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# Metabolic imaging using SPECT

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**Abstract**

In normal condition, the heart obtains more than two-thirds of the energy from oxidative metabolism of the long chain fatty acids, although a wide variety of substrates such as glucose, lactate, keton bodies and aminoacids are also utilized. In ischemic myocardium, on the other hand, oxidative metabolism of free fatty acid is suppressed and anaerobic glucose metabolism play a major role for residual oxidative metabolism. Therefore, metabolic imaging can be an important technique for the assessment of various cardiac diseases and conditions. In SPECT, up to the present, several iodinated fatty acid traces have been introduced and studied. Of these, I-123 labeled 15-(p-iodophenyl)3R, S-methylpentadecanoic acid (BMIPP) has been the most commonly used tracers in clinical studies, especially in some of the European countries and Japan. In this review article the

characterization of the several fatty acid tracers for SPECT are described and basic and clinical utility of BMIPP are further discussed.

## Introduction

The cardiac muscle metabolizes a variety of substrates by selecting appropriate ones available in the particular myocardial condition. In normal condition, fatty acids and glucose are the most preferred substrate for energy production, followed by lactate, amino acids, keton bodies. Approximately two-thirds or more of the total energy produced by myocardium is derived from fatty acid oxidation and the most of the remaining energy is covered by the glucose metabolism. Both fatty acid and glucose are catabolized to acetyl-COA through beta-oxidation and glycolysis and the metabolite is oxidized in the tricarboxylic acid (TCA) cycle. In various pathological conditions the myocardial metabolism can be changed significantly, for instance, in ischemia, oxidative metabolism of free fatty acid is decreased because ß-oxidation of fatty acid in mitochondria requires a large amount of oxygen, and glucose becomes the preferred substrate for anaerobic glycolysis that requires less oxygen consumption [1, 2]. Therefore, imaging tracers that permit direct assessment of myocardial metabolism are desired to evaluate the pathophysiological changes in various heart disease. Current available tracers for metabolic imaging are several fatty acid tracers, $^{18}$F-FDG for the evaluation of glucose metabolism, and $^{11}$C-acetate for the assessment of oxygen consumption. Of these tracers, only $^{123}$I-labeled fatty acid tracers are currently available for SPECT imaging.

## Myocardial fatty acid uptake and metabolism

Due to hydrophobic nature of fatty acids, they are delivered to the heart by binding to plasma albumin or lipoproteins. After dissociating from albumin or lipoprotein, fatty acids can pass through the sarcolemmal membrane by diffusion or a facilitated transport mechanism. In the past it has been proposed and believed that passive diffusion account for the uptake

mechanism. However, absent uptake of BMIPP in a small minority of patients even without significant cardiac abnormality raised the question about the mechanism of fatty acid transport into the cells [3, 4]. It has been proved that the patients with deficient myocardial uptake of BMIPP correspond to the patients with type I CD36 deficiency (neither platelets nor monocytes expresse CD36) [5-7], and biopsy specimen from the patients with absent myocardial BMIPP uptake and type I CD36 deficiency demonstrated no expression of CD36 on the myocardial capillary endothelial cells [8]. PET study demonstrated that the patients without BMIPP cardiac uptake showed compensatory increased FDG uptake [9, 10]. Furthermore, the absent myocardial BMIPP uptake is hereditable [3] and several gene abnormalities related to CD36 deficiency have been reported [11, 12]. Based on these clinical data and other animal experiments, it has been proved that CD36 plays a crucial role in fatty acid transport into the cells [13]. Intracellularly, fatty acids are activated as acyl-CoAs and are consequently trapped inside the cell. This process requires one molecule of adenosine-5'-triphosphate (ATP) for each fatty acid. Then the acyl-CoAs are taken up by mithochondria via an acyl carnitine carrier system and is rapidly catabolized by ß-oxidation into 2-carbon fragments, acetyl-CoAs, which enter the TCA cycle for further oxidation to become water and carbon dioxide. The half-life of ß-oxidation is fast and in the order of minutes but is dependent on the adequate oxygen availability. The remaining part of the total fatty acid entering the myocyte is incorporated into the lipid pool, mainly in the form of triglycerides and phospholipids, or into myocardial structural lipids and presents in the myocardium for a long time. Turnover in the lipid pool is much slower with the half-life of the order of hours.

**Development of iodinated fatty acid compounds for SPECT** (Table. 1)

In mid 1970's, several iodinated long chain fatty acids were developed by introducing radioiodine to the terminal position of fatty acids without altering extraction efficiency compared with the natural compound [14-16]. These straight chain fatty acids, $^{123}$I-hexadecanoic acid (IHXA) and $^{123}$I

