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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 β -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 express 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 hereditary [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 mitochondria via an acyl carnitine carrier system and are rapidly catabolized by β -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 β -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 β -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 β -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 β -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 β -oxidation [21]. Through β -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 β -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 β -carbon position to slow myocardial clearance by inhibiting β -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 ± 0.05 and 1.00 ± 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 β -oxidation, and this water soluble intermediate metabolite, 3MNA, is rapidly cleared from the myocardium. Clinical trial 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.

¹²³I-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 β oxidation is blocked by β -methyl branching), followed by β 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 palmitoyltransferase 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 β -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 chronic 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 $^{99\text{m}}\text{Tc}$ labeled perfusion tracers instead of thallium and the effectiveness of scatter correction for accurate comparison of BMIPP and $^{99\text{m}}\text{Tc}$ -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 $^{99\text{m}}\text{Tc}$ -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 infarction (>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 territory 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 sestamibi 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 cardiomyopathic 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 β -blocker, decrease in BMIPP uptake in patients with DCM did not respond well to the therapy, however, BMIPP uptake improved after β -blocker therapy in only non-responder, indicating that β -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 β -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 β -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 persists for a longer period [127]. These findings 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 permits 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 β -oxidation by introducing methyl branching at β -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 antero-septal 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 antero-septal 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 antero-septal 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 antero-septal 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 antero-septal 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.

References

1. Liedtke AJ. Alterations of carbohydrate and lipid metabolism in the acutely ischemic heart. *Prog Cardiovasc Dis* 1981;23:321-36
2. Camici P, Ferrannini E and Opie LH. Myocardial metabolism in ischemic heart disease: basic principles and application to imaging by positron emission tomography. *Prog Cardiovasc Dis* 1989;32:217-38
3. Hwang EH, Yamashita A, Takemori H, Taki J, Nakajima K, Bunko H, et al. Absent myocardial I-123 BMIPP uptake in a family. *Ann Nucl Med* 1996;10:445-8
4. Hashimoto J, Koseki S, Kinoshita F, Kubo A, Iwanaga S, Mitamura H, et al. Absent myocardial accumulation of two different radioiodinated pentadecanoic acids. *Ann Nucl Med* 1998;12:43-6
5. Tanaka T, Okamoto F, Sohmiya K and Kawamura K. Lack of myocardial iodine-123 15-(p-iodiphenyl)-3-R,S-methylpentadecanoic acid (BMIPP) uptake and CD36 abnormality--CD36 deficiency and hypertrophic cardiomyopathy. *Jpn Circ J* 1997;61:724-5
6. Hwang EH, Taki J, Yasue S, Fujimoto M, Taniguchi M, Matsunari I, et al. Absent myocardial iodine-123-BMIPP uptake and platelet/monocyte CD36 deficiency. *J Nucl Med* 1998;39:1681-4
7. Yoshizumi T, Nozaki S, Fukuchi K, Yamasaki K, Fukuchi T, Maruyama T, et al. Pharmacokinetics and metabolism of 123I-BMIPP fatty acid analog in healthy and CD36-deficient subjects. *J Nucl Med* 2000;41:1134-8
8. Watanabe K, Ohta Y, Toba K, Ogawa Y, Hanawa H, Hirokawa Y, et al. Myocardial CD36 expression and fatty acid accumulation in patients with type I and II CD36 deficiency. *Ann Nucl Med* 1998;12:261-6
9. Fukuchi K, Nozaki S, Yoshizumi T, Hasegawa S, Uehara T, Nakagawa T, et al. Enhanced myocardial glucose use in patients with a deficiency in long-chain fatty acid transport (CD36 deficiency). *J Nucl Med* 1999;40:239-43
10. Kudoh T, Tamaki N, Magata Y, Konishi J, Nohara R, Iwasaki A, et al.

