Original article

Discrepancy between myocardial perfusion and fatty acid metabolism following acute myocardial infarction for evaluating the dysfunctional viable myocardium

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KEYWORDS

Acute myocardial infarction
Fatty acid metabolism
Myocardial perfusion
Perfusion-metabolism mismatch
Single photon emission computed tomography

ABSTRACT

Objective: Following acute myocardial infarction (AMI) the area of myocardial perfusion and metabolism mismatch is designated as dysfunctional viable myocardium. ¹²³I-beta-methyl iodophenyl pentadecanoic acid (BMIPP) is clinically very useful for evaluating myocardial fatty acid metabolism, and ^{99m}Tc-Tetrofosmin (TF) is a widely used tracer for myocardial perfusion. This study was designed to evaluate the degree of discrepancy between BMIPP and TF at the subacute state of AMI. **Methods:** Fifty-two patients (aged 59 ± 10 years; mean 46 years) with AMI were enrolled, and all of them underwent percutaneous coronary intervention (PCI). Patients were classified according to ST-T change and PCI timing. ¹²³I-beta-methyl iodophenyl pentadecanoic acid and TF cardiac scintigraphy were performed on 7 ± 3.5 days of admission using a dual headed gamma camera. Perfusion and fatty acid metabolism defect were scored on a 17 segments model. **Results:** The mean BMIPP defect score on early and delayed images were 16.67 ± 10.19 and 16.25 ± 10.40, respectively. The mean TF defect score was 10 ± 7.69. Defect score of BMIPP was significantly higher than that of the TF ($P < 0.0001$; 95% CI 4.32–7.02), and there was a strong correlation between perfusion and metabolism defect score ($r = 0.89$, $P < 0.00001$). Forty-seven (90%) patients showed mismatched defect (BMIPP > TF), and 5 (10%) patients showed matched defect (BMIPP = TF). Mismatched defect score (MMDS) was significantly higher in patients with ST-segment elevation myocardial infarction (STEMI) than that of non-ST-segment elevation myocardial infarction (NSTEMI) ($P < 0.041$; 95% CI 0.11–5.19). **Conclusion:** At the subacute state of AMI, most of the patients showed perfusion-metabolism mismatch, which represents the dysfunctional viable myocardium, and patients with STEMI showed higher mismatch.

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Introduction

During the acute phase of myocardial infarction, the majority of myocyte loss in the infarct zone occurs via coagulation necrosis and proceeds to inflammation, phagocytosis of necrotic myocytes, and repair eventuating in scar formation.¹ As the extent of myocardial infarction is a major determinant of patient's care and rehabilitation with acute myocardial infarction (AMI) it is very important to differentiate dysfunctional viable segments 'stunned myocardium' from the infarcted

segments in the area of abnormal left ventricular function early after AMI.^{2,3}

Among several iodinated fatty acid tracers studied for SPECT, ¹²³I-15-(p-iodophenyl)-3-(R, S)-methylpentadecanoic acid (¹²³I-BMIPP) has been the most commonly used tracer in evaluating ischaemic heart disease, especially in Europe and Japan.⁴ Gated myocardial perfusion imaging with technetium labelled tetrofosmin (^{99m}Tc-TF) permits the assessment and quantification of various parameters of global and regional left ventricular (LV) function.⁵ A combined study of metabolic tracer with perfusion tracer is useful for assessing salvaged myocardium after revascularisation in patients with AMI.^{3,6–8}

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Previous studies remarked that following AMI, and after coronary reperfusion therapy, there is decreased ^{123}I -BMIPP uptake compared to ^{201}Tl uptake, this discordant BMIPP uptake may relate to stunned myocardium.^{6,9} Franken et al. also reported that mismatching of BMIPP and sestamibi uptake is predictive of long-term functional recovery following AMI.¹⁰ In contrast, segments with matched defects contain only scar tissue and absence of functional improvement, and it is noteworthy that combined BMIPP and sestamibi scintigraphy offers increased accuracy compared to dobutamine echocardiography. Thus, scoring of discordant BMIPP uptake may play a pivotal role in estimating salvaged myocardium early after coronary reperfusion therapy.

