5. Fleming JS, Alaamer AS, Perring S. A technique for the absolute quantification of ^{131}I radiopharmaceuticals using SPECT. *Nucl Med Commun* 1993;14:498–505.
6. Axelsson B, Msaki P, Israelsson A. Subtraction of Compton scattered photons in SPECT. *J Nucl Med* 1984;25:490–494.
7. Msaki P, Axelsson B, Dahl CM, Larsson S. Generalized scatter correction method in SPECT using point scatter distribution functions. *J Nucl Med* 1987;28:1861–1869.
8. Fleming JS. A technique for using CT images in attenuation correction and quantification in SPECT. *Nucl Med Commun* 1989;10:83–97.
9. Alaamer AS, Fleming JS, Perring S. Evaluation of the factors affecting the accuracy and precision of a technique for quantification of volume and activity in SPECT. *Nucl Med Commun* 1994;15:758–771.
10. Fleming JS, Simpson DE. A technique for simulation of the point spread function of a gamma camera. *Phys Med Biol* 1994;39:1457–1473.

Metabolic Fate of Iodine-123-BMIPP in Canine Myocardium after Administration of Etomoxir

Ryohei Hosokawa, Ryuji Nohara, Yasuhisa Fujibayashi, Kazumi Okuda, Motonari Ogino, Tatsuhiko Hata, Masatoshi Fujita, Nagara Tamaki, Junji Konishi and Shigetake Sasayama

Third Division, Department of Internal Medicine and Department of Nuclear Medicine, Kyoto University Hospital and Department of Genetic Biochemistry, Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan

To clarify the metabolic fate of ^{123}I-(-p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) in dysfunctional myocardium, a comparison between normal dogs and those with etomoxir administration was studied using an open-chest canine model. **Methods:** Using open-chested dogs under anesthesia, we created a system to release all the blood in the great cardiac vein outside without recirculation, if necessary. Iodine-123-BMIPP was directly injected into the left anterior descending artery, its extraction, retention and washout rate in the early phase were calculated, and the metabolites in the myocardium were evaluated using a high-performance liquid chromatography. Moreover, these factors were compared between normal dogs and those pretreated with etomoxir, that creates a condition similar to ischemia. **Results:** Although rapid extraction of BMIPP from the plasma into the myocardium and the subsequent retention were unchanged, early washout (8 min) of radioactivity significantly increased (49.6%±13.3% → 70.5%±10.7%, $p < 0.05$) with etomoxir. The levels of the full metabolite formed by complete oxidation of BMIPP decreased significantly with etomoxir (21.4%±10.9% → 5.5%±3.5%, $p < 0.01$). In addition, back diffusion of BMIPP increased (25.1%±8.0%→41.9%±12.0%, $p < 0.05$) in the etomoxir-treated animals without affecting the levels of alpha-oxidation metabolite and the intermediate metabolites. **Conclusion:** BMIPP is very sensitive to etomoxir and is suitable for assessing mitochondrial dysfunction. Iodine-123-BMIPP might be a promising radiopharmaceutical for the evaluation of ischemic heart disease, cardiomyopathy and mitochondrial encephalomyopathy.

Key Words: fatty acid metabolism; BMIPP; etomoxir; mitochondrial function

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Iodine-123-(ρ-iodophenyl)-3-R,S-methylpentadecanoic acid (^{123}I-BMIPP) is a radioiodinated fatty acid analog in which a methyl group has been introduced into the beta (3) position of the fatty acid chain to inhibit rapid myocardial catabolism (*1,2*). Therefore, BMIPP has a long retention in the myocardium by incorporation into the triglyceride pool (*3,4*) and good characteristics for clinical SPECT imaging. Clinical protocols using BMIPP have been performed at several institutions in western Europe (*5–8*) and Japan (*9–11*) to evaluate impairment of myocardial fatty acid metabolism and myocardial viability. Although ^{123}I-BMIPP is now widely used in Japan as an approved radiopharmaceutical and studies with more than 50,000 patients have been completed (Yamada H, *unpublished data*, 1995), the metabolic fate and pathway for catabolism of BMIPP in the myocardium are still not completely elucidated. However, this agent does not show ideal irreversible retention like the ^{123m}Te-containing fatty acids (*12*) or beta-dimethyl substituted fatty acids (*3*), and a part of BMIPP is metabolized through alpha-oxidation followed by beta-oxidation to small catabolites in a recirculating isolated rat heart (*13*).