-heptadecanoic acid (IHDA) were proved to be an indicator of myocardial perfusion in canine model and human [15, 16]. After rapid initial myocardial extraction these traces showed biexponential clearance (rapid and slow components) similar to that of $^{11}$C-palmitate. It was generally thought that the rapid and slow components of clearances represented ß-oxidation of fatty acids and fatty acids storage in lipid pool, respectively. However, their ability to assess myocardial metabolism has been questioned. A canine study revealed that myocardial counts peaked at 5 min after $^{131}$I-IHDA infusion to the left atrium followed by decrease with a half life of 36 min, although, the myocardial activity of radiolabeled fatty acids remained constant after an initial increase, indicating that washout rate of radioactivity from the heart is determined by the back diffusion of deiodinated free iodine not by ß-oxidation [17]. A clinical study using IHDA demonstrated high quality image early after injection, but the image quality deteriorated rapidly because of rapid reduction of myocardial counts and increase in background counts by deiodinated radioiodine [18]. Accordingly, these characteristics of the tracers make IHDA and IHXA unattractive for clinical use, especially for SPECT study. To overcome the problem of these alkyl fatty acids, including release of free iodine resulting in a rapid loss of image quality and poor dependency of elimination rate on ß-oxidation, the phenyl fatty acid was developed by attaching iodide to the para position of phenyl ring (IPPA) [19]. Because this agent demonstrated high myocardial uptake and no essential release of free radioiodide into circulation, the image quality was excellent. Animal experiment demonstrated that the IPPA accumulated rapidly to myocardium followed by a two-component tracer clearance similar to $^{14}$C-palmitate, permitting estimation of metabolic rate [20]. The uptake of IPPA during exercise was related to myocardial perfusion and its catabolism follows the usual metabolic pathway for ß-oxidation [21]. Through ß-oxidation IPPA is metabolized to iodobenzoic acid and its metabolite iodohippurate and these are rapidly excreted from the kidneys with the iodine still attached, resulting in high image quality with low background by preventing the buildup of free radioiodide [22]. Coronary occlusion and

reperfusion blunted the uptake of IPPA and prolonged the clearance, but permanent coronary occlusion decreased the uptake significantly and accelerated the clearance, indicating that the IPPA can be used to localize the area of myocardial ischemia and infarction [23]. For routine clinical use, however, the rate of metabolism and clearance of IPPA is still relatively fast for SPECT imaging, even in multiple detector SPECT system. For initial IPPA uptake imaging, acquisition time should be shortened to prevent progressive undersampling due to rapid count decrease from the myocardium, resulting in the deterioration of image quality, and dynamic SPECT study may be necessary for kinetic analysis of ß-oxidation. Accordingly, a new fatty acid tracer with more prolonged cardiac retention has been developed to improve quantitative image quality. For this purpose methyl branching was introduced at ß-carbon position to slow myocardial clearance by inhibiting ß-oxidation, and 2 forms of iodine labeled modified fatty acids, 15-p-iodophenyl-3(RS)-methylpentadecanoic acid (BMIPP) and 15-p-iodophenyl)-3,3-dimethylpentadecanoic acid (DMIPP), has been developed [24, 25]. In fasted rats, myocardial half-time value of BMIPP and DMIPP greatly increased to 30-45 min and 6-7 hr, respectively, compared with that of IPPA (5-10 min) [25]. In human, DMIPP showed higher liver uptake than that of BMIPP (heart/liver ratio was $0.39 \pm 0.05$ and $1.00 \pm 0.12$, respectively: $p<0.001$), suggesting that BMIPP is more favorable cardiac SPECT agent [26]. Eventually BMIPP has been widely used to investigate the clinical significance as well as basic properties, especially in Japan and some European countries. Another alternative of branched fatty acid analogue is a 15-p-iodophenyl-9(RS)-methylpentadecanoic acid (9MPA) [27]. This tracer had been designed to be cleared from myocardium at medium rate by introducing a methyl branch at 9th-carbon position, permitting conversion of 9MPA to iodophenyl-3-methyl-nonanoic acid (3MNA) after 3 cycles of ß-oxidation, and this water soluble intermediate metabolite, 3MNA, is rapidly cleared from the myocardium. Clinical trail of this tracer was performed in Japan and abnormal uptake of this tracer was well described in patients with chronic ischemic heart disease and acute

coronary syndrome [28-30]. Ability of identifying ischemic region by 9MPA is comparative or even better than that by BMIPP [30], however unfortunately, this agent was not approved for health care service provided by health insurance.

## $^{123}$I-BMIPP

*Basic characteristics of the tracer and mechanism of discordant BMIPP uptake less than perfusion tracers:*

Among the various radio-labeled fatty acids, BMIPP has been studied extensively in clinical settings as well as in animal experiments. This compound is designed for SPECT imaging, which requires long myocardial retention of the tracer for good image quality as described previously. Clinical importance of fatty acid imaging depends on whether incremental information over perfusion tracers can be obtained or not. Accumulated clinical experience of BMIPP imaging has demonstrated that discordant BMIPP uptake less than perfusion tracers are often observed in various heart diseases especially in ischemic heart disease, and this finding may provide a key issue for assessing the pathophysiology of the heart condition. Therefore, comparison of BMIPP uptake with that of the perfusion tracers is cardinal for the interpretation and exploring the clinical utility of BMIPP as a metabolic tracer.