- Metabolism substrate with negative myocardial uptake of iodine-123-BMIPP. *J Nucl Med* 1997;38:548-53
11. Nozaki S, Tanaka T, Yamashita S, Sohmiya K, Yoshizumi T, Okamoto F, et al. CD36 mediates long-chain fatty acid transport in human myocardium: complete myocardial accumulation defect of radiolabeled long-chain fatty acid analog in subjects with CD36 deficiency. *Mol Cell Biochem* 1999;192:129-35
 12. Tanaka T, Nakata T, Oka T, Ogawa T, Okamoto F, Kusaka Y, et al. Defect in human myocardial long-chain fatty acid uptake is caused by FAT/CD36 mutations. *J Lipid Res* 2001;42:751-9
 13. Brinkmann JF, Abumrad NA, Ibrahimi A, van der Vusse GJ and Glatz JF. New insights into long-chain fatty acid uptake by heart muscle: a crucial role for fatty acid translocase/CD36. *Biochem J* 2002;367:561-70
 14. Robinson GD, Jr. and Lee AW. Radioiodinated fatty acids for heart imaging: iodine monochloride addition compared with iodide replacement labeling. *J Nucl Med* 1975;16:17-21
 15. Poe ND, Robinson GD, Jr., Graham LS and MacDonald NS. Experimental basis of myocardial imaging with 123I-labeled hexadecenoic acid. *J Nucl Med* 1976;17:1077-82
 16. Poe ND, Robinson GD, Jr., Zielinski FW, Cabeen WR, Jr., Smith JW and Gomes AS. Myocardial imaging with 123I-hexadecenoic acid. *Radiology* 1977;124:419-24
 17. Visser FC, van Eenige MJ, Westera G, Den Hollander W, Duwel CM, van der Wall EE, et al. Metabolic fate of radioiodinated heptadecanoic acid in the normal canine heart. *Circulation* 1985;72:565-71
 18. Freundlieb C, Hock A, Vyska K, Feinendegen LE, Machulla HJ and Stocklin G. Myocardial imaging and metabolic studies with [17-123I]iodoheptadecanoic acid. *J Nucl Med* 1980;21:1043-50
 19. Machulla HJ, Marsmann M and Dutschka K. Biochemical concept and synthesis of a radioiodinated phenylfatty acid for in vivo metabolic studies of the myocardium. *Eur J Nucl Med* 1980;5:171-3
 20. Reske SN, Sauer W, Machulla HJ and Winkler C.

- 15(p-[123I]Iodophenyl)pentadecanoic acid as tracer of lipid metabolism: comparison with [1-14C]palmitic acid in murine tissues. *J Nucl Med* 1984;25:1335-42
21. Caldwell JH, Martin GV, Link JM, Krohn KA and Bassingthwaite JB. Iodophenylpentadecanoic acid-myocardial blood flow relationship during maximal exercise with coronary occlusion. *J Nucl Med* 1990;31:99-105
 22. Ercan M, Senekowitsch R, Bauer R, Reidel G, Kriegel H and Pabst HW. In vivo and in vitro studies with omega-[rho-123I-phenyl]-pentadecanoic acid in rats. *Int J Appl Radiat Isot* 1983;34:1519-24
 23. Rellas JS, Corbett JR, Kulkarni P, Morgan C, Devous MD, Sr., Buja LM, et al. Iodine-123 phenylpentadecanoic acid: detection of acute myocardial infarction and injury in dogs using an iodinated fatty acid and single-photon emission tomography. *Am J Cardiol* 1983;52:1326-32
 24. Goodman MM, Kirsch G and Knapp FF, Jr. Synthesis and evaluation of radioiodinated terminal p-iodophenyl-substituted alpha- and beta-methyl-branched fatty acids. *J Med Chem* 1984;27:390-7
 25. Knapp FF, Jr., Ambrose KR and Goodman MM. New radioiodinated methyl-branched fatty acids for cardiac studies. *Eur J Nucl Med* 1986;12 Suppl:S39-44
 26. Sloof GW, Visser FC, van Lingen A, Bax JJ, Eersels J, Teule GJ, et al. Evaluation of heart-to-organ ratios of 123I-BMIPP and the dimethyl-substituted 123I-DMIPP fatty acid analogue in humans. *Nucl Med Commun* 1997;18:1065-70
 27. Chouraqui P, Maddahi J, Henkin R, Karesh SM, Galie E and Berman DS. Comparison of myocardial imaging with iodine-123-iodophenyl-9-methyl pentadecanoic acid and thallium-201-chloride for assessment of patients with exercise-induced myocardial ischemia. *J Nucl Med* 1991;32:447-52
 28. Hashimoto J, Kubo A, Iwasaki R, Fujii H, Kunieda E, Iwanaga S, et al. Scintigraphic evaluation of myocardial ischaemia using a new fatty acid

