

The Role of Fatty Acids in Cardiac Imaging*

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Nuclear medicine has progressed in conjunction with the recent growth of molecular medicine. Myocardial energy metabolism has long been investigated in experimental models with the use of Langendorff's method or coronary sinus blood sampling. However, the introduction of a variety of radiopharmaceutical agents has now made possible easy visualization of myocardial energy metabolism in vivo with nuclear medicine techniques.

Key Words: emission CT; myocardial ischemia; cardiomyopathy; metabolism

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The heart is an active organ that requires a high uptake of oxygen to provide sufficient energy for balancing mechanical requirements. Oxygen consumption increases in almost a direct ratio with increases in workload. When the oxygen supply is inadequate for the demand, reversible or irreversible metabolic changes may occur. Such an imbalance is most often observed in severe coronary artery disease, in which the oxygen supply is limited because of stenosis or occlusion of major arteries. Energy is also required to maintain membrane potential for regulating ion concentrations in the cells.

Glucose and free fatty acids are major energy sources, or substrates, for the myocardium. Substrates require enzymatic conversion before breakdown, and their uptake by the heart partially depends on their arterial concentration. In the fasting state, the level of free fatty acids in the plasma and their uptake by the myocardium are high, and glucose oxidation is suppressed. When glucose or insulin levels are high, such as after a meal, glucose oxidation increases and fatty acid use is suppressed (1).

Long-chain fatty acids are the principle energy source for the normoxic myocardium and are rapidly metabolized by β -oxidation. Approximately 60%–80% of adenosine triphosphate (ATP) produced in aerobic myocardium derives from fatty acid oxidation. Long-chain free fatty acids easily pass through the sarcolemmic membrane to be activated as acyl coenzyme A (CoA). Acyl CoA is carried into mitochondria through an acyl carnitine carrier system to enter the β -oxida-

tion pathway, which cuts off 2-carbon fractions. After β -oxidation, acetyl CoA is formed and enters the tricarboxylic acid cycle for further oxidation to become water and carbon dioxide. Some part of free fatty acids is not oxidized but is formed into triglycerides and myocardial structural lipids and stays in the myocardium for a long time.

Glucose is not normally the major myocardial fuel but can become so after a high-carbohydrate meal with its subsequent increases in plasma insulin levels. In ischemia, glucose plays a major role in residual oxidative metabolism, whereas oxidation of long-chain fatty acids is greatly suppressed (2,3). Thus, an alteration of fatty acid oxidation is considered to be a sensitive marker of ischemia and myocardial damage. Because fatty acids are a major energy source in the myocardium, several radiolabeled fatty acid analogs have been introduced to assess myocardial cellular function (Fig. 1).

PET

Tracers

Pathways of intracellular metabolism that have been studied in animal tissues can be traced in humans by PET. PET has the unique characteristic of allowing in vivo tracing of physiologic and biochemical functions using radiolabeled physiologic compounds. Thus, PET allows noninvasive monitoring of myocardial metabolic pathways with the use of suitable radiotracers (4,5). FDG is often used for identifying ischemic but viable myocardium. [^{11}C]palmitate, a radiolabeled long-chain saturated fatty acid compound, is most commonly used for assessing myocardial fatty acid metabolism in PET studies.

[^{11}C]palmitate participates in the metabolic fate of its natural counterpart. Once the tracer is esterified to acyl CoA, a fraction proceeds through the carnitine shuttle into mitochondria. Then, β -oxidation catabolizes the long-chain fatty acids into 2-carbon fragments that are oxidized through the tricarboxylic acid cycle and released from the myocardium in the form of [^{11}C]carbon dioxide (Fig. 2). The remaining fraction of acyl CoA enters the intracellular lipid pool mainly in the form of triglycerides and phospholipids. Dynamic PET after intracoronary administration of [^{11}C]palmitate indicates biexponential washout from the myocardium as a metabolic fate of the tracer (6,7). The rapid-clearance fraction corresponds to β -oxidation, whereas the slow-washout fraction reflects the turnover rate of the intracellular lipid pool. Similar biexponential clearance