Initial myocardial BMIPP uptake depends on regional perfusion and is transported into myocardial cells via fatty acid translocase/ CD36 involvement [5, 6, 8, 11-13], followed by a rapid incorporation into triglycerides through the enzymatic conversion to BMIPP-CoA [25, 31]. Canine study revealed that BMIPP first pass extraction is rather high and 74% of BMIPP is extracted from plasma into the myocardium within 30 sec of intracoronary BMIPP infusion, followed by a small fraction of washout (8.7% of infused BMIPP) for the next 30 min [32]. The washed out radioactive metabolites consist of backdiffused BMIPP (24% of all washed out radioactivity), α oxidation metabolite (27%), intermediate metabolites (33%), and full metabolite (16%), suggesting only small amount of

BMIPP-CoA transported into mitochondria is metabolized by α oxidation (because first ß oxidation is blocked by ß-methyl branching), followed by ß oxidation. The high uptake and low washout of the tracer indicates that BMIPP can be substantially considered as a metabolically trapped tracer like FDG. Early washout from the myocardium may reflect back diffusion of non metabolized BMIPP. Severe ischemia with 30min coronary occlusion and reperfusion increased early back diffusion of nonmetabolized BMIPP from 25.1% to 34.7%, and in mild ischemia (10 min occlusion) back diffusion of BMIPP was closely correlated with lactate production (marker of ischemic severity) [33]. Etomoxir, one of the carnitine palmotoyltransferase I inhibitor and inhibits the transport of long chain lipids into the mitochondria, enhanced early washout (until 8 min after injection) of radioactivity due to increased back diffusion of BMIPP (25.1% to 41.9%) [34]. These authors speculate that this early 8 min washout period in dogs might correspond to usual SPECT initiation time in human (around 15 to 20 min after injection of BMIPP). If so, clinical BMIPP SPECT image represents the BMIPP retention status after the completion of the non metabolized BMIPP back diffusion. In the first step of the common pathway of fatty acid metabolism BMIPP also converted to BMIPP-CoA by consuming ATP and once BMIPP-CoA is synthesized, it is hard to back out of the cell [35, 36]. Therefore, ATP level of the cells may relate to the amount of BMIPP back diffusion, in other word, BMIPP myocardial retention. BMIPP uptake correlated with the ATP level in mouse myocardium treated with an electron transport uncoupler, dinitrophenol, which reduced intracellular ATP level without affecting acyl-CoA synthetase activity or Coenzyme-A level [37]. In acutely damaged canine myocardium introduced by coronary occlusion and reperfusion, BMIPP uptake also correlated with the tissue ATP levels [38].

In a clinical study with dynamic SPECT demonstrated that the BMIPP washout was observed early after BMIPP injection (2-6 min after injection) in the segments with reversible thallium defects but not in the segments with normal thallium uptake and fixed thallium defects [39]. In addition, early dynamic BMIPP SPECT images in acute coronary syndrome showed similar

BMIPP uptake with thallium in spite of the discordant BMIPP uptake less than thallium in usual 30 min BMIPP images [40]. These clinical and animal experimental findings suggest that, in ischemic myocardium, initial myocardial distribution of BMIPP may represent blood flow, followed by a back diffusion of free BMIPP which is not incorporated into triglyceride pool after conversion to BMIPP-CoA, resulting in discordant BMIPP uptake less than thallium on the static images obtained 20-30 min after BMIPP injection.

On the contrary, during acute phase of ischemia, reduced availability of oxygen suppresses ß-oxidation and increases the proportion of fatty acid in the triglyceride pool. At this moment BMIPP may enter into this enlarged triglyceride pool. Accordingly, BMIPP uptake may possibly be increased in acute ischemia [41, 42]. In early canine experiments with occlusion and reperfusion model showed higher BMIPP uptake than thallium (reverse mismatch) which is an opposite finding observed in clinical studies [41, 43]. BMIPP injection after 15 or 60 min coronary occlusion and 3 hr reperfusion demonstrated that BMIPP uptake in TTC-positive areas was 27% higher than in TTC-negative areas and 9 % higher than in normal area after the normalization by perfusion, suggesting that greater BMIPP uptake than perfusion at acute phase of post-ischemia are characteristic of ischemically stunned but viable myocardium [41]. However, BMIPP uptake may change as a function of time after ischemia. A recent rat study with 20 min coronary occlusion and reperfusion demonstrated that BMIPP uptake was higher than thallium at 1 day after reperfusion but, at 5 day after reperfusion, BMIPP was similar to or lower than thallium uptake [44]. In addition, another rat study with 20 min coronary occlusion and reperfusion revealed that BMIPP uptake was higher than thallium at 20 min and 1 day after reperfusion, followed by similar uptake at 3 days after reperfusion and significant reduction of BMIPP uptake than thallium at 7 days after reperfusion, though, BMIPP uptake recovered to normal level at 30 days after reperfusion [45]. Furthermore, clinical study in patients with stunned myocardium showed BMIPP uptake reduction in area at risk was minimal within 27 hr of onset followed by

significant reduction at 5 to 12 days later, but normalized at 1 month later [46]. These findings indicate that BMIPP imaging may offer metabolic information independent of perfusion at different stages of ischemic insults after ischemia. Usual mismatch, discordant BMIPP uptake less than perfusion tracers, seen in clinical study may reflect the myocardial alteration of subacute phase of ischemia or cumulative or chromic ischemic status. Although most of the discrepant uptake of BMIPP and perfusion tracers in daily clinical practice is less BMIPP uptake than perfusion tracers, less perfusion tracer uptake than BMIPP (reverse mismatch) can be observed occasionally. In normal subjects % uptake of BMIPP is higher than thallium in septum to inferior wall [47] and most of the reverse mismatch is observed in inferior septum to inferior wall in patients with coronary artery disease [48-50], suggesting that reverse mismatch in these area might be generated by the greater photon attenuation of thallium than $^{123}$I. Such artifact might be reduced by using $^{99m}$Tc labeled perfusion tracers instead of thallium and the effectiveness of scatter correction for accurate comparison of BMIPP and $^{99m}$Tc-MIBI is proposed [51].