In our previous study using open-chested canines and analysis with high-performance liquid chromatography (HPLC), myocardial metabolism of BMIPP in normal dogs was studied (*14*), and BMIPP was found to be well retained in the myocardium and to have the same metabolic fate as observed with BMIPP administered to isolated rat hearts (*13*). Still to be clarified, however, is how alpha- and beta-oxidation, and/or backdiffusion of nonmetabolized BMIPP might contribute to the washout of BMIPP from dysfunctional myocardium such as ischemic heart disease or cardiomyopathy.

The aim of this study is to evaluate myocardial metabolism of BMIPP with etomoxir, which creates a condition similar to ischemia, and to assess the potential usefulness of BMIPP for ischemic heart disease, cardiomyopathy and mitochondrial encephalomyopathy.

MATERIALS AND METHODS

Iodine-123-BMIPP and standard samples for HPLC were generously donated by the Nihon Medi-physics Co. Ltd. (Tokyo, Japan). Iodine-125-bovine serum albumin (^{125}I-BSA) was prepared by the conventional chloramine T method. Etomoxir was obtained from ASAT AG (Zug, Switzerland).

Surgical Preparation

The surgical preparation is illustrated in Figure 1, which followed the method previously reported (*15*) with some modifications. After overnight fasting, male mongrel dogs, weighing 18.5–32.0 kg, received an intramuscular injection of ketalar (2.5 mg/kg) for induction of anesthesia and an intravenous injection of pentobarbital (25 mg/kg) for its maintenance. For respiration, an endotracheal tube was connected to a dual-phase control respirator through which 100% 2l/min oxygen was supplied. The fifth intercostal space was opened and the epicardium was immobilized in the form of a cradle. The left anterior descending artery (LAD) was dissected free for radioisotope administration, and the great

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For correspondence or reprints contact: Ryuji Nohara, MD, Third Division, Department of Internal Medicine, Kyoto University Hospital, 54 Kawaracho, Shogoin, Sakyoku, Kyoto City, 606 Japan.

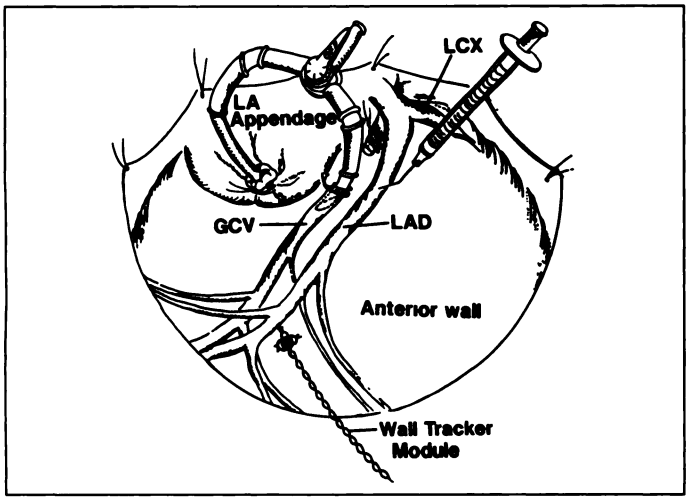

FIGURE 1. Illustration of heart instrumentation. The wall tracker module was attached to the myocardial wall of the left ventricle where the LAD dominated. LAD = left anterior descending artery; LCX = left circumflex artery; GCV = great cardiac vein; LA = left atrium.