- analogue: iodine-123-labelled 15-(p-iodophenyl)-9-(R,S)-methylpentadecanoic acid (9MPA). *Eur J Nucl Med* 1999;26:887-93
29. Fujiwara S, Takeishi Y, Tojo T, Yamaoka M, Nitobe J, Takahashi K, et al. Fatty acid imaging with ¹²³I-15-(p-iodophenyl)-9-R,S-methylpentadecanoic acid in acute coronary syndrome. *J Nucl Med* 1999;40:1999-2006
 30. Fukuchi K, Hasegawa S, Ito Y, Yamaguchi H, Yoshioka J, Uehara T, et al. Detection of coronary artery disease by iodine-123-labeled iodophenyl-9-methyl pentadecanoic acid SPECT: comparison with thallium-201 and iodine-123 BMIPP SPECT. *Ann Nucl Med* 2000;14:11-6
 31. Ambrose KR, Owen BA, Goodman MM and Knapp FF, Jr. Evaluation of the metabolism in rat hearts of two new radioiodinated 3-methyl-branched fatty acid myocardial imaging agents. *Eur J Nucl Med* 1987;12:486-91
 32. Fujibayashi Y, Nohara R, Hosokawa R, Okuda K, Yonekura Y, Tamaki N, et al. Metabolism and kinetics of iodine-123-BMIPP in canine myocardium. *J Nucl Med* 1996;37:757-61
 33. Hosokawa R, Nohara R, Fujibayashi Y, Okuda K, Ogino M, Hata T, et al. Myocardial kinetics of iodine-123-BMIPP in canine myocardium after regional ischemia and reperfusion: implications for clinical SPECT. *J Nucl Med* 1997;38:1857-63
 34. Hosokawa R, Nohara R, Fujibayashi Y, Okuda K, Ogino M, Hata T, et al. Metabolic fate of iodine-123-BMIPP in canine myocardium after administration of etomoxir. *J Nucl Med* 1996;37:1836-40
 35. Fox KA, Abendschein DR, Ambos HD, Sobel BE and Bergmann SR. Efflux of metabolized and nonmetabolized fatty acid from canine myocardium. Implications for quantifying myocardial metabolism tomographically. *Circ Res* 1985;57:232-43
 36. Duwel CM, Visser FC, van Eenige MJ and Roos JP. Variables of myocardial backdiffusion, determined with 17-iodo-¹³¹I heptadecanoic acid in the normal dog heart. *Mol Cell Biochem* 1989;88:191-4

37. Fujibayashi Y, Yonekura Y, Takemura Y, Wada K, Matsumoto K, Tamaki N, et al. Myocardial accumulation of iodinated beta-methyl-branched fatty acid analogue, iodine-125-15-(p-iodophenyl)-3-(R,S)methylpentadecanoic acid (BMIPP), in relation to ATP concentration. *J Nucl Med* 1990;31:1818-22
38. Nohara R, Okuda K, Ogino M, Hosokawa R, Tamaki N, Konishi J, et al. Evaluation of myocardial viability with iodine-123-BMIPP in a canine model. *J Nucl Med* 1996;37:1403-7
39. Matsunari I, Saga T, Taki J, Akashi Y, Hirai J, Wakasugi T, et al. Kinetics of iodine-123-BMIPP in patients with prior myocardial infarction: assessment with dynamic rest and stress images compared with stress thallium-201 SPECT. *J Nucl Med* 1994;35:1279-85
40. Kobayashi H, Kusakabe K, Momose M, Okawa T, Inoue S, Iguchi N, et al. Evaluation of myocardial perfusion and fatty acid uptake using a single injection of iodine-123-BMIPP in patients with acute coronary syndromes. *J Nucl Med* 1998;39:1117-22
41. Miller DD, Gill JB, Livni E, Elmaleh DR, Aretz T, Boucher CA, et al. Fatty acid analogue accumulation: a marker of myocyte viability in ischemic-reperfused myocardium. *Circ Res* 1988;63:681-92
42. Schwaiger M, Schelbert HR, Keen R, Vinten-Johansen J, Hansen H, Selin C, et al. Retention and clearance of C-11 palmitic acid in ischemic and reperfused canine myocardium. *J Am Coll Cardiol* 1985;6:311-20
43. Nishimura T, Sago M, Kihara K, Oka H, Shimonagata T, Katabuchi T, et al. Fatty acid myocardial imaging using 123I-beta-methyl-iodophenyl pentadecanoic acid (BMIPP): comparison of myocardial perfusion and fatty acid utilization in canine myocardial infarction (occlusion and reperfusion model). *Eur J Nucl Med* 1989;15:341-5
44. Noriyasu K, Mabuchi M, Kuge Y, Morita K, Tsukamoto T, Kohya T, et al. Serial changes in BMIPP uptake in relation to thallium uptake in the rat myocardium after ischaemia. *Eur J Nucl Med Mol Imaging* 2003;30:1644-50
45. Higuchi T, Taki J, Nakajima K, Kinuya S, Namura M and Tonami N.

