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Review article

# Iodine-123-labelled fatty acids for myocardial single-photon emission tomography: current status and future perspectives

F.F. (Russ) Knapp, Jr.[1], J. Kropp[2]

[1] Nuclear Medicine Group, Health Sciences Research Division, Oak Ridge National Laboratory (ORNL), Oak Ridge, TN 37831-6229, USA
[2] Klinik und Poliklinik für Nuklearmedizin des Universitätsklinikums der Technischen Universität, Fetscher Strasse 74, D-01307 Dresden, Germany

**Abstract.** Renewed interest in the clinical use of iodine-123-labelled fatty acids is currently primarily focused on the use of iodine-123-labelled 15-(*p*-iodophenyl)pentadecanoic acid (IPPA) and "modified" fatty acid analogues such as 15-(*p*-iodophenyl)-3-*R,S*-methylpentadecanoic acid (BMIPP) which show delayed myocardial clearance, thus permitting single-photon emission tomographic imaging. Interest in the use of BMIPP and similar agents results from the differences which have often been observed in various types of heart disease between regional myocardial uptake patterns of [$^{123}$I]BMIPP and flow tracer distribution. Although the physiological basis is not completely understood, differences between regional fatty acid and flow tracer distribution may reflect alterations in important parameters of metabolism which can be useful for patient management or therapy planning. These tracers may also represent unique metabolic probes for correlation of energy substrate metabolism with regional myocardial viability. The two agents currently most widely used clinically are $^{123}$I-labelled IPPA and BMIPP. While [$^{123}$I]IPPA is commercially available as a radiopharmaceutical in Europe (Cygne) and Canada (Nordion), multicenter trials are in progress in the United States as a prelude to approval for broad use. [$^{123}$I]BMIPP was recently introduced as Cardiodine for commercial distribution in Japan (Nihon Medi-Physics, Inc.). [$^{123}$I]BMIPP is also being used in clinical studies on an institutional approval basis at several institutions in Europe and the United States. In this review, the development of a variety of radioiodinated fatty acids is discussed. The results of clinical trials with [$^{123}$I]IPPA and [$^{123}$I]BMIPP are discussed in detail, as are the future prospects for fatty acid imaging.

*Key words:* Iodine-123 – 15-(*p*-Iodophenyl)pentadecanoic acid – 15-(*p*-Iodeophenyl)-3-*R,S*-methylpentadecanoic acid – Single-photon emission tomography

*Correspondence to:* F.F. Knapp, Jr.

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## Introduction

Naturally occurring long-chain fatty acids (palmitic, stearic, etc.) are the principal energy source for the normoxic myocardium and are rapidly metabolized by β-oxidation (Figs. 1, 2). Such agents thus represent potential probes to evaluate differences in oxidative metabolism which are present in various types of cardiac disease. While the clinical use of $^{123}$I-labelled fatty acids has been pursued for nearly 30 years, the potential routine use of such agents in nuclear cardiology has only recently been seriously accepted. Until the last decade, studies had focused on the use of $^{123}$I-labelled straight-chain fatty acids (Fig. 3), most of which are rapidly metabolized (vide infra), requiring the use of planar imaging systems and often special procedures with the reinjection of sodium [$^{123}$I]iodide to correct for blood pool activity of free iodide. Because of the importance of the availability of a new generation of more slowly metabolized $^{123}$I-labelled fatty acid analogues which permit the use of single-photon emission tomographic (SPET) imaging, various "modified" fatty acids have been developed and are now in clinical use.

The time required by SPET for camera rotation a priori requires minimal tracer redistribution during the acquisition period. The design and development of various $^{123}$I-labelled modified fatty acids which would not interfere with myocardial extraction, but which would inhibit subsequent β-oxidative catabolism, have thus been pursued. The principal approach which has been successfully followed is introduction of methyl substitution. As a key example, the expected inhibitory effects of methyl substitution in delaying myocardial tracer clearance are illustrated in Fig. 4. Ideally, myocardial tracer uptake should be similar to natural fatty acid uptake following intravenous administration, but the initial uptake pattern

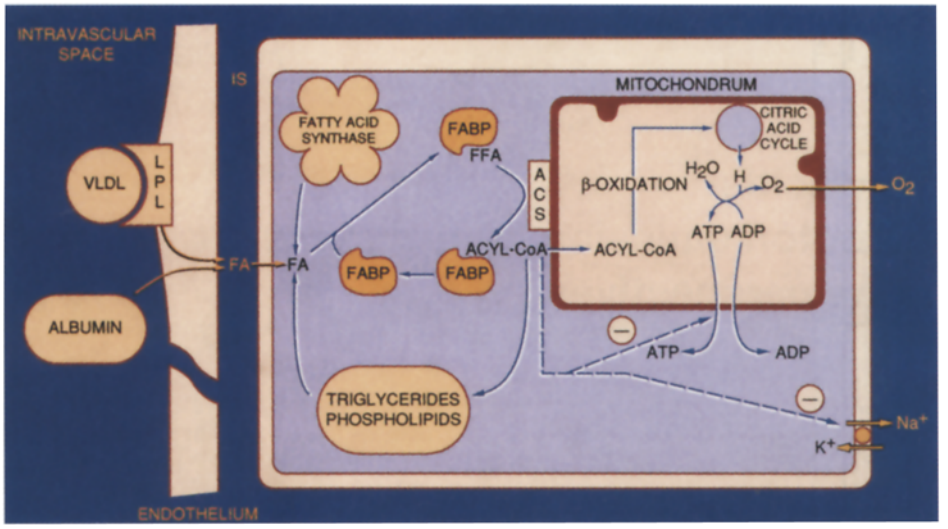


**Fig. 1.** Generalized depiction of the cytosolic binding and transport of fatty acids and their derivatives in myocytes. *VLDL*, Very low-density lipoprotein; *LPL*, lipoprotein lipase; *FA*, fatty acid; *FABP*, fatty acid binding protein; *FFA*, free fatty acid; *IS*, interstitial space; *ACS*, acyl-CoA synthetase, *dotted lines*, possible interactions with the adenine-nucleotide translocator and Na-K-ATPase. (Modified from Glatz et al. [177])

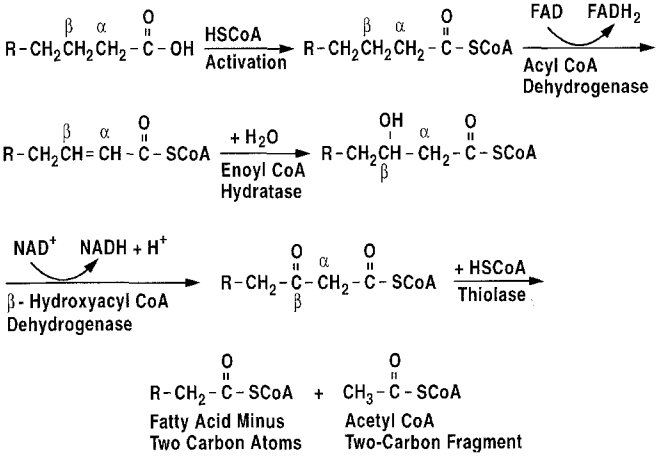


**Fig. 2.** β-Oxidation of fatty acids in the mitochondria

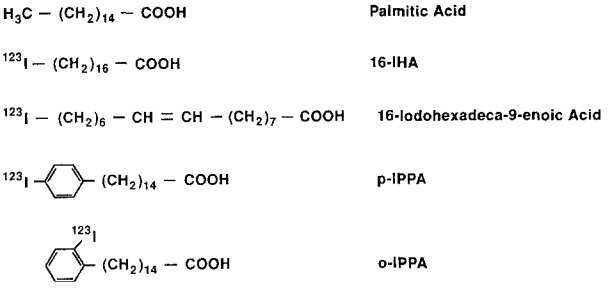


**Fig. 3.** Structures of representative $^{123}$I-labelled straight-chain (linear) fatty acid analogues

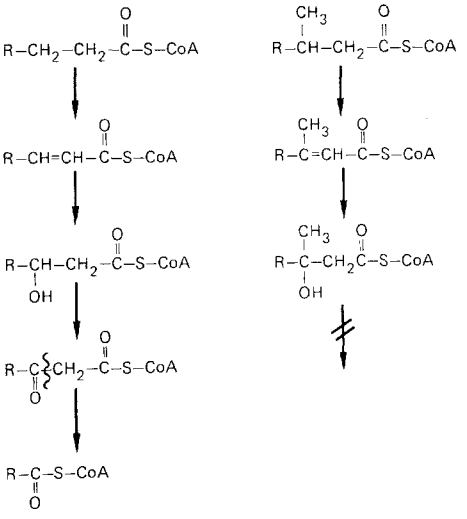

**Fig. 4.** Possible mechanism for inhibition of β-oxidation and subsequent catabolism of fatty acid analogues containing a methyl-group in the β (3)-position. Since no hydrogen is available on the β-carbon, the β-methyl group inhibits oxidation of the β-hydroxy group to the β-ketone, which is catalyzed by the β-hydroxyacyl CoA dehydrogenase enzyme

should change only slowly, permitting SPET analysis of the regional fatty acid uptake pattern. Delayed myocardial tracer clearance permits SPET acquisition with minimal changes in distribution occurring during the imaging protocol. These "modified" fatty acids must be compatible with myocyte recognition and subsequent extraction similar to endogenous fatty acids following intravenous administration. The effects of structural changes of the "modified" and "natural" fatty acids are reflected in their relative washout kinetics following extraction. Several recent publications have discussed various aspects of the development and use of radioiodinated methyl-branched fatty acids [1–4].

