Cardiac SPECT with Iodine-123-Labeled Fatty Acids: Evaluation of Myocardial Viability with BMIPP

F.F. (Russ) Knapp, Jr., P. Franken and J. Kropp

Nuclear Medicine Group, Health Sciences Research Division, Oak Ridge National Laboratory, Oak Ridge Tennessee; Department of Nuclear Medicine, Free University Hospital (VUB), Brussels, Belgium; Clinic and Polyclinic for Nuclear Medicine, Technical University, Dresden, Germany

The use of ^{123}I-labeled fatty acids is witnessing a resurgence of interest, primarily because of data from recent clinical protocols comparing regional myocardial uptake of ^{123}I-labeled 15-(p-iodophenyl)-3-(R,S)-methylpentandecanoic acid (BMIPP) with flow tracers. Comparison of mismatches in BMIPP and flow tracer distribution (BMIPP < flow tracer) has demonstrated the usefulness of evaluating myocardial viability with BMIPP. BMIPP was introduced in 1993 as "Cardiodine" as an approved radiopharmaceutical in Japan by Nihon Medi-Physics, Inc. This article reviews the clinical use of BMIPP in the assessment of cardiomyopathy, myocardial infarction, ischemic heart disease and for the evaluation of myocardial viability in comparison with PET tracers. The results of two specific protocols demonstrating the utility of using BMIPP to detect viable myocardium are described in detail. The first study compares BMIPP and sestamibi uptake to wall motion and inotropic reserve after acute myocardial infarction in conjunction with two-dimensional echocardiography and low-dose dobutamine stimulation. The second example describes results of a triple SPECT technique using BMIPP reinjection for the assessment of ischemia.

Key Words: myocardial viability; single-photon emission computed tomography; iodine-123-BMIPP

J Nucl Med 1995; 36:1022–1030

Iodine-123-BMIPP [15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid is a 3-methyl-branched fatty acid analog (Fig. 1) which shows considerably longer myocardial retention in comparison to the straight-chain analog (*1–4*). The first reported patient studies with [^{123}I]BMIPP were performed by Dudczack et al., who showed excellent delineation of the myocardium by planar imaging with high myocardial extraction and high myocardial-to-lung and myocardial-to-blood ratios (*5*). Although initial clinical studies with [^{123}I]-BMIPP by Dudczak et al. had demonstrated the rapid, high myocardial extraction of this agent in patients by planar imaging (*5*), the more detailed evaluation of regional BMIPP uptake required SPECT studies. In addition to the prolonged myocardial retention exhibited by BMIPP, an unexpected and added benefit is the "mismatching" pattern often observed between regional BMIPP and flow tracer distribution, which has been correlated with viable myocardium. Clinical SPECT with [^{123}I]BMIPP was thus prompted because of the striking discordance between regional BMIPP and flow tracer distribution initially observed by autoradiographic studies of hearts from hypertensive and cardiomyopathic animals (*6–11*). Another indication of the unique behavior of BMIPP and its potential utility for the evaluation of myocardial viability was from the studies by Miller et al. that demonstrated differences in BMIPP and ^{201}Tl distribution in the ischemic border zone region of a canine model (*12*).

The significance and potential importance of this mismatch between regional BMIPP uptake in comparison to flow tracer distribution was not fully realized until confirmation in human studies. More importantly, these studies demonstrated the expected prolonged myocardial retention, which was consistent with previous results of extensive animal studies. Because of the benefits of tomography, current studies with BMIPP exclusively use SPECT, and high quality images of the left ventricular myocardium are obtained even with SPECT imaging after injection with as low as 3-5 mCi of [^{123}I]BMIPP. An important question to be raised is what role will [^{123}I]BMIPP have in nuclear cardiology? From an extrapolation of the results from extensive preclinical studies with BMIPP for its possible clinical use, the potential advantages for using [^{123}I]BMIPP and flow tracers for dual-isotope SPECT include:

1. Evaluation of myocardial viability with [^{123}I]BMIPP as an alternative to PET with [^{18}F]-2-FDG.
2. Expected cost-effectiveness of dual-isotope studies with [^{123}I]BMIPP, in comparison to flow tracers, us-

Received Mar. 22, 1995; accepted Mar. 22, 1995.

Reprints may be obtained from any of the authors.

For correspondence contact: F.F. (Russ) Knapp, Jr., PhD, Group Leader, Nuclear Medicine Group, Oak Ridge National Laboratory, P.O. 2008, Oak Ridge, TN 37831-6229, E-mail JKP @ ornl.gov.

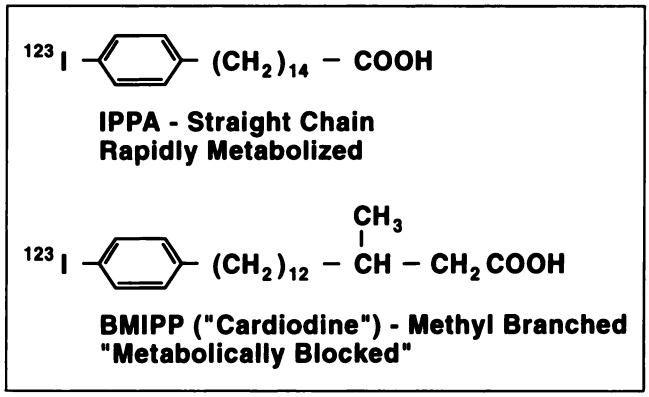

FIGURE 1. Fatty acid structures. The 3-methyl group present in BMIPP results in prolonged myocardial retention.

ing SPECT systems widely available in most nuclear medicine departments in most community hospitals.

BMIPP STUDIES IN CARDIOMYOPATHY

Results from several recent clinical studies have shown that [^{123}I]BMIPP SPECT appears useful for detection characterization of cardiomyopathy. Extensive clinical studies by Japanese investigators have evaluated the use of BMIPP in cardiomyopathy and differences in [^{123}I]BMIPP and ^{201}Tl distribution have been assessed in patients with hypertrophic cardiomyopathy (*13–16*). In one key study, SPECT imaging was conducted at rest 20 min and 3 hr following administration of [^{123}I]BMIPP (*14*) in 14 patients with left ventricular hypertrophy. Studies were also conducted in the patients within 1 wk with ^{201}Tl. Quantitative analysis of the regional uptake and clearance of both BMIPP and ^{201}Tl demonstrated mismatching where the regional distribution of BMIPP was more heterogeneous than that observed with ^{201}Tl. Lower uptake of BMIPP in anteroseptal regions was often noted in comparison with the posterolateral wall (BMIPP < ^{201}Tl). Although ^{201}Tl uptake was normal or increased in the anteroseptal wall, BMIPP exhibited both decreased uptake and increased clearance in these same regions. In contrast to regions with only mild hypertrophy, a general finding was that thickened wall segments showed lower BMIPP uptake and faster clearance.

