

Dynamic changes in cardiac fatty acid metabolism in the stunned human myocardium

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Background: The chronological changes or mechanisms in cardiac fatty acid metabolism under clinical conditions of hypoxia and ischemia have not been fully elucidated. ^{123}I -15-(*p*-iodophenyl)-3-*R,S*-methylpentadecanoic acid (BMIPP) can be used with single photon emission computed tomography (SPECT) to evaluate myocardial fatty acid metabolism. We investigated chronological changes in energy metabolism in the stunned human myocardium by means of ^{123}I -BMIPP myocardial SPECT.

Methods and Results: We conducted ^{123}I -BMIPP myocardial SPECT in 10 patients with stunned myocardium during the acute, subacute and chronic phases after onset. The left ventricle was divided into 9 regions on SPECT, and the degree of abnormalities in each region was scored in four grades from normal (0) to defect (4). We also examined wash-out rates on BMIPP images. The scores on early BMIPP images in the acute, subacute and chronic phases were 5.6 ± 1.8 , 13.4 ± 3.5 and 2.5 ± 1.1 , respectively, and the score was highest in the subacute phase ($p < 0.001$). Similarly, scores on the late images were 2.3 ± 1.7 , 18.3 ± 4.5 and 4.7 ± 2.6 , respectively, and highest in the subacute phase ($p < 0.001$). The wash-out rates (normal: $18.2 \pm 2.1\%$) in the acute, subacute and chronic phases were $12.1 \pm 4.8\%$, $44.9 \pm 10.0\%$ and $23.1 \pm 4.6\%$, respectively, with the value being lowest during the acute phase ($p < 0.05$), and highest during the subacute phase ($p < 0.001$).

Conclusion: These results suggested that fatty acid metabolism in the stunned human myocardium changes dynamically over time.

Key words: myocardial fatty acid metabolism, myocardial stunning, ^{123}I -BMIPP

INTRODUCTION

THE HEART REQUIRES CONSIDERABLE AMOUNTS of energy to maintain the pumping function that supplies blood to all systemic organs. The energy metabolism of the myocardium has unique characteristics appropriate to the demands placed on the heart. Fatty acids, glucose and lactic acid are energy sources. The proportions of these substrates metabolized in the myocardium vary with physiological changes resulting from meals and exercise.

Under aerobic conditions and at rest while fasting, 60% to 90% of the energy requirement is supplied by fatty acid metabolism, which is the most efficient means of energy production. Under hypoxic or ischemic conditions, fatty acid metabolism, which needs a large amount of oxygen, is believed to be suppressed and replaced by glucose metabolism which requires less oxygen consumption, but the chronological changes that occur in myocardial metabolism or in the mechanism operating in clinical hypoxia or ischemia have not been fully elucidated.

Fatty acid metabolism can be evaluated in the myocardium by means of ^{11}C -palmitate and positron emission tomography (PET),^{1,2} but this procedure is available at only a few facilities. On the other hand, the straight chain fatty acid ^{123}I -iodophenyl pentadecanoic acid (IPPA)³ and the branched chain fatty acid ^{123}I -15-(*p*-iodophenyl)-

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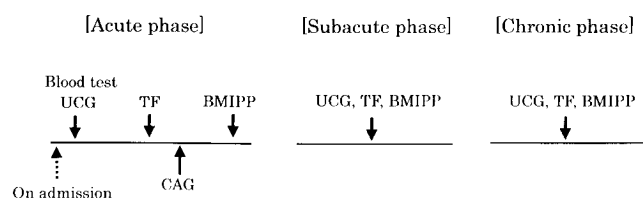
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Table 1 Clinical characteristics