An important use of $^{123}$I-labelled fatty acids would be for the provision of complementary information on myocardial viability, for example, to identify and assess the presence of salvageable tissue. Because of the relatively long acquisition periods required for SPET, structurally modified fatty acids have been developed to inhibit myocardial catabolism and delay tracer clearance. $^{123}$I-labelled fatty acid cardiac SPET may have an important role, for example, because of false-positive results often

encountered with traditional thallium-201 and technetium-99m sestamibi (MIBI) SPET in the identification of threatened viable myocardium.

Cardiac imaging in humans with fatty acids was first demonstrated in 1965 with $^{131}$I-labelled "iodooleic acid" [5]. Since these early studies, use of radiolabelled fatty acids for myocardial imaging has fascinated many investigators. $^{123}$I is now accepted as the radioisotope of choice for radiolabelling fatty acids for SPET, although $^{99m}$Tc would be expected to be the best candidate because of low cost and availability. A variety of $^{99m}$Tc-labelled fatty acid analogues have been synthesized and evaluated, but the structural and stereochemical consequences of the relatively large chelating groups required for attachment of $^{99m}$Tc to fatty acid analogues significantly decrease myocardial uptake [6]. Introduction of iodine introduces a relatively modest structural alteration, and because of excellent imaging properties and the wide variety of chemical methods available for attachment to organic molecules, $^{123}$I is the best radioisotope for fatty acid labelling for single-photon imaging. Research in the SPET area has thus focused on the development of $^{123}$I-labelled methyl-branched fatty acids. High-purity $^{123}$I is routinely available in many countries and decreasing costs would be expected to increase availability and use.

## Fatty acid analogues which are rapidly metabolized

In the 1970s and early 1980s, measurement of myocardial washout of free radioiodide released from rapid myocardial catabolism of radioiodinated straight-chain iodoalkyl-substituted fatty acids was extensively evaluated and promoted as a method to evaluate "metabolism" by planar imaging. Although this review is primarily focused on a discussion of the 15-(*p*-iodophenyl)pentadecanoic acid (IPPA) and 15-(*p*-iodophenyl)-3-*R*,*S*-methylpentadecanoic acid (BMIPP) analogues, a brief discussion of the various straight-chain analogues is important to illustrate the basis on which the second-generation modified agents have been developed.

### *16-Iodohexadeca-9-enoic acid*

An early example of a fatty acid in the iodoalkyl-substituted series is 16-[$^{123}$I]-iodohexadeca-9-enoic acid (Fig. 3), which was described after the initial description of the use of iodooleic acid [7, 8]. As observed with other straight-chain analogues, this fatty acid is also rapidly degraded in the myocardium but was used in early patient studies [8] and provided the stimulus for later studies with 17-iodoheptadecanoic acid.

### *17-Iodoheptadecanoic acid (IHA).*

The IHA agent (Fig. 3) is an analogue of stearic acid, since the terminal iodine substituent is about the same size as a methyl group [9]. Much of the impetus for the current, expanding interest in $^{123}$I-labelled fatty acids for myocardial imaging was stimulated by the early work with [$^{123}$I]IHA, which was developed as a tracer of fatty acid oxidative metabolism using sequential planar imaging to generate time-activity curves of regions of interest. Because of the rapid appearance in the blood of free [$^{123}$I]iodide released from metabolism of the IHA tracer, however, special "correction" procedures involving the intravenous administration of sodium [$^{123}$I]iodide are required to differentiate the myocardial mass from free blood activity. Since the use of IHA represents an interesting and useful approach, over the last 20 years many papers have evaluated the metabolism of this tracer in a variety of animal models and humans [10–16]. Because of the inability of performing tomography, which is the preferred imaging modality for clear delineation of the myocardium, over the last few years there have been only occasional reports describing clinical studies with [$^{123}$I]IHA [17, 18].

### *15-(*p*-Iodophenyl)pentadecanoic acid (IPPA or* p*-IPPA)*

In order to stabilize the $^{123}$I attached to the fatty acid and overcome the rapid loss of free [$^{123}$I]iodide, which requires correction procedures, for example, with the use of [$^{123}$I]IHA, the IPPA tracer was developed by Machulla and co-workers as an alternative for myocardial metabolic studies [19]. The clinical use of this tracer, as is discussed in some detail, has the added advantage that tomography can be performed, although the timing of the tomographic period must be carefully controlled, especially in the case of stress. The development of ω-phenyl-substituted straight-chain fatty acids [20] involved attachment of the iodine radiolabel to either the *para* or the *ortho* position of the terminal phenyl ring (Fig. 3).

Iodide attached in this manner is considered stable against deiodination by the deiodinase enzymes. These developments were based on the pioneering work of Knoop [21], who proved with ω-phenylated straight-chain fatty acids their catabolism by β-oxidation. These ideas led to the development and relatively broad use of the IPPA agent [22]. Although the results of studies of the effects of the total chain length of terminal *p*-iodophenyl-substituted fatty acid analogues have not yet been reported, studies using Langendorff perfused rat hearts have demonstrated that IPPA behaves similarly to the physiological substrate, palmitic acid [23]. The metabolism of IPPA is therefore linked to myocardial oxygen supply and consumption [24], which is closely related to blood flow. The catabolism of IPPA follows the normal biochemical pathways for fatty acids [25] and the uptake is linearly correlated to myocardial blood flow as well [26].

### *Investigation protocols for clinical studies*

Both early patient studies with the [$^{123}$I]IPPA tracer [27, 28] and more recent investigations [29] on the diagnosis

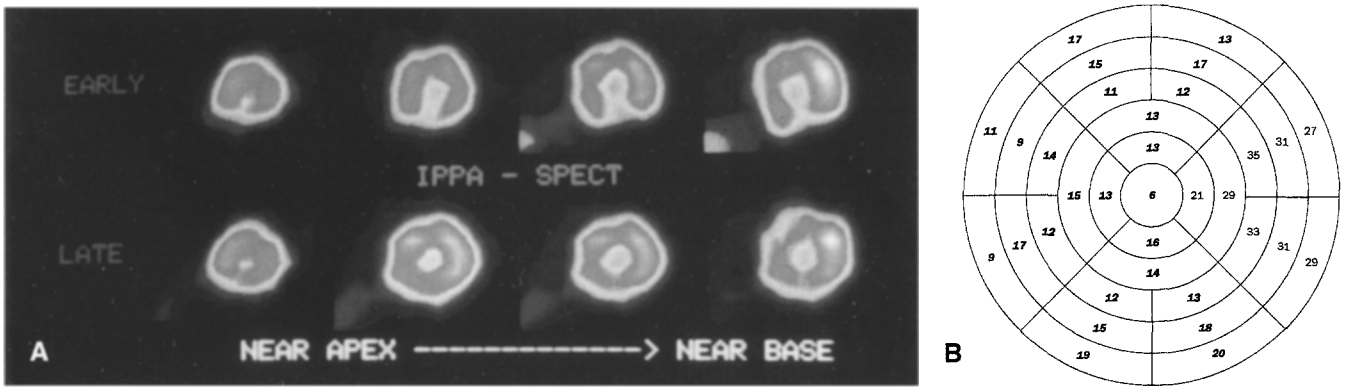


**Fig. 5a,b.** Example of a study with [$^{123}$I]IPPA in a patient with CAD. **A** Four short-axis slices of the early and late IPPA SPET studies of a patient with 95% stenosis of the RCA and 75% narrowing of the LAD. **B** Segmental bull's-eye plot of the turnover rates of the same patient. Pathologic values are printed in bold italics

of coronary artery disease (CAD) have used a maximal stress protocol to induce acute ischemia. The results are somewhat disappointing, however, which might be due to the serum lactate levels, which have been reported to increase sixfold during a maximal stress protocol [30]. The presence of lactate interferes with β-oxidation of fatty acids [31] because lactate is a competing substrate for the myocardial cell for energy production, and accounts for >85% of the energy generated by substrate oxidation, as has been demonstrated in anesthetized animals [32, 33] as well as in human volunteers and in awake animals [34–36]. There is at least an indication that lactate also plays the predicted role in IPPA patient studies [37] in delaying the release kinetics of IPPA from the myocardial cell. In addition, there is evidence from animal experiments that pyruvate interferes with β-oxidation of fatty acids in the same sense as lactate [38]. The assumption that in the early studies lactate serum levels interfered with the metabolic fate of IPPA is supported by the fact that in one of these studies [27] the rest studies of normal volunteers showed a 50% faster IPPA turnover compared to normals after maximal exercise, which might be explained by the increased serum lactate, although lactate levels were not measured in this study. The authors of the study stated that semiquantification of IPPA scans is advantageous over visual inspection and that about 30% of the segments could be considered as "ischemic" only due to their prolonged turnover. In another study [28] the same tendency was described, although it was not as pronounced. This may be due to the study protocol, which utilized a long period between the injection and the initiation of imaging, and the increased rotation time during the SPET acquisitions. Under these conditions the initial SPET image will already have been influenced by tracer turnover. Again, the authors emphasized that quantification of the turnover improves the accuracy in detecting CAD. A recently published study compared the turnover in normal volunteers at various work loads [39]. The authors found an increase in turnover from 17% to 24% if resting values were compared to values after submaximal stress, and a fall in turnover to 13% if the individuals were exercised maximally.

Because of these factors it was initially suggested that a submaximal stress protocol with either successive [40] or single [41] stress tests be used to enhance uptake of the tracer, rather than to induce acute ischemia, but that increasing serum levels of competing substrates should be avoided because IPPA extraction and metabolism are uncoupled at high work loads [42]. It has also been shown that the increase in these competing substrates during a submaximal exercise is statistically not significant [43], even for pyruvate [44]. These protocols were used in conjunction with sequential SPET acquisitions and are especially valuable if semiquantification of the tracer kinetics is to be achieved.