The distribution of [^{123}I]BMIPP and ^{201}Tl in fasted patients at rest with hypertrophic cardiomyopathy (HCM) and with the dilated subtype was also assessed (*16*). The protocol involved initial SPECT imaging 30 min following BMIPP administration and a second late SPECT 3.5 hr later. Thallium-201 SPECT was performed 4–6 days after the BMIPP study. Normally contracting apical and septal hypertrophic regions of patients with hypertrophic cardiomyopathy demonstrated reduced [^{123}I]BMIPP uptake 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.

Nishimura et al. investigated 16 patients with hypertrophic cardiomyopathy (*13*). This protocol involved simultaneous rest BMIPP/^{201}Tl SPECT following administration of both tracers. The "early" SPECT was initiated 15–30 min after tracer administration and the "delayed" SPECT was obtained 40–60 min after injection. Increased thallium uptake was often observed in apical and postlateral hypertrophic myocardial regions which showed reduced BMIPP uptake in the same regions in both early and delayed scans (BMIPP < ^{201}Tl). In 68 segments with increased thallium uptake, 33 segments (49%) demonstrated normal BMIPP uptake, while the remaining showed reduced BMIPP accumulation. In 207 segments with normal thallium uptake, 41 segments (20%) clearly showed reduced BMIPP accumulation. These combined data clearly demonstrate that "mismatching," with reduced accumulation of BMIPP in comparison with ^{201}Tl uptake, is often observed in hypertrophic myocardium, and that [^{123}I]BMIPP fatty acid SPECT in conjunction with flow tracer assessment is adequate to assess myocardial functional integrity.

MYOCARDIAL INFARCTION: RESIDUAL VIABILITY

Discrepancies between BMIPP and regional myocardial blood flow have also been reported in patients with myocardial infarction (*17–19*). In their preliminary clinical study, Saito et al. (*17*) found mismatching between BMIPP and ^{201}Tl distribution in four of six patients investigated after an acute myocardial infarction. More reduced fatty acid uptake was found in the three patients who had successful reperfusion. The other patient showed segments with higher BMIPP uptake than ^{201}Tl uptake.

In a larger series including 28 patients with myocardial infarction, Tamaki et al. (*18*) found that BMIPP uptake was decreased compared to ^{201}Tl in 17 patients (61%) and in 49 of 196 myocardial segments (25%). Such discordant BMIPP uptake was observed more often in areas of acute, as opposed to chronic, myocardial infarction, and more often in reperfused, as opposed to nonreperfused, areas. In addition, a discordant decrease in BMIPP was frequently seen in areas showing a regional wall motion abnormality with relatively preserved perfusion. Thus, mismatching with decreased regional BMIPP uptake (BMIPP < flow tracer) may indicate a persistent metabolic abnormality associated with the failure of functional recovery after revascularization, particularly in patients with acute myocardial infarction.

Nishimura et al. investigated 25 patients with myocardial infraction (*13*). In this study, BMIPP and ^{201}Tl were administered simultaneously and myocardial SPECT was performed 15–30 min later. A dissociation between thallium and BMIPP defects (BMIPP < ^{201}Tl) was frequently observed in successfully reperfused segments in comparison with those regions with no reperfusion and chronic myocardial infarction. More importantly, the severity scores for BMIPP uptake determined by SPECT correlated

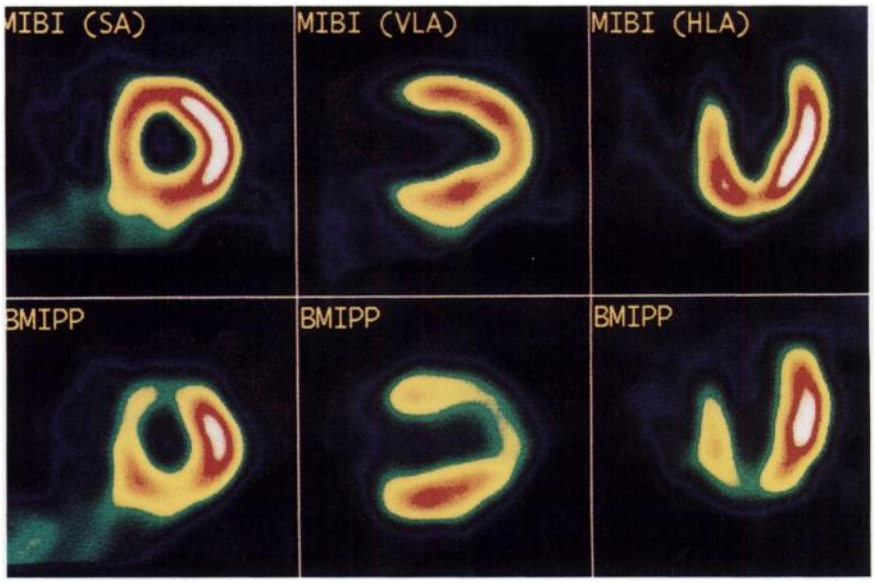

FIGURE 2. Example of mismatched defects. Sestamibi (MIBI) and BMIPP left ventricular short-axis (SA), vertical long-axis (VLA) and horizontal long-axis (HLA) slices were obtained in a patient with left ventricular dysfunction 1 wk after acute anterior myocardial infarction. BMIPP (148 MBq) was injected intravenously under resting conditions after an overnight fast of the day after the resting sestamibi study (740 MBq). The study shows reduced BMIPP but normal sestamibi uptake in the infarct-related coronary artery territory, indicating the presence of viable, jeopardized myocardium.

well with ventricular function as determined by ventricular ejection fraction measurement.

Similar findings were observed by De Geeter et al. (*19*) by using ^{99m}Tc-sestamibi as the flow tracer. The use of a ^{99m}Tc myocardial perfusion agent limited the problem of differential attenuation and scatter. In this way, no physical element could contribute significantly to the observed differences observed between metabolic and flow distribution. In this study, 26 patients were investigated within 2 wk after an acute myocardial infarction. Ten patients had a history of previous infarction. BMIPP and sestamibi SPECT were performed after rest injection within 4 days of one another. Forty segments were defined on apical, midventricular and basal slices. Of the 477 abnormal segments for at least one tracer, 47% showed defects of similar intensity, 42% showed more reduced BMIPP than sestamibi uptake and 11% showed a relative excess of BMIPP. Coronary arteriography and contrast ventriculography were obtained for each patient. Ninety-five percent of the defects occurred either in the infarct-related coronary artery (77%) or in territories subserved by significant coronary stenosis (18%). Regions with relatively decreased BMIPP uptake occurred much more frequently in patients who had undergone thrombolysis and/or PTCA in the early phase of infarction and appeared more often in areas supplied by patent arteries as opposed to occluded coronary arteries. In some areas, relative excess of BMIPP was observed at the periphery of previous infarction and severe regional wall motion abnormalities, presumably reflecting the increased metabolic requirements of myocardium which undergoes passive systolic wall stretch.