Case No.	Gender/age	ECG: ST elevation and/or depression	CAG findings	Treatment	Left ventricular ejection fraction (%) acute/chronic phase	Level of CPK-MB (-25 IU/l)
1	M/73	I, aV ₁ , V ₂₋₆	diffuse spasm in LAD and LCX	medicinal treatment	44%→68%	27
2	M/55	II, III, aV _F , V ₃₋₆	total occlusion in proximal segment of LAD	direct PTCA	52%→62%	47
3	M/69	II, III, aV _F , V ₄₋₆	99% stenosis in proximal segment of LAD	direct PTCA	55%→75%	35
4	F/65	I, aV ₁ , III, aV _F , V ₃₋₆	diffuse spasms in LAD, LCX and RAC	medicinal treatment	37%→62%	18
5	M/58	II, III, aV _F , V ₃₋₆	95% stenosis in proximal segment of LAD	direct PTCA	55%→65%	46
6	F/62	I, aV ₁ , V ₂₋₆	normal	medicinal treatment	42%→80%	25
7	F/75	II, III, V ₃₋₆	75% stenosis in proximal segment of LAD	medicinal treatment	52%→73%	21
8	F/49	II, aV _F , V ₃₋₆	spasm in proximal segment of LAD	medicinal treatment	44%→67%	36
9	M/68	V ₂₋₆	90% stenosis in proximal segment of LAD	direct PTCA	45%→62%	19
10	M/75	III, V ₄₋₆	normal	medicinal treatment	53%→69%	43

CAG: coronal arteriography, CPK-MB: MB fraction of creatine phosphokinase, ECG: electrocardiogram, F: female, LAD: left anterior descending coronary artery, LCX: left circumflex coronary artery, M: male, PTCA: percutaneous transluminal coronary angioplasty, RCA: right coronary artery



CAG: coronary angiography. UCG: ultrasonic echocardiography. BMIPP: ¹²³I-BMIPP myocardial SPECT. TF: ^{99m}Tc-tetrofosmin myocardial SPECT

Fig. 1 Study protocol.

3-*R,S*-methylpentadecanoic acid (BMIPP)^{4,5} can be used for single photon emission computed tomography (SPECT) at far more institutions. The clearance of BMIPP from the blood is faster than that of IPPA, and BMIPP accumulates in the heart, making it appropriate for SPECT evaluation. Moreover, because low levels accumulate in the liver and the lungs, heart imaging is very clear. Therefore, this procedure is widely applied to diagnosing ischemic heart diseases and evaluating pathological conditions.^{6,7}

We examined energy metabolism over time in the stunned human myocardium by means of ¹²³I-BMIPP myocardial SPECT.

MATERIALS AND METHODS

Subjects

Ten patients with stunned myocardium (Table 1) satisfied the following criteria (6 males and 4 females; mean age, 64.9 ± 8.8 years):

- 1) First episode without a history of angina pectoris or myocardial infarction.
- 2) Marked wall motion abnormalities during the acute phase, with normalized motion during the chronic phase.
- 3) Myocardial escape enzyme levels remaining below double the upper limit of the normal range over time.

All participants in this study gave written informed consent to all necessary procedures.

Imaging of myocardial fatty acid metabolism

¹²³I-BMIPP myocardial SPECT was conducted after coronary angiography during the acute phase within 27 hours of onset (mean 18 ± 4 hours), during the subacute phase between 5 and 12 days after onset, and during the chronic phase one month after onset (Fig. 1). While fasting at rest, 111 MBq of BMIPP (Nihon Medi-Physics Co., Nishinomiya, Japan) was intravenously injected, then early and late images were obtained by SPECT starting 15 minutes and 3 hours after injection respectively, with a digital gamma camera 901A (Toshiba Co., Tokyo, Japan) to which a collimator exclusively for ¹²³I was attached. Data were collected from a 64 × 64 matrix in 32 directions, namely every 6° between a left posterior oblique angle of

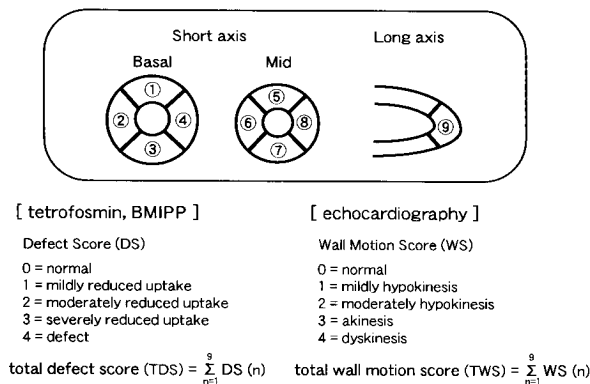


Fig. 2 Schematic representation of left ventricular segmentation. Left ventricle was divided into 9 segments on SPECT and on two-dimensional echocardiography: 1 and 5, anterior; 2 and 6, septal; 3 and 7, inferior; 4 and 8, lateral; 9, apical.