A clinical example is presented in Fig. 5 of a patient with a 95% stenosis of the right coronary artery (RCA) and 75% narrowing of the left anterior descending artery (LAD). The patient had no history of a myocardial infarction. Reduced uptake in the inferior wall is visible on the early SPET, with significant activity retention in this area on the late SPET, representing decreased IPPA turnover and thus ischemia. Visually, there is no sign of ischemia in the LAD-supplied region. The "bull's-eye" plot of the turnover rates (Fig. 5B), however, reveals pathologic values in the LAD-supplied area, matching the findings of coronary arteriography. No persistent defect is visible in the tomograms, corresponding to the patient's history.

Studies at rest have recently been suggested in conjunction with semiquantification for detection of myocardial viability or for the prediction of functional recovery after revascularization [45] as well as in comparison with rest-redistribution $^{201}$Tl imaging [46]. In these studies myocardial uptake of IPPA was found to predict left ventricular function and abnormalities of IPPA metabolism aided in predicting functional recovery.

Evidence of hibernating myocardium in the sequential IPPA SPET studies predicted improvement in ejection fraction and wall motion after revascularization. Similar studies were conducted with planar imaging [47,

48] and acquisition of time-activity curves in spite of the limitations of this technique, most notably the superimposition of disease-free and diseased areas. Another group suggested low-dose and hence low-cost dynamic IPPA studies with a planar technique using a multi-crystal camera [49, 50]. This technique was reported to have both high sensitivity (92%) and high specificity (86%) in detecting for metabolically viable myocardium.

Only a limited number of studies have compared pure flow tracers with [$^{123}$I]IPPA. Planar imaging was used to compare IPPA studies with the results of $^{201}$Tl scans in the same patients, but again with a maximal symptom-limited exercise, which has an unfavorable impact on fatty acid kinetics [51], although the results were slightly better with IPPA. Some studies have compared [$^{123}$I]IPPA and [$^{99m}$Tc]-MIBI and $^{201}$Tl [52–54]. These authors found that, compared with MIBI, IPPA scans have a similar or even better sensitivity in detecting CAD, but with a higher specificity due to lower numbers of fixed defects, especially in the inferior wall. Other authors have also indicated that IPPA might be more helpful than MIBI in the estimation of myocardial viability [55]. In the case of $^{201}$Tl the authors stated that IPPA shows an improved detection of viability since 47% of the segments with a fixed defect in the Tl scan showed IPPA uptake, whereas $^{201}$Tl was slightly better for the detection of ischemia.

Other investigators have attempted to evaluate the use of influx rate constants in dual radioisotope procedures as a diagnostic tool [56, 57]. Unfortunately, these procedures are possible only using the planar technique and due to the maximal exercise there is some uncertainty about the indistinct "back-diffusion" rate, which is enhanced especially in ischemic areas [58]. The contribution of back-diffusion cannot be calculated and hence net uptake is a source of uncertainty. In addition, biochemical changes, such as an increase in serum levels of competing substrates, cannot be taken into account in these methods because a maximal symptom-limited exercise is used, although there is evidence that the uptake, and hence the fatty acid influx rate, is not affected by competing substrates, at least in the normal perfused heart. An additional, interesting, and potentially very important observation from these studies is the apparent demonstration that fatty acid influx is at least in part a carrier-mediated process [59].

*Catabolism of IPPA*

There is controversy in the literature concerning the identity of the final metabolite(s) of IPPA. In one study gas-liquid chromatography was used to separate the metabolites before mass spectral evaluation of the metabolites (GC-MS) [60], while other investigators have more recently used high-performance liquid chromatography (HPLC) and fast atom bombardment-mass spectrometry (FAB-MS) [38]. Since esterification or other derivatization techniques are required for GC-MS, further degradation of the compounds may occur. In addition, sensitive compounds may decompose more easily due to the thermalization and ionization processes of electron bombardment in GC-MS. The FAB-MS technique is performed under much milder conditions and has provided evidence that 3-(*p*-iodophenyl)propenoic acid is the major metabolite of IPPA, rather than the 1-(*p*-iodophenyl)benzoic acid identified by the GC-MS procedure. These different findings may result from different experimental conditions and will require further investigation. It should be emphasized, however, that the results of both studies have demonstrated the stability of the radioiodine label on the fatty acid metabolite(s) and that the original tracer undergoes β-oxidation.

*Coronary artery disease*

The results of several clinical studies have provided evidence that ischemia can be detected with high accuracy if coronary arteriography is considered to be the "gold standard" [61]. These studies were performed using sequential SPET tomograms with a semiquantitative evaluation of metabolic rates which were compared to a normal data base.

The advantages of using [$^{123}$I]IPPA in comparison to the use of pure flow tracers include:

1. Lower radiation dose to patients compared with $^{201}$Tl or $^{99m}$Tc-MIBI
2. Possible use in patients who are unable to perform maximal exercise
3. Reliable diagnosis in high-risk patients, since studies are possible even at rest
4. No evidence thus far to discontinue any drug therapy without changing the accuracy of the method
5. Improved specificity, possibly due to lower numbers of "false-positive" persistent defects compared to pure flow markers
6. Independence of the severity of stenoses (complex status of the coronary artery system) and therefore no dependency of the accuracy in detecting ischemia on the culprit lesion.
7. Dedicated tracer for evaluation of cardiac involvement in diseases such as cardiomyopathies and systemic myopathies with cellular metabolic defects.

Although it is not generally accepted that it might be possible to detect ischemia by submaximal exercise, there is some evidence from the physiology literature that the oxidation of fatty acids for energy production is critically dependent on oxygen supply [62] and thus blood flow, so that the catabolism of fatty acids might be impaired in very early stages of ischemia which might be traced with labelled fatty acids. A potentially very important advantage of using fatty acid SPET scintigraphy is that the alteration of flow is not the basis of the diagnostic principle (as it is with pure flow tracers) but rather the disturbance of a very sensitive metabolic system due to the alterations of flow which are reflected by

the changes in the metabolic rates of a tracer which follow the metabolic pathways of that system.

This premise is supported by the results of Parker et al., who paced the hearts of patients with CAD and measured myocardial lactate production [63]. As described earlier, this parameter can be considered as a sign of the change of the myocardial cell to an anaerobic state of metabolism which occurs within seconds after initiation of pacing, far in advance of any observed ECG changes or the onset of anginal pain. Kurien and Oliver deduced similar conclusions from their experimental work, which showed that fatty acids tend to undergo esterification into the storage pool of triglycerides rather than β-oxidation even in mild and symptomless stages of ischemia [64]. There have not yet been reports on the prognostic significance or the value of risk stratification of fatty acid scintigraphy, as have been presented in respect of other nuclear cardiology procedures like $^{201}$Tl studies.

*Evaluation of viability with IPPA*

The potential use of $^{123}$I-labelled fatty acids in conjunction with flow tracers for the assessment of myocardial viability would be expected to be one of the most important applications. There are some reports dealing with the detection of myocardial viability, including a recently published editorial [65] and an ongoing phase I/II multicenter study [66]. Kuikka et al. [67] found in patients with prior myocardial infarction that IPPA uptake was still detectable in 39% of the segments with persistent MIBI defects and was completely normal in 25% of those segments. In other studies [68, 69] dynamic IPPA scans were compared to transmural myocardial biopsies and thallium reinjection. Compared to biopsy, viability could be detected with a sensitivity of 92% and a specificity of 86%. Compared to thallium reinjection, which is considered to be the state of the art SPET imaging procedure for the detection of viability, IPPA could frequently show viability when Tl did not (51% Tl viable vs 74% IPPA viable). In another study using stress sonography as the gold standard for the detection of wall motion recovery after revascularization [37] it could be shown that IPPA turnover compared to sonography at rest was the best predictor of outcome in terms of recovery of wall motion abnormalities. To detect hibernating myocardium another study was performed [70] comparing MIBI, metaiodobenzylguanidine (MIBG), and IPPA uptake and revealed an improvement in the metabolic reserve over a follow-up period of 1 year without any change in the perfusion and the innervation defect.

*Evaluation of cardiomyopathies and cardiac involvement from systemic myopathies with IPPA*

Only a limited number of studies have described metabolic imaging employing [$^{123}$I]IPPA in patients with cardiomyopathies using the dynamic double-nuclide technique [71] or in patients with myocardial involvement in systemic diseases of the muscle [72] using sequential SPET acquisitions. In the latter diseases (Kearns-Sayre-Shy disease, carnitine-palmitoyl transferase deficiency or dystrophies, etc.), fatty acids might serve as dedicated tracers because metabolic defects are often described that directly or indirectly involve fatty acid transport, activation, or metabolism [73, 74]. The lack of IPPA studies may result from the almost indefinite number of diseases, since there are "as many diseases as enzymes and metabolic steps." In addition, these diseases are relatively rarely encountered, and thus only a limited number of centers are confronted with these patients. A pathognomonic diagnostic procedure for the regional evaluation of myocardial involvement would be very desirable, because the prognosis is often determined by the heart function in these diseases [75, 76] and because myocardial biopsies are often unspecific and morphological changes are observed in only some of the diseases [77–79]. In addition, retrieval of biopsies is invasive and regionally limited and often unreproducible.

*Application of IPPA for other types of heart diseases*

Free fatty acid extraction was evaluated in patients with hypertensive heart disease [71] and the values were depressed in hypertrophic and dilated cardiomyopathies even in children [80]. Also with tomographic techniques abnormalities in IPPA metabolism could be shown [81]. With various techniques traceable alterations in IPPA metabolism have been observed in patients with diabetes mellitus [82, 83], aortic stenosis (assessment performed to evaluate prognosis and timing of surgical treatment) [84], suspected small vessel disease [82, 85], or transplanted hearts [82, 86]; SPET utilizing IPPA has also been employed for therapy control after percutaneous transluminal coronary angioplasty [87]. In addition, at least one study has been performed in animals to test the hypothesis that doxorubicin cardiotoxicity might be traceable with radioiodine-labelled IPPA [88].