- Time course of discordant BMIPP and thallium uptake after ischemia and reperfusion in a rat model. *J Nucl Med* 2005;46:172-5
46. Ito K, Sugihara H, Kawasaki T, Katoh S, Azuma A and Nakagawa M. Dynamic changes in cardiac fatty acid metabolism in the stunned human myocardium. *Ann Nucl Med* 2001;15:343-50
 47. Takahashi N, Ishida Y, Hirose Y, Kawano S, Fukuoka S, Hayashida K, et al. [Detection of myocardial 123I-BMIPP distribution abnormality in patients with ischemic heart disease based on normal data file in bull's-eye polar map]. *Kaku Igaku* 1995;32:1089-98
 48. Taki J, Nakajima K, Matsunari I, Bunko H, Takada S and Tonami N. Impairment of regional fatty acid uptake in relation to wall motion and thallium-201 uptake in ischaemic but viable myocardium: assessment with iodine-123-labelled beta-methyl-branched fatty acid. *Eur J Nucl Med* 1995;22:1385-92
 49. Ueshima K, Miyakawa T, Taniguchi Y, Nishiyama O, Musha T, Saitoh M, et al. The incidence of discrepant regional myocardial uptake between 201 thallium and 123 I-BMIPP SPECT in patients with coronary heart disease. *Int J Cardiovasc Imaging* 2002;18:273-8
 50. Tamaki N, Kawamoto M, Yonekura Y, Fujibayashi Y, Takahashi N, Konishi J, et al. Regional metabolic abnormality in relation to perfusion and wall motion in patients with myocardial infarction: assessment with emission tomography using an iodinated branched fatty acid analog. *J Nucl Med* 1992;33:659-67
 51. Dobbeleir AA, Hambye AS and Franken PR. Influence of methodology on the presence and extent of mismatching between 99mTc-MIBI and 123I-BMIPP in myocardial viability studies. *J Nucl Med* 1999;40:707-14
 52. Franken PR, De Geeter F, Dendale P, Demoor D, Block P and Bossuyt A. Abnormal free fatty acid uptake in subacute myocardial infarction after coronary thrombolysis: correlation with wall motion and inotropic reserve. *J Nucl Med* 1994;35:1758-65
 53. Ito T, Tanouchi J, Kato J, Morioka T, Nishino M, Iwai K, et al. Recovery

- of impaired left ventricular function in patients with acute myocardial infarction is predicted by the discordance in defect size on 123I-BMIPP and 201Tl SPET images. *Eur J Nucl Med* 1996;23:917-23
54. Hashimoto A, Nakata T, Tsuchihashi K, Tanaka S, Fujimori K and Iimura O. Postischemic functional recovery and BMIPP uptake after primary percutaneous transluminal coronary angioplasty in acute myocardial infarction. *Am J Cardiol* 1996;77:25-30
 55. Franken PR, Dendale P, De Geeter F, Demoor D, Bossuyt A and Block P. Prediction of functional outcome after myocardial infarction using BMIPP and sestamibi scintigraphy. *J Nucl Med* 1996;37:718-22
 56. Naruse H, Arii T, Kondo T, Morita M, Ohyanagi M, Iwasaki T, et al. Clinical usefulness of iodine 123-labeled fatty acid imaging in patients with acute myocardial infarction. *J Nucl Cardiol* 1998;5:275-84
 57. Nishimura T, Nishimura S, Kajiya T, Sugihara H, Kitahara K, Imai K, et al. Prediction of functional recovery and prognosis in patients with acute myocardial infarction by 123I-BMIPP and 201Tl myocardial single photon emission computed tomography: a multicenter trial. *Ann Nucl Med* 1998;12:237-48
 58. Hambye AS, Vervaet A, Dobbeleir A, Dendale P and Franken P. Prediction of functional outcome by quantification of sestamibi and BMIPP after acute myocardial infarction. *Eur J Nucl Med* 2000;27:1494-500
 59. Katsunuma E, Kurokawa S, Takahashi M, Fukuda N, Kurosawa T and Izumi T. Usefulness of BMIPP SPECT to evaluate myocardial viability, contractile reserve and coronary stenotic progression after reperfusion in acute myocardial infarction. *Jpn Heart J* 2001;42:435-49
 60. Seki H, Toyama T, Higuchi K, Kasama S, Ueda T, Seki R, et al. Prediction of functional improvement of ischemic myocardium with (123I-BMIPP SPECT and 99mTc-tetrofosmin SPECT imaging: a study of patients with large acute myocardial infarction and receiving revascularization therapy. *Circ J* 2005;69:311-9
 61. Furutani Y, Shiigi T, Nakamura Y, Nakamura H, Harada M, Yamamoto T,