cardiac vein (GCV) was also dissected free, cannulated and a three-way valve was attached to switch blood flow to the left appendage of the heart for recirculation or to the open port for venous blood sampling. Through the catheter, which was inserted into the left appendage, colored microspheres were injected for use in determining the absolute value of regional blood flow. The wall tracker module using ultrasonography was attached to the myocardium of the left ventricle for measurement of regional myocardial thickening. A catheter was introduced into one femoral artery to monitor blood pressure, and another catheter for arterial blood sampling was inserted into the abdominal aorta through the opposite femoral artery. A catheter was also introduced into the femoral vein for the fluid infusion and the injection of anesthetic drugs.

BMIPP Extraction

This study followed our previous protocol (*14*) and involved the collection of all blood from the GCV for 60 sec immediately after the injection of a mixture of ^{123}I-BMIPP (0.5 mCi) and ^{125}I-BSA (0.5 mCi) in 100 μl of saline. The collected blood samples were weighed and the radioactivity was measured by a well-type scintillation counter. The actual radioactive content of ^{123}I and ^{125}I in the samples was calculated using the crosstalk ratio obtained from the ^{123}I standard sample. Crosstalk from ^{125}I to ^{123}I was negligible. The average flow rate of the GCV was calculated from the weight of the blood samples and the extraction fraction as follows:

$$\text{Extraction fraction} = 1 - \frac{[^{123}\text{I in the blood (0–30 sec)}]/[^{123}\text{I injected}]}{[^{125}\text{I in the blood (0–30 sec)}]/[^{125}\text{I injected}]}.$$

BMIPP Retention and Metabolism

Just after the extraction study, ^{123}I-BMIPP (2 mCi, 0.2 ml) was injected into the LAD, and both venous blood from the GCV and arterial blood from the abdominal aorta were collected into heparinized tubes at various time intervals (30 sec and 1, 2, 5, 10, 15 and 30 min after injection). Plasma samples were separated by centrifugation at 3000 rpm for 10 min and the radioactivity of a 0.1-ml aliquot was measured by a well-type scintillation counter as soon as possible. The remainder of the plasma was extracted twice with a 2:1 mixture of chloroform and methanol (*16*). The organic layer was then collected, evaporated and the residue dissolved in 500 μl of methanol for HPLC analysis. An LC-6A chromatographic system (Shimadzu Co. Ltd., Kyoto, Japan) with a YMC-Pack ODS Column (20 x 150 + 20 × 50 mm; YMC Co. Ltd., Kyoto, Japan) was used for the HPLC analysis. The mobile phase was methanol:water:acetic acid (*96:4:1*) with a flow rate of 6 ml/min. After injection of the sample, the eluate was collected in 1-min fractions with a fraction collector. The radioactivity of each fraction was then measured with the well-type scintillation counter.

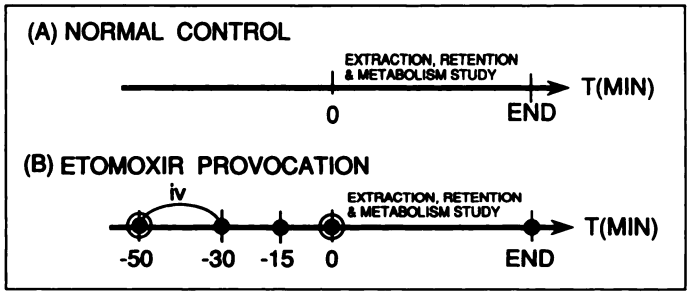

FIGURE 2. Illustration of experimental time schedule. The starting time of extraction, retention and metabolism studies was defined as zero (min). Iv = etomoxir injection into a femoral vein; ● = measurement of wall thickening, oxygen saturation, NEFA, blood sugar and lactate; [○] = measurement of microspheres flow.

Data Calculation

By fitting time-activity data with a three-exponential curve, the area under the curve (AUC) was calculated. The following parameters were also calculated:

Cumulative dose = Injected dose × Extraction fraction.