In conclusion, the metabolism of [$^{123}$I]IPPA is well understood and its unique properties for tracing perfusion and fatty acid turnover by the myocytes in one single investigation have resulted in numerous clinical studies in a great variety of myocardial diseases. However, its high costs and the rapid metabolism, resulting in myocardial slices with poor statistics, have prevented its widespread use. It might be that clinical interest in IPPA will decrease compared with the intereest in tracers with prolonged retention, but the use of IPPA will continue to be important in clinical situations in which the SPET technique is used and when turnover rates of fatty acids are required for the final diagnosis.

## Modified fatty acids which have prolonged retention for myocardial SPET

Even with the use of low levels of exercise to delay washout kinetics of [$^{123}$I]IPPA, the timing of SPET must

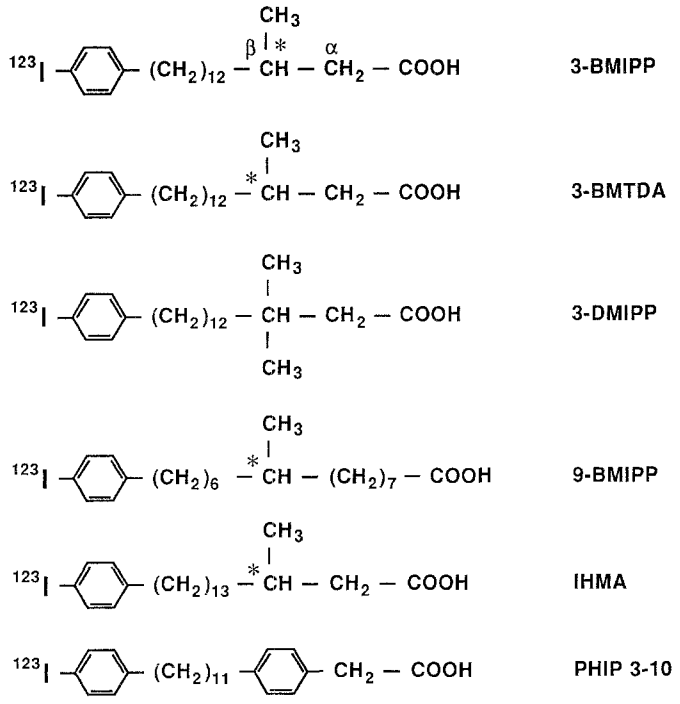


**Fig. 6.** Structures of various $^{123}$I-labelled structurally modified fatty acid analogues. The *stars* denote the asymmetric β-carbon atoms indicating that the four substituents can be oriented differently in space and the carbon can have either the *R* (*rectus*) or *S* (*sinister*) configuration. The monomethyl-substituted fatty acids shown are all racemic mixtures of the *R* and *S* isomers

be very precise, and often it may not be possible, especially in patients who cannot exercise. Because of the relatively long period required for SPET imaging with single- and even double-headed cameras, various approaches have been explored which would interfere with the usually rapid fatty acid metabolism and myocardial tracer washout. Early studies pursued the concept of a "heteroatom insertion" in the alkyl chain of the modified fatty acids in order to inhibit "metabolism" for SPET imaging. These studies represented the first demonstration that such a drastic modification could be made without interfering with myocardial fatty acid extraction [89–91]. Incorporation of the radioactive tellurium-123m heteroatom into the fatty acid chain was the first approach to the development of a modified fatty acid in which a structural perturbation was introduced to inhibit or interfere with β-oxidation, and thus prolong the myocardial residence time of the radiolabelled agent following flow-dependent myocardial extraction. These studies demonstrated that the modified fatty acids were extracted in similar fashion to natural fatty acids, and as expected, the total chain length was an important factor [92].

Because of the long 119-day half-life and low specific activity of reactor-produced $^{123m}$Te, an alternative strategy involving "bifunctional" analogues was pursued in which the nonradioactive tellurium heteroatom was inserted within the fatty acid chain to increase myocardial retention. Radioiodine was then attached to the terminus of the fatty acid by stable attachment as a *para*-iodophenyl group [93–95] or a *trans* vinyl iodide [96–99]. These analogues demonstrated high myocardial extraction and prolonged retention and structure-activity studies demonstrated that both total chain length and position of the heteroatom were important structural features affecting myocardial extraction and clearance kinetics. The development of these analogues thus represented an important basis for further development of the concept of metabolic blocking using radioiodinated methyl-branched fatty acid analogues (Fig. 6) for cardiac imaging.

### *15-(o-Iodophenyl)pentadecanoic acid (o-IPPA)*

The *o*-IPPA analogue (Fig. 3) of IPPA is an interesting example of the effects of fatty acid molecular structure on myocardial uptake and retention. In this analogue, $^{123}$I is introduced into the *ortho* rather than the *para* position, as in *p*-IPPA. The *o*-IPPA analogue is unique since its myocardial retention properties in man are completely different from those observed in most lower animal species. While *o*-IPPA exhibits rather rapid myocardial washout kinetics in rodents ($t_{1/2}$ rats, 8.6 min) [100], the [$^{123}$I]*o*-IPPA analogue exhibits nearly irreversible myocardial retention in man ($t_{1/2}$>200 min) [101–103]. The different behavior of the *o*-IPPA isomer in animals compared with man thus does not allow the use of well-controlled animal models for the prediction of its clinical behavior and interest in the broad use of this agent has not developed.

### *16-[$^{123}$I]-Iodo-3-methylhexadecanoic acid (IMHA)*

IMHA is an example of a methyl-branched analogue in which $^{123}$I has not been chemically stabilized on the fatty acid chain. In one study [104] the IMHA analogue was compared with $^{201}$Tl reinjection techniques and 3-[$^{18}$F]fluorodeoxyglucose (3-FDG), which is considered to be the "gold standard" for detection of viability. The authors detected viability in noninfarcted areas with a comparable sensitivity with all three techniques. In infarcted areas, however, 56% of the segments indicated to be nonviable by $^{201}$Tl scans were considered viable on the 3-FDG scans, whereas only 16% were considered viable on the fatty acid scans.

### *$^{123}$I-labelled "phenylene" substituted fatty acid analogues*

Use of this class of fatty acid analogues represents an alternative approach to methyl substitution which has been pursued to interfere with rapid myocardial metabolism. This promising new class of compounds are metabolically trapped analogues serving as a "metabolic micro-

sphere," behaving similarly to the tellurium-substituted fatty acids described earlier. The phenylene analogues were first introduced by Eisenhut [105] following the synthesis of a series of compounds to evaluate the optimal chain length and the best position of the phenyl bridge. These studies identified 13-(*p*-[I*]-3-(*p*-phenylene)tridecanoic acid (PHIPA 3-10) as the most promising tracer, and it is currently in clinical trials [106, 107]. The most interesting result from animal experiments with this agent is the identification of only one metabolite in the lipid hydrolysis by HPLC analyses of the extracted rat heart lipids. From the HPLC behavior the identity of the isolated metabolite is assumed to be the α,β-unsaturated analogue of PHIPA 3-10.

### *15-(*p*-Iodophenyl)-9-*R,S*-methylpentadecanoic acid (9-BMIPP)*

9-BMIPP is an analogue of BMIPP developed by Mallinckrodt, Inc. In this analogue (Fig. 6) methyl substitution has been introduced in the 9-position, compared to the 3-position in BMIPP. Only one clinical study has thus far been reported [108]; it compared 9-BMIPP with $^{201}$Tl, and suggested its suitability for the diagnosis of myocardial diseases.

### *15-(*p*-Iodophenyl)-3-*R,S*-methylpentadecanoic acid (BMIPP)*

The use of methyl-branched fatty acids is based on the expected inhibition of β-oxidation by the presence of a methyl group in the β-position (Fig. 4). We developed 15-(*p*-iodophenyl)-3-*R,S*-methylpentadecanoic acid analogue (BMIPP) at ORNL [109–111] with radioiodine stabilized by attachment to the *para* position of the terminal phenyl ring based on the linear structure of IPPA [19–20] (Fig. 6). The IPPA analogue has been widely studied in both animals and humans, and its metabolism is well understood [112].

Although a discussion of the chemical development and use of various radioiodination strategies is beyond the scope of this paper, significant research efforts have been conducted at many institutions for over a decade. Other analogues in which radioiodine is stabilized on methyl-branched fatty acids by attachment to a terminal vinyl iodide have also been evaluated. One example is 19-iodo-3-*R,S*-methyl-18-octadecenoic acid (BMIVN), which also exhibits prolonged myocardial retention in comparison to a linear, straight-chain analogue, and is stored by incorporation into triglycerides [113–117]. The corresponding 3,3-dimethyl analogue shows increased myocardial retention in comparison with the β-monomethyl analogue, a difference similar to the relative myocardial retention of BMIPP and DMIPP described earlier [115, 118]. A variety of other examples are illustrated in Fig. 6, and include the 14-(*p*-iodophenyl)-3-*R,S*-methyltetradecanoic acid (BMIPT) analogue, which has an alkyl chain containing one less carbon atom than BMIPP [119, 120].