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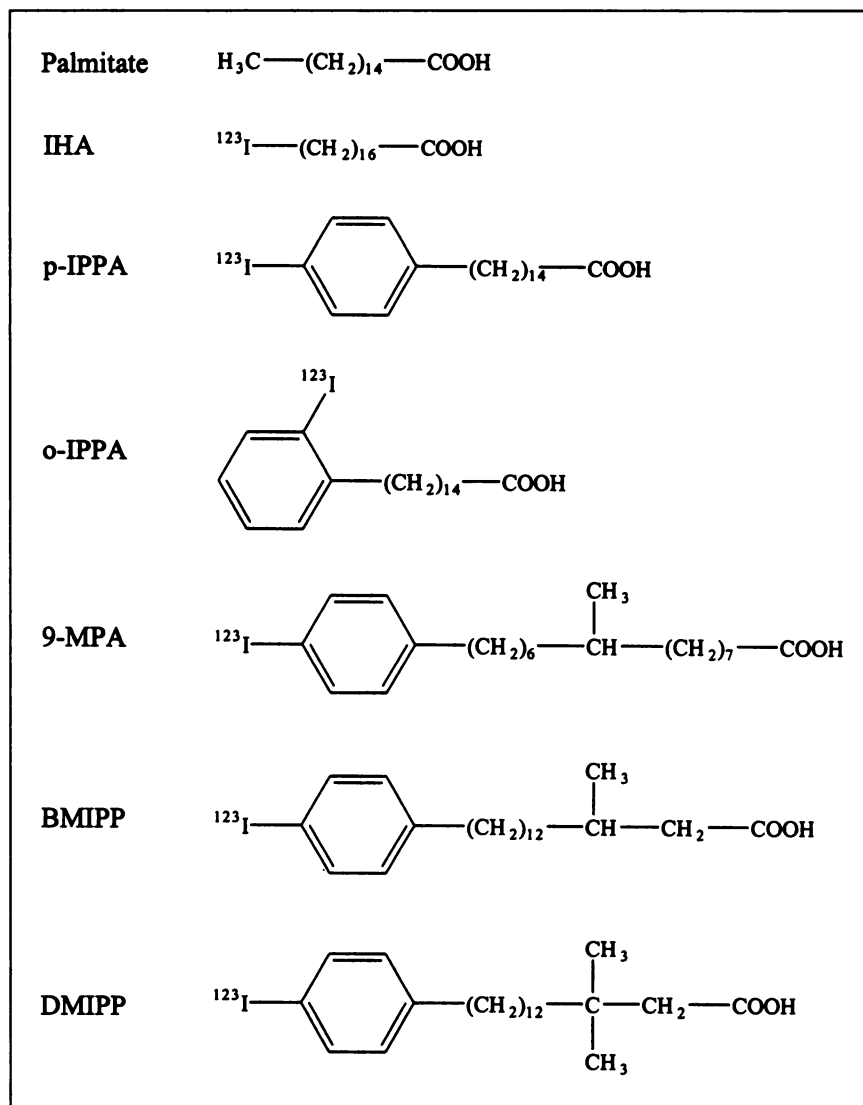


FIGURE 1. Structures of various radiolabeled fatty acid analogs. BMIPP = 15-(*p*-iodophenyl)-3-(*R,S*)-methylpentadecanoic acid; DMIPP = 15-(*p*-iodophenyl)-3,3-dimethylpentadecanoic acid; IHA = 17-iodoheptadecanoic acid; IPPA = 15-(*p*-[^{123}I]iodophenyl)pentadecanoic acid (*o* = ortho position; *p* = para position); 9-MPA = (*p*-[^{123}I]iodophenyl)-9-(*R,S*)-methylpentadecanoic acid.

curves have been obtained with intravenous administration of the tracer (8–10). The size of the rapid-clearance fraction has correlated well with myocardial oxygen consumption (10).

Clinical Applications

In ischemic myocardium, fatty acid use is suppressed with the reduction of β -oxidation. Decreases in the single-pass extraction fraction of [^{11}C]palmitate are probably caused by an increase in shunting into the triglyceride pool and diffusion back into the coronary venous circulation (10). Thus, regional uptake of [^{11}C]palmitate is reduced in severely ischemic myocardium. In the clinical setting, myocardial infarction has been quantitatively estimated and characterized through the defect size on the early [^{11}C]palmitate images (11,12). Although most of the [^{11}C]palmitate studies have included qualitative and semiquantitative evaluation of fatty acid metabolism, the quantitative value of myocardial fatty acid use and oxidation is difficult to estimate in absolute units (milliequivalents of free fatty acid per minute per gram of myocardium).

Schon et al. (10) nicely demonstrated clearance of radioactivity from the myocardium after intravenous administration of [^{11}C]palmitate. Clearance of [^{11}C]palmitate showed 2 components consistent with incorporation of the tracer into at least 2 pools with different turnover rates (Fig. 3). Because the clearance rate of the fast component is closely correlated with [^{11}C]carbon dioxide clearance, this component is considered to represent β -oxidation of [^{11}C]palmitate. The slow component of the tracer washout may reflect slow turnover of the triglycerides and phospholipids. A significant reduction in the size and rate of the fast-clearance component of the activity was shown in ischemic myocardium, indicating reduced β -oxidation of free fatty acids (10).

For better differentiation of metabolic alterations in ischemic myocardium, metabolic studies during certain interventions are often required. Grover-McKay et al. (13) used atrial pacing for delineating ischemic myocardium. Tamaki et al. (14) used dobutamine infusion, which enhanced separation of ischemia from normal myocardium on the basis of differences in clearance response. The abnormal

