIBI-delayed and BMIPP images. NAA of MIBI-delayed images and BMIPP images after AMI reperfusion revealed a strong correlation, with $r = 0.983$, $r = 0.984$ at day 7 and day 60 respectively.

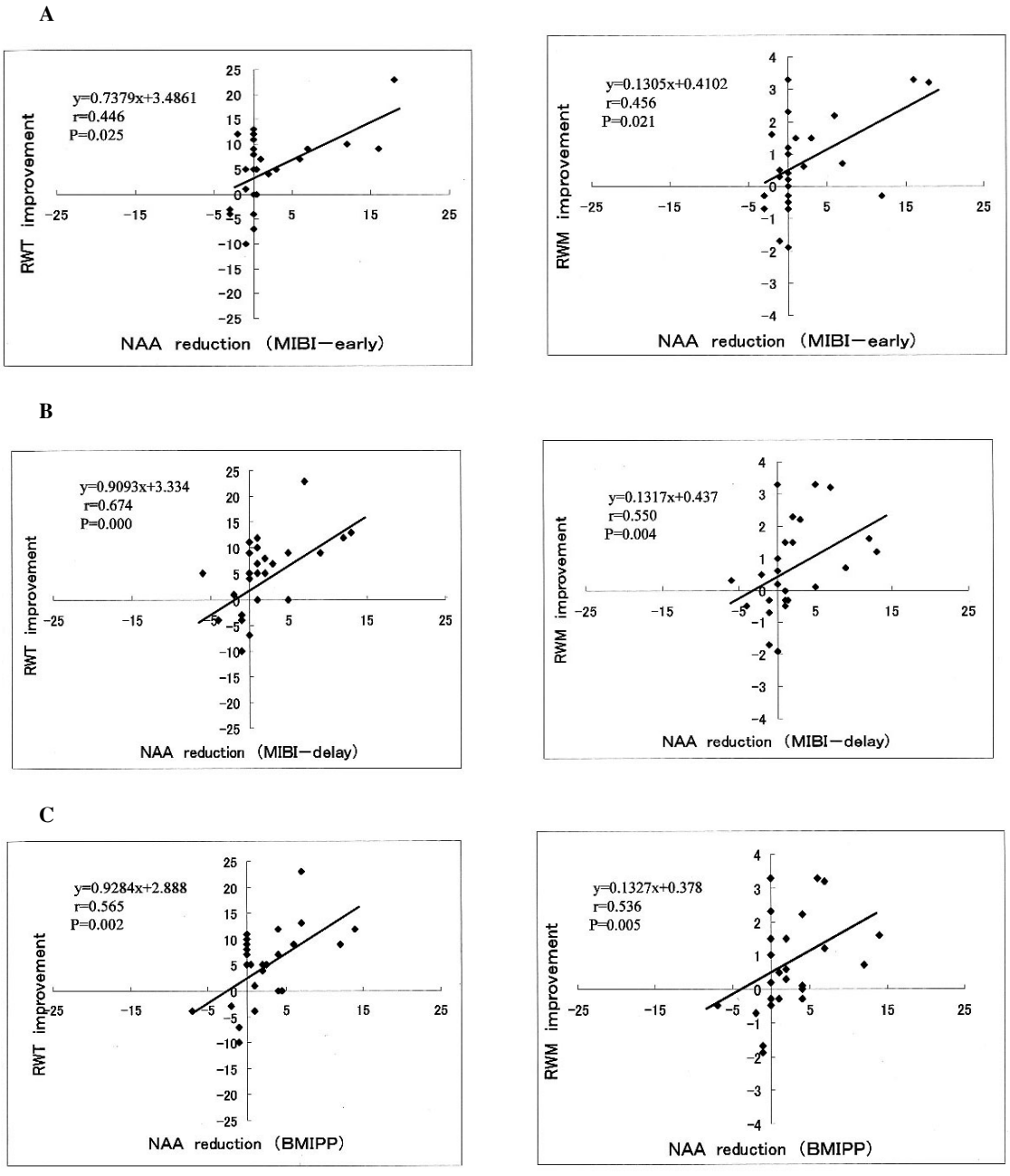

Fig. 2 Correlation between changes over time in cardiac function and in NAA of MIBI-early, delayed, and BMIPP images. "NAA reduction" was defined as NAA (7 days) minus NAA (60 days). "RWM improvement" was defined as RWM (60 days) minus RWM (7 days). The definition of "RWT improvement" was the same as RWM improvement. A: Correlation between MIBI-early NAA reduction and improvement of RWM (mm)/RWT (%). B: Correlation between MIBI-delay NAA reduction and improvement of RWM (mm)/RWT (%). C: Correlation between BMIPP NAA reduction and improvement of RWM (mm)/RWT (%).

Change in cardiac function

Change in cardiac function is shown in Table 2. Significant improvement was recognized with mild from the subacute (7 days) through to the chronic (60 days) stage ($p < 0.05$). But no significant improvement was observed in volume (ns).