- et al. Quantification of area at risk in acute myocardial infarction by tomographic imaging. *J Nucl Med* 1997;38:1875-82
62. Kawai Y, Tsukamoto E, Nozaki Y, Kishino K, Kohya T and Tamaki N. Use of 123I-BMIPP single-photon emission tomography to estimate areas at risk following successful revascularization in patients with acute myocardial infarction. *Eur J Nucl Med* 1998;25:1390-5
 63. Mochizuki T, Murase K, Higashino H, Miyagawa M, Sugawara Y, Kikuchi T, et al. Ischemic "memory image" in acute myocardial infarction of 123I-BMIPP after reperfusion therapy: a comparison with 99mTc-pyrophosphate and 201Tl dual-isotope SPECT. *Ann Nucl Med* 2002;16:563-8
 64. Tamaki N, Tadamura E, Kudoh T, Hattori N, Inubushi M and Konishi J. Recent advances in nuclear cardiology in the study of coronary artery disease. *Ann Nucl Med* 1997;11:55-66
 65. Kawamoto M, Tamaki N, Yonekura Y, Tadamura E, Fujibayashi Y, Magata Y, et al. Combined study with I-123 fatty acid and thallium-201 to assess ischemic myocardium: comparison with thallium redistribution and glucose metabolism. *Ann Nucl Med* 1994;8:47-54
 66. Tateno M, Tamaki N, Yukihiro M, Kudoh T, Hattori N, Tadamura E, et al. Assessment of fatty acid uptake in ischemic heart disease without myocardial infarction. *J Nucl Med* 1996;37:1981-5
 67. Suzuki A, Takada Y, Nagasaka M, Kato R, Watanabe T, Shimokata K, et al. Comparison of resting beta-methyl-iodophenyl pentadecanoic acid (BMIPP) and thallium-201 tomography using quantitative polar maps in patients with unstable angina. *Jpn Circ J* 1997;61:133-8
 68. Takeishi Y, Fujiwara S, Atsumi H, Takahashi K, Sukekawa H and Tomoike H. Iodine-123-BMIPP imaging in unstable angina: a guide for interventional strategy. *J Nucl Med* 1997;38:1407-11
 69. Takeishi Y, Sukekawa H, Saito H, Nishimura S, Shibu T, Sasaki Y, et al. Impaired myocardial fatty acid metabolism detected by 123I-BMIPP in patients with unstable angina pectoris: comparison with perfusion imaging by 99mTc-sestamibi. *Ann Nucl Med* 1995;9:125-30

70. Kawai Y, Tsukamoto E, Nozaki Y, Morita K, Sakurai M and Tamaki N. Significance of reduced uptake of iodinated fatty acid analogue for the evaluation of patients with acute chest pain. *J Am Coll Cardiol* 2001;38:1888-94
71. Nakajima K, Shimizu K, Taki J, Uetani Y, Konishi S, Tonami N, et al. Utility of iodine-123-BMIPP in the diagnosis and follow-up of vasospastic angina. *J Nucl Med* 1995;36:1934-40
72. Matsunari I, Fujino S, Taki J, Senma J, Aoyama T, Wakasugi T, et al. Impaired fatty acid uptake in ischemic but viable myocardium identified by thallium-201 reinjection. *Am Heart J* 1996;131:458-65
73. Tamaki N, Ohtani H, Yonekura Y, Nohara R, Kambara H, Kawai C, et al. Significance of fill-in after thallium-201 reinjection following delayed imaging: comparison with regional wall motion and angiographic findings. *J Nucl Med* 1990;31:1617-23
74. Ohtani H, Tamaki N, Yonekura Y, Mohiuddin IH, Hirata K, Ban T, et al. Value of thallium-201 reinjection after delayed SPECT imaging for predicting reversible ischemia after coronary artery bypass grafting. *Am J Cardiol* 1990;66:394-9
75. Dilsizian V, Bateman TM, Bergmann SR, Des Prez R, Magram MY, Goodbody AE, et al. Metabolic imaging with beta-methyl-p-[(123)I]-iodophenyl-pentadecanoic acid identifies ischemic memory after demand ischemia. *Circulation* 2005;112:2169-74
76. Kim SJ, Peppas A, Hong SK, Yang G, Huang Y, Diaz G, et al. Persistent stunning induces myocardial hibernation and protection: flow/function and metabolic mechanisms. *Circ Res* 2003;92:1233-9
77. Camici PG and Rimoldi OE. Myocardial blood flow in patients with hibernating myocardium. *Cardiovasc Res* 2003;57:302-11
78. Gerber BL, Vanoverschelde JL, Bol A, Michel C, Labar D, Wijns W, et al. Myocardial blood flow, glucose uptake, and recruitment of inotropic reserve in chronic left ventricular ischemic dysfunction. Implications for the pathophysiology of chronic myocardial hibernation. *Circulation* 1996;94:651-9