The purpose of this study was: (1) to evaluate the degree of impaired myocardial perfusion and fatty acid metabolism at the subacute state of AMI; (2) to assess the discrepancy between myocardial perfusion tracer (TF) and fatty acid metabolic tracer (BMIPP) in a view to assess the dysfunctional viable myocardium even after successful percutaneous coronary intervention (PCI).

Materials and methods

Patient population

This prospective and cross-sectional study was carried out in 52 consecutive patients (mean age 59 ± 10 years; mean 46 years) with first attack of AMI who got admission in this hospital between April 2007 and October 2008. The diagnosis of AMI was made on the basis of ≥ 2 of the following criteria: (1) typical chest pain lasting for >30 minutes; (2) typical ST-T change in at least two contiguous electrocardiographic (ECG) leads; and (3) raised cardiac biomarkers (troponin I and creatine kinase). Patients with old myocardial infarction, cardiogenic shock, severe congestive heart failure, conduction abnormalities, and valvular heart disease were excluded from this study.

Patient classification

According to the timing of PCI patients were classified as: (i) emergency PCI group, those who underwent PCI within 6 hours of attack and (ii) delayed PCI group, those who underwent PCI >6 hours of attack. Again on the basis of ST-T change they were divided into 2 groups: (i) patients with chest pain, ST-segment elevation on ECG, and elevation of troponin level were considered as ST-segment elevation myocardial infarction (STEMI); (ii) patients with ischaemic discomfort without ST-segment elevation on ECG but elevation of troponin level were considered as non-ST-segment elevation myocardial infarction (NSTEMI).

Study protocol

Both STEMI and NSTEMI patients were managed according to American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.^{11,12} All patients underwent PCI.

^{123}I -BMIPP and ^{99}mTc -TF cardiac scan were performed on 7 ± 3.5 days of admission. Cardiac biomarkers were checked serially and the peak level was recorded. Written and informed consent were taken from all patients and the study protocol was approved by the human research ethics committee of our institution.

Estimation of cardiac biomarkers

Venous blood was collected immediately after the patient arrived in the emergency department for the analysis of cardiac biomarkers. Cardiac troponin I (TP-I) was measured using chemiluminescent enzyme immuno assay (CLEIA), and creatine kinase-myocardial band (CK-MB) by enzyme immuno assay (EIA). The normal level of TP-I of our institute is <0.06 ng/mL and for CK-MB it is 0.6–3.5 ng/mL. The levels also checked serially while the patients were in the coronary care unit, and the peak concentration was recorded accordingly.

Coronary angiography and reperfusion

Selective coronary cine angiography was performed to ascertain the infarct-related coronary artery soon after admission. Patients with STEMI and NSTEMI with high-risk¹² patients arriving 6 hours after attack underwent emergency PCI. Experienced interventional cardiologists reviewed the angiograms without having any prior information about the study design. The anterior and septal segments were considered to be in the left anterior descending coronary artery distribution (LAD), the lateral segments in the left circumflex coronary artery distribution (LCx) and the inferior segments in the right coronary artery distribution (RCA). Coronary flow in the infarct-related artery before and after percutaneous intervention was graded according to the classification of the thrombolysis in myocardial infarction (TIMI) trial.¹³ Percutaneous coronary intervention was considered successful in the presence of TIMI-grade 3 coronary flow in the treated vessel, with a residual stenosis $<20\%$.¹⁴

Radiopharmaceuticals

^{123}I -BMIPP (Cardiodine; 111 MBq/0.03–0.01 mg) was purchased from Nihon Medi-Physics Co. Ltd. Japan. ^{99}mTc -TF was prepared using a kit vial of tetrofosmin (Myoview; Nihon Medi-Physics Co. Ltd., Japan) and freshly eluted ^{99}mTc -pertechnetate from ^{99}mTc generator system.