## Clinical Utility of $^{123}$I-BMIPP imaging

*Acute myocardial infarction*

In patients with coronary artery disease, discrepant uptake between BMIPP and thallium has been reported initially in patients with acute myocardial infarction. Tamaki et al. found discordant BMIPP uptake less than thallium in 17 of 28 patients with myocardial infarction. Such discordant BMIPP uptake was observed more often in areas of acute than chronic myocardial infarction (59% at <4 week versus 31% at >4 week after onset), and more often in areas supplied with revascularized than non-revascularized arteries (74% versus 28%, respectively). In addition, regional wall motion was more severely impaired in such perfusion-metabolic mismatching area [50]. In comparison between BMIPP and $^{99m}$Tc-MIBI 4 to 10 days after coronary thrombolysis demonstrated that the segments with more reduced BMIPP uptake than MIBI uptake

(mismatching) showed either normal wall motion or demonstrated inotropic reserve during dobutamine stimulation [52]. These findings suggested that mismatching is indicative of jeopardized but viable myocardium and may correspond to stunned myocardium where functional abnormality is prolonged in association with sustained metabolic abnormalities (metabolically stunned myocardium) after perfusion recovery by successful reperfusion procedures (Fig. 1). Several studies have supported this concept, that is, areas of discordant BMIPP uptake less than perfusion tracers in acute or subacute stages of myocardial infarction demonstrated improvement of wall motion abnormality on the subsequent follow-up periods [53-60]. These studies also indicated that mismatched BMIPP uptake less than perfusion tracers may be a predictor of functional recovery in acute myocardial infarction. For the evaluation of area at risk in acute myocardial infarction, reduction of BMIPP uptake is also shown to be useful. BMIPP defect size in subacute phase of myocardial infarction correlated well with the risk area revealed by contrast ventriculography or echocardiography [56, 61], and the area with BMIPP reduction 1 week after the onset of myocardial infarction corresponded well to the area with perfusion defect which was demonstrated before revascularization therapy at admission [62]. These observations suggested that BMIPP imaging obtained in subacute phase of myocardial infarction can be called “ischemic memory imaging” because it reflects prior ischemic damage or metabolically stunned myocardium even after the restoration of perfusion abnormality [56, 63, 64].

In chronic phase of myocardial infarction, mismatched uptake of BMIPP less than thallium is not an uncommon finding. The study compared resting BMIPP uptake and exercise-redistribution thallium scintigraphy in 26 patients with prior myocardial infarction (>4 week after onset) without revascularization therapy demonstrated that 67% of the segments with discordant BMIPP uptake less than redistribution thallium showed reversible thallium defects, 21% showed fixed thallium defects and 12% showed normal thallium uptake, indicating that the myocardium with mismatched BMIPP uptake less than redistribution thallium uptake were mostly exposed

to stress induced ischemia [39]. In subacute to chronic phase of infraction (>2 week after onset), similar findings were reported, with most of the mismatched segments (22/27) is associated with reversible thallium defect [65].

*Unstable angina pectoris*

In patients with unstable angina, mismatched BMIPP uptake less than thallium has also been observed frequently [66-69]. Comparison of BMIPP image in 19 patients with unstable angina without prior myocardial infarction and stress thallium scan performed after stabilization of their condition demonstrated that BMIPP decrease was associated with stress perfusion abnormality in 44 of 57 (77%) segments and degree of BMIPP reduction correlated with the degree of perfusion abnormality at stress, degree of wall motion abnormality, and severity of coronary artery stenosis [66]. BMIPP imaging performed in 20 patients with unstable angina after medication and elimination of chest pain disclosed that patients with abnormal BMIPP uptake (n=11) had more severe coronary artery stenosis exceeding 90% (10/11 vs 4/9), 99% stenosis (9/11 vs 0/9) and more collateral opacification (4/11 vs 0/9) than patients without BMIPP abnormality (n=9). In addition, revascularization was performed in 82% of patients with abnormal BMIPP images, while in only 22% of patients with normal BMIPP images, accordingly, BMIPP imaging may be helpful in decision-making for interventional treatment [68]. In a study of 111 consecutive patients with acute chest pain without myocardial infarction, BMIPP (performed 2 days after chest pain) abnormality was observed in 74% of coronary abnormalities, while only 38% showed tetrofosmin (within 24 hr after chest pain) abnormality [70]. These findings indicate that reduced BMIPP uptake in patients with unstable angina may represent persistent metabolic abnormality reflecting prior severe ischemia or repetitive ischemic insults, thus the concept of ischemic memory imaging could be extended and applied to these patients population. In other words, BMIPP imaging could extend time window for detecting previous ischemic event

after the resolution of perfusion abnormality. In addition, ischemic memory concept can be applied to the patients with vasospastic angina pectoris. In the patients repetitive ischemia may cause metabolic alteration and this metabolic alteration can be detected as a reduction of BMIPP uptake, however, stress perfusion SPECT often failed to detect ischemia because exercise or vasodilator stress usually does not provoke vasospasm. Accordingly, BMIPP imaging should be considered as one of the noninvasive diagnostic methods [71].