45° and a right anterior oblique angle of 45°, and for 30 seconds per direction. Data were entered into an on-line nuclear medicine data processor, GMS550U (Toshiba Co., Tokyo, Japan). The original image was reconstituted by smoothing at 5 points. Tomographic images along the vertical long, horizontal long and short axes were created with a Shepp & Logan filter. The threshold level was 20% and absorption was not corrected. The SPECT image of the left ventricle was divided into nine segments for semi-quantitative analysis. Short-axis slices were separated into four segments at the basal and midventricular levels. The apical portion of one segment was evaluated on vertical long-axis slices. Each segment was graded visually with scores between 0 and 4 (0, normal uptake; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; 4, defective) in a blinded manner by three experienced cardiologists. Differences of opinion were resolved by consensus. The sum of each score was defined as the total defect score, reflecting the severity of impaired myocardial fatty acid metabolism (Fig. 2).

With polar coordinate presentations of the early and late images, the wash-out rate (WR) (%) between 15 minutes and 3 hours after the intravenous injection of ^{123}I -BMIPP in the ischemic and non-ischemic regions was calculated with the following equation: $(\text{count at 15 minutes} - \text{count at 3 hours}) / (\text{count at 15 minutes}) \times 100$.

Imaging of myocardial blood flow

We conducted $^{99\text{m}}\text{Tc}$ -tetrofosmin myocardial SPECT⁸⁻¹⁰ immediately before coronary angiography during the acute phase, and during the subacute and chronic phases (Fig. 1). Images were obtained with a low energy, high-resolution, parallel-hole collimator 10 minutes after the patient received an intravenous injection of $^{99\text{m}}\text{Tc}$ -tetrofosmin (370 MBq) (Nihon Medi-Physics Co., Nishinomiya, Japan). The conditions were the same as those for ^{123}I -BMIPP, except that the time spent for imaging in one direction was changed to 20 seconds. The

SPECT image of the left ventricle was divided into 9 segments, and the degree of accumulation in each region was expressed according to 5 defect score (DS) grades as described above. The sum of each score was defined as TDS, reflecting the severity of impaired myocardial perfusion (Fig. 2).

Segments with defect scores of 1 to 4 on $^{99\text{m}}\text{Tc}$ -tetrofosmin images during the acute phase (mildly reduced to defective uptake) were regarded as ischemic. Those with scores of 0 (normal uptake) at the same time were regarded as non-ischemic.

Wall motion

Two-dimensional echocardiography was conducted on admission, during the subacute phase between 5 and 12 days after onset, and during the chronic phase one month after onset (Fig. 1). Patients were examined by two-dimensional echocardiography with a Sonos 5500 device (Hewlett-Packard, Cal, USA). The tomographic image of the left ventricle obtained from the short axial image of the sternal left edge and the long axial image of the apex of the heart was divided into 9 segments. Each segment was graded visually with scores between 0 and 4 (0, normal; 1, mild hypokinesis; 2, moderate hypokinesis; 3, akinesis; 4, dyskinesis) in a blinded manner by three experienced cardiologists. Differences of opinion were resolved by consensus. The sum of each score was defined as the total wall motion score (TWS), reflecting the severity of impaired left ventricular wall motion (Fig. 2).

Statistic analysis

Data are expressed as the means \pm standard deviation. The F test of ANOVA examined differences in mean values. The level of statistical significance was set at a probability (p) of 0.05.

RESULTS

The TWS values on two-dimensional echocardiography during the acute, subacute and chronic phases were 15.1 ± 5.3 , 3.5 ± 3.0 , and 1.0 ± 1.3 , respectively. The score was highest during the acute phase ($p < 0.001$) (Fig. 3).