In the iodoakyl-substituted series, one example is 17-iodo-3-*R,S*-methylheptadecanoic acid analogue [121], which Fagret and colleagues used to evaluate time-activity curves of the efflux of radioactivity from rat hearts perfused by the Langendorff technique following bolus administration of radioiodinated fatty acids into the inflow. The α-*R,S*-monomethyl, α,α-dimethyl, β-*R,S*-monomethyl, and β,β-dimethyl analogues of 16-iodohexadecanoic acid were also evaluated. These studies demonstrated that the β,β-dimethyl analogue exhibited the longest myocardial retention [122]. Fagret et al. evaluated the global myocardial uptake and clearance kinetics of these analogues in both mice and dogs, demonstrating that the 16-iodo-3-*R,S*-methylhexadecanoic acid analogue had the longest retention and identifying it as a candidate for human studies [123]. To achieve a greater understanding of the effects of methyl branching on metabolism, more recent studies have evaluated the metabolism of these methyl-branched analogues in primary cultures of isolated rat hepatocytes, comparing the metabolism of the various $^{125}$I-labelled analogues with that of [1-$^{14}$C]palmitic acid [124]. While all of the analogues exhibited significant deiodination, the monomethyl-branched analogues exhibited greater esterification in triglycerides than the corresponding dimethyl analogues.

Our studies also aimed to evaluate the influence of the methyl group in BMIPP on myocardial metabolism in rat hearts in vivo [125, 126] and isolated Langendorff-perfused rat hearts [127–131], and demonstrated incorporation of BMIPP into triglyceride storage products, correlating with the observed myocardial retention. Other studies in rats in vivo [132, 133] and isolated Langendorff-perfused rat hearts, however, have demonstrated that cellular accumulation of radioactivity involves accumulation of free BMIPP with minimal incorporation into the triglyceride pool. Studies using high-resolution autoradiographic techniques have also clearly demonstrated differences in BMIPP and flow tracer distribution in the hearts of hypertensive animals [134, 135]. The results of these key studies have direct clinical relevance and have stimulated interest in the clinical applications of [$^{123}$I]BMIPP, to be discussed below.

Results of detailed triple-label studies comparing the relative uptake and clearance kinetics of IPPA, BMIPP and DMIPP [the germinal 3,3-dimethyl analogue of BMIPP, 15-(*p*-iodophenyl)-3,3-dimethylpentadecanoic acid] in rat hearts in vivo clearly illustrated the expected effects of 3-methyl substitution. Animal studies with radioiodinated BMIPP also evaluated the regional myocardial distribution of this tracer in various cardiac disease models, and paved the way for subsequent human studies (vide infra). Significant differences between flow tracer ($^{201}$Tl) and methyl-branched fatty acid distribution have been observed in the free wall of the left ventricle and septal regions of hearts from hypertensive rats [134,

135] and rat and hamster models with hypertrophic and cardiomyopathic heart disease [136–138]. BMIPP has also been used to evaluate cocaine-induced regional myocardial metabolic changes in hypertensive rats by comparison of regional perfusion of $^{201}$Tl with differences in 2-deoxyglucose (2-DG) and radioiodinated BMIPP uptake [139, 140]. While global perfusion is increased with cocaine, 2-DG uptake decreases with a concomitant increase in BMIPP uptake. These studies may help to delineate the physiological factors which lead to sudden cardiac death, often encountered among high-risk hypertensive cocaine abusers.

DMIPP (Fig. 6) shows much longer retention than BMIPP [115, 116, 118, 141]. Since BMIPP exhibits slow myocardial washout, the introduction of two methyl groups was expected to inhibit β-oxidation more effectively and to prolong retention. The significantly longer myocardial retention of DMIPP in comparison with BMIPP in rats has been confirmed in isolated perfused swine hearts [141, 142] and an in vivo canine model [143]. Other examples of methyl-branched iodophenyl-substituted analogues which have been evaluated in animal models include the racemic 9-methyl analogue of BMIPP [108, 144] (Fig. 6) and BMIPT [119, 120, 145].

The 3-methyl group in BMIPP was expected to inhibit β-oxidation and result in longer myocardial retention, as has been demonstrated in in vivo studies in rats, dogs, and humans. Since the kinetics of myocardial washout are slow, both the "working" [130] and "non-working" [127–131] Langendorff-perfused rat heart systems were used to isolate the radioactive species present in the outflow. The major radioactive species represented an unidentified polar metabolite, which has also been observed in plasma samples from humans following intravenous administration of [$^{123}$I]BMIPP [146–148]. Earlier studies had predicted that the slow washout of BMIPP may result from initial α-oxidation with formation of the α-methyl metabolite [111, 116, 118]. Since the impediment of the β-methyl group is not present, α-methyl fatty acids can proceed through the β-oxidative pathway. Consistent with these predictions, more recent studies have identified the major metabolite of BMIPP as the α-methyl analogue, 14-(*p*-iodophenyl)-2-*R*,*S*-methyltetradecanoic acid (AMIPT). Two other metabolites were also found and assigned the structures of (*p*-iodophenyl)acetic acid (PIPA) and 12-(*p*-iodophenyl)dodecanoic acid ($PIPC_{12}$); these represent metabolites formed from β-oxidation. The structures of these compounds were assigned by comparison of their chromatographic properties with the authentic synthetic compounds [149].

HPLC has been used to examine the incorporation of radioiodinated BMIPP and IPPA into phospholipid fractions of myocardial lipids isolated from both rats and dogs. While the IPPA straight-chain analogue is incorporated into lecithin (phosphatidylcholine) in rat hearts, BMIPP is primarily found in the cephalin (phosphatidylethanolamine) fraction [25, 150]. Thin-layer chromatographic studies have evaluated the incorporation of IHA, IPPA, and DMIPP into the complex lipids of dog hearts in vivo using a biopsy punch technique to obtain myocardial samples. Fatty acid structure dramatically affects incorporation into various phospholipid fractions [15, 151], thus while IHA is incorporated primarily into both phosphatidylinositol and phosphatidylcholine, IPPA is incorporated into the phosphatidylcholine fraction. The dimethyl DMIPP analogue shows only low incorporation into the phospholipid fraction.

Although the DMIPP analogue exhibits longer myocardial retention than BMIPP, radioiodinated BMIPP is currently the agent of choice in the iodophenyl series, since its clearance kinetics represent a compromise between having enough time for evaluation of regional distribution by SPET, but exhibiting clearance kinetics which can be measured by successive SPET acquisitions. [$^{123}$I]BMIPP may thus offer the first opportunity to construct regional time-activity curves from successive SPET studies, and is now commercially available through Nihon Medi-Physics, Inc., in Japan.

Animal research which has direct correlation with clinical data include studies that have elucidated the metabolic fate and physiological factors affecting myocardial uptake of BMIPP, including triglyceride storage and myocardial clearance kinetics, altered uptake in diabetic myocardium [152], discordance between blood flow and uptake in lactate infusion [153], tumor uptake [154], uptake in adriamycin-induced cardiomyopathy [155], and the effects of ATP on BMIPP uptake [156]. More recent studies have investigated the correlation between myocardial ATP levels and BMIPP uptake in normal rats following administration of tetradecylglycidic acid (TDGA), an inhibitor of mitochondrial carnitine acyltransferase I, and in salt-sensitive Dahl strain rats [157]. Rats pretreated with TDGA showed a positive correlation between ATP levels and BMIPP uptake, in agreement with the results of earlier studies. In these studies, however, immediate myocardial BMIPP uptake was not influenced by acute inhibition of β-oxidation by the inhibitor. These results support the expected importance of ATP levels for the retention of BMIPP resulting from cytosolic activation of BMIPP to BMIPP-CoA, with slow shunting into triglyceride storage products. In contrast, a negative correlation was observed between ATP levels and severely compromised myocardial BMIPP uptake in hypertrophied hearts of Dahl rats. These contrasting results were explained by differences in separate ATP pools available in the mitochondria and cytosol.

Several early studies evaluated the properties of radioiodinated BMIPP in an ischemic canine model [158–160]. The uptake and clearance of [$^{123}$I]BMIPP has also been studied by planar imaging in a canine occlusion-reperfusion model [161]. In this protocol sequential gamma camera images obtained following intravenous administration of $^{201}$Tl and [$^{123}$I]BMIPP were evaluated, and the hearts were also excised and then imaged. Two

dogs served as controls, one group of eight dogs had a 6-h occlusion by ligation of the LAD before reflow (chronic), and two dogs had a 3-h occlusion followed by 1 h of reperfusion (acute). While all dogs with the longer occlusion showed persistent defects with BMIPP and $^{201}$Tl, five of the dogs (80%) in the second group with a much shorter occlusion period showed a mismatch of BMIPP/thallium uptake, with greater uptake of BMIPP than $^{201}$Tl.

In summary, these developmental studies and biological and metabolic studies of various radioiodinated methyl-branched fatty acid analogues have provided the foundation for studies in humans, in particular with the BMIPP agent. Although the DMIPP analogue shows nearly irreversible retention in all animal and in preliminary patient studies (S.N. Reske, F.F. Knapp, J. Kropp, and H.-J. Biersack, unpublished data), clinical studies with this agent have not been pursued further. This is primarily because BMIPP has been most extensively studied in animal experiments, and the kinetics of myocardial washout of activity following intravenous BMIPP administration offer the best compromise between sufficient retention for SPET and fast enough kinetics to allow evaluation of washout in successive SPET studies [162]. The following sections provide a brief overview of clinical protocols with [$^{123}$I]BMIPP.