79. Kageyama H, Morita K, Katoh C, Tsukamoto T, Noriyasu K, Mabuchi M, et al. Reduced ¹²³I-BMIPP uptake implies decreased myocardial flow reserve in patients with chronic stable angina. *Eur J Nucl Med Mol Imaging* 2006;33:6-12
80. Udelson JE, Bonow RO and Dilsizian V. The historical and conceptual evolution of radionuclide assessment of myocardial viability. *J Nucl Cardiol* 2004;11:318-34
81. Srinivasan G, Kitsiou AN, Bacharach SL, Bartlett ML, Miller-Davis C and Dilsizian V. [¹⁸F]fluorodeoxyglucose single photon emission computed tomography: can it replace PET and thallium SPECT for the assessment of myocardial viability? *Circulation* 1998;97:843-50
82. Tamaki N, Tadamura E, Kawamoto M, Magata Y, Yonekura Y, Fujibayashi Y, et al. Decreased uptake of iodinated branched fatty acid analog indicates metabolic alterations in ischemic myocardium. *J Nucl Med* 1995;36:1974-80
83. Hambye AS, Vaerenberg MM, Dobbeleir AA, Van den Heuvel PA and Franken PR. Abnormal BMIPP uptake in chronically dysfunctional myocardial segments: correlation with contractile response to low-dose dobutamine. *J Nucl Med* 1998;39:1845-50
84. Hambye AS, Dobbeleir AA, Vervaet AM, Van den Heuvel PA and Franken PR. BMIPP imaging to improve the value of sestamibi scintigraphy for predicting functional outcome in severe chronic ischemic left ventricular dysfunction. *J Nucl Med* 1999;40:1468-76
85. Kudoh T, Tadamura E, Tamaki N, Hattori N, Inubushi M, Kubo S, et al. Iodinated free fatty acid and ²⁰¹Tl uptake in chronically hypoperfused myocardium: histologic correlation study. *J Nucl Med* 2000;41:293-6
86. Taki J, Nakajima K, Matsunari I, Bunko H, Takata S, Kawasuji M, et al. Assessment of improvement of myocardial fatty acid uptake and function after revascularization using iodine-123-BMIPP. *J Nucl Med* 1997;38:1503-10
87. Sato H, Iwasaki T, Toyama T, Kaneko Y, Inoue T, Endo K, et al. Prediction of functional recovery after revascularization in coronary

- artery disease using (18)F-FDG and (123)I-BMIPP SPECT. *Chest* 2000;117:65-72
88. Tamaki N, Tadamura E, Kudoh T, Hattori N, Yonekura Y, Nohara R, et al. Prognostic value of iodine-123 labelled BMIPP fatty acid analogue imaging in patients with myocardial infarction. *Eur J Nucl Med* 1996;23:272-9
 89. Nakata T, Kobayashi T, Tamaki N, Kobayashi H, Wakabayashi T, Shimoshige S, et al. Prognostic value of impaired myocardial fatty acid uptake in patients with acute myocardial infarction. *Nucl Med Commun* 2000;21:897-906
 90. Nanasato M, Hirayama H, Ando A, Isobe S, Nonokawa M, Kinoshita Y, et al. Incremental predictive value of myocardial scintigraphy with 123I-BMIPP in patients with acute myocardial infarction treated with primary percutaneous coronary intervention. *Eur J Nucl Med Mol Imaging* 2004;31:1512-21
 91. Fukuzawa S, Ozawa S, Shimada K, Sugioka J and Inagaki M. Prognostic values of perfusion-metabolic mismatch in Tl-201 and BMIPP scintigraphic imaging in patients with chronic coronary artery disease and left ventricular dysfunction undergoing revascularization. *Ann Nucl Med* 2002;16:109-15
 92. Chikamori T, Fujita H, Nanasato M, Toba M and Nishimura T. Prognostic value of I-123 15-(p-iodophenyl)-3-(R,S) methylpentadecanoic acid myocardial imaging in patients with known or suspected coronary artery disease. *J Nucl Cardiol* 2005;12:172-8
 93. Nohara R, Hosokawa R, Hirai T, Okuda K, Ogino M, Fujibayashi Y, et al. Effect of metabolic substrate on BMIPP metabolism in canine myocardium. *J Nucl Med* 1998;39:1132-7
 94. Kurata C, Wakabayashi Y, Shouda S, Mikami T, Takei Y, Tawarahara K, et al. Influence of blood substrate levels on myocardial kinetics of iodine-123-BMIPP. *J Nucl Med* 1997;38:1079-84
 95. Matsuki T, Tamaki N, Nakata T, Doi A, Takahashi H, Iwata M, et al. Prognostic value of fatty acid imaging in patients with angina pectoris