Correlation between NAA reduction and improvement of regional wall motion indexes over subacute and chronic phases

The NAA reduction in MIBI-early, MIBI-delayed, and BMIPP images over time from the subacute phase (7 days) to the chronic phase (60 days) was compared with the RWM improvement and RWT improvement, and the

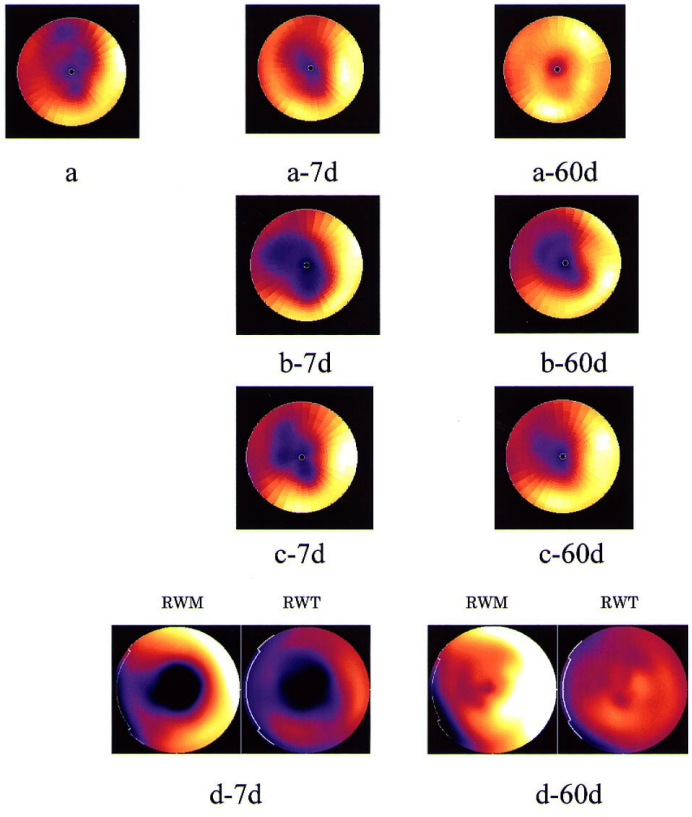

Fig. 3 A 76-year-old AMI patient (woman). Emergency CAG was performed and revealed 100% stenosis in the LAD lesion, which was treated by PTCA with stent implantation and restored to 0%. Myocardial SPECT pre image (a) showed a wide-range defect in LAD area with NAA of 24, which eventually diminished to zero in 60 days (a-60d). On the other hand, MIBI-delayed (b) and BMIPP (c) images presented similar NAA reduction patterns, with mild improvement between 7 days (7d) and 60 days (60d) but not without defective segments. According to the regional wall thickening and regional wall motion image by QGS program (d), regional wall thickening recovered from 12% at 7d to 35% at 60d, regional wall motion recovered from 2.5 mm at 7d to 5.7 mm at 60d.