Kinetics of Fatty Acids

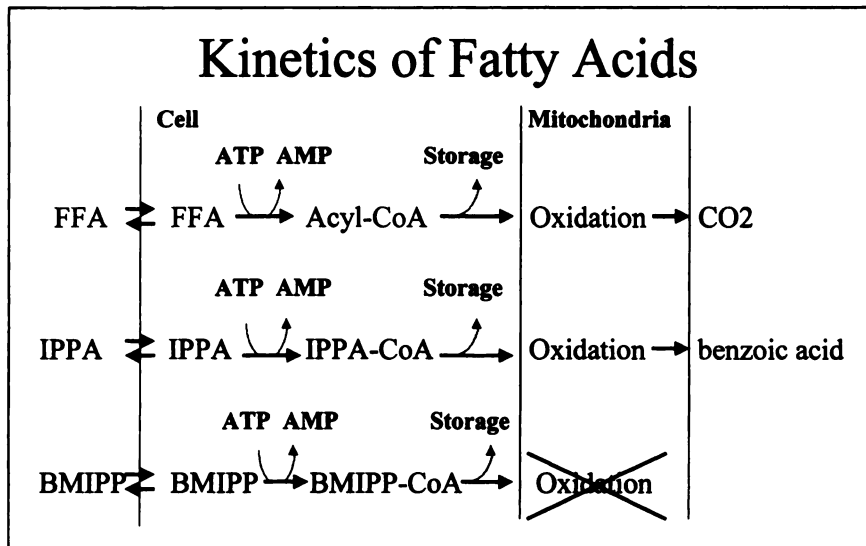


FIGURE 2. Tracer kinetics of radiolabeled free fatty acids (FFA), such as [^{11}C]palmitate; iodinated straight-chain fatty acid compounds, such as the para position of 15-(p -[^{123}I]iodophenyl)pentadecanoic acid (IPPA); and iodinated branched-chain fatty acid compounds, such as 15-(p -iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP). FFA and IPPA are oxidized in mitochondria and washed out from myocardium as carbon dioxide and [^{123}I]benzoic acid, respectively. On the contrary, BMIPP is retained in myocardium without rapid oxidation. AMP = adenosine 5'-monophosphate; CoA = coenzyme A.

response (delayed clearance of [^{11}C]palmitate) was more often observed in patients with severe coronary artery stenosis. The metabolic response under stress is thought to have a key role in differentiating reversible ischemia from irreversible scar tissue through a concept similar to that of low-dose dobutamine echocardiography; however, this role has not been fully validated for [^{11}C]palmitate.

[^{11}C]acetate has been used to assess pathophysiologic conditions in patients with coronary artery disease and cardiomyopathy. After administration, [^{11}C]acetate is activated to acetyl CoA, oxidized in mitochondria by the tricarboxylic acid cycle, and washed out from the myocardium as [^{11}C]dioxide. The early clearance rate in the myocardium measured by PET corresponds closely to release of [^{11}C]dioxide, indicating oxidative metabolism. The basic kinetics

and clinical applications of this tracer have been fully described (15).

Because of the limited availability of PET, only the few institutions that have a PET camera and a cyclotron can study myocardial energy metabolism in vivo. However, a variety of [^{123}I]labeled fatty acid compounds have been introduced to probe myocardial energy metabolism in vivo in routine clinical nuclear medicine facilities.

TWO TYPES OF IODINATED FATTY ACIDS

[^{123}I] is an appropriate choice for labeling metabolic substrates because its chemical properties allow replacement of a molecular methyl group through a halogen exchange reaction and because it is widely applicable to clinical

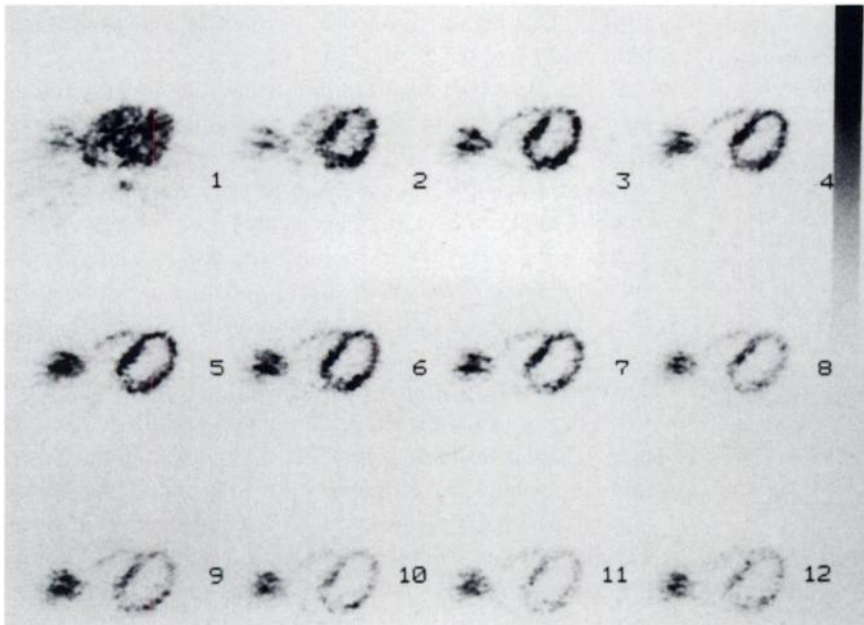


FIGURE 3. Serial dynamic images (2 min per frame) of myocardium after administration of [^{11}C]palmitate to healthy volunteer. Note high myocardial uptake in early stage, with rapid washout from myocardium.

practice. Thus, ^{123}I -labeled fatty acids have received great attention for assessing myocardial metabolism in vivo (16–18).