*Chronic coronary artery disease*

In chronic stable coronary artery disease even without history of myocardial infarction, discordant BMIPP uptake less than perfusion tracer is not a rare finding (Fig. 2). Comparison between BMIPP uptake and stress-reinjection thallium SPECT in 45, patients with chronic coronary artery disease demonstrated that most of the segments (118/124) with discordant BMIPP uptake less than reinjection-thallium were associated with reversible thallium defects, indicating ischemic myocardium [48]. When reversible thallium defects were analyzed, 118 out of 237 segments evidenced discordant BMIPP uptake less than reinjection thallium, suggesting that approximately half of the segments with ischemic myocardium have more severe metabolic abnormality than expected from the degree of resting perfusion abnormality. On the other hand, 71 (79%) of 90 segments with fixed thallium defects demonstrated concordant uptake of both tracers, suggesting myocardium with poor viability has metabolic abnormality similar to the degree of resting perfusion abnormality. When reversible thallium defects were analyzed with respect to the evidence of discordant BMIPP uptake less than thallium and regional wall motion abnormality, wall motion was more severely impaired in the segments with discordant BMIPP uptake less than thallium than those without such discordance in both subset of patients with and without old myocardial infarction. However, severity of coronary artery stenosis was similar in the vascular teritory with discordant BMIPP uptake less than reinjection thallium and those without such

discordance. Similar findings were also reported in 12 patients with stable angina without prior myocardial infarction, with location and degree of BMIPP decrease was associated with those of stress-induced hypoperfusion on thallium imaging, but no significant correlation between BMIPP reduction and coronary artery stenosis was found [66]. In 55 patients with stable coronary artery disease who had persistent thallium defects in at least one segment on stress-redistribution thallium imaging, BMIPP uptake in the segments with new fill-in after thallium reinjection was investigated [72]. Discordant BMIPP uptake less than thallium was observed in 37% of the segments with thallium redistribution after exercise, on the contrary, such discordance was observed in 82% of the segments with no redistribution but new fill-in after thallium reinjection. In addition, such discordance was observed in only 19% of the segments with fixed defects. In previous studies using stress-redistribution-reinjection thallium, the myocardium with new fill-in after thallium reinjection is characterized as severely ischemic but viable myocardium with frequent wall motion abnormalities that may recover after revascularization [73, 74]. Accordingly, these observation may indicate that mismatched uptake is suggestive of the myocardium jeopardized by more severe ischemia.

The concept of ischemic memory imaging of BMIPP has been tested in 32 patients with exercise-induced ischemia on thallium SPECT by injecting BMIPP at rest within 30 hrs of ischemia which was induced and confirmed by exercise thallium SPECT [75]. In more than 90 % of patients, BMIPP identified suppressed fatty acid uptake area corresponding to the ischemia detected by stress thallium study up to 30 hrs after ischemic episode, therefore, the authors concluded that BMIPP can identify sustained metabolic abnormality as a ischemic memory imaging at least until 30 hrs after stress induced ischemic episodes. Accumulated data in patients with chronic ischemic heart disease in Japan, however, demonstrated that reduced BMIPP uptake was frequently observed independent of prior radionuclide and ECG stress tests but related to severe ischemia and wall motion abnormality, raise the possibility that BMIPP reduction reflects the substrate

shift from fatty acid to glucose as a results of repeated myocardial ischemia rather than reflecting the single episode of metabolic stunning. Myocardium exposed to repetitive ischemia or stunning is subsequently adapted metabolically into chronic ischemic myocardium, so called hibernation [76-78]. In hibernating myocardium, energy substrate is shifted from fatty acid to glucose, contractility is impaired but with recruitable inotropic reserve, and myocardial flow reserve is severely impaired. In relation to this issue, recent investigation of the relationship between BMIPP uptake and myocardial blood flow measured by PET in patients with chronic stable angina without previous myocardial infarction demonstrated that rest myocardial blood flow was preserved independent of BMIPP uptake. However, hyperemic myocardial blood flow was decreased in the area with reduced BMIPP uptake, resulting in the severity of impaired myocardial flow reserve correlated to the reduction of BMIPP uptake [79]. Hence, reduced BMIPP uptake implies impaired myocardial flow reserve and may reflects substrate shifts in hibernating myocardium.

*Viability assessment and prediction of functional recovery in chronic coronary artery disease*

Improvement of regional or global systolic function can be achieved if revascularization of viable myocardium is successfully performed. Therefore, assessment of residual myocardial viability in the setting of dysfunctional myocardium due to significant coronary artery disease is a key issue in making clinical decisions with respect to revascularization procedures. On scintigraphy using perfusion tracers, the hallmarks of myocardial viability supplied by a stenosed or occluded coronary artery are the perfusion defect with thallium redistribution on stress-redistribution or rest-redistribution images, fill-in of thallium, setamibi, and tetrofosmin after reinjection, or significant uptake on resting or reinjection images (usually more than 50-60% uptake of normal area). However, the ability of perfusion tracers to differentiate viable from non-viable myocardium is not completely satisfactory as evidenced by recent viability studies using perfusion tracers

[80, 81].