The TDS values on tetrofosmin images during the acute, subacute and chronic phases were 14.4 ± 4.6 , 1.3 ± 1.3 and 0.8 ± 1.3 , respectively, and the score was highest during the acute phase ($p < 0.001$) (Fig. 4).

The TDS values on the early BMIPP images during the acute, subacute and chronic phases were 5.6 ± 1.8 , 13.4 ± 3.5 and 2.5 ± 1.1 , respectively, and the score was highest during the subacute phase ($p < 0.001$) (Fig. 4).

The TDS values on the late BMIPP images in the acute, subacute and chronic phases were 2.3 ± 1.7 , 18.3 ± 4.5 and 4.7 ± 2.6 , respectively, and the score was highest during the subacute phase ($p < 0.001$) (Fig. 4).

On early and late BMIPP images, the TDS value was high on the early image during the acute phase ($p < 0.05$),

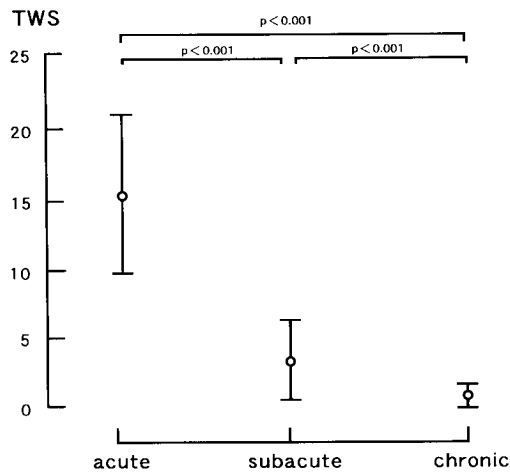


Fig. 3 Serial change of tetrofosmin and BMIPP images—case presentation. (A) Acute phase: Although myocardial ischemia was severe on tetrofosmin images, uptake was not reduced on early BMIPP images. Redistribution was observed in apex on late BMIPP images. The wash-out rate of BMIPP was reduced in the entire left ventricle. (B) Subacute phase: Although myocardial perfusion was normalized on tetrofosmin images, uptake was reduced on early BMIPP images. Redistribution was reversed in the anterior wall. The wash-out rate of BMIPP was remarkably increased on the entire left ventricle. (C) Chronic phase: Early and late BMIPP images and wash-out rate of BMIPP were normalized.

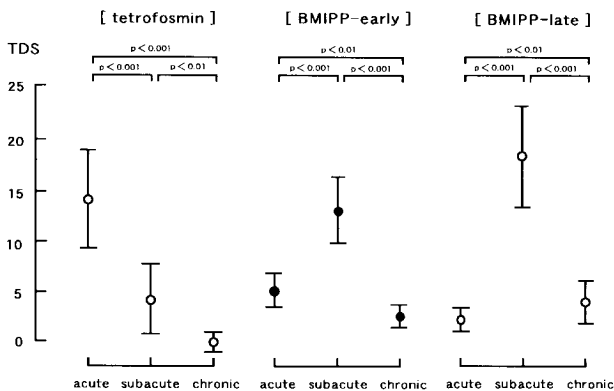


Fig. 4 Serial change of total wall motion score (TWS) on two-dimensional echocardiography. TWS values on two-dimensional echocardiography reflecting that severity of impaired left ventricular wall motion was highest during the acute phase.

and on the late image during the subacute phase ($p < 0.05$), but no differences were significant during the chronic phase.

The wash-out rates in the entire left ventricle (normal: $18.2 \pm 2.1\%$) during the acute, subacute and chronic phases were $12.1 \pm 4.8\%$, $44.9 \pm 10.0\%$ and $23.1 \pm 4.6\%$, respectively. The wash-out rates were $9.8 \pm 4.7\%$, $47.4 \pm 9.1\%$ and $24.7 \pm 5.0\%$ in the ischemic region, and $14.9 \pm 5.3\%$, $39.9 \pm 5.3\%$ and $21.0 \pm 5.1\%$ in the non-ischemic