To determine whether BMIPP uptake can be used to differentiate viable myocardium from scar tissue soon after myocardial infarction, Franken (*et al. 20*) compared the relative uptake of BMIPP and sestamibi to regional wall motion and to contractile reserve assessed by two-dimen-

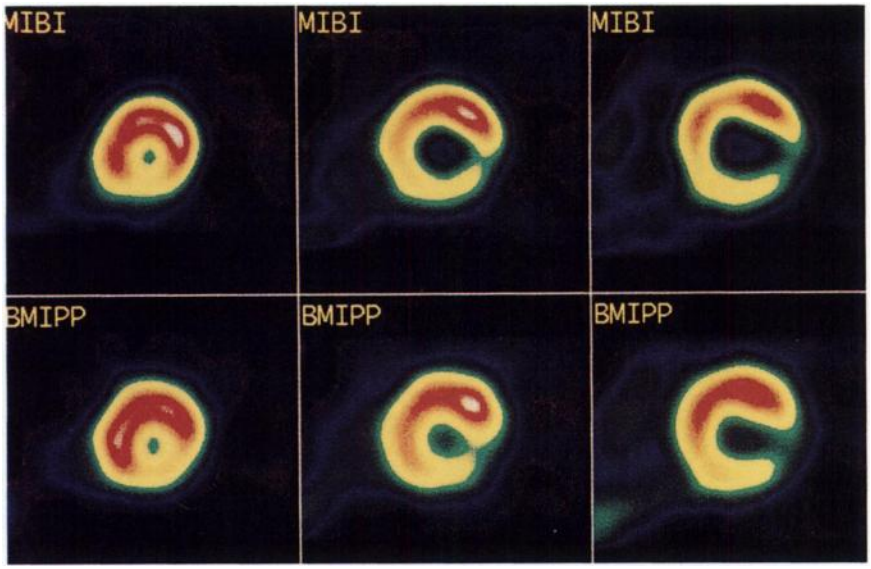

FIGURE 3. Example of matched defects. Sestamibi (MIBI) and BMIPP left ventricular short-axis slices were obtained in a patient with recent acute inferolateral myocardial infarction. There is a mild-to-moderate matched defect of both tracers in the infarct-related coronary artery territory suggesting absence of residual viability. Regional dysfunction did not improve after revascularization of this patient.

sional echocardiography and low-dose dobutamine stimulation. Twenty-two patients with a first acute myocardial infarction were investigated 4 to 10 days after coronary thrombolysis. BMIPP was injected intravenously under resting conditions after an overnight fast and SPECT images were obtained 20 min after injection. Three segmental patterns were identified in the infarct-related coronary artery territory: normal uptake of both tracers, mismatched defects with more reduced BMIPP uptake than sestamibi uptake (BMIPP < sestamibi) and matched defects (BMIPP = sestamibi). Examples of typical results from patients with matched and mismatched defects are shown in Figures 2 and 3. All segments with both normal BMIPP and sestamibi uptake showed normal wall motion. Evidence of residual viability was found in 72% of the segments showing mismatching, i.e., wall motion was either normal at rest or demonstrated inotropic reserve during low-dose dobutamine stimulation. In segments with dysfunction, mismatching was significantly associated with inotropic reserve ($p < 0.001$). All segments that improved function during dobutamine stimulation showed a mismatched BMIPP/sestamibi uptake. In contrast, segments with matched defects always showed abnormal wall motion and none demonstrated inotropic reserve, regardless of the severity of sestamibi defect. It was concluded from this study that mismatching is indicative of jeopardized but viable myocardium, and that matched defects are associated with scar tissue.

The prognostic value of combined BMIPP and sestamibi SPECT to predict functional outcome, after acute myocardial infarction, has been recently addressed by the same group (*21*). Rest BMIPP, rest sestamibi SPECT and dobutamine echocardiography were obtained in 18 patients presenting with wall motion abnormalities on two-dimensional echocardiography the week following acute myocardial infarction. All patients received the appropriate treatment according to standard indications, including percutaneous transluminal coronary angioplasty (PCTA) in seven patients and coronary artery bypass grafting (CABG) in six patients. Six months after infarction, all patients underwent a second echocardiographic study to assess functional outcome. Wall motion improved in at least 50% of the dysfunctional segments in nine patients and was unchanged in the nine other patients. Baseline clinical data, findings on coronary arteriography before hospital discharge and the occurrence and type of revascularization procedure were similar in patients with improved function and in patients where function was not improved.

On the other hand, a highly significant association ($p < 0.001$) was found between the functional outcome and the relative uptake of BMIPP and sestamibi. Wall motion improved in 27 of the 33 segments (82%) showing mismatching (BMIPP < sestamibi) and was unchanged in 19 of the 21 segments (90%) with matched defects (BMIPP = sestamibi). The overall accuracy of combined BMIPP and sestamibi SPECT in predicting segmental functional outcome was 85%. An important outcome of this study is that these values are similar to those obtained with metabolic studies using PET and 2-[^{18}F]fluoro-2-deoxyglucose (2-FDG) for differentiating viable from nonviable myocardium. The study shows that the probability of observing functional improvement in a patient was directly related to the extent of mismatching between BMIPP and sestamibi. When more than 75% of the dysfunctional segments showed a mismatched pattern, the probability for functional improvement was 90% (9 of 10 patients). In contrast, none of the eight patients with less than 75% of mismatching improved function at 6 mo follow-up. The sensitivity, specificity and predictive accuracy values of combined BMIPP and sestamibi scintigraphy for patient functional improvement were 100%, 89% and 94%, respectively.

The incremental value of combined BMIPP and sestamibi to predict segmental functional outcome over that provided by either sestamibi uptake alone or by low-dose dobutamine echocardiography was also evaluated in this study. By using an arbitrary cutoff of 50% of the maximal activity as criterion for myocardial viability, sestamibi uptake alone had a positive predictive value of 84% and a negative predictive value of 72%. These values improved to 95% and 89%, respectively, when the relative uptake of BMIPP is also considered (mismatched versus matched defects). Improvement in wall thickening during low-dose dobutamine stimulation had a positive predictive value of 80% and a negative predictive value of 62%. These values both increased to 94% when the relative uptake of BMIPP and sestamibi was also considered.