Imaging protocol

BMIPP and TF cardiac scintigraphy was performed at the same day using a dual headed SPECT gamma camera (ADAC, VERTEX-plus EPIC, USA) well-equipped with a low-energy general purpose (LEGP) collimator. After an overnight fast early imaging of BMIPP began 20 minutes after intravenous injection of 111 MBq of ^{123}I -BMIPP. Before SPECT data acquisition, an anterior chest planar image was acquired for 360 seconds in a 128×128 matrix. Immediately after planar imaging, 64 projection images were obtained in a 64×64 matrix for 55 seconds each, with 180° rotation and an energy window of 10% centred at 160 keV. Delayed planar imaging and SPECT imaging were performed 4 hours after the injection following the same acquisition mode.

After finishing BMIPP scan, standard electrocardiographically quantitative gated SPECT (QGS) of TF was performed on an RR interval divided into 16 frames per cardiac cycle. Images were taken 20 minutes after intravenous administration of 740 MBq of ^{99m}Tc -TF radiotracer. Planar images were taken for 120 seconds in a 128×128 matrix. Immediately after planar imaging, for SPECT images 64 projection images were obtained in a 64×64 matrix for 30 seconds each with an energy window of 10% centred at 140 keV.

A series of contiguous transaxial images of 5.12 mm thickness were reconstructed without attenuation correction by a filtered back-projection algorithm for BMIPP and TF studies. After preprocessing with a Butterworth filter (order, 5; cut-off frequency, 0.44 cycle/pixel), transaxial images were reconstructed with a ramp filter. Long and short axial slices were then produced by axial reorientation (SPECT imaging protocol, Figure 1).

Perfusion and metabolism defect score

Two experienced nuclear cardiologists independently interpreted the result unaware of the patient clinical information, and disagreements were resolved by consensus. Perfusion and metabolism defects in this study were graded in a 17 segments

model according to the quality assurance (QA) committee of the American Society of Nuclear Cardiology for semiquantitative visual analysis¹⁵ (Figures 2A and B). For interpretation of radiotracer defect in the LV anterior, inferior, septal, and lateral wall short axis slices were considered; for apical region vertical long axis slices were considered. ^{123}I BMIPP and ^{99m}Tc -TF uptake was scored in each segment using a visual five-grade scale: 0, normal; 1, mildly decreased uptake; 2, moderately decreased uptake; 3, severely decreased uptake; and 4, complete defect. When BMIPP defect score was higher than that of the TF defect score, it was considered as mismatched defect, and when BMIPP defect score was similar to the TF defect score it was considered as matched defect.

Statistical analysis

Statistical analysis was performed using the statistical package for social science (SPSS) (Version 12 for windows; Chicago, USA). Continuous variables were expressed as the mean $\pm$ SD. To find out significant intergroup differences Student's unpaired *t* test was used and paired *t* test was applied for detecting significant differences of variables in a certain group. Correlations between continuous variables were assessed using linear regression analysis. A *P* < 0.05 was considered statistically significant.

Figure 1 SPECT imaging protocol. About 20 minutes and 4 hour after intravenous (i.v.) administration of BMIPP, initial and delayed images were taken, respectively. Quantitative gated SPECT was performed 20 minutes after i.v. administration of TF. BMIPP: ^{123}I -beta-methyl iodophenyl pentadecanoic acid, TF: ^{99m}Tc -Tetrofosmin.

Results

The clinical information of the patients with AMI have been summarised in the Table 1. Out of 52 patients 46 (88%) were males, and the mean $\pm$ SD age of the patients was 59 ± 10 years. Twenty-five patients (48%) had inferior, 14 (35%) had anterior, and rest 6 (17%) had lateral myocardial infarction. Among the patients, 27 (52%) had STEMI, and rest 25 (48%) NSTEMI. Out of 27 STEMI patients 23 (85%) and out of 25 NSTEMI patients 10 (40%) underwent emergency PCI. Subsequently, 33 (64%) patients underwent emergency PCI and the rest 19 underwent delayed PCI. Forty (77%) patients received stent during PCI, rest of the patients received peripercutaneous balloon angioplasty (POBA) or combination of both.