In chronic coronary artery disease, the hallmark of viability of perfusion tracers is the significant tracer uptake, although, the hallmark of viability in BMIPP imaging is the relative reduction of BMIPP uptake compared to perfusion tracers. There are several substantial evidences that discordant BMIPP uptake less than perfusion tracers is a marker of viability. Firstly, as previously described, such mismatch is associated with ischemic myocardium as evidenced by stress perfusion studies. Secondly, increased FDG uptake was observed in areas with discordant BMIPP uptake less than thallium and higher oxidative metabolism by $^{11}$C-acetate PET was observed in mismatched area than the area with concordant reduction of BMIPP and perfusion [82]. Thirdly, myocardial areas with BMIPP uptake less than sestamibi were more likely to have a positive response to dobutamine than areas with matched defect [83, 84]. Lastly, histologic examination in patients with bypass surgery demonstrated that BMIPP uptake reduction against % fibrosis looked biphasic, with steep reduction of BMIPP uptake within 20% of fibrosis, although, thallium uptake reduction correlated linearly to % fibrosis. Thus, the areas with discordant BMIPP uptake less than thallium had less than 20% fibrosis [85].

More directly, functional recovery after revascularization has been investigated in relation to BMIPP uptake abnormality. In patients with chronic stable coronary artery disease, discordant BMIPP uptake less than thallium could predict functional recovery after revascularization more precisely than exercise-reinjection thallium study. In addition, the extent of discordant uptake of BMIPP less than reinjection thallium before revascularization were a good predictor of global ejection fraction improvement after revascularization [86]. Similarly, in patients with chronic ischemic left ventricular dysfunction, area with discordant BMIPP uptake less than sestamibi measured by quantitative analysis was highly predictive of improvement of ejection fraction, wall motion and free fatty acid utilization after revascularization [84]. Interestingly, the comparison of FDG, BMIPP, and sestamibi uptake in patients with old myocardial infarction and

stable ischemic regional wall motion abnormalities demonstrated that extent of discordant BMIPP uptake less than FDG uptake before revascularization highly correlated with ejection fraction improvement after revascularization ($r = 0.74$) and also the extent of discordant BMIPP uptake less than sestamibi correlated significantly with ejection fraction improvement ($r = 0.50$). However, no significant correlation was observed between the area with discordant FDG uptake more than sestamib and ejection fraction recovery [87]. The results are quite intuitive because, in ischemic and viable myocardium, substrate shift from fatty acid to glucose would take place, hence, mismatch of FDG and BMIPP uptake should be prominent but mismatch between BMIPP and sestamibi might be modest. These data suggest that discordant BMIPP uptake less than perfusion may represent reversible ischemic myocardial injury or hibernating myocardium and that the regional and global dysfunction will improve after revascularization in patients with chronic stable coronary artery disease.

*Risk stratification and prognostic value*

Assessment of prognostic value of BMIPP imaging over perfusion tracers in patients with coronary artery disease is a matter of clinical importance. The initial study in 50 consecutive patients with myocardial infarction was performed to investigate the prognostic implications of BMIPP and stress-reinjection thallium imaging (obtained at 2 week to 6 month after infarction) with a mean follow up period of 23 months [88]. During the follow-up period 9 patients had cardiac events and 8 of the 9 patients with cardiac events showed discordant BMIPP uptake less than reinjection thallium, whereas only 20 of 41 patients without cardiac events did so. When all the clinical and radionuclide variables were analyzed by Cox regression analysis, presence of discordant BMIPP uptake was the best, and an independent, predictor of future cardiac events followed by the number of coronary stenosis. BMIPP and thallium imaging performed within 1 month of acute myocardial infarction demonstrated that impaired BMIPP uptake and mismatched BMIPP uptake less than thallium are related to a high

probability of fatal and non-fatal cardiac events [89] and the defect score of BMIPP and mismatched BMIPP uptake less than thallium provided incremental predictive value for future cardiac events [90]. In addition clinical value of BMIPP imaging is also revealed in the patients with chronic stage of myocardial infarction. BMIPP imaging performed before revascularization in 76 patients with chronic stable ischemia (including 61 patients with myocardial infarction after at least 3 month of onset) with left ventricular dysfunction has been analyzed [91]. Patients with large amount of discordant BMIPP uptake less than thallium demonstrated greater ejection fraction improvement after revascularization and, interestingly, showed significantly better event free survival than patients with small amount or no perfusion and metabolic mismatch. These data indicate that patients with significant amount of discordant BMIPP uptake less than thallium may benefit from revascularization. It has been also demonstrated that BMIPP imaging is also valuable for risk stratification in chronic coronary artery disease without old myocardial infarction. In 270 patients with known or suspected coronary artery disease without previous myocardial infarction, BMIPP defect score was analyzed with respect to cardiac event during a median follow-up of 3.9 years [92]. Kaplan-Meier survival estimates revealed a hard event-free survival rate of 98% at 3 years in patients with a summed BMIPP defect score lower than 5 but 93% in those with a defect score of 5 or greater ($P = 0.03$) and all event-free survival rate of 92% at 3 years in patients with a summed BMIPP defect score lower than 5 but 80% in those with a defect score of 5 or greater ($P = 0.0003$). More importantly, BMIPP was able to select a high-risk subgroup among patients with diabetes mellitus as well as non-diabetic patients, with 41% event rate in diabetic patients with BMIPP defect score 5 or more but only 4% event rate in non-diabetic patients with BMIPP defect score lower than 5. This ability of BMIPP imaging for risk stratification in diabetic patients is advantageous against FDG PET imaging, because myocardial BMIPP uptake is not affected by blood substrate contents but FDG uptake is influenced significantly [93, 94]. Another strength of BMIPP imaging is its simplicity

since it offers metabolic information without stress procedure. It is a matter of great interest whether resting BMIPP imaging offers complementary or additional prognostic information over conventional stress perfusion imaging or not. Consecutive 167 patients with angina pectoris but without prior myocardial infarction who had undergone both BMIPP and stress thallium imaging were followed up for 48 months [95]. For overall cardiac events (5 hard and 29 soft events), multivariate Cox's analysis revealed that reduced BMIPP uptake, stress perfusion score, diabetes, and left ventricular ejection fraction were the significant predictors. No hard event was observed with normal BMIPP uptake, whereas 2 patients with nearly normal stress perfusion with impaired BMIPP uptake had a hard event. The authors concluded that resting BMIPP imaging may provide significant prognostic information independent of stress myocardial perfusion imaging.