Comparison of BMIPP and flow tracer uptake (^{201}Tl or ^{99m}Tc-sestamibi) thus clearly allows the characterization of the complete spectrum of postischemic myocardium, i.e., from complete functional recovery (when the uptake of both tracers is normal) to complete transmural necrosis without residual viability (when the uptake of both tracers is severely and similarly reduced). Mismatching with more severely depressed fatty acid metabolism than expected on the basis of the flow is indicative of jeopardized but viable myocardium and is predictive for long-term functional recovery following acute myocardial infarction. Matched defects are associated with scar. The additional information provided by BMIPP substantially increases the accuracy of sestamibi uptake alone or dobutamine echocardiography alone to predict functional outcome early after acute myocardial infarction.

MYOCARDIAL ISCHEMIA: DETECTION OF CAD

The expected inhibition of beta-oxidation by methyl-branching in BMIPP results in prolonged myocardial retention, and in the patient population described in the studies below, the average activity loss over 3 hr was only 18.7% ± 5.1% in regions perfused by nonstenosed coronary arteries. Prolonged imaging periods are thus possible, but the lack of BMIPP redistribution makes a second injection (reinjection) necessary to detect ischemic but viable myocardium. In contrast to [^{123}I]BMIPP studies at rest, a

TABLE 1
Scores of BMIPP Uptake in Relation to Wall Motion in 180 Segments

BMIPP score	Wall motion score			
	3	2	1	Total
3	97	9	2	108
2	10	30	2	42
1	2	18	10	30
Total	109	57	14	180

BMIPP uptake score: 3 = normal; 2 = reduced with refill; 1 = absent. LVCV score: 3 = normal; 2 = hypokinesia; 1 = akinesia. No dyskinetic segments in this patient group.

TABLE 2
Turnover and Refill Values for Nonischemic Myocardial Areas

	LAD	RCA	LCX
T	21.9 ± 6.4	17.42 ± 4.5	16.8 ± 4.2
Rf1	11.6 ± 2.6	10.9 ± 3.8	10.0 ± 4.2
Rf2	−1.7 ± 0.6	2.5 ± 1.0	1.8 ± 1.7

The mean "normal" values of turnover (T) and standard deviation values were calculated by the comparison of decay-corrected slices from the SPECT I (stress) and SPECT II (3 hr postinjection) tomogram. Mean refill values were calculated by the comparison of the SPECT I and SPECT II tomogram (Rf1) and from the SPECT II and SPECT III tomogram (Rf2). The latter values were corrected for the assumed fraction of back diffusion of BMIPP from Rf1.

T = turnover; Rf1 = refill 1; Rf2 = refill 2; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

"triple SPECT" approach with maximal exercise prior to tracer administration has also been developed (*23*). In this protocol, the myocardial distribution of activity following administration of a standard 5-mCi dose of [^{123}I]BMIPP radiotracer is determined by an early SPECT I (stress) 15 min postinjection, and represents blood flow. A second acquisition is obtained (SPECT II) 3 hr later, and a third acquisition (SPECT III, reinjection) is acquired 30 min after reinjection of 2 mCi BMIPP at rest. For an example of this protocol, 20 strictly fasted patients were investigated who had coronary artery disease (CAD) substantiated by quantitative coronary arteriography and biplane left ventricular cineventriculography. The SPECT slices of the left ventricle were first analyzed visually to grade BMIPP uptake and detect fill in ("refill") of BMIPP in 10 segments (Table 1). Comparison of the differences in relative regional tracer concentration in myocardial segments between SPECT I and SPECT II is defined as "metabolism" and SPECT III represents viable myocardium where refilling of the defect is observed. Regional wall motion in the cineventriculographgic study was scored in the same ten segments as in the BMIPP tomogram (Table 1).

The regions supplied by the left anterior descending, left circumflex and right coronary arteries without stenosis exhibited "normal" BMIPP turnover values, which are summarized in Table 2, with the values for refill. Turnover values in regions supplied by a stenosed artery were considered significantly decreased if they differed from the normal mean value by more than 1 s.d. Figure 4A illustrates four short-axis slices of the complete set of tomograms of a patient with an occluded left anterior descending coronary artery, and Figure 4B illustrates the computer printout of the coronary arteriogram of this patient who had an infarction in the distal anterior wall with akinesia in this region (Fig. 4C). Reduced uptake in the anterior wall is observed in the SPECT I (stress) slices and is consistent with the vessel narrowing observed by arteriography. The regional uptake in SPECT II (3 hr postinjection) shows no major uptake differences compared to SPECT I. In the SPECT III (reinjection) tomogram, there is normal uptake (refill) in the noninfarcted regions of the anterior wall (arrows), indicating ischemic but viable myocardium. In addition, there is a persistent defect in the distal anterior wall which matches the infarcted area observed by cineventriculography. There were 15 infarctions which were substantiated anamnestically and by typical enzyme changes, electrocardiographic signs and cineventriculography (akinetic or hypokinetic). In 14 patients (93%), BMIPP-SPECT corresponded with the clinical findings as persistent uptake defects.

Figure 5 summarizes these results concerning the diagnosis of ischemia with regard to the findings in coronary arteriogram and the mode of analysis of the BMIPP images. The maximum sensitivity and specificity for detection of ischemia were 86% and 94%, respectively, and infarcted areas were excluded in this analysis. For the analysis based on turnover values, the specificity could not be calculated due to the mode of calculation of the normal values. Finally, two patients with no evidence of stenoses by arteriography had normal homogeneous uptake of BMIPP in all tomograms. The results of this study demonstrate that left ventricular myocardial imaging with BMIPP and the triple SPECT tomographic technique provides reliable information for identifying ischemic but viable myocardium. There is also good correlation with the results from regional wall motion studies and the anatomy of the coronary artery system. Semiquantification could improve the accuracy of the method in detecting ischemic rather than infarcted areas.