The 2 groups of iodinated fatty acid compounds include straight-chain fatty acids and modified branched fatty acids (Table 1). The straight-chain fatty acids are generally metabolized through β -oxidation and released from the myocardium (Fig. 2). Therefore, fatty acid use can be directly assessed by the washout kinetics of the tracer, as for [^{11}C]palmitate. However, rapid washout from the myocardium may require fast dynamic acquisition for imaging after tracer administration. This requirement may become a critical problem for tomography with a rotating gamma camera. Inadequate image quality with a low target-to-background ratio may often be observed. In addition, back-diffusion and metabolites should be considered in the kinetic model for quantitative analysis of fatty acid metabolism.

The introduction of modified fatty acids is based on the concept of myocardial retention from metabolic trapping (Fig. 2). Thus, excellent myocardial images are obtained with long acquisition times. However, their uptake may not directly reflect fatty acid oxidation but may, instead, be based on the fatty acid uptake and turnover rate of the lipid pool. Therefore, combined imaging of iodinated fatty acids and perfusion is required to show perfusion–metabolism mismatching and to characterize fatty acid use.

^{123}I -LABELED STRAIGHT-CHAIN FATTY ACIDS

Tracers

The introduction of radioiodine to the terminal position of fatty acids has made great progress without altering extraction efficiency compared with the naturally occurring com-

pound. A chain length of 15–21 carbon atoms has effected the best myocardial extraction, and a chain length of 16 or 17 carbon atoms has appeared optimal for myocardial imaging (19). An early example of an iodinated straight-chain fatty acid—16- ^{123}I iodohexadecanoic acid—is rapidly degraded in the myocardium in experimental studies (20). The mathematic model of the metabolism of this fatty acid has been created for quantitative analysis of the metabolism of many fatty acids (21). Van der Wall et al. (22) initially applied this agent to show reduced tracer uptake in ischemic regions in metabolic assessments of patients with coronary artery disease.

Similar kinetic studies of metabolism have been performed in experimental models and clinical settings using 17-iodoheptadecanoic acid (IHA) (23–27). IHA is an analog of stearic acid that has expanded interest in the use of ^{123}I -labeled fatty acids for myocardial imaging. Kinetic studies have assessed fatty acid oxidative metabolism using sequential planar imaging after administration of IHA to create time–activity curves.

Several clinical investigations have used ^{123}I -labeled heptadecanoic acid (28–32). The half-time of tracer washout varied significantly, and background subtraction may be required for better imaging and more accurate assessment of washout. In addition, an inability to perform tomography because of rapid washout may limit the clinical usefulness of IHA.

New biochemical methods have been proposed to avoid high background activity in imaging studies and to eliminate rapid deiodination by stabilizing the ^{123}I attached to the fatty acid. In particular, stable iodinated fatty acid compounds with iodide attached to the para or ortho position of the phenyl ring have been developed. Machulla et al. (33) introduced the terminally phenylated iodinated straight-chain fatty acid 15-(*p*- ^{123}I iodophenyl)pentadecanoic acid (IPPA). This agent has shown no essential release of free radioiodide into the circulation.

Kaiser et al. (34) analyzed differences between the tracer kinetics of the para and ortho positions of iodophenyl pentadecanoic acid. IPPA is rapidly excreted from the myocardium as [^{123}I]benzoic acid (Fig. 1). On the contrary, ortho-iodophenyl pentadecanoic acid is readily taken up and is retained a long time in the myocardium. Because ortho-PPA undergoes β -oxidation, it has potential for evaluating fatty acid transport into mitochondria. IPPA has been more widely investigated. Reske et al. (35,36) showed rapid accumulation of tracer in the heart after administration of IPPA, with fast clearance from the myocardium in the biexponential fashion characteristic of [^{11}C]palmitate. Preliminary studies have shown high myocardial uptake in normal myocardium, in contrast to decreased uptake in areas supplied by an occluded coronary artery. In addition, Caldwell et al. (37) compared IPPA uptake and perfusion during exercise and found a linear correlation.

TABLE 1
Characteristics of Straight-Chain and Branched-Chain Fatty Acids

Characteristic	Straight-chain fatty acids	Branched-chain fatty acids
PET tracers	[^{11}C]palmitate	3-(<i>R,S</i>)-[^{11}C]methylheptadecanoic acid
SPECT tracers	16- ^{123}I iodohexadecanoic acid	15-(<i>p</i> - ^{123}I iodophenyl)-3-(<i>R,S</i>)-methylpentadecanoic acid (BMIPP)
	17- ^{123}I iodoheptadecanoic acid (IHA)	15-(<i>p</i> - ^{123}I iodophenyl)-3,3-dimethylpentadecanoic acid (DMIPP)
	para-15-(<i>p</i> - ^{123}I iodophenyl)pentadecanoic acid (IPPA)	(<i>p</i> - ^{123}I iodophenyl)-9-(<i>R,S</i>)-methylpentadecanoic acid (9MPA)
Measurement	Uptake and clearance	Uptake (metabolic trapping)
Advantages	β -oxidation assessment	Suitable for SPECT Excellent image quality

Clinical Applications

IPPA imaging has been applied to patients with coronary artery disease. A segmental reduction of IPPA correlated well with regional perfusion defects on thallium scans (38,39). Reske et al. (35) showed the IPPA defects to be generally more prominent than thallium defects, probably because of a lower extraction fraction for IPPA in ischemic areas. This finding indicates that IPPA studies at rest are useful for the detection of coronary artery disease.