correlation was evaluated (Fig. 2). The regression equation and correlation coefficient in relation to RWM improvement were: MIBI-early image, $y = 0.130x + 0.410$ ($r = 0.456$, $p = 0.021$); MIBI-delayed image, $y = 0.131x + 0.437$ ($r = 0.550$, $p = 0.004$); BMIPP image, $y = 0.132x + 0.378$ ($r = 0.536$, $p = 0.005$). Those in relation to RWT improvement were: MIBI-early image, $y = 0.737x + 3.486$ ($r = 0.446$, $p = 0.025$); MIBI-delayed image, $y = 0.909x + 3.33$ ($r = 0.674$, $p = 0.000$); BMIPP image, $y = 0.928x + 2.88$ ($r = 0.565$, $p = 0.002$). Each revealed significant correlation, with the highest value shown with the MIBI-delayed image.

Figure 3 shows an example of changes with time revealed in MIBI (early/delayed) and BMIPP images.

DISCUSSION

Tc-99m-Hexakis-2-Methoxyisobutyl Isonitrile (MIBI) is a myocardial perfusion agent that is taken up in myocardial cells in proportion to blood flow, immediately after injection.[5] It is recognized that almost 90% of MIBI inside myocardial cells combines with mitochondria[6] and is retained for a relatively long time without any significant change in distribution.[7] This characteristic of MIBI has enabled use of the "freeze method," which is drawing attention today as a means of preoperative risk area assessment in AMI. This method detects the risk area by injecting MIBI intravenously prior to revascularization therapy such as PTCA, and then postoperatively performing SPECT imaging. Some reports have pointed out that, if a delayed image (4–6 h after injection) is obtained during the subacute phase of AMI, several hours after MIBI injection, the image reveals reverse redistribution and an increase in washout of the agent from cardiac muscle, and the findings are very indicative of a risk area.[8–12] As the role of depressed mitochondrial function is important, detailed research in kinetics is called for.

According to previous research, the myocardium utilizes fatty acids, glucose and amino acids as energy substrates. The tricarboxylic acid cycle with beta-oxidation

of fatty acids works with such high energy efficiency that the myocardium draws 60 to 70% of its energy from the fatty acid metabolism. Iodine-123-βmethyl-p-iodophenyl-pentadecanoic acid (BMIPP) undergoes a metabolic process analogous to that of free fatty acids, although somewhat different from long chain fatty acids, and, for that reason, is assumed to reflect the fatty acid metabolism taking place in the myocardium. Once inside the body, BMIPP moves along a concentration gradient into myocardial cytoplasm, stays in lipid pools in the form of stored fatty acid, and then enters the mitochondrial tricarboxylic acid cycle.[13,14] The myocardial accumulation of BMIPP is known to reflect the changes in the concentration of adenosine triphosphate (ATP) in the cells.[15] Decreased BMIPP accumulation presumably reflects depressed mitochondrial function or cell membrane dysfunction caused by myocardial diseases such as myocardial ischemia.[16] Assessment of BMIPP accumulation can be an effective means of determining the severity of myocardial damage, if the mismatch with myocardial perfusion is properly evaluated.

Thus both MIBI-delayed and BMIPP SPECT findings are closely related to mitochondrial function including the production of ATP. The images are not only close to each other but also probably reflect the pattern of improvement of wall motion in AMI patients.

In this study, the results of a series of MIBI SPECT (early and delayed) and BMIPP SPECT images for AMI post-reperfusion patients, conducted over time through to the chronic phase, were utilized in the evaluation of the recovery patterns as shown in SPECT in terms of correlation with the pattern of improvement of cardiac function.

MIBI is taken into the normal myocardium through passive transport in proportion to blood flow, and then retained without undergoing washout. This characteristic of MIBI can be useful in the cases of acute myocardial infarction, in that it enables the quantitative assessment of a pre-reperfusion risk area by the pre-PTCA injection of MIBI followed by postoperative SPECT. Nevertheless, when the pattern of improvement of myocardial blood flow was assessed by MIBI-early images, it showed swift recovery in the pre-images to 7 day-images, but the process slowed down thereafter, and this is the same tendency as discussed in our previous study on Tc-99m Tetrofosmin imaging[3] caused by post-ischemia-reperfusion disorder after surgical treatment. This suggests that a certain length of time is needed before the salvaging effect of revascularization therapy can be determined with any degree of accuracy with regard to the range of the salvaged area. Meanwhile, there were some individual cases in which blood flow increased even in the chronic phase (at 60 days).