Figure 2 Left ventricular segmentation. (A) Diagrammatic representation of a circumferential polar plot of 17 segmental model of the LV for perfusion and metabolism defect scoring (modified from American Society of Nuclear Cardiology (ASNC) recommendations¹⁵): 1, basal anterior; 2, basal anteroseptal; 3, basal inferoseptal; 4, basal inferior; 5, basal inferolateral; 6, basal anterolateral; 7, mid anterior; 8, mid anteroseptal; 9, mid inferoseptal; 10, mid inferior; 11, mid inferolateral; 12, mid anterolateral; 13, apical anterior; 14, apical septal; 15, apical inferior; 16, apical lateral; 17, apex. (B) Myocardial slices according to coronary artery territories (modified from ASNC recommendations¹⁵): assignment of the 17 myocardial segments to the territories of the left anterior descending (LAD), right coronary artery (RCA), and the left circumflex coronary artery (LCx).

Table 1

Baseline patients' characteristics (n=52).

Age (yr±SD)	59±10
Gender (M:F)	46:6
BMI (kg/m ²)	24.26±3.5
Risk factors	
Smoking	31 (60%)
Diabetes	15 (29%)
Hypertension	25 (48%)
Hyperlipidaemia	13 (25%)
ST elevation AMI	27 (52%)
Biomarkers	
Peak TP-I (ng/mL)	76±94
Peak CK-MB (ng/mL)	210±219
Myocardial infarct-related coronary artery	
RCA	25 (48%)
LAD	14 (35%)
LCx	6 (17%)
Time to cardiac scintigraphy (d)	7±3.5
Emergency PCI (≤6 hr of AMI)	33 (64%)
TIMI flow grade 3 after PCI	50 (96%)

AMI: acute myocardial infarction, BMI: body mass index, CK-MB: creatine kinase-myocardial band, LAD: left anterior descending, LCx: left circumflex, PCI: percutaneous coronary intervention, RCA: right coronary artery, SD: standard deviation, TIMI: thrombolysis in myocardial infarction, TP-I: troponin-I.

The PCI was successful (TIMI-grade 3) in 50 (96%) patients, and no patients had major cardiac events or fatal outcome during the procedure and first 1 week in the hospital.

Cardiac scintigraphy findings

The mean BMIPP defect score on early and delayed images were 15.67 ± 10.19 and 16.25 ± 10.40 , respectively, but the difference was not significant ($P=0.20$; 95% CI -1.47 to 0.32). The mean TF defect score was 10 ± 7.69 . Defect score of BMIPP (early) was significantly higher (16 ± 10) than that of the TF defect score (10 ± 8) ($P<0.0001$; 95% CI $4.32-7.02$), and there was a significant positive correlation between the BMIPP defect score and TF defect score ($r=0.89$, $P<0.00001$) (Figure 3). Heart to mediastinum ratio (H/M) of BMIPP on early and delayed planar images were 2.30 ± 0.25 and 2.03 ± 0.22 , respectively, and the overall washout rate retrieved from the polar map of BMIPP images was 21 ± 7.34 .

Out of the 52 patients, 47 (90%) had mismatched defect, and only 5 (10%) patients had matched defect. The mismatch defect score (MMDS) was 5.78 ± 4.7 considering BMIPP early images. Considering the subgroups: MMDS was significantly higher in patients with STEMI than that in patients with NSTEMI (7.77 ± 4.49 vs 4.81 ± 4.86 ; $P<0.053$; 95% CI -0.04 to 6.32); MMDS was higher in emergency PCI group than that of delayed PCI but did not show significant difference (7.77 ± 5.26 vs 3.83 ± 2.51 ; $P=0.07$; 95% CI -0.28 to 6.35). Additional information we got from the gated SPECT: ejection fraction (EF%), end diastolic volume (EDV), and end systolic volume (ESV) were $60 \pm 12\%$, 94 ± 23 mL, and 39 ± 17 mL, respectively.