## Clinical studies with [$^{123}$I]BMIPP

### *General features*

High-quality images of the left ventricular myocardium are obtained with SPET imaging even after injection of as little as 3–5 mCi of [$^{123}$I]BMIPP. A discussion of the clinical studies with [$^{123}$I]BMIPP through 1992 has recently been published [162]. The first clinical studies with [$^{123}$I]BMIPP by Dudczack and co-workers used planar imaging and demonstrated that this agent exhibited the expected prolonged myocardial retention and provided excellent delineation of the myocardium [146]. Because of the benefits of tomography, current studies with BMIPP exclusively use SPET, and various protocols have been employed which evaluate regional distribution with or without stress. In some cases, such as for the evaluation of hypertension and cardiomyopathies, the agent is administered at rest. In other cases, such as for the evaluation of ischemic heart disease, BMIPP can also be administered after symptom-limited maximal exercise. In the latter case, a second SPET acquisition can be obtained later at rest to evaluate redistribution. A second BMIPP tracer injection at rest is included in one protocol. Formulation and administration of [$^{123}$I]BMIPP are straightforward. The BMIPP is complexed to albumin solution and intravenously administered in an antecubital or other peripheral vein [162]. The rapidly increasing interest in the clinical use of $^{123}$I-labelled fatty acids for myocardial SPET is particularly well illustrated by the significant number of papers describing patient studies with [$^{123}$I]BMIPP reported at the Society of Nuclear Medicine Meeting held in Orlando, Florida, USA, in June 1994, and at the 6th World Congress of Nuclear Medicine and Biology, held in Sydney, Australia, on 23–28 October 1994.

### *BMIPP studies in cardiomyopathy*

[$^{123}$I]BMIPP cardiac SPET has been used in patients with hypertrophic cardiomyopathy [163–166]. In one study, 14 patients with left ventricular hypertrophy were evaluated at rest following administration of [$^{123}$I]BMIPP and by SPET studies conducted 20 min and 3 hours later [164]. Studies were also conducted in the patients within 1 week using $^{201}$Tl. Quantitative analysis of the regional uptake and clearance of both BMIPP and $^{201}$Tl demonstrated that the regional distribution of BMIPP was more heterogeneous than that of $^{201}$Tl. Important relative differences included lower uptake of BMIPP in the anteroseptal wall than in the posterolateral wall. Although $^{201}$Tl uptake was normal or increased in the anteroseptal wall, BMIPP exhibited both decreased uptake and increased clearance in this region. In contrast to regions with only mild hypertrophy, a general finding was that thickened wall segments showed lower BMIPP uptake and faster clearance.

More recently these studies have been extended. In 17 patients with hypertrophic cardiomyopathy and two patients with the dilated subtype, SPET was used to assess the distribution of [$^{123}$I]BMIPP and $^{201}$Tl, employing a protocol using resting SPET following fasting. The protocol involved an initial SPET study 30 min following BMIPP administration and a second SPET study 3.5 h later. $^{201}$Tl SPET was performed 4–6 days after the BMIPP study. Among normally contracting apical and septal hypertrophic regions in patients with hypertrophic cardiomyopathy, reduced [$^{123}$I]BMIPP uptake was demonstrated in those thickened regions which showed normal or high $^{201}$Tl uptake. Such heterogeneous distribution of the two tracers was also observed in patients with hypertrophy and systolic dysfunction and patients with dilated cardiomyopathy. Although the physiological mechanisms resulting in such distribution patterns are not well understood, the significant differences often observed between flow tracer distribution and BMIPP uptake are felt to represent abnormalities of myocardial fatty acid metabolism in cardiomyopathic myocardium, reflecting an "intrinsic" impairment of myocardial free fatty acid utilization.

A number of other investigators in Japan have also evaluated [$^{123}$I]BMIPP SPET in patients with cardiomyopathy. Nishimura et al. investigated [$^{123}$I]BMIPP SPET in 25 patients with myocardial infraction and 16 patients with hypertrophic cardiomyopathy [163]. This protocol involved simultaneous rest BMIPP/$^{201}$Tl SPET following administration of both tracers. The "early" SPET was

initiated 15–30 min after tracer administration and the "delayed" SPET was obtained 40–60 min after injection. Although the energy discriminators were entered on each photo peak (75 and 159 keV), "cross-talk" was not visually assessed during the studies. An important observation was that among the patients with infarction, dissociation between BMIPP and thallium defects was more often observed in those patients with successful reperfusion ($n$ = 7) than in those without reperfusion ($n$ = 7) or with chronic myocardial infarction ("old" infarctions, $n$ = 10). More importantly, the "severity scores" for BMIPP uptake determined by SPET correlated well with ventricular function, determined by ventricular ejection fraction measurement. In the patients with cardiomyopathy, increased thallium uptake was often observed in apical and posterolateral hypertrophic myocardial regions which showed reduced BMIPP uptake in both early and delayed scans. Of 68 segments with increased thallium uptake, 33 (49%) demonstrated normal BMIPP uptake, while the remainder showed reduced BMIPP accumulation. Of 207 segments with normal thallium uptake, 41 (20%) showed reduced BMIPP accumulation. These data clearly show that reduced accumulation of BMIPP in comparison with thallium uptake is often observed in hypertrophic myocardium. The above results demonstrate that [$^{123}$I]BMIPP fatty acid SPET in conjunction with flow tracer assessment is adequate to assess myocardial functional integrity.

*BMIPP in CAD: myocardial infarction/ischemia*

Several recent studies have described regional myocardial uptake and clearance of [$^{123}$I]BMIPP in patients with myocardial infarction and ischemia [163, 167, 168]. One study protocol consisted of SPET imaging at rest with [$^{123}$I]BMIPP and $^{201}$Tl in four normal controls and 28 patients with myocardial infarction [167]. Contrast ventriculography of each patient also provided an opportunity to correlate tracer uptake and washout with regional wall motion abnormalities. The SPET studies were obtained with each tracer independently within 1 week of each other. Image analysis consisted of a 4-point grading system of the uptake of tracer in seven segments of the left ventricular myocardium with quantitative analysis by generation of time-activity curves and creation and analysis of bull's-eye polar maps. An important observation from these studies was decreased global myocardial uptake of BMIPP in 17/28 patients (61%) and in 49/196 myocardial segments (25%). This mismatch between BMIPP uptake and perfusion tracer distribution was more often observed in areas which had suffered an acute myocardial infarction and in revascularized rather than nonrevascularized areas. Most importantly, lower BMIPP uptake was more often observed in segments which exhibited wall motion scores lower than perfusion scores than in segments showing a concordant decrease in both wall motion and perfusion scores.

Another approach currently used with [$^{123}$I]BMIPP utilizes maximal exercise to promote ischemia prior to tracer administration [148, 169]. This protocol evolved from the "dual SPET" approach developed earlier by Kropp and co-workers for use with [$^{123}$I]IPPA, in which the distribution of radioiodinated IPPA in the early SPET study (SPET-I) represents blood flow, and 15 min later a second acquisition (SPET-II) is obtained at rest [41]. Comparison of the differences in relative regional tracer concentration in myocardial segments between SPET-I and SPET-II is defined as "metabolism" [41]. For this analysis there is no actual "redistribution" of radioactivity between the early and late SPET studies in the usual sense. Rather, the more rapid washout of radioactivity from normal, oxygenated segments is contrasted with significantly delayed washout from ischemic segments. Relative differences can thus be used to differentiate between normal and ischemic segments which can be detected with appropriate timing of successive SPET acquisitions.

A similar protocol with [$^{123}$I]BMIPP has recently been employed in a group of 20 patients who were also evaluated by coronary angiography and left ventricular cineventriculography [148]. An initial SPET-I study was performed after administration of 5 mCi [$^{123}$I]BMIPP following maximal exercise, with a second acquisition (SPET-II) 3 h later at rest. A SPET-III study was then performed at rest following a second tracer injection of 2 mCi of [$^{123}$I]BMIPP. Short-axis slices were analyzed by the bull's eye display. In this initial patient group, 98% of infarctions could be detected as persistent defects. The sensitivity and specificity for detection of ischemia were 89% and 91%, respectively. A total of 94% of noninfarcted segments exhibited reduced or absent uptake of BMIPP on SPET-I and SPET-II and regularly showed no major differences in activity distribution. These segments had normal BMIPP uptake after reinjection in SPET-III, demonstrating the attractive properties of BMIPP for differentiation between irreversibly damaged and ischemic but still viable myocardium. An example of this protocol is shown in Fig. 7, which illustrates four short-axis slices of the complete set of tomograms of a patient with an occluded but reopened LAD and a small akinetic region in the anterior wall near the apex. In the exercise ECG, ischemia could not be substantiated although the patient exercised maximally. In the stress slices there is a reduced uptake in the anterior wall, matching the findings of coronary arteriography. The uptake in the 3-h p.i. SPET study shows no major uptake differences compared to the stress tomogram. In the reinjection tomogram there is normal uptake (refill) in the non-infarcted regions of the anterior wall, indicating ischemic but viable myocardium. In addition, there is a persistent defect in the distal anterior wall matching the findings of left ventricular cineventriculography and representing the infarcted area.