Washout dose (0.5 to 30 min) = AUC of (radioactivity in GCV plasma − radioactivity in arterial plasma)

$$\times \text{ Average flow rate of GCV} \times \frac{100 - \text{hematocrit}}{100}.$$

Retention fraction at 30 min = 1 − Washout dose/Cumulative dose

$$\text{\% Washout in the early phase (8 min)} = \frac{\text{Washout dose (8 min)}}{\text{Washout dose (30 min)}} \times 100$$

Percent cumulative metabolite washout fraction (0.5–30 min).

From the total radioactivity in plasma and the fraction of each metabolite obtained by HPLC, the plasma metabolite levels were calculated. Washout of each metabolite from the myocardium was then estimated from the difference in the metabolite levels of arterial and GCV plasma. BMIPP extraction from the arterial plasma was considered as follows:

Washout of BMIPP = GCV content − arterial content × (1 − Extraction fraction).

Metabolite washout was fitted to a three-exponential curve and the AUC was calculated. The cumulative metabolite washout fraction (1–30 min) was then calculated as follows:

Cumulative metabolite washout fraction
= AUC of metabolite/Sum of each metabolite AUC.

Provocation of Etomoxir

The experimental protocol with etomoxir is summarized in Figure 2. Sodium 2 [6(4-chlorophenoxy) hexyl] oxirane-2-carboxylate dehydrate (generic name of etomoxir) is one of the carnitine palmotoyltransferase I inhibitors and inhibits the transport of long-chain lipids into the mitochondria. Inhibition with etomoxir is thus similar to the clinical situation of ischemia. Etomoxir (20 mg/kg in 40 ~ 50 ml distilled water) was continuously injected into the femoral vein for 20 min. To stabilize canine hemodynamics, the injection was administered 30 min prior to the above studies.

TABLE 1
Extraction and Retention Studies. Comparison between Control and Etomoxir Provocation

	Control	Etomoxir provocation
Extraction (30 sec)	74% ± 12%	67% ± 18%
Retention (30 min)	89% ± 9%	86% ± 15%
% Washout (8 min)	50% ± 13%	71% ± 11%*

*$p < 0.05$ versus control.

Measurement of Regional Myocardial Blood Flow

Colored nonradioactive microspheres were used to measure blood flow. At the time of the control and 30 min after etomoxir injection (Fig. 2), about 200,000 microspheres/kg were injected into the catheter in the left auricle of the heart, and the blood was simultaneously aspirated from the abdominal aorta at a rate of 10 ml/min. Tissue and blood samples were routinely processed (*17*), and the number of microspheres was counted under a microscope. The absolute blood flow value was obtained from the ratio of microspheres in the tissue to those in the blood.

Measurement of Myocardial Thickening

Myocardial thickening was assessed with a wall tracker module (WT-10, Crystal Biotech, Hopkinton, MA) as described in a previous report (*18*). The beginning and end of the systolic interval were determined from the onset of the initial uptake of left ventricular dP/dt and 20 msec before peak negative dP/dt, respectively. Regional left ventricular wall function was estimated as net systolic thickening. The thickening fraction was calculated by dividing the transmural net systolic thickening by the end diastolic wall thickness.

Measurement of Metabolic Parameters

The oxygen saturation of blood in the GCV or the abdominal aorta was continuously monitored by OXIMETRIX® 3 (Abbot Laboratories, Abbot Park, IL), and the change of the difference between venous blood and arterial blood values was considered to represent ischemia or flow reduction. Blood sampling from the GCV and the abdominal aorta were performed to measure lactate, blood sugar and nonesterified fatty acids (NEFA). Lactate production was calculated as follows:

$$\text{Lactate production} = \frac{\text{arterial lactate (mg/dl)} - \text{venous lactate (mg/dl)}}{\text{arterial lactate (mg/dl)}} \times 100\ (\%).$$

Statistical Analysis

All measured values were