Kuikka et al. (40) found in the study of viability assessment that preserved IPPA uptake was seen in 39% of segments with a persistent methoxyisobutyl isonitrile (MIBI) defect and normalized in 25% of these segments, indicating the value of IPPA imaging over MIBI perfusion studies. Murray et al. (41) compared dynamic IPPA study data using a multicrystal camera with data from transmural biopsies and thallium scanning and concluded that the viability findings from IPPA studies were quite similar to those from biopsy and such viability findings were more often seen than the thallium scans. Recent studies have shown the clinical value of IPPA SPECT at rest for assessing viability on the basis of a prediction of functional recovery after revascularization (42,43). Hansen et al. (42) found the areas showing intermediate-range IPPA washout (less than normal washout but more than washout from infarcted areas) to represent ischemic but viable myocardium. Iskandrian et al. (43) indicated that reversibility of IPPA imaging was seen more often for IPPA imaging than that of rest-redistribution thallium imaging. The semiquantitative analysis possible with IPPA kinetics was suggested to be an advantage over rest-redistribution thallium imaging.

IPPA has also been applied to other myocardial disorders. Ugolini et al. (44) studied IPPA SPECT at rest in patients with dilated cardiomyopathy and showed that IPPA uptake was more heterogeneous and washout was faster in these patients than in healthy volunteers. Wolfe et al. (45) studied stress IPPA imaging in patients with left ventricular hypertrophy secondary to arterial hypertension. Reduced uptake and delayed washout of IPPA from the myocardium indicated regional myocardial ischemia in hypertrophic myocardium. Although stress thallium studies did not show abnormal perfusion, such regional heterogeneity of fatty acid metabolism suggests impaired microcirculation in hypertrophic myocardium. However, whether such metabolic abnormalities may precede regional perfusion abnormalities is uncertain.

The tracer kinetics of IPPA are well documented, and its unique properties of probing perfusion and fatty acid turnover have enabled many important clinical studies. Of particular use is the reduced initial uptake and slow washout of IPPA commonly seen in ischemic myocardium. Kinetic studies have a key role in assessing myocardial viability, although relatively rapid washout from the myocardium may create difficulties for kinetic analysis with a conventional SPECT camera. Broader clinical experience is needed

to confirm the usefulness of these agents for detecting coronary artery disease and assessing tissue viability.

¹²³I-LABELED MODIFIED FATTY ACIDS

Tracers

Methyl branching of the fatty acid chain is thought to protect these compounds against metabolism by β -oxidation while retaining some physiologic properties such as fatty acid uptake and the turnover rate of the triglyceride pool. The degree of branching and the length of the chain determines myocardial uptake of these tracers.

Several iodinated branched-chain fatty acids have been introduced to assess fatty acid use. These are particularly useful for SPECT with a conventional gamma camera, because they are retained in the myocardium for long time (metabolic trapping). One example is (*p*-[¹²³I]iodophenyl)-9-(*R,S*)-methylpentadecanoic acid (9MPA). This tracer is trapped in the myocardium with a mechanism similar to that for free fatty acids. Whereas other branched fatty acid analogs stay in the myocardium for a long time, this tracer is thought to be converted to iodophenyl-3-methylnonanoic acid (3MNA) after 3 cycles of β -oxidation. The water-soluble intermediate metabolite, 3MNA, is rapidly washed out from the myocardium. Thus, this tracer is designed to trace both fatty acid uptake and some part of β -oxidation. Chouraqui et al. (46), in their clinical study, found a high uptake and retention in the myocardium shortly after 9MPA administration. However, the postexercise study showed findings comparable with those of a stress thallium study. Unfortunately, these investigators did not evaluate the clinical importance of metabolism more than perfusion. Clinical trials of 9MPA have been performed in Japan, and abnormal uptake of this tracer was well shown in ischemic regions (47-49). The results seem to be comparable with or even better than those for 15-(*p*-iodophenyl)-3-(*R,S*)-methylpentadecanoic acid (BMIPP) in identifying ischemic myocardium (49). In addition, some washout from the myocardium occurs, with the rate seeming to differ in various myocardial disorders. Because the washout rate of this compound was slower than that of the straight-chain fatty acid, IPPA, 9MPA is more feasible for washout analysis with SPECT.

16-[¹²³I]iodo-3-methylhexadecanoic acid (IMHA) is another example of a methyl-branched analog. Marie et al. (50) showed that reversibility of a defect was more often observed on IMHA imaging than on rest-reinjection thallium imaging, indicating the value of IMHA for identifying ischemic myocardium. Marie et al. also indicated that IMHA imaging is a better marker of reversible ischemic myocardium after revascularization than is rest-reinjection ²⁰¹Tl imaging in patients with prior myocardial infarction (51). Thus, preserved uptake of IMHA in the hypoperfused areas is considered to be a better marker of tissue viability than are the findings of conventional thallium imaging.