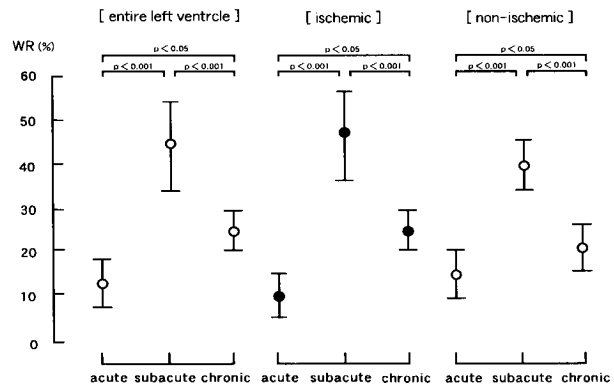


Fig. 5 Serial changes in total defect score (TDS) on tetrofosmin and BMIPP images. TDS values on tetrofosmin images reflecting severity of impaired myocardial perfusion were highest in the acute phase ($p < 0.001$). TDS values on early and late BMIPP images reflecting severity of impaired myocardial fatty acid metabolism were highest in the subacute phase ($p < 0.001$).

region, during the respective phases. In all regions, the value was lowest during the acute phase ($p < 0.05$), and highest during the subacute phase ($p < 0.001$) (Fig. 5).

CASE PRESENTATION

A 65-year-old woman consulted our hospital with a chief complaint of chest discomfort. Electrocardiography showed ST segment elevation in V_2 to V_6 leads. Although no stenotic lesion was revealed by coronary arteriography, ^{99m}Tc -tetrofosmin myocardial SPECT showed decreased accumulation in the area from the anterior wall and septum to the apex. Contraction was absent in the area from the anterior wall and septum to the apex on images of the left ventricle during the acute phase, but the condition normalized in the chronic phase. The early image during the acute phase revealed that BMIPP accumulation was slightly decreased at the apex, but not at any other site. On the late images, BMIPP was redistributed mainly at the apex. The wash-out rate was decreased in the entire left ventricle. On the early BMIPP image during the subacute phase, uptake was conspicuously decreased from the anterior wall and septum to the apex, and the wash-out rate was faster in the same area on the late image. The wash-out rate was accelerated over the entire left ventricle. The early and late images and the wash-out rate normalized during the chronic phase (Fig. 6).

DISCUSSION

Under aerobic conditions, cardiac muscle cells efficiently oxidize fatty acids to produce high levels of energy. Free fatty acids incorporated from the blood are acylated with ATP as an energy source and β -oxidized in mitochondria. Some fatty acids accumulate in the lipid pool and are