The attempt to diagnose ischemia by using semiquantification of the tomograms (turnover rates) was based on the assumption that the metabolism of BMIPP is, at least in part, dependent on oxygen supply and consumption. Because the usual beta-oxidative process is apparently inhibited by the methyl group, an alternative metabolic pathway is suggested which might involve initial α-oxidation. To assess the time course of metabolite formation, blood samples were withdrawn from patients at 3 min, 20 min and 3 hr postinjection and lipids were extracted from the serum and analyzed by thin-layer chromatography (TLC). Iodobenzoic acid [metabolite of 15-(p-iodophenyl)pentade-

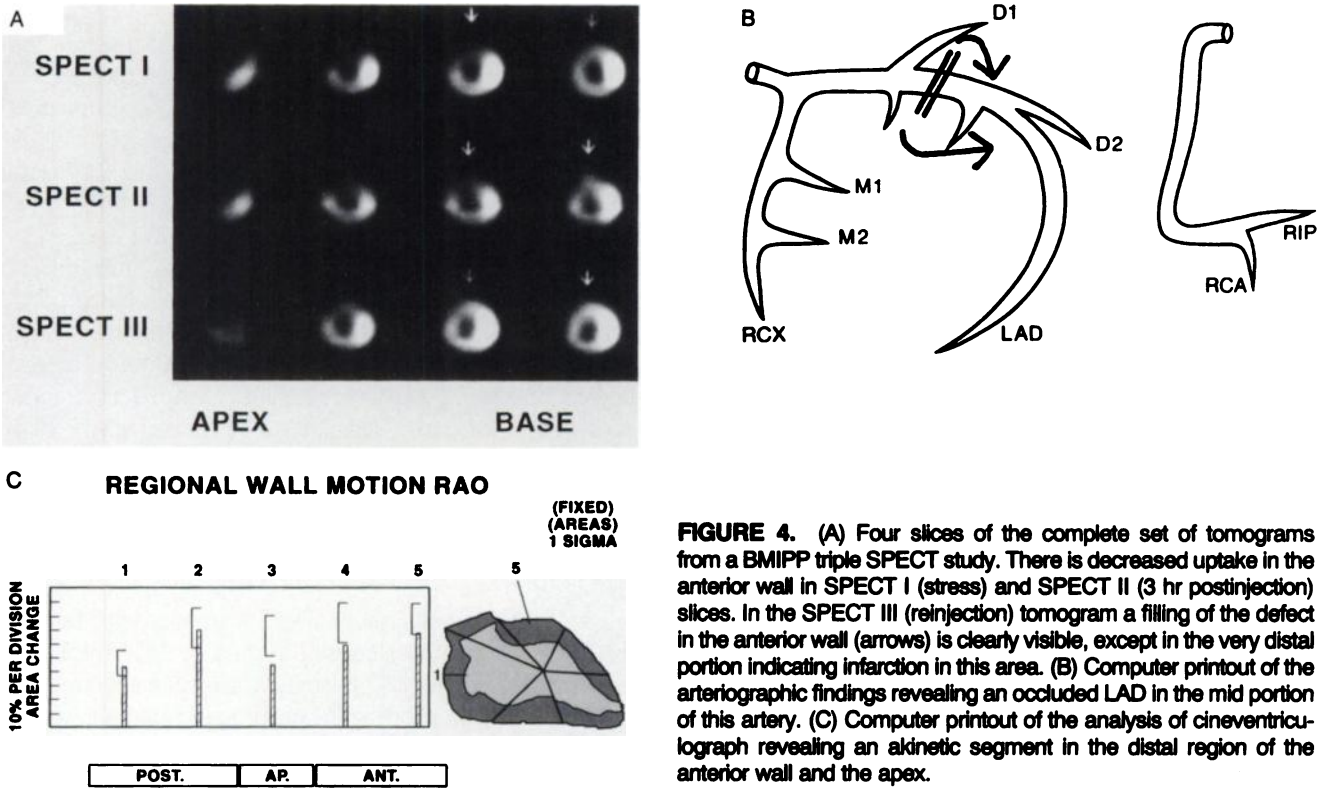

FIGURE 4. (A) Four slices of the complete set of tomograms from a BMIPP triple SPECT study. There is decreased uptake in the anterior wall in SPECT I (stress) and SPECT II (3 hr postinjection) slices. In the SPECT III (reinjection) tomogram a filling of the defect in the anterior wall (arrows) is clearly visible, except in the very distal portion indicating infarction in this area. (B) Computer printout of the arteriographic findings revealing an occluded LAD in the mid portion of this artery. (C) Computer printout of the analysis of cineventriculograph revealing an akinetic segment in the distal region of the anterior wall and the apex.

canoic acid], authentic BMIPP and tripalmitin were also applied to the chromatographic plates as reference standards. After solvent development, the TLC plates were cut into 15 segments and counted. The measured activities were expanded to the total blood volume, which was calculated from weight and height (*24*) of the patient, and this value was compared to the injected activity. The chromatographic properties of the serum lipids were also evaluated, which showed an increasing fraction of radioactivity which was chromatographically more polar than BMIPP. These results are summarized in Table 3.

The TLC analysis of blood lipids showed a metabolite more polar than the BMIPP standard and even more polar than the p-iodobenzoic acid metabolite of 15-(p-iodophenyl)pentadecanoic acid, which corresponds to the principal metabolite identified by Yamamichi et al. (*25–26*). The polar fraction from BMIPP metabolism increased slowly. The polar component observed in TLC analysis appears to correspond with the same metabolite of BMIPP found in isolated heart experiments (*27*), since both compounds exhibited identical chromatographic mobility (relative R_f mobility value of 0.20). This metabolite is expected to be the initial product resulting from alpha-oxidation, since it is known to occur in ischemic conditions. Because this metabolite was also detected in patients without stenoses and a normal scan, this metabolic pathway might also be at

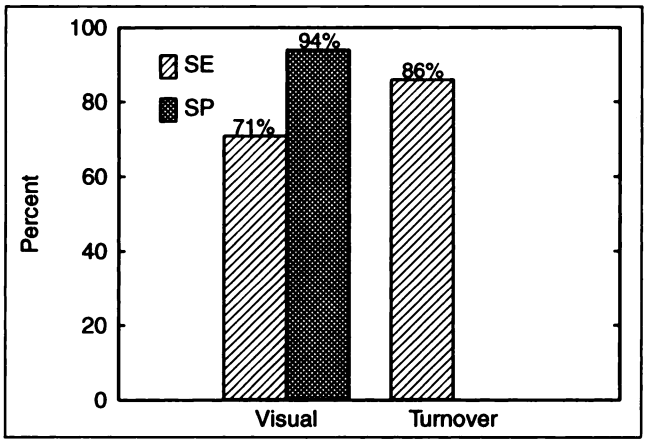

FIGURE 5. Sensitivity (SE) and specificity (SP) for the diagnosis of ischemia with regard to the mode of analysis of the BMIPP-scans. The CA findings were taken as the gold standard, where greater than 50% narrowing of an artery was regarded significant for coronary artery disease.