Another approach for labeling a metabolically trapped analog is to use a phenylene substituted fatty acid analog.

13-*p*-[¹²³I]-3-(*p*-phenylene)tridecanoic acid (PHIPA) is considered the most promising tracer for myocardial imaging. PHIPA is extracted by the myocardium in a manner similar to that of the unmodified fatty acid analog, IPPA. Retention of the tracer results from the presence of the *p*-phenylene group, which prevents more than 1 β -oxidation cycle (52). In a cardiac transplantation study in humans, Jonas et al. (53) observed mismatching of fatty acid uptake and ^{99m}Tc sestamibi perfusion, indicating residual viable myocardium, whereas a matched defect was associated with a myocardial scar. More clinical experience is warranted to confirm the value of this agent for assessing viability.

Methyl-branched fatty acid is based on the expected inhibition of β -oxidation by the presence of a methyl group in the β -position. Knapp et al. (54) first introduced BMIPP and 15-(*p*-iodophenyl)-3,3-dimethylpentadecanoic acid (DMIPP). Animal experiments showed slow clearance of BMIPP (approximately 25% in 2 h), whereas DMIPP showed no clearance. The fractional distribution of these compounds at 30 min after tracer injection in rats indicated that 65%–80% of the total activity resided in the triglyceride pool. Sloof et al. (55) compared these 2 compounds in humans and concluded that BMIPP was more favorable because of lower liver counts. BMIPP has been the most widely used tracer to investigate basic kinetics and clinical implications, particularly in Japan and Europe.

Several studies have investigated tracer kinetics in the myocardium with the use of BMIPP. Fujibayashi et al. (56), in a canine study, found that 74% of the injected dose of BMIPP was extracted from the plasma into the myocardium and approximately 65% was retained after intracoronary injection, with only an 8.7% washout fraction. The slow washout from the myocardium was seen as α - and β -oxidation metabolites (56–58). Hosokawa et al. (59) showed enhanced rapid washout from the myocardium by a long-chain fatty acid transporter inhibitor, etomoxir, that may produce conditions similar to those of myocardial ischemia. Fujibayashi et al. (60,61) indicated that BMIPP uptake correlated with ATP concentration in acutely damaged myocardium treated with dinitrophenol or tetradecylglycidic acid, inhibitors of mitochondrial carnitine acyltransferase I. Nohara et al. (62) also showed that BMIPP uptake correlated with ATP levels in the occlusion–reperfusion canine model and concluded that BMIPP may be useful for differentiating ischemic from infarcted myocardium in their model. The importance of ATP levels in the retention of BMIPP, probably because of cytosolic activation of BMIPP into BMIPP CoA, is supported by these results.

In the occlusion–reperfusion canine model, higher uptake of BMIPP than of thallium has been reported for in vivo and ex vivo studies (63,64). Such BMIPP and perfusion mismatching (more BMIPP uptake than perfusion) conflicts with clinical findings, because less BMIPP uptake than perfusion is observed in most clinical studies. Such conflicting results may be partly explained by fatty acid uptake, which is influenced by both residence time in the capillary

bed and the rate of metabolism extracted into myocytes. In acute ischemia, prolonged residence may cause higher retention of fatty acid analogs in the myocardium, with washout similar to that in normal myocardium. In chronic ischemia, on the other hand, the single-pass extraction fraction of the tracer decreases with an increase in back-diffusion into the coronary venous circulation. In a canine ischemic model, Hosokawa et al. (65) nicely showed this increase in back-diffusion of nonmetabolized BMIPP in the coronary sinus sampling after BMIPP administration. Thus, regional uptake of BMIPP may be reduced in severely ischemic myocardium.

BMIPP was usually injected under fasting conditions, and SPECT was performed approximately 20–30 min after tracer administration. BMIPP uptake in the myocardium was not influenced by the plasma substrate levels in the human study (66). In approximately 0.2%–1% of all patients who undergo clinical BMIPP imaging, no accumulation of BMIPP is seen in the myocardium (67). Clearance of blood-pool activity is reduced in these patients. But comparative imaging has indicated a reduction in [¹¹C]palmitate uptake and enhancement of FDG uptake in the myocardium in these patients, indicating metabolic shifting from free fatty acid use to glucose use under fasting conditions (67). Absence of BMIPP uptake in the myocardium may be related to absence of membrane fatty acid transporter CD-36, which may relate to BMIPP uptake in these patients (68).