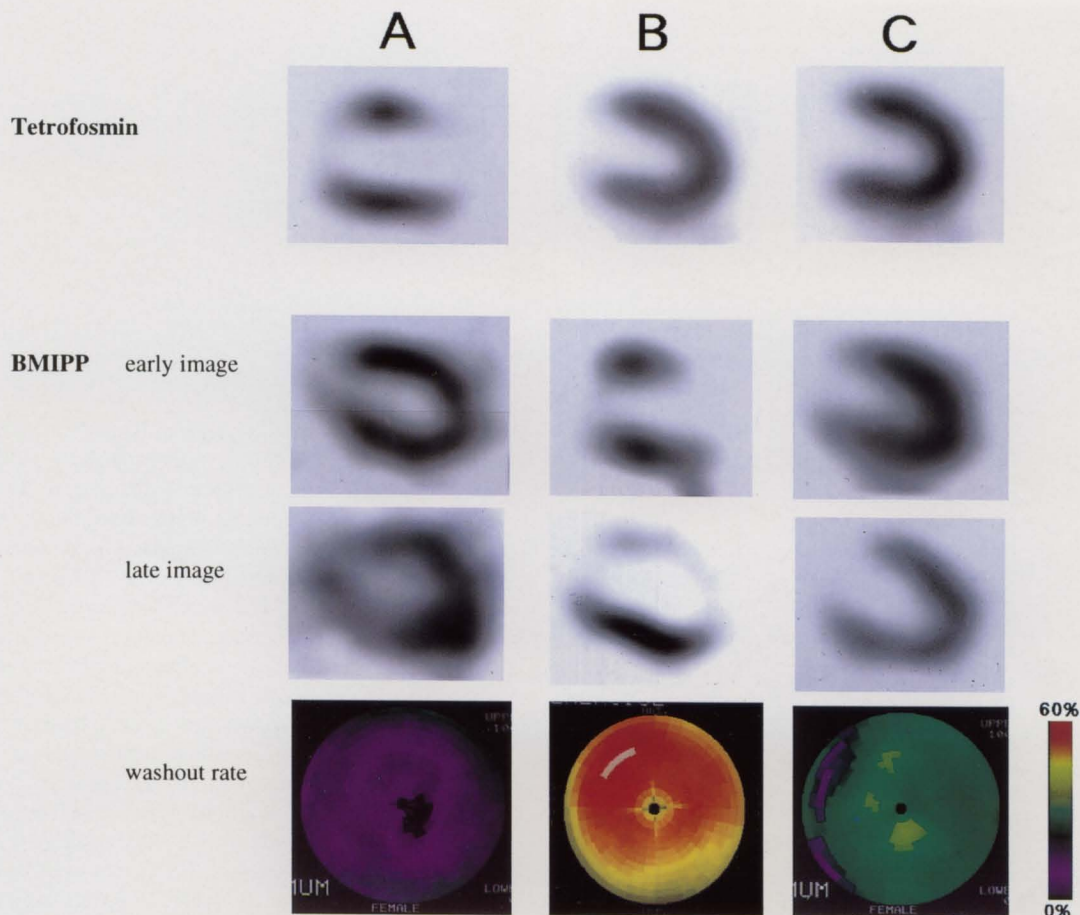


Fig. 6 Serial changes in the wash-out rates on BMIPP images in the entire left ventricle, ischemic regions and non-ischemic regions. Wash-out rates on BMIPP images (normal: $18.2 \pm 2.1\%$) were lowest and highest during acute and subacute phases, respectively, in the entire left ventricle, ischemic and non-ischemic regions.

again metabolized upon demand. When severe ischemia persists and cardiac muscle cells undergo necrosis, mitochondria and lipid pools are irrevocably destroyed. On the other hand, if ischemia is reversible, energy production in the mitochondria shifts from β -oxidation to glucose metabolism.¹¹⁻¹³ When cardiac muscle cells become ischemic, the blood catecholamine concentration increases and the degradation of fat tissues is accelerated throughout the body. Excess free fatty acids produced as a result may exert adverse effects on cardiac muscle cells, including the induction of fatal arrhythmias,^{14,15} decreased cardiac contractility^{16,17} and membranous dysfunction.^{18,19} To prevent these events, the lipid pool in cardiac muscle cells expands, and incorporates excess free fatty acids. Moreover, free fatty acids incorporated into the expanded lipid pool are retained in this pool without being metabolized or being washed away into the bloodstream.^{1,2,20,21} Animal experiments show that the extent of lipid pool expansion is about 2.5-fold higher in ischemic, than in non-ischemic regions,²⁰ and that this continues for several days even after recovery from ischemia.^{11-13,22} Myocar-

dial fatty acid metabolism during the acute phase of ischemia has been examined with BMIPP mainly in animal experiments.²³ Few reports have described changes in fatty acid metabolism during the acute phase of ischemia and after recovery from ischemia in the human myocardium,²⁴ and many issues remain unresolved. The present study examined the stunned human myocardium over time starting from the acute phase of ischemia with ¹²³I-BMIPP myocardial SPECT, and detected dynamic changes in myocardial fatty acid metabolism. The metabolism and kinetics of BMIPP in cardiac muscle cells are believed to be determined by the following factors (Fig. 7)^{22,25-29}: incorporation from the blood into cardiac muscle cells via CD36-positive fatty acid binding protein on the cardiac muscle cell membrane, back diffusion (early back diffusion) from inside cardiac muscle cells into the blood, which occurs immediately after incorporation, accumulation in the lipid pool (about 70%); metabolism into *p*-iodophenyl acetic acid (PIPA) via α - and β -oxidization in mitochondria and back diffusion from the lipid pool into the blood (late back diffusion).