- without prior myocardial infarction: comparison with stress thallium imaging. *Eur J Nucl Med Mol Imaging* 2004;31:1585-91
96. Yonekura Y, Brill AB, Som P, Yamamoto K, Srivastava SC, Iwai J, et al. Regional myocardial substrate uptake in hypertensive rats: a quantitative autoradiographic measurement. *Science* 1985;227:1494-6
 97. Kubota K, Som P, Oster ZH, Brill AB, Goodman MM, Knapp FF, Jr., et al. Detection of cardiomyopathy in an animal model using quantitative autoradiography. *J Nucl Med* 1988;29:1697-703
 98. Kurata C, Kobayashi A and Yamazaki N. Dual tracer autoradiographic study with thallium-201 and radioiodinated fatty acid in cardiomyopathic hamsters. *J Nucl Med* 1989;30:80-7
 99. Yamamoto K, Som P, Brill AB, Yonekura Y, Srivastava SC, Meinken GE, et al. Dual tracer autoradiographic study of beta-methyl-(1-14C) heptadecanoic acid and 15-p-(131I)-iodophenyl-beta-methylpentadecanoic acid in normotensive and hypertensive rats. *J Nucl Med* 1986;27:1178-83
 100. Kagaya Y, Kanno Y, Takeyama D, Ishide N, Maruyama Y, Takahashi T, et al. Effects of long-term pressure overload on regional myocardial glucose and free fatty acid uptake in rats. A quantitative autoradiographic study. *Circulation* 1990;81:1353-61
 101. Kurata C, Tawarahara K, Taguchi T, Aoshima S, Kobayashi A, Yamazaki N, et al. Myocardial emission computed tomography with iodine-123-labeled beta-methyl-branched fatty acid in patients with hypertrophic cardiomyopathy. *J Nucl Med* 1992;33:6-13
 102. Taki J, Nakajima K, Bunko H, Shimizu M, Taniguchi M and Hisada K. 123I-labelled BMIPP fatty acid myocardial scintigraphy in patients with hypertrophic cardiomyopathy: SPECT comparison with stress 201Tl. *Nucl Med Commun* 1993;14:181-8
 103. Takeishi Y, Chiba J, Abe S, Tonooka I, Komatani A and Tomoike H. Heterogeneous myocardial distribution of iodine-123 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) in patients with hypertrophic cardiomyopathy. *Eur J Nucl Med* 1992;19:775-82

104. Ohtsuki K, Sugihara H, Kuribayashi T and Nakagawa M. Impairment of BMIPP accumulation at junction of ventricular septum and left and right ventricular free walls in hypertrophic cardiomyopathy. *J Nucl Med* 1999;40:2007-13
105. Nishimura T, Nagata S, Uehara T, Morozumi T, Ishida Y, Nakata T, et al. Prognosis of hypertrophic cardiomyopathy: assessment by ¹²³I-BMIPP (beta-methyl-p-(¹²³I)iodophenyl pentadecanoic acid) myocardial single photon emission computed tomography. *Ann Nucl Med* 1996;10:71-8
106. Shimizu M, Ino H, Okeie K, Emoto Y, Yamaguchi M, Yasuda T, et al. Cardiac dysfunction and long-term prognosis in patients with nonobstructive hypertrophic cardiomyopathy and abnormal (¹²³I)-15-(p-Iodophenyl)-3(R,S)-methylpentadecanoic acid myocardial scintigraphy. *Cardiology* 2000;93:43-9
107. O'Gara PT, Bonow RO, Maron BJ, Damske BA, Van Lingen A, Bacharach SL, et al. Myocardial perfusion abnormalities in patients with hypertrophic cardiomyopathy: assessment with thallium-201 emission computed tomography. *Circulation* 1987;76:1214-23
108. von Dohlen TW, Prisant LM and Frank MJ. Significance of positive or negative thallium-201 scintigraphy in hypertrophic cardiomyopathy. *Am J Cardiol* 1989;64:498-503
109. Cannon RO, 3rd, Dilsizian V, O'Gara PT, Udelson JE, Schenke WH, Quyyumi A, et al. Myocardial metabolic, hemodynamic, and electrocardiographic significance of reversible thallium-201 abnormalities in hypertrophic cardiomyopathy. *Circulation* 1991;83:1660-7
110. Matsuo S, Nakamura Y, Takahashi M, Mitsunami K and Kinoshita M. Myocardial metabolic abnormalities in hypertrophic cardiomyopathy assessed by iodine-123-labeled beta-methyl-branched fatty acid myocardial scintigraphy and its relation to exercise-induced ischemia. *Jpn Circ J* 1998;62:167-72
111. Ishida Y, Nagata S, Uehara T, Yasumura Y, Fukuchi K and Miyatake