*Cardiomyopathy*

In patients with cardiomyopathy, evaluation of the metabolic status in addition to perfusion may offer a clue for the assessment of the underlying pathophysiology of the disease. Animal experiments with autoradiography using methyl-branched fatty acids in cadiomyopathic hamsters and hypertensive rats demonstrated that fatty acid uptake was heterogeneous and lower than thallium in endocardium [96-100]. In patients with cardiomyopathy, including hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM), it has been reported that BMIPP distribution is inhomogeneous and discordant BMIPP uptake less than thallium is a general finding especially in patients with HCM (Fig. 3). In patients with HCM discordant BMIPP uptake less than thallium in the disproportionately thickened septum was a common finding [101, 102] and mismatched BMIPP uptake less than thallium in the hypertrophied septum and the degree of BMIPP abnormality was correlated with the severity of hypertrophy [103]. In addition, BMIPP accumulation was significantly less in the septal portion of the anterior and the posterior wall and the apex than in the lateral segments. The patients with such BMIPP defects in the septal

portion of anterior and posterior segments had a more frequent family history of HCM, sudden death, and severe cardiac dysfunction [104] and the severity of BMIPP abnormality was a significant predictor of cardiac events including heart failure and cardiac death [105, 106]. Several studies employing stress thallium scintigraphy in patients with HCM have revealed that, despite the normal epicardial coronary arteries, the reversible perfusion defect is a commonly seen findings, which could be eliminated by verapamil, and that ischemia may account for the phenomenon [107-109]. When the relationship between BMIPP uptake and ischemia defined by reversible perfusion defect in stress-redistribution thallium scintigraphy in HCM patients was investigated, mismatched BMIPP uptake less than thallium in hypertrophied areas often accompanied reversible thallium defects [102, 110]. Furthermore, BMIPP imaging depicts disease associated abnormality even at early stages [102]. In 5 patients with NYHA class 1, all patients showed normal stress thallium and only 1 showed reduced BMIPP uptake. In 6 patients with NYHA class 2, all showed reduced BMIPP uptake less than redistribution thallium and 4 showed stress induced ischemia in the mismatched area and 2 showed normal thallium findings. In 6 patients with NYHA class 3, all showed reduced BMIPP uptake less than redistribution thallium with 4 showing additional matched defect simultaneously and only 2 showed stress induced ischemia in the mismatched area. Together with other recent studies, the discordant BMIPP less than thallium in hypertrophic areas with high frequency of reversible thallium defects suggests that myocardial ischemia or impaired coronary flow reserve may play a considerable role in impaired fatty acid utilization or metabolism [110, 111] and that mismatched uptake may be an early marker of HCM followed by matched defect at later stage [102]. A recent study with positron emission tomography demonstrated that, in patients with HCM, the reduction of BMIPP uptake was the most sensitive indicator of metabolic abnormalities followed by the abnormal oxidative metabolism and FDG uptake [112]. As for the ventricular function in patients with HCM, BMIPP uptake abnormality correlated well with regional function and also correlated well

with global ejection fraction, while thallium abnormality did not, hence the ventricular function correlated more closely with metabolic abnormality than perfusion [113-116].

In patients with DCM, both BMIPP and thallium distribution was heterogeneous, and BMIPP abnormality correlated well with ventricular dysfunction, whereas, thallium abnormality did not [117]. In addition, the extent of the BMIPP abnormality reflects the severity of haemodynamic deterioration and histopathological changes [118]. BMIPP imaging is useful for therapy monitoring and risk stratification in DCM patients. In the therapy with ß-blocker, decrease in BMIPP uptake in patients with DCM did not respond well to the therapy, however, BMIPP uptake improved after ß-blocker therapy in only non-responder, indicating that ß-blocker therapy may lead to metabolic improvement even without functional improvement [119, 120]. However, controversial results have also been reported. DCM patients with reduced BMIPP uptake also did not respond to ß-blocker therapy but BMIPP uptake improved in only responders after treatment [121]. By the treatment with coenzyme Q10, BMIPP uptake abnormality in patients with DCM improved, while the percent fractional shortening measured by echocardiography did not changed, suggesting that BMIPP imaging could be a more sensitive indicator than functional parameter [122]. These data indicates that BMIPP uptake may predict the response to ß-blocker therapy in DCM, however, in the monitoring of therapeutic effect, role of BMIPP imaging should warrant further investigation.

BMIPP imaging might provide helpful information for the differential diagnosis of patients with severe LV dysfunction. Ischemic cardiomyopathy and DCM are the main cause of congestive heart failure and share similar clinical features, such as dilated ventricle, diffuse hypokinesis with severely reduced ejection fraction. However, the therapeutic approach in both diseases is quite different. When discordant BMIPP uptake less than thallium is investigated, ischemic cardiomyopathy and dilated form of HCM showed high prevalence of mismatched uptake, while idiopathic DCM, alcoholic and hypertensive cardiomyopathy showed lower incidence of mismatched

uptake [123].