An additional recent example is a study protocol involving administration of [$^{123}$I]BMIPP at rest and com-

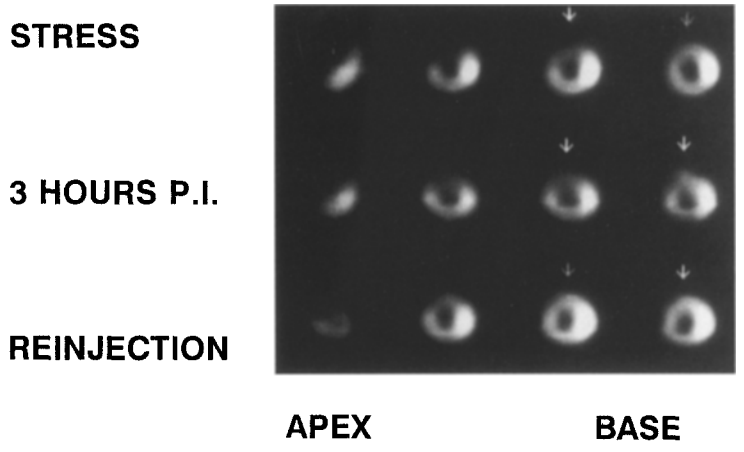


**Fig. 7.** Example of a patient study with [$^{123}$I]BMIPP, using the reinjection technique. Four slices of the complete set of a BMIPP tomographic study are shown. There is decreased uptake in the anterior wall in the stress and 3-h p.i. slices. In the reinjection tomogram fill-in is clearly visible in the anterior wall (*arrows*) except in the very distal portion, indicating infarction in this area

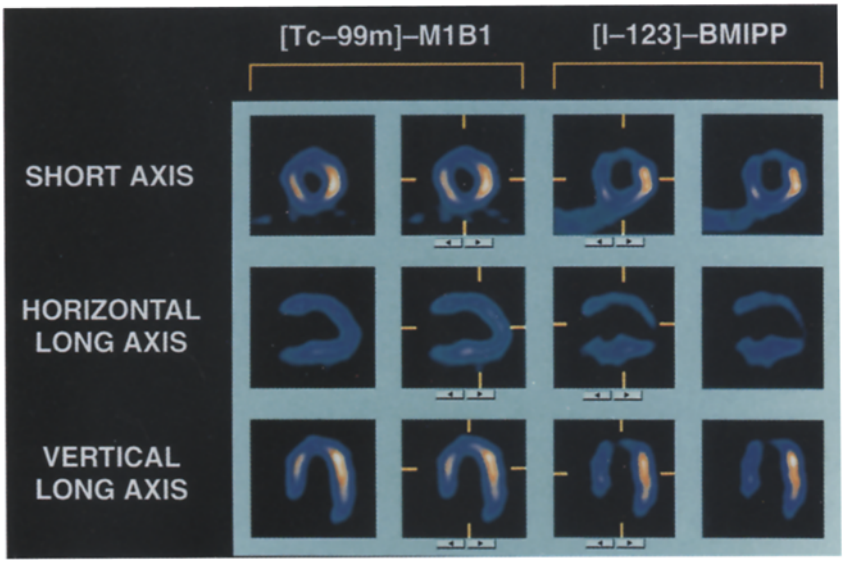


**Fig. 8.** Study comparing [$^{123}$I]BMIPP and $^{99m}$Tc-MIBI in a patient with CAD. There is mismatch of uptake of the two tracers in the anterior wall. (Courtesy of Philippe Franken, M.D., Department of Nuclear Medicine, Free University Hospital, Brussels, Belgium)

parison with the myocardial distribution of $^{99m}$Tc-MIBI [170, 171]. These studies are also being complemented with two-dimensional echocardiography and ECG-gated magnetic resonance imaging (MRI) to provide information on the evolution of wall motion during heart contraction. The goal is to correlate functional changes with changes in tracer distribution observed in the radionuclide studies and to determine whether such differences can identify ischemic but viable myocardium. In one study, [$^{123}$I]BMIPP (4 mCi) and $^{99m}$Tc-MIBI (25 mCi) were administered at a 1-day interval after overnight fasting. The SPET results from 15 patients with recent myocardial infarction were compared with regional wall motion obtained with gated-MRI at rest and during low-dose dobutamine infusion (10 μg/kg per min) to identify ischemic but viable myocardium. Nine segments were defined on apical, midventricular and basal slices to compare SPET and gated-MRI data. A total of 60 segments had either abnormal BMIPP or MIBI uptake: 37 of these segments (62%) exhibited concordant BMIPP and MIBI uptake, while 23 (38%) exhibited decreased BMIPP activity relative to MIBI. The wall motion of these 23 segments with discordant BMIPP and MIBI uptake was normal in seven cases and improved with low-dose dobutamine in 11. On the other hand, only 3 of the 37 segments with concordantly decreased BMIPP and MIBI uptake showed evidence of residual viability on the dobutamine MRI study. These results demonstrate that comparison of MIBI SPET (perfusion) with BMIPP SPET is useful in identifying viable myocardium after acute myocardial infarction.

The results of one typical study of the mismatch between [$^{123}$I]BMIPP and $^{99m}$Tc-MIBI are shown in Fig. 8. This patient was investigated 8 days after an anterior myocardial infraction. The anterior wall motion was severely depressed at that time (akinesis) but had improved significantly when evaluated 3 months later at follow-up. This is an excellent example demonstrating that reduced areas of BMIPP uptake at rest corresponding to normal flow tracer uptake can identify jeopardized but viable myocardium. Identification of jeopardized myocardial regions by such a dual-tracer technique could be important as an indication for revascularization. As described above, those regions which show matched defects (con-

cordance) nearly always represent scar tissue. A more recent study by these same investigators [172] has evaluated the regional uptake of BMIPP and MIBI in 22 patients with subacute myocardial infarction 4–10 days after coronary thrombolysis controlled by echocardiography and dobutamine stimulation. All segments with normal MIBI and BMIPP uptake showed normal wall motion. There was no segment with a larger MIBI uptake defect compared to BMIPP. Out of 32 segments with dysfunction, 23 showed a larger BMIPP uptake defect than did MIBI SPET ("mismatched defects") while nine had "matched defects." Of the 23 segments with mismatched defects, 15 showed improved systolic wall thickening during dobutamine stimulation. In contrast, none of the nine segments with matched defects showed evidence of inotropic reserve. Hence, in dysfunctional segments, mismatching may correspond either to stunned or to hibernating myocardium.

*Comparison of [$^{123}$I]BMIPP with palmitate and 3-FDG PET tracers*

Recent important studies have compared [$^{123}$I]BMIPP SPET with [1-$^{11}$C]palmitate and [$^{18}$F]-labelled 2-fluorodeoxyglucose (3-FDG) PET. On the basis of earlier studies of ischemic myocardium, segments which are viable but have decreased contraction would presumably be expected to concentrate. In this regard, comparisons of BMIPP uptake, ventricular function, and 2-FDG are desirable in order to evaluate the factors which result in decreased fatty extraction in myocardial segments that have adequate perfusion but demonstrate significantly reduced contractile function.

One recent study [173] has compared the regional uptake and clearance kinetics of [$^{123}$I]BMIPP and [1-$^{11}$C]palmitate by means of successive SPET and PET studies in the same patients. Patients were studied at rest and the protocol consisted of initiation of the BMIPP SPET study 20 min after injection following overnight fasting. Some patients were also studied with thallium SPET conducted within 2 weeks of the BMIPP study, with imaging initiated 15 min after injection at rest. In six patients, palmitate PET study was conducted with 2-min serial dynamic scans for 40 min, which permitted a comparison of the BMIPP, thallium, and palmitate uptake by, and clearance kinetics from, the same segments. In another set of ten patients, 2-FDG static images were obtained 60 min after administration. Comparison of the data demonstrated that BMIPP accumulation patterns corresponded well with palmitate PET findings in the majority of the segments studied. In the six patients studied with both BMIPP and palmitate, of 15 segments showing decreased BMIPP accumulation, 12 exhibited decreased late uptake of palmitate, and 11 showed decreased early uptake and delayed clearance. Of 27 segments with normal BMIPP uptake, 23 had normal palmitate uptake and clearance. BMIPP accumulation thus appears to parallel palmitate uptake and retention. The results of a typical study, in a patient with acute inferior wall myocardial infarction, are shown in Fig. 9 [174]. The short-axis slices clearly show decreased BMIPP uptake compared to $^{201}$Tl uptake in the inferior wall and lateral regions. Corresponding myocardial perfusion images obtained with [$^{13}$N]ammonia and 2-FDG also showed hypoperfusion, with increased 2-FDG uptake in

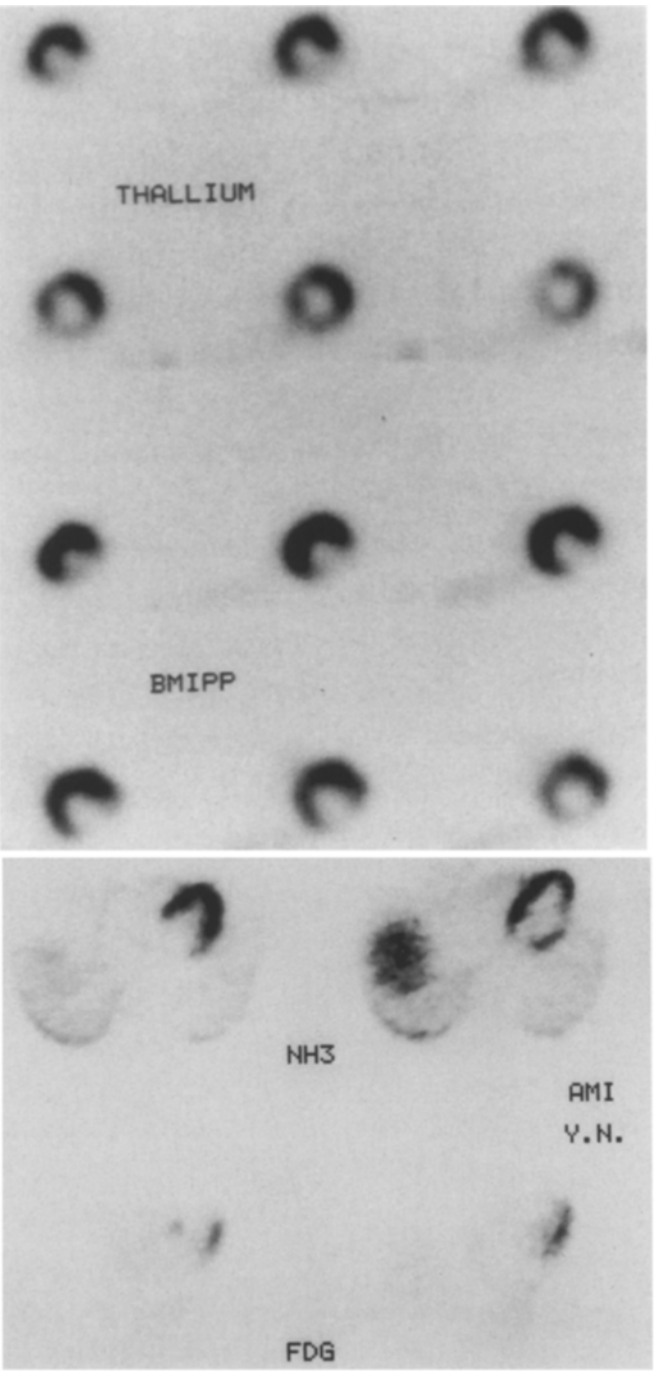


**Fig. 9.** Example of resting studies in a patient with acute inferior wall myocardial infarction, comparing regional distribution of [$^{123}$I]BMIPP, $^{201}$Tl, [$^{13}$N]ammonia, and 2-FDG. (Courtesy of N. Tamaki, M.D., Department of Nuclear Medicine, Kyoto University Hospital, Kyoto, Japan)

the inferolateral regions where discordant BMIPP uptake was observed.