Clinical Applications

In clinical studies, rapid and high myocardial uptake and long retention have been observed after BMIPP administration, with low background activity and low uptake in the liver and lungs 60 min later. High-quality SPECT images can be obtained by collecting myocardial images for approximately 20 min. Generally, BMIPP uptake has been similar to thallium perfusion. Therefore, BMIPP distribution is carefully assessed to identify regional decreases in tracer distribution as areas of altered fatty acid uptake and metabolism. Regional BMIPP uptake is also compared with regional perfusion to detect the presence of a perfusion–metabolism mismatch. Less BMIPP uptake than perfusion (discordant BMIPP uptake) is often observed in ischemic myocardium. However, when BMIPP distribution and thallium perfusion are compared, differences in photon attenuation should be considered. More BMIPP uptake than thallium perfusion is occasionally observed in septal and inferior regions in healthy volunteers, probably because of greater photon attenuation from thallium in these areas. Such technical errors may be minimized by comparing BMIPP uptake with ^{99m}Tc perfusion agents with similar photon attenuation effects. Differences in acquisition and processing may significantly modify the areas of mismatched patterns. Dobbeleir et al. (69) pointed out the importance of scatter correction for accurate estimates of such areas on BMIPP SPECT. Sequential dynamic SPECT was performed using a triple-head camera and found that the initial distribution was similar to perfusion and that 20- to 30-min images may

reflect more metabolic function (70,71). Therefore, a single injection of BMIPP may provide information on both perfusion and metabolism without the use of a perfusion tracer. However, the quality of initial BMIPP images 2–5 min after BMIPP administration may be adequate for reliable interpretation. Recently, gated BMIPP SPECT has been introduced for simultaneous assessment of myocardial metabolism and ventricular function (72).

Tamaki et al. (73) first applied BMIPP imaging in patients with myocardial infarction and showed that less BMIPP uptake than thallium perfusion was frequently seen in patients with a recent onset of infarction, recanalized arteries, or severe wall motion abnormalities. Less BMIPP uptake than ^{99m}Tc -sestamibi perfusion in patients with subacute myocardial infarction was also reported by a European group (74,75). This group suggested that the finding resulted from stunning, or delayed recovery of metabolism after recovery of perfusion. Furutani et al. (76) indicated that the size of a defect seen with BMIPP may identify the area at risk in patients with successful revascularization after acute myocardial infarction. Kawai et al. (77) proved that the defect areas found during the subacute phase with BMIPP correlated with areas at risk calculated by perfusion imaging during the acute phase of myocardial infarction, at hospital admission. These authors suggested that BMIPP may reflect prior severe ischemia after recovery of perfusion, or so-called ischemic memory. Many investigators have shown that areas of less BMIPP uptake than perfusion in the acute and subacute phases of myocardial infarction show improvement of wall motion abnormalities on follow-up studies, suggesting that such areas represent stunned myocardium (78–81). In an extension of the concept of ischemic memory imaging, BMIPP at rest has been used for identifying ischemic myocardium (82–86). In addition, decreases in BMIPP uptake have been shown to be often associated with regional wall motion abnormalities in subjects without a history of myocardial infarction (85,86). The sensitivity of BMIPP imaging for detecting coronary artery lesions, ranging from only 40% to 60%, may not be satisfactory compared with conventional stress perfusion imaging. However, imaging does not require a provocative test, and therefore, this imaging method is suitable for patients with unstable angina or severe coronary artery disease. In addition, metabolic alterations are most often seen in patients with vasospastic angina, probably as a result of repetitive ischemic episodes, but stress perfusion studies may not reveal regional perfusion abnormalities. Therefore, in these patients, BMIPP imaging is considered the method of choice for noninvasively showing that regional abnormalities represent ischemic memory.

It is important to know whether a discordance between BMIPP uptake and perfusion represents reversible myocardial ischemia. Matsunari et al. (70) and Kawamoto et al. (87) reported that areas with reduced uptake of BMIPP showed thallium redistribution on stress-delayed scans (Fig. 4). Tamaki et al. (17,88) showed that reduced BMIPP uptake

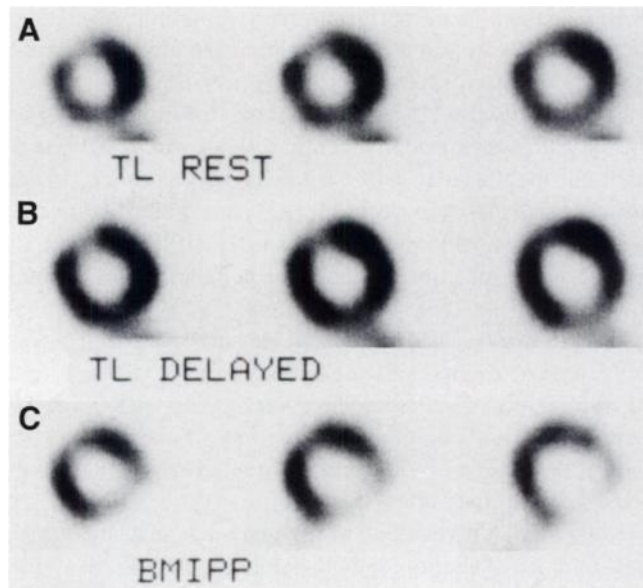


FIGURE 4. Series of short-axis slices of resting (A) and delayed (B) thallium (TL) scans and resting BMIPP scan (C) of patient with unstable angina. Although thallium did not show definite perfusion abnormalities, decreased BMIPP uptake was noted in lateral region.

was observed in areas with increased FDG uptake from exogenous glucose use. On PET images, the areas with discordant BMIPP uptake were most likely to show ischemia, whereas a concordant decrease in both BMIPP and thallium might have reflected scarring. In addition, such areas showed preserved oxidative metabolism as assessed by [^{11}C]acetate PET studies. In ischemic myocardium, fatty acid oxidation is easily suppressed, and glucose metabolism provides a major energy source. In addition, dysfunctional areas—those with a mismatched BMIPP–perfusion pattern—were more likely to have residual inotropic reserves under dobutamine infusion than were areas with a matched pattern (89). Furthermore, Kudoh et al. (90) showed that areas of BMIPP–thallium mismatching had less than 10% fibrosis on histologic examination during cardiac surgery. These data indicate that a discordance between BMIPP uptake and thallium perfusion may represent myocardial ischemia.