- K. Clinical analysis of myocardial perfusion and metabolism in patients with hypertrophic cardiomyopathy by single photon emission tomography and positron emission tomography. *J Cardiol* 2001;37 Suppl 1:121-8
112. Tadamura E, Kudoh T, Hattori N, Inubushi M, Magata Y, Konishi J, et al. Impairment of BMIPP uptake precedes abnormalities in oxygen and glucose metabolism in hypertrophic cardiomyopathy. *J Nucl Med* 1998;39:390-6
 113. Shimonagata T, Nishimura T, Uehara T, Hayashida K, Kumita S, Ohno A, et al. Discrepancies between myocardial perfusion and free fatty acid metabolism in patients with hypertrophic cardiomyopathy. *Nucl Med Commun* 1993;14:1005-13
 114. Nishimura T, Uehara T, Shimonagata T, Nagata S and Haze K. Clinical results with beta-methyl-p-(123I)iodophenylpentadecanoic acid, single-photon emission computed tomography in cardiac disease. *J Nucl Cardiol* 1994;1:S65-71
 115. Nakata T, Tanaka S, Hamagami S, Miyamoto K, Oh-hori K and Iimura O. Detection of impaired fatty acid metabolism and dyskinesia in hypertrophic cardiomyopathy with iodine-123-BMIPP. *J Nucl Med* 1996;37:1679-81
 116. Narita M and Kurihara T. Is I-123-beta-methyl-p-iodophenyl-methylpentadecanoic acid imaging useful to evaluate asymptomatic patients with hypertrophic cardiomyopathy? I-123 BMIPP imaging to evaluate asymptomatic hypertrophic cardiomyopathy. *Int J Cardiovasc Imaging* 2003;19:499-510
 117. Hashimoto Y, Yamabe H and Yokoyama M. Myocardial defect detected by 123I-BMIPP scintigraphy and left ventricular dysfunction in patients with idiopathic dilated cardiomyopathy. *Ann Nucl Med* 1996;10:225-30
 118. Yazaki Y, Isobe M, Takahashi W, Kitabayashi H, Nishiyama O, Sekiguchi M, et al. Assessment of myocardial fatty acid metabolic

- abnormalities in patients with idiopathic dilated cardiomyopathy using 123I BMIPP SPECT: correlation with clinicopathological findings and clinical course. *Heart* 1999;81:153-9
119. Yoshinaga K, Tahara M, Torii H and Kihara K. Predicting the effects on patients with dilated cardiomyopathy of beta-blocker therapy, by using iodine-123 15-(p-iodophenyl)-3- R,S-methylpentadecanoic acid (BMIPP) myocardial scintigraphy. *Ann Nucl Med* 1998;12:341-7
 120. Yoshinaga K, Tahara M, Torii H, Akimoto M, Kihara K and Tei C. Myocardial scintigraphy using iodine-123 15-(p-iodophenyl)-3-R, S-methylpentadecanoic acid predicts the response to beta-blocker therapy in patients with dilated cardiomyopathy but does not reflect therapeutic effect. *J Cardiol* 2000;35:343-51
 121. Ito T, Hoshida S, Nishino M, Aoi T, Egami Y, Takeda T, et al. Relationship between evaluation by quantitative fatty acid myocardial scintigraphy and response to beta-blockade therapy in patients with dilated cardiomyopathy. *Eur J Nucl Med* 2001;28:1811-6
 122. Kim Y, Sawada Y, Fujiwara G, Chiba H and Nishimura T. Therapeutic effect of co-enzyme Q10 on idiopathic dilated cardiomyopathy: assessment by iodine-123 labelled 15-(p-iodophenyl)-3(R,S)-methylpentadecanoic acid myocardial single-photon emission tomography. *Eur J Nucl Med* 1997;24:629-34
 123. Ishida Y, Yasumura Y, Nagaya N, Fukuchi K, Komamura K, Takamiya M, et al. Myocardial imaging with 123I-BMIPP in patients with congestive heart failure. *Int J Card Imaging* 1999;15:71-7
 124. Kawai S, Suzuki H, Yamaguchi H, Tanaka K, Sawada H, Aizawa T, et al. Ampulla cardiomyopathy ('Takotusbo' cardiomyopathy)--reversible left ventricular dysfunction: with ST segment elevation. *Jpn Circ J* 2000;64:156-9
 125. Tsuchihashi K, Ueshima K, Uchida T, Oh-mura N, Kimura K, Owa M, et al. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. *Angina Pectoris-Myocardial Infarction Investigations in*

- Japan. J Am Coll Cardiol 2001;38:11-8
126. Kurisu S, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Nishioka K, et al. Myocardial perfusion and fatty acid metabolism in patients with tako-tsubo-like left ventricular dysfunction. J Am Coll Cardiol 2003;41:743-8
127. Ito K, Sugihara H, Kinoshita N, Azuma A and Matsubara H. Assessment of Takotsubo cardiomyopathy (transient left ventricular apical ballooning) using 99mTc-tetrofosmin, 123I-BMIPP, 123I-MIBG and 99mTc-PYP myocardial SPECT. Ann Nucl Med 2005;19:435-45