Transient left ventricular apical ballooning is a newly defined syndrome in Japan and has been called Takotsubo cardiomyopathy or transient left ventricular apical ballooning syndrome. It is characterized by sudden onset of chest symptoms, electrocardiographic changes, transient left ventricular wall motion abnormalities particularly involving in the apical region, low-grade cardiac enzyme elevation, and absence of significant coronary stenosis [124, 125]. In subacute phase (around 5 days after onset) thallium uptake reduction was mild but marked BMIPP uptake reduction was observed in the regions with an apical asynergy. Resolution of apical asynergy was observed around 15 days after onset, while normalization of impaired BMIPP uptake was observed about 1 month after the onset [126]. Recent study demonstrated that tetrofosmin uptake immediately after the onset was severely depressed in the area that corresponded to the large apical dysfunction. The tetrofosmin uptake abnormality and apical dysfunction recovered rapidly at subacute stage, but BMIPP abnormality persiste for a longer period [127]. These finding suggested that the transient ventricular dysfunction in this disease may essentially be stunned myocardium, although the etiology is still unknown.

## Conclusions

In normal condition approximately two-thirds or more of the total energy produced by myocardium is derived from fatty acid oxidation and myocardial substrates may change significantly in various pathological conditions such as ischemia. Accordingly, many fatty acid tracers for SPECT imaging have been introduced. However, straight chain fatty acid analogue has not been used widely in clinical studies because of its rapid washout is not suitable for SPECT imaging. On the contrary, methyl branched fatty acid analogue permit SPECT imaging more easily because of its prolonged myocardial retention. BMIPP, one of the methyl branched fatty acid analogues, is the only approved fatty acid tracer for daily clinical use at present. The concept of BMIPP imaging is metabolic trapping, like FDG, by

inhibiting ß-oxidation by introducing methyl branching at ß-carbon position. Myocardial BMIPP uptake more likely reflects activation of BMIPP into BMIPP-CoA and reflects indirectly cellular ATP production by fatty acid metabolism. Hence, under the condition of ischemia, the reduction of BMIPP uptake is observed by reflecting the reduction of ATP production due to depressed oxidative fatty acid metabolism and substrate shift from fatty acids to glucose. Reduced utilization of fatty acids or reduced uptake of BMIPP at rest is often observed in ischemic myocardium independent of the uptake of perfusion tracers. Through comparison with perfusion, BMIPP image can detect previous myocardial ischemia as an ischemic memory imaging (stunned myocardium) and viable but chronically dysfunctional myocardium (hibernating myocardium). In addition, BMIPP image may offer incremental prognostic information in ischemic heart disease. In cardiomyopathy, BMIPP imaging may be useful for the early detection of HCM and differentiation of ischemic cardiomyopathy from idiopathic DCM, and also for the prediction of prognosis. Through the basic and clinical studies, it has become clear that BMIPP imaging has a high potential utility in clinical nuclear cardiology practice. Thus world wide clinical use of fatty acid imaging is desired.

## Figure legends

Fig. 1.
Short-axis slices and horizontal long axis slices of $^{99m}$Tc-tetrofosmin, $^{123}$I-BMIPP and gated blood pool images. Patient was admitted with acute myocardial infarction (AMI) and emergency coronary angiography revealed 90% stenosis of the proximal left anterior descending coronary artery. Direct angioplasty was performed successfully. Maximum creatine kinase was 460 IU/L. Gated blood pool study demonstrated severe hypokinesis of apex to anteroseptal wall at 3 days after the onset. 6 days after the onset of AMI, tetrofosmin did not show definite perfusion abnormality, though, reduced BMIPP uptake was noted in the anteroseptal wall. 3 month later BMIPP uptake improved and wall motion abnormality disappeared. The area with discordant BMIPP uptake less than perfusion may represent metabolically and functionally stunned myocardium and area at risk as an “ischemic memory”.

Fig. 2.
Horizontal long axis and sagittal slices of $^{201}$Tl, $^{123}$I- BMIPP and gated blood pool images. The patient with diabetes mellitus and nephrotic syndrome had electrocardiographic abnormality, therefore, the thallium and BMIPP SPECT were performed. Discordant BMIPP uptake less than thallium in apex to anteroseptal wall was observed and the area demonstrated severe hypokinesis in gated blood pool scintigraphy. Coronary angiography showed left anterior descending coronary artery (LAD) obstruction and 90% stenosis of the left circumflex coronary artery. Coronary angioplasty of the LAD was performed successfully and BMIPP uptake and wall motion abnormality improved 1 month later. The discordant BMIPP uptake less than thallium depicted the dysfunctional but viable myocardium or hibernating myocardium in apex to anteroseptal wall.

Fig. 3.

Sagittal, horizontal long axis and short axis slices of $^{201}$Tl, $^{123}$I- BMIPP in patients with hypertrophic cardiomyopathy (HCM). Thallium demonstrated increased uptake in apex to anteroseptal wall, but BMIPP uptake showed reduction of uptake in the area. Discordant BMIPP uptake less than thallium in hypertrophic area is rather early phenomenon of HCM.

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