Several reports have indicated that discordant BMIPP uptake represents ischemia that is reversible and for which regional function may improve after revascularization. Franken et al. (78) showed that in areas for which BMIPP uptake was less than ^{99m}Tc -sestamibi uptake, cardiac function improved shortly after myocardial infarction. Ito et al. (79) also showed recovery of regional dysfunction after myocardial infarction in areas with a discordance in defect size between BMIPP imaging and thallium imaging. The degree of perfusion–metabolism mismatching may correlate with subsequent improvement of postischemic dysfunction (80,91). In addition, Taki et al. (85) showed that areas of discordance between BMIPP uptake and reinjection thallium uptake before revascularization were a good predictor of improvement of ejection fraction. These data show that less

BMIPP uptake than perfusion may represent reversible ischemic myocardium and that regional and global dysfunction will improve in coronary patients.

Because discordant BMIPP uptake may represent ischemic and jeopardized myocardium, combined BMIPP and thallium imaging may have value for risk stratification in coronary patients. Tamaki et al. (92) surveyed 50 consecutive patients who underwent follow-up BMIPP and thallium scanning at a mean of 23 mo after myocardial infarction. Among various clinical, angiographic, and radionuclide indices, discordant BMIPP uptake was the best predictor of future cardiac events. The number of coronary stenoses was the second best predictor. These preliminary data suggest that BMIPP and thallium imaging may have prognostic value through identifying high-risk subgroups among patients with coronary artery disease.

Evaluation of myocardial metabolism may play an important role in assessing pathophysiology in patients with cardiomyopathy. Alterations of fatty acid metabolism are frequently observed on [¹¹C]palmitate or [¹¹C]acetate PET images of patients with hypertrophic cardiomyopathy. BMIPP distribution has been extensively studied in patients with hypertrophic cardiomyopathy in Japan and has been shown to be heterogeneous in hypertrophied myocardium independent of thallium perfusion (93–96). Although thallium uptake is somewhat heterogeneous in hypertrophied septal regions, BMIPP uptake is strikingly decreased, indicating a perfusion–metabolism mismatch. Thus, BMIPP may permit detection of altered fatty acid metabolism independent of perfusion. Compared with abnormalities seen on PET images, decreased BMIPP uptake seems to be an early sign of cardiomyopathy (96). Because most patients with hypertrophic cardiomyopathy showed a discordance between BMIPP uptake and perfusion in septal regions, combined BMIPP and perfusion tracer imaging may differentiate patients with cardiomyopathy from patients with hypertrophic myocardial conditions, such as hypertensive heart disease, in which no such discordant distribution is observed.

BMIPP imaging has also been applied to patients with idiopathic dilated cardiomyopathy. Hashimoto et al. (97) showed a defect of BMIPP uptake in relation to the severity of left ventricular dysfunction. The percentage of fractional shortening measured by echocardiography correlated significantly with BMIPP defect scores but not with thallium defect scores, indicating that ventricular function correlates more closely with metabolic information than with perfusion. Yoshinaga et al. (98) suggested that a decrease in BMIPP uptake in patients with dilated cardiomyopathy may indicate that the patients will not respond well to β -blocker therapy. Although these data remain preliminary, they may provide new insights into pathophysiology and treatment strategies in patients with poor left ventricular function.

CONCLUSION

The results of basic and preliminary clinical studies have suggested 3 potential clinical roles for fatty acid imaging:

detection of myocardial ischemia and ischemic history, assessment of viability through areas of perfusion–metabolism mismatching, and early detection and classification of cardiomyopathy. Although fatty acids are a major energy source in normal myocardium, fatty acid oxidation is easily suppressed in ischemic and postischemic myocardium. Thus, assessment of fatty acid metabolism by radionuclide techniques has an important role in early detection of myocardial ischemia and assessment of the severity of ischemic heart disease. Reduced use of fatty acids at rest has often been observed in severely ischemic myocardium and possibly in postischemic myocardium despite normal perfusion at rest. Attention has recently focused on the role of metabolic imaging in identifying postischemic insult as ischemic memory imaging (99). Although we need basic studies and more clinical experience to prove this concept, it may expand the use of metabolic imaging in the evaluation of coronary artery disease. Segments in which BMIPP uptake is less than perfusion were often seen in patients with coronary artery disease and may represent ischemic but viable myocardium. Therefore, combined imaging using fatty acid analogs and perfusion markers permits detection of ischemic but viable myocardium based on alterations of myocardial energy metabolism. Furthermore, BMIPP holds promise for showing early alterations in energy metabolism in a variety of myocardial disorders. Although the tracers we have discussed in this article are now available in only a few countries, worldwide use is soon expected.

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