Comparison of 2-FDG static images and BMIPP results in ten patients indicated that nearly all segments (35/37, 95%) with normal thallium and BMIPP patterns had normal 2-FDG PET images [174]. With regard to 25 segments showing decreases in both BMIPP and thallium uptake, 2-FDG PET showed ischemia in five segments and scar in 20. In contrast, among eight segments with decreased BMIPP accumulation in comparison with thallium uptake, PET showed ischemia in seven and scar in only one. These initial, preliminary data from a small patient group indicate that segments exhibiting decreased (discordant) BMIPP accumulation often have increased 2-FDG uptake and thus represent ischemic, viable myocardium. These combined studies illustrate the potential usefulness of BMIPP accumulation studies in conjunction with flow tracer distribution in detecting myocardial ischemia.

## Summary

Renewed interest in the clinical use of $^{123}$I-labelled fatty acids has resulted from several factors which include the potentially unique importance of these agents in assessing myocardial viability in stunned and/or hibernating myocardium. Table 1 summarizes some of the physiological properties (blood clearance, myocardial extraction, metabolism, etc.) of the $^{123}$I-labelled fatty acids that are most extensively used clinically. The commercial availability of [$^{123}$I]IPPA in Europe and more recently the approval and commercial introduction of [$^{123}$I]BMIPP as Cardiodine in Japan have made these agents more widely available. Interest in the use of [$^{123}$I]BMIPP has steadily grown and this agent is also in use at several institutions in Europe and in Japan: estimates indicate that more than 2000 patient studies are currently performed each month with Cardiodine in Japan. Over 50,000 patient studies have been completed through December 1994. As has been discussed in detail earlier, combined use of [$^{123}$I]BMIPP with the appropriate flow tracers may provide information on myocardial viability which cannot be obtained with flow tracers alone. How deficits in regional BMIPP uptake observed in the SPET cross-sectional images correlate with factors which affect the mechanism of fatty acid uptake or metabolism has not yet been elucidated. Static PET canine imaging studies with [1-$^{11}$C]palmitate have demonstrated the correlation of reduced regional fatty acid uptake with delayed contractile function recovery following reperfusion after coronary artery occlusion [175]. Decreased extraction of exogenous fatty acids in viable myocardial regions may result from alterations in fatty acid binding protein(s) involved in the transfer of fatty acids [57, 176, 177] or from arrested turnover of fatty acid pool(s). With BMIPP, the phenomenon of mismatch between flow tracer distribution and regional fatty acid

**Table 1** Comparison of physiological properties of various $^{123}$I-labelled fatty acids in humans

| Compound | Blood clearance | Myocardial clearance | Myocardial extraction | Metabolism | Heart/liver ratio |
|---|---|---|---|---|---|
| IPPA | $T_{1/2}$ ca. 3 min [179] | Three slopes in normals: $T_{1/2}$ I:0.24–0.5 min, $T_{1/2}$ II: 6–10 min, $T_{1/2}$ III: 40–60 min. CAD: One slope: $T_{1/2}$: 26–67 min [179] Biexponential: $T_{1/2}$ I:12.2±1.8, $T_{1/2}$ II: 99.2±18.7 [182] | Normals: 45%–53% CAD: 34%–61% [179] | [GC-MS, 60]. *p*-iodobenzoic acid [FAB-MS, 38]. 3-(*p*-iodophenyl) propenoic acid | 0.87 [116] |
| IHA | $T_{1/2}$ ca. 1.5 min [181] or 2 min [9] | 10–24 min [181]. Biexponential: $T_{1/2}$ I: 9.6±1.4, $T_{1/2}$ II: 54.9±18.2 [182] | 70%–80% [180], 78% [4] | $CO_2$ and free iodide | Rabbits and dogs: 0.9–1.3 [182] |
| BMIPP | $T_{1/2}$ ca. 2.5 min [184] | Normal regions: Biexponential: $T_{1/2}$ I: 11.2±4.3 min; $T_{1/2}$ II: 153.7±47.9 min. Diseased regions: Biexponential: $T_{1/2}$ I: 19.7±12.7 min; $T_{1/2}$ II:160.1±64.2 min [116] | 65% | 7.7%±2.1% after 3 h [169] metabolized to: 2-(*p*-iodophenyl)acetic [183] and/or iodophenyltetradecanoic acid [149] | 1.1 [116], 1.2 [169] |

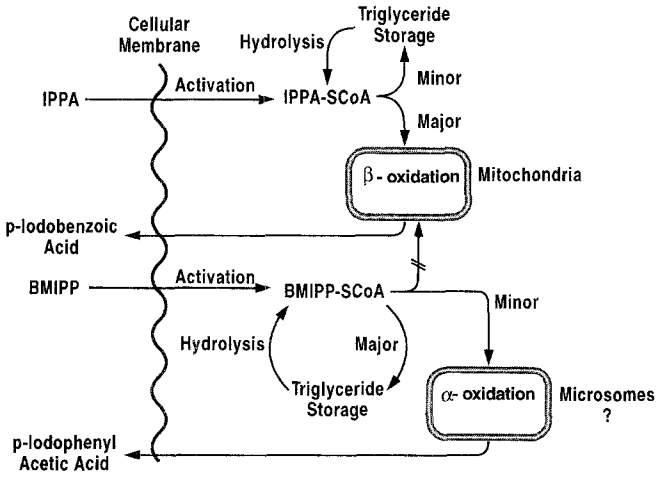


**Fig. 10.** Scheme comparing the relative intracellular metabolism of IPPA and BMIPP ("Cardiodine"). While IPPA can undergo immediate $\beta$-oxidation, the apparent obligatory initial $\alpha$-oxidation of BMIPP (i.e. loss of carboxyl carbon) is required before the resulting $\alpha$-methyl product can undergo subsequent cycles of $\beta$-oxidation. Although not understood, the sensitivity of cellular uptake of BMIPP may be a factor in explaining the unique regional "mismatch" often observed between relative regional uptake of flow tracers and BMIPP. Such a mismatch apparently has not been reported for IPPA

uptake patterns in animal studies has now been observed in many patient studies; assessment of the significance and potential usefulness of qualitative analyses of this discordance has undoubtedly also stimulated interest in the use of these agents.

Better understanding of the importance and limitations of the use of [$^{123}$I]BMIPP, for instance, would be expected to evolve as results become available from the retrospective evaluation of the large amount of patient data. In addition, as more patient information becomes available from the increasing number of clinical studies, especially in respect of [$^{123}$I]BMIPP, patterns may be expected to emerge that will allow the identification of those cases where this fatty acid, probably in conjunction with flow tracers, may have an important application.

The answers to several important questions which should be pursued on the basic research side include the potential effects of the absolute configuration of monomethyl substitution at the asymmetric carbon center (i.e., β-carbon of BMIPP, Fig. 6). BMIPP and all other monomethyl-substituted fatty acids which have been evaluated to date in animal models and/or humans consist of racemic mixtures of the *R* and *S* isomers. Because of the well-established importance of molecular configuration for the binding of many biologically molecules to macromolecules, transport, metabolism, etc., it may be expected that either the 3(*R*)-methyl-or the 3(*CS*)-methyl-isomer of BMIPP, for instance, may show more specific myocardial uptake and perhaps less localization in non-target organs. Other factors which should be studied further in animal models and which might be expected to provide additional insight include biochemical and histological analysis of biopsy segments removed from myocardial regions which have decreased fatty acid uptake.

One discrepancy which has not yet been evaluated in the same patient group and not discussed in the literature is the apparently unique regional uptake behavior of BMIPP in comparison with flow tracers. This behavior appears very different than that observed with IPPA. Why does BMIPP often show a regional mismatch with well-established flow tracers in situations where such a mismatch has not been observed with IPPA? Furthermore, what is the significance of this mismatch and how can it be used as an effective diagnostic tool? One key may be the different metabolic fates of the two tracers. While IPPA is primarily shuttled to the mitochondrial compartment for β-oxidation (Fig. 10), BMIPP appears to be primarily activated in the cytosol and incorporated into triglyceride storage products [178]. The fraction of BMIPP which is released from the myocardium represents the metabolites formed from α-oxidation [149] with some contribution from back-diffusion. An understanding of this different behavior may be expected to require the evaluation of both tracers in the same patients. For this purpose, and to achieve a better understanding of the physiological factors which affect BMIPP distribution and metabolism, additional carefully controlled patient studies will be necessary. Finally, evidence is beginning to accumulate that the use of [$^{123}$I]BMIPP in conjunction with flow tracers may represent a unique opportunity for the evaluation of myocardial viability with SPET.

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