Figure 3 Linear regression analysis of BMIPP and TF defect score. Plots of linear regression analysis between the BMIPP defect score and TF defect score, showing a strong positive correlation between them. BMIPP: ¹²³I-beta-methyl iodophenyl pentadecanoic acid, TF: ^{99m}Tc-Tetrofosmin.

The SPECT images of one representative case of our study is presented in Figure 4.

Discussion

We noticed some important findings in this study that was carried out at the subacute state (day 7±3 days) of myocardial infarction. The present study demonstrated that most of the patients (90%) revealed discrepancy between myocardial perfusion and fatty acid metabolism which is designated as dysfunctional viable myocardium “stunning” following acute myocardial infarction. The rest 10% patients showed perfusion-metabolism matched defect which denoted the non-viable area. The area of perfusion-metabolism mismatch was significantly higher in patients with STEMI than that of NSTEMI. As the stunned myocardium is important indeed for future cardiac events, for better risk stratification this combined cardiac scintigraphy findings would be very informative for watchful waiting for a cardiologist.

Kinetics of ¹²³I-beta-methyl iodophenyl pentadecanoic acid

The precise uptake mechanism of BMIPP is still unclear. It is distributed in the myocardium according to regional blood flow and subsequently incorporated into the endogenous lipid pool in the myocardium.^{16,17} Free fatty acid (FFA) is a major myocardial energy source involving β -oxidation after the tri-carboxylic acid cycle in the basal oxygen state. The BMIPP is a methyl-branched fatty acid analogue—designed to resist β -oxidation.¹⁸ Most injected BMIPP is transported into myocytes, followed by adenosine triphosphate (ATP) dependent activation to coenzyme A; subsequently, substantial quantities of BMIPP are esterified and retained in the triglyceride pool.^{19,20} Therefore, the myocardial BMIPP image is related

Figure 4 Representative case: SPECT images of BMIPP and TF. BMIPP-TF mismatched defect score in a patient with STEMI: SPECT images of BMIPP and TF cardiac scintigraphy showing defect in the anteroseptal and apical wall. Upper row showing the early images, middle row showing the delayed images of BMIPP, and the lower row showing the TF images. BMIPP defect score on early and delayed images were 22 and 24, respectively, and TF defect score was 12. BMIPP: ^{123}I -beta-methyl iodophenyl pentadecanoic acid, HLA: horizontal long axis, TF: $^{99\text{m}}\text{Tc}$ -Tetrofosmin, VLA: vertical long axis.

predominantly to the triglyceride pool. Ischaemic insult is known to increase the size of the triglyceride pool, and elevated BMIPP uptake observed just after AMI should be a reflection of increased capacity of the triglyceride pool.^{21,22}

Under aerobic condition 60–90% of myocardial energy metabolism is provided by the fatty acids which require a large amount of oxygen. Conversely under ischaemic state, fatty acid metabolism is replaced by glucose metabolism with less oxygen consumption.²³ ^{123}I -labelled 15-(*p*-iodophenyl)-3-*R*, *S*-methyl pentadecanoic acid (^{123}I -BMIPP) can demonstrate myocardial fatty acid metabolism and clinically very useful to evaluate myocardial infarction, angina pectoris and their prognosis.^{23,24} In ischaemic state blood catecholamine concentration increases and the degradation of fat tissues are accelerated throughout the body. Excess FFA produced in this way may exert adverse effects on cardiac muscle cells, including the induction of fatal arrhythmias, decreased cardiac contractility, and membranous dysfunction.^{25,26} To prevent these events, the lipid pool in cardiac muscle cells expands, and incorporates excess free fatty acids.^{27,28}