TABLE 3
Results of Blood Lipid TLC Analysis

	% ID	
Time p.i.	BMIPP	Metabolite
3 min	26.5 ± 4.8	0
30 min	2.8 ± 0.5	5.2 ± 1.8
3 hr	0	7.7 ± 2.1

Values are expressed as the mean and s.d. and are expanded to the patient total blood volume.

least partly an alternative to beta-oxidation in the normal perfused myocardium. Since the myocardial washout of BMIPP is slow and catabolism of BMIPP in myocytes from animal studies is only small, serum levels of activity could also represent metabolites from the liver or other body compartments.

These data are consistent with the results of several other groups that demonstrate that BMIPP or similar derivatives are useful in the diagnosis of various diseases of the heart (*18–28*). Visual inspection of the scans with regard to infarcted areas reveals high accuracy and correlation to clinical findings, including regional wall motion, as found by other investigators (*18*). In contrast, the more rapid washout of radioactivity from normal, oxygenated segments is contrasted in comparison to 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 SPECT acquisitions.

The analysis of turnover rates improved the sensitivity for the detection of ischemia in patients with CAD, compared to the visual inspection, if a greater than 50% narrowing of an artery was considered significant and coronary arteriography as the gold standard for CAD. This result implies that the degradation of BMIPP is oxygen-dependant and the rate of turnover is decreased under ischemic conditions. A refill value of about 10% in the SPECT III slices compared to SPECT I in nonischemic areas (Table 2) might be due to backdiffusion of unmetabolized tracer under stress. This fraction is assumed to be enhanced in ischemic areas (*29*), especially under maximal stress. Such kinetic behavior of the BMIPP tracer was also found in isolated rat heart experiments (*30*) and occurred also in normally perfused segments in clinical studies, indicating that ischemia is not a necessary supposition for backdiffusion and might result from increased lactate serum levels which interfere with fatty acid metabolism.

COMPARISON OF IODINE-123-BMIPP SPECT AND PET TRACERS

Since the use of 2-FDG with PET is often considered the gold standard for evaluation of regional myocardial viability, comparison of [^{123}I]BMIPP and 2-FDG in conjunction with flow tracers is crucial. Such studies are based on the supposition that myocardial segments which are viable but have decreased contraction are expected to concentrate 2-FDG. Comparative regional uptake and clearance kinetics of [^{123}I]BMIPP and [1-^{11}C]palmitate have been evaluated in the same patients by Tamaki et al. using SPECT and PET, respectively (*31*).

Patients were fasted overnight and studied at rest. The BMIPP-SPECT study was initiated 20 min after injection of [^{123}I]BMIPP. For those patients also studied with thallium-SPECT, this study was conducted within 2 wk of the BMIPP study, with images initiated 15 min after injection at rest. The palmitate PET studies involved six patients with 2 min-serial dynamic scans for 40 min. The protocol allowed a comparison of relative BMIPP and thallium uptake and palmitate uptake and clearance kinetics from the same segments. Static 2-FDG images were also obtained 60 min after administration to 10 patients. BMIPP accumulation patterns corresponded well with palmitate PET data in the majority of segments, and in general, BMIPP accumulation appeared to parallel palmitate uptake and retention in the majority of segments studied (Fig. 6). In the six patients studied with both BMIPP and palmitate, of 15 segments showing decreased BMIPP accumulation, 12 segments exhibited decreased late uptake of palmitate and 11 showed decreased early uptake and delayed clearance. Twenty-three of the 27 segments with normal BMIPP uptake had normal palmitate uptake and clearance.

Comparison of FDG-PET results with [^{123}I]BMIPP SPECT have been summarized and clearly suggest that BMIPP/^{201}Tl mismatch is significant and can be corroborated by PET data (*32*). Normal BMIPP uptake correlated well with PET results, since 35/37 segments with normal BMIPP uptake were diagnosed normal by FDG-PET and 2/37 as scar. BMIPP/^{201}Tl mismatch has been shown to be a sensitive indicator for the localization of ischemic, viable myocardium. A high percentage of segments (80%, 20/25) were diagnosed as normal for both BMIPP and ^{201}Tl and showed the presence of scar on FDG-PET; five of the 25 were judged ischemic. Significantly, 7/8 segments diagnosed ischemic by FDG-PET had less BMIPP localization than ^{201}Tl, while only 1/8 showed scarring. Verification of these data in a larger patient population will further support the combined BMIPP/^{201}Tl mismatch phenomenon as a method which can be conducted without PET for the detection of ischemic but viable myocardium in patients with coronary heart disease.

CONCLUSION

After significant investment in research funds and effort during the last 30 yr, the use of ^{123}I-labeled fatty acids for routine assessment of cardiac disease may now be a reality with the introduction of BMIPP. Iodine-123-fatty acid cardiac SPECT imaging may have an important role because of false-positive results often encountered with ^{201}Tl SPECT in identifying threatened but viable myocardium. The use of ^{123}I-labeled fatty acids may provide complementary information on myocardial viability, for example, for identifying and assessing the presence of salvageable tissue. Although it is not yet clear if there is a "best" flow tracer for comparison with [^{123}I]BMIPP, similar mismatching seems to be a consistent phenomenon which has been observed using ^{201}Tl, sestamibi and ^{13}N-ammonia. The consistent results from data evolving from clinical studies with BMIPP-SPECT in comparison to flow tracers indicates that mismatching (less BMIPP uptake than flow tracer) is an indicator of viable myocardium and suggests that the availability of this technique will permit assessment of myocardial viability using SPECT systems widely