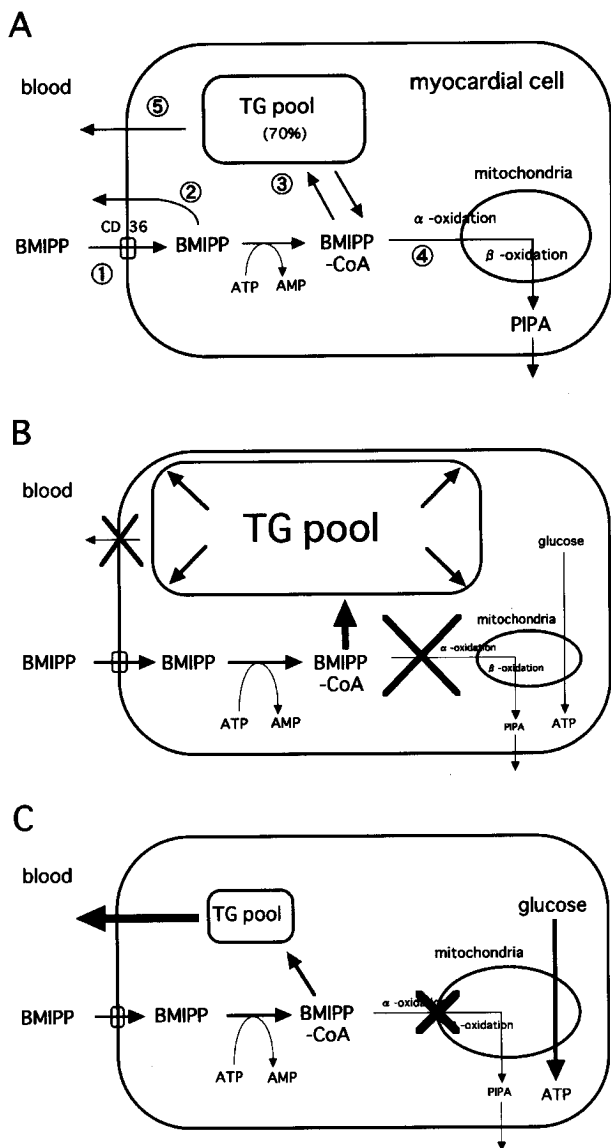


Fig. 7 Metabolism and kinetics of BMIPP in cardiac muscle cells. (A) Normal conditions: The metabolism and kinetics of BMIPP in cardiac muscle cells are believed to be determined by the following factors: incorporation from blood into cardiac muscle cells via CD36-positive fatty acid binding protein on cardiac muscle cell membrane; back diffusion (early back diffusion) from inside cardiac muscle cells into blood that occurs immediately after incorporation; accumulation in the lipid pool (about 70%); metabolism into *p*-iodophenyl acetic acid (PIPA) via α and β -oxidization in mitochondria and back diffusion from the lipid pool into blood (late back diffusion). (B) Acute phase: To prevent catecholamine induced myocardial damage after severe ischemia, the lipid pool is considered to respond by expanding, thus incorporating and retaining excess free fatty acids. The lipid pool contained BMIPP. The wash-out rate decreased, which can probably be explained by a decrease in turnover resulting from the need to retain incorporated BMIPP. (C) Subacute phase: Although wall motion abnormalities and tetrofosmin findings were improved during the subacute phase, BMIPP accumulation decreased. These findings suggested that fatty acid metabolism is suppressed, and that glucose metabolism supplies energy. Moreover, BMIPP wash-out was accelerated, probably because the lipid pool that had expanded during the acute phase was reduced during this period, and BMIPP was washed into the bloodstream.