Among various clinical, angiographic, and radionuclide indices, discrepant BMIPP uptake was the best predictor of future cardiac events.²⁹ It has been shown that the additional information provided by BMIPP substantially increases the accuracy of perfusion tracer uptake alone or dobutamine echocardiography alone to predict functional outcome early after AMI.³⁰ Recently, Higuchi et al.³¹ in an animal experiment noticed that BMIPP uptake was higher than ^{201}Tl uptake in the acute phase (20 minutes and 1 day), lower than ^{201}Tl during the subacute phase (7 day), and BMIPP uptake was similar to ^{201}Tl uptake in the chronic phase (30 day) of acute ischaemia followed by reperfusion. The present study also demonstrated the perfusion and metabolism mismatch (BMIPP uptake lower

than TF) on cardiac scintigraphy at 7 ± 3.5 days following acute MI even after establishment of reperfusion. There was a strong correlation between the BMIPP and TF defect score, and BMIPP defect score was characteristically higher than that of the TF defect score (Figure 4).

One important thing is that we were intended to know the perfusion-metabolism mismatch at the subacute state (7 ± 3.5 days) of AMI. Because Tanaka et al.³² suggested that a 7 day interval should be placed between reperfusion therapy and $^{99\text{m}}\text{Tc}$ -TF SPECT to evaluate a salvage effect (i.e. SPECT imaging immediately after reperfusion therapy underestimates the salvaged area) and that TF delayed images and BMIPP images were both useful in estimating the risk area. Moreover, we classified the patients according to ST-T change on ECG, and according to PCI timing. We noticed that MMDS was significantly higher in patients with STEMI than that of NSTEMI, and MMDS was higher in patients underwent emergency PCI than that of delayed PCI though the difference not significant. This is for the first time we observed such findings; further study is needed to explore the possible mechanism.

We took the delayed images of BMIPP, because delayed image is important for calculating the washout rate as in this study it was higher (21 ± 7.34) than the reference normal value ($18.2 \pm 2.1\%$),²³ and very much justified following AMI. Akashi et al.³³ very recently suggested that the wide receiver (WR) accelerates in patients with chronic heart failure and stable angina. Hence, WR reflects the degree of cardiac damage. That data strongly suggested that the delayed H/M ratio and myocardial WR of ^{123}I -BMIPP enhances the assessment of impaired myocardial fatty acid metabolism in patients with heart disease in both masked and unmasked conditions.

Although the exact pathophysiology of dysfunctional but viable myocardium 'myocardial stunning' is still unclear and

remains controversial the potential for functional recovery has clinical relevance. It is well established that ischaemically compromised myocardium is associated with severe impairment of contractile function and heart failure. However, in contrast to infarct-related or scar tissue, dysfunctioning but viable myocardium has the potential to regain contractile function.^{34,35}

Among various clinical, angiographic, and radionuclide indices, discrepant BMIPP uptake was the best predictor of future cardiac events in patients with myocardial infarction.³³ Another study on the multicentre trials showed that BMIPP defect score was the most powerful index for predicting future cardiac events among various clinical and radionuclide parameters.²⁴

Limitations

The BMIPP and TF defect was scored by quantitative visual estimation, so there might be some subjective error. The other important limitation is the small number of patients which might influence the statistical result to make a difference for MMDS between 2 groups of patients (depending on ECG change and PCI timing).

Conclusion

Fatty acid metabolism defect score was significantly higher than the perfusion defects score in 90% of the studied patients at the subacute state of AMI even after successful PCI. The MMDS was significantly higher in patients with STEMI than that of patients with NSTEMI. We could speculate that for the evaluation of viable dysfunctional myocardium which is potentially related to the functional recovery or adverse cardiac events, ¹²³I-BMIPP and ^{99m}Tc-TF combined cardiac scintigraphy might be very important for risk stratification and patient management.

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Conflict of interest

None.

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