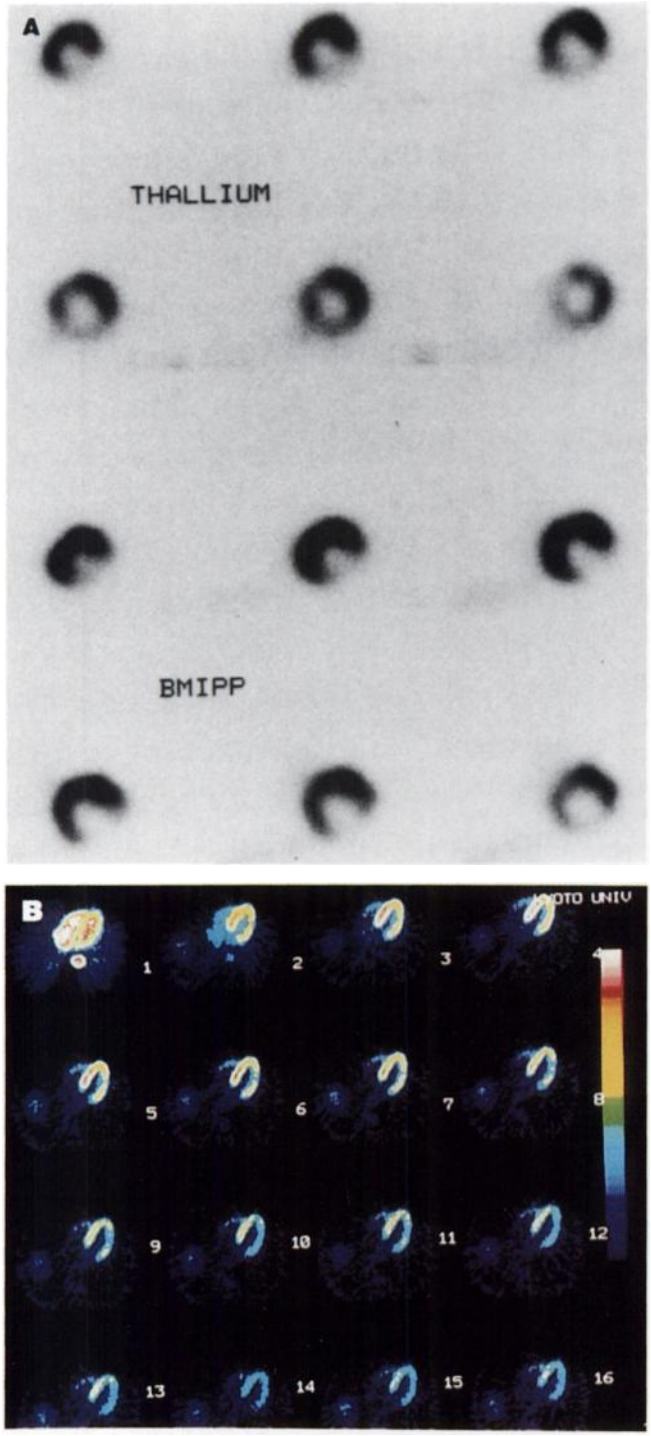

FIGURE 6. Results from a 76-yr-old patient with inferior wall myocardial infraction. The series of short-axis ^{201}Tl slices show a small perfusion defect in the inferior region. The BMIPP study, decreased uptake of the fatty acid tracer is observed in the posterolateral and inferior regions, illustrating the discordance between flow tracer and BMIPP uptake. The accompanying serial PET images in the same patient with [1-^{11}C]-palmitate also shows decreased uptake in the posterolateral region with delayed clearance. [Reprinted with permission from: Tamaki N,. et al. Assessment of fatty acid metabolism using ^{123}I branched fatty acid: comparison with positron emission tomography. *Annals of Nuclear Medicine* 1993;7:41–48].

available in community hospitals, thus precluding the routine requirement for PET.

Factors requiring further study in animal models include biochemical and histological analysis of biopsy segments removed from myocardial regions which have decreased fatty acid relative to flow tracer uptake. The important goal of these studies should be the identification of the factor(s) affecting reduced BMIPP uptake compared to flow, since the physiological mechanisms resulting in such distribution patterns is 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 which reflects an "intrinsic" impairment of myocardial free fatty acid uptake or utilization.

In addition, evaluation of the kinetics of tissue uptake and metabolite release of the 3R and 3S isomers of radioiodinated BMIPP should be evaluated. It is quite probable that the target-to-nontarget ratios can be further improved, since one isomer may have more favorable characteristics when compared to racemic 3-(R,S)-BMIPP, which is currently available for clinical use. Opportunities for clinical studies would include use of the rapid acquisition capability of three-head SPECT systems since [^{123}I]BMIPP may offer the first opportunity to construct regional time-activity curves from successive SPECT studies. In this manner, one would expect that [^{123}I]BMIPP could be used with SPECT similar to palmitate for PET to measure differences in washout between normal and ischemic myocardial segments.

Several issues requiring further evaluation before [^{123}I]BMIPP SPECT is more widely accepted include:

1. Are dual-radioisotope studies with ^{201}Tl or ^{99m}Tc flow tracers and [^{123}I]BMIPP practical in the routine clinical setting and is the expense justifiable?
2. Is the metabolism/catabolism of BMIPP understood well enough in animal models to translate the use of this agent to routine clinical cardiac SPECT?
3. Can information on viability be uniquely obtained in the routine clinical setting with [^{123}I]BMIPP without access to PET?
4. Is the cost sufficiently low, and can ^{123}I be regularly available in the large amounts which may be required for routine clinical use of [^{123}I]BMIPP?
5. Is the combined radiation exposure from repeat dual-radioisotope studies within acceptable limits?

Over 2500 patient studies per month are currently conducted in Japan with Cardiodine in over 300 hospital-based nuclear medicine departments. This is estimated to represent about 14% of all nuclear cardiology studies in Japan; through December 1994, over 50,000 patient studies had been completed. The results of these studies, in conjunction with clinical studies being pursued at several institutions described in this article and at other institutions in Europe, would hopefully stimulate use of Cardiodine in the United States. We would expect that the extensive data

being documented on the use of [^{123}I]BMIPP in the diagnosis of various myocardial disorders and the comparison of these results with commonly used flow tracers will answer these questions and provide the basis by which the broader possible role of BMIPP in nuclear cardiology will be further assessed.

ACKNOWLEDGMENTS

Research at ORNL is supported by the Office of Health and Environmental Research, U.S. Department of Energy, under contract DE-AC05-85OR21400 with Martin Marietta Energy Systems, Inc. The authors also wish to express their appreciation to the many colleagues who have provided stimulating discussions on the clinical use of [^{123}I]BMIPP.