In the present study the ST segment on ECG was elevated, accumulation on ^{99m}Tc -tetrofosmin myocardial SPECT was decreased and left ventricular wall motion abnormalities were significant during the acute phase. These findings suggest that energy production in mitochondria is decreased by ischemia. In other words, the source of energy in the myocardium is considered to have shifted from fatty acids to glucose, but BMIPP accumulation was not decreased on the early images despite the presence of ischemia and this may be explained by the following mechanism. Excess free fatty acids are produced in the blood as a result of catecholamine increase due to ischemia, and the lipid pool responds by expanding to absorb these free fatty acids. During late images of the acute phase, BMIPP was redistributed mainly in the ischemic region. The wash-out rates of 10% and 14% in the ischemic and non-ischemic regions, respectively, were both below the normal value adopted at our institution

(18%). The decreased wash-out rate may be explained by the suppression of fatty acid metabolism, or by suppressed wash-out from the lipid pool into the blood. The present study found significant wall motion abnormalities in the ischemic region during the acute phase, indicating that fatty acid metabolism is significantly suppressed in the mitochondria. Moreover, wash-out from the lipid pool into the bloodstream also appeared to have been suppressed, so that excess fatty acids, which are harmful to cardiac muscle cells, would be retained in the lipid pool. The present study found decreased wash-out rates in the non-ischemic region. Experiments on animal models of acute ischemia have also identified an expanded lipid pool and accelerated mitochondrial glucose metabolism in the non-ischemic region.¹¹ These findings suggest that wash-out from the lipid pool into the bloodstream decreases in the non-ischemic region to suppress responses such as expansion of the lipid pool, decreased fatty acid metabo-

lism and increased free fatty acid concentrations in the blood.

Early images showed decreased BMIPP accumulation during the subacute phase. This indicated that the lipid pool, which had expanded during the acute phase, had become smaller than normal and that fatty acid metabolism had decreased. Moreover, left ventricular wall motion was improved. This finding suggests that while fatty acid metabolism is suppressed, accelerated glucose metabolism may provide compensatory energy production. The decreased accumulation on early BMIPP images during the subacute phase closely corresponded with the findings of left ventricular wall motion abnormalities during the acute phase, and with those of ^{99m}Tc -tetrofosmin myocardial SPECT. The BMIPP images from this phase appear to provide the best memory of ischemic disorder during the acute phase.^{6,7,29,30} On late images of the ischemic region from the subacute phase, the wash-out rate was accelerated, and either increased mitochondrial fatty acid metabolism or increased back diffusion from the lipid pool into the bloodstream could account for this phenomenon. Judging from the findings on the early images, fatty acid metabolism remains suppressed during this period. Therefore, this phenomenon may be caused by accelerated wash-out from the lipid pool into the bloodstream. Since catecholamines were not secreted and the free fatty acid concentration was not increased during the subacute phase, excess fatty acid must have been washed out of the lipid pool.

In the meantime, the wash-out rate was also accelerated in the non-ischemic region. Since wall motion in this region did not significantly differ from that in the chronic phase, and animal experiments with palmitate have not revealed significant differences in lipid metabolism between the subacute and chronic phases in the non-ischemic region,¹¹ a mechanism involving accelerated lipid metabolism can be ruled out. Therefore, accelerated wash-out from the lipid pool into the bloodstream can increase the BMIPP wash-out rate.

The major findings of our study are as follows. First, early BMIPP images are thought to reflect the size of the lipid pool. Second, fatty acid metabolism in mitochondria and the degree of wash-out from the lipid pool into the bloodstream can be evaluated by comparing additional late and early images. Third, the myocardial viability in patients with stunned myocardium could be estimated with BMIPP images during the acute phase. Fourth, the area of myocardial ischemia during the acute phase could be assessed with BMIPP imaging during the subacute phase.

Since BMIPP in combination with FDG-PET and palmitate-PET allows the simultaneous evaluation of glucose metabolism and β -oxidization of fatty acids, changes in myocardial energy metabolism during ischemia and after recovery can be visualized more clearly. Acute coronary syndrome is treated mainly by reperfusion techniques

such as percutaneous transluminal coronary angioplasty, but our study revealed that myocardial metabolic disorders persist even after recovery from ischemia. Therefore, treatment from the viewpoint of myocardial energy metabolism appears to be necessary. At present, glucose, insulin, and potassium (GIK) regimens, as well as nicotinic acid therapy, are applied, but none is fully utilized in a clinical setting.^{31,32} More effective treatment methods are required that consider both myocardial blood flow and myocardial energy metabolism.

CONCLUSION

We concluded that fatty acid metabolism in the stunned human myocardium dynamically changes over time.

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