Aggressive factors associated with post-ischemia-reperfusion disorders include a lowering of myocardial ATP levels, myocardial Ca^{2+} overload, free radicals, microcirculatory failure, activation of adhesion molecules, and apoptosis. It is assumed that these factors delay the restoration of myocardial perfusion even when reperfusion therapy is performed in the MIBI-early stage of ischemia.[17–22]

Compared to the recovery process as shown in MIBI-early images, the recovery in MIBI-delayed and BMIPP images was slow to start and mild though significant. The latter two agreed well with each other at each observation point. Although a branched chain fatty acid, BMIPP's accumulation mechanism in the myocardium is so analogous to that of free fatty acids (FFA) that, as reported by many,[13–16] it can possibly reflect the state of myocardial fatty acid metabolism. In our cases of AMI, mitochondria and other myocardial cell organelles had presumably been injured severely; particularly triglycerol storerooms for fatty acid energy playing an important role in myocardial energy production.[23] SPECT revealed a lowering in BMIPP intake levels in the myocardium, visualized as defects on images.

When myocardial cells are injured by ischemia, Ca^{+} accumulation within cells causes the mitochondria to suffer massive swelling, decline in activity, and have a consequent loss of ATP generating potential. Furthermore, increase in proton leakage from the respiration chain is important from the perspective of mitochondrial respiration.[24–27] When this happens, a smaller number of protons can only be pumped out of the matrix, so that the mitochondrial membrane potential becomes lowered. It also lowers the MIBI retention rate, which is closely related to mitochondrial membrane potential, and so increases the washout in the damaged myocardium. As far as our study goes, the mechanism accounts for the lowering of the MIBI accumulation level indicated by the MIBI-delayed images. The abnormal findings in the evaluation of images and their change over time revealed a high degree of agreement between the MIBI-delayed and BMIPP SPECT, pointing to the close correlation of these agents with AMI post-reperfusion mitochondrial dysfunction as well as with fatty acid metabolic defect.

As for the cardiac function indices for the damaged myocardium, the improvement was significant over 7 days from the reperfusion treatment, then mild yet significant through to the 60th day. As the myocardial blood flow is restored by degrees, the oxygen supply increases in the myocardial cells, but it is known to take longer for the patient to recover satisfactory cardiac functions, probably because the mitochondrial function remains impaired and continues to depress the ATP synthesis potential in the citric acid cycle, thus allowing only a low-level, glucose-based ATP production.[28] In this study, there was a mild but significant improvement in wall motion between the subacute phase (7 days) and the chronic phase (60 days), and the same was true with MIBI-delayed and BMIPP findings. Furthermore, there were significant positive correlations between the improvement of regional cardiac function indexes and the recovery of these images (Fig.

3). It can therefore be deduced that the process of recovery of impaired cardiac function is closely related to the decrease in NAA in MIBI-delayed and BMIPP SPECT. This, in turn may suggest the possibility of MIBI-delayed images reflecting the state of fatty acid metabolism. The possibility has yet to be discussed in detail, since factors such as glycolytic pathway, abnormality in the ATP utilization process, as well as free radical actions, make it difficult to evaluate point-by-point correspondence. This study has raised the possibility of MIBI-delayed and BMIPP imagings being indicative of the state of AMI post-reperfusion stunned myocardium. Further study is needed to assess effectiveness over time in predicting prognosis and choosing medical therapy, by performing either dual-time-point MIBI or combined MIBI-early and BMIPP SPECT.

CONCLUSION

We conclude that insufficient ATP production caused by mitochondrial dysfunction in stunned myocardium is closely related to MIBI-delayed and BMIPP images. Furthermore, MIBI-delayed imaging as well as BMIPP imaging will provide a clue to the state of stunned myocardium after reperfusion therapy in patients with AMI.

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