REFERENCES

1. Knapp FF Jr, Kropp J. Iodine-123-labeled fatty acids for myocardial single-photon emission tomography: current status and future perspectives. *Eur J Nucl Med* 1995;22:361–381.
2. Knapp FF Jr, Kropp J, Goodman MM, et al. The development of iodine-123-methyl-branched fatty acids and their applications in nuclear cardiology. *Ann Nucl Med* 1993;7:1–14.
3. Goodman MM, Kirsch G, Knapp FF Jr. Synthesis and evaluation of radioiodinated terminal p-iodophenyl-substituted α- and β-methyl-branched fatty acids. *J Med Chem* 1984;27:390-397.
4. Knapp Jr FF, Ambrose KR, Goodman MM. New radioiodinated methyl-branched fatty acids for cardiac imaging. *Eur J Nucl Med* 1986;12:S539–544.
5. Dudczak R, Schmoliner R, Angelberger P, et al. Structurally-modified fatty acids: clinical potential as tracers of metabolism. *Eur J Nucl Med* 1986;12: 45–48.
6. Yonekura Y, Brill AB, Som P, et al. Quantitative autoradiographic measurement of regional myocardial substrate utilization in hypertensive rats. *Science* 1985;227:1494–1496.
7. Yamamoto K, Som P, Brill AB, et al. Dual tracer autoradiographic study of β-methyl-(1-^{14}C) heptadecanoic acid and 15-p-(^{131}I)-iodophenyl-β-methyl-pentadecanoic acid in normotensive and hypertensive rats. *J Nucl Med* 1986;27:1178–1183.
8. Kurata C, Kobayashi A, Yamazak A. Dual-tracer autoradiographic study with ^{201}Tl and radioiodinated fatty acid in cardiomyopathic hamsters. *J Nucl Med* 1989;30:80–87.
9. Som P, Oster ZH, Goodman MM, et al. Microimaging studies with myocardial substrate utilization and perfusion in two models of non-coronary heart disease. *NucCompact/Eur Am Commun Nucl Med* 1990;21:259–262.
10. Som P, Wang G-J, Oster ZH, et al. Myocardial uptake of cocaine and effects of cocaine on myocardial substrate utilization and perfusion in hypertensive rats. *Ann Nucl Med* 1993;7:19–26.
11. Wang G-J, Som P, Oster, ZH, Volkow ND, Knapp FF Jr, Sacker DF. Quantitative autoradiographic measurement of cocaine-induced regional myocardial metabolic changes in hypertensive rats. *Nucl Med Biol* 1994;21: 245–250.
12. Miller DD, Gill JB, Livni E, et al. Fatty acid analogue accumulation: a marker of myocyte viability in ischemic-reperfused myocardium. *Circ Res* 1988;63:681–693.
13. Nishimura T, Uehara T, Shimonagata T, Nagata S, Haze K. Clinical experience of ^{123}I-BMIPP myocardial imaging for myocardial infarction and hypertrophic cardiomyopathy. *Ann Nucl Med* 1993;7:35–40.
14. Takeishi Y, Chiba J, Abe S, et al. Heterogeneous myocardial distribution of iodine-123 15-(p-iodophenyl)-3-R,S-methylpentadecanoic avid (BMIPP) in patients with hypertrophic cardiomyopathy. *Eur J Nucl Med* 1992;19:775–782.
15. Morita K, Yanagimoto S, Otsuka N, et al. Iodine-123-BMIPP scintigraphy in seven cases with cardiomyopathy. *Ann Nucl Med* 1993;7:101–107.
16. Kurata C, Tawahara K, Okayama K, et al. Myocardial imaging with radioiodinated beta-methyl-branched fatty acid in cardiomyopathy. *Ann Nucl Med* 1993;7:27–34.
17. Saito S, Yasuda T, Gold HK, et al. Differentiation of regional perfusion and fatty acid uptake in zones of myocardial injury. *Nucl Med Commun* 1991; 12:663–675.
18. Tamaki N, Kawamoto M, Yonekura Y, et al. Regional metabolic abnormality in relation to perfusion and wall motion in patients with myocardial infarction: assessment with emission tomography using an iodinated branched fatty acid analog. *J Nucl Med* 1992;33:659–667.
19. De Geeter F, Franken PR, Knapp FF Jr, Bossuyt A. Relationship between blood flow and fatty acid metabolism in subacute myocardial infarction: a study by means to Tc-99m MIBI and 1-123 beta-methyl iodophenyl pentadecanoic acid. *Eur J Nucl Med* 1994;21:283–291.
20. Franken PR, De Geeter F, Dendale P, Demoor D, Block P, Bossuyt A. Abnormal free fatty acid uptake in subacute myocardial infarction after coronary thrombolysis: correlation with wall motion and inotropic reserve. *J Nucl Med* 1994;35:1758–1765.
21. Franken PR, Demoor D, De Sadeleer C, Block P, Bossuyt A. Free fatty acid uptake in myocardium with postischemic dysfunction: comparison with dobutamine echocardiography to predict long term functional recovery [Abstract]. *J Nucl Med* 1994;35(suppl):50P.
22. Tomiguchi S, Oyama Y, Nabeshima M, et al. Quantitative evaluation of BMIPP in patients with ischemic heart disease. *Ann Nucl Med* 1993;7:107–112.
23. Kropp J, Juergans M, Glaenzer K, Luederitz B, Biersack H-J, Knapp FF Jr. Evaluation of ischemia and myocardial viability in patients with coronary artery disease (CAD) with iodine-123-labeled (15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP). *Ann Nucl Med* 1993;7:93–100.
24. Nadler SB, Hidalgo JU, Bloch T. Prediction of blood volume in normal human adults. *Invest Surg* 1961;51:224–232.
25. Yamamichi Y, Hideo BS, Kusuoka H, et al. Metabolism of ^{123}I-labeled 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) in perfused rat hearts: the evidence for initial α-oxidation and subsequent cycles of β-oxidation, and dependency on substrates. *J Nucl Med* 1995;36:1031–1038.
26. Knapp FF Jr, Myocardial metabolism of radioiodinated BMIPP ("Cardiodine") [Editorial]. *J Nucl Med* 1995;36:1039–1042.
27. Knapp FF Jr, Goodman MM, Reske SN, et al. Radioiodinated methyl-branched fatty acids—evaluation of catabolites formed in vivo. *NucCompact/Eur Am Commun Nucl Med* 1990;21:229–231.
28. Kurata C, Tawarahara K, Taguchi T, et al. Myocardial emission computed tomography with iodine-123-labeled beta-methyl-branched fatty acid in patients with hypertrophic cardiomyopathy. *J Nucl Med* 1992;33:6–13.
29. Fox KAA, Abendschein DR, Ambos HD, et al. Efflux of metabolized and nonmetabolized fatty acid from canine myocardium. *Circ Res* 1985;57:232–243.
30. Kropp J, Ambrose KR, Knapp FF Jr, et al. Der washout von 15-(p-Jodphenyl)-3-R,S-methylpentadecansaeure (BMIPP) repraesentiert sowohl rueckdiffusion als auch katabolismus. In: Hoefer R, Bergman H, Sinzinger H, eds. Radioaktive Isotope in Klinik und Forschung. Stuttgart: Schattauer Verlag; 1991:93–97.
31. Tamaki N, Kawamoto M, Yonekura Y, et al. Assessment of fatty acid metabolism using I-123 branched fatty acid: comparison with positron emission tomography. *Ann Nucl Med* 1993;7:41–48.
32. Kawamoto M, Tamaki N, Yonekura Y, et al. Combined study with I-123 fatty acid and ^{201}Tl to assess ischemic myocardium: Comparison with thallium redistribution and glucose metabolism. *Ann Nucl Med* 1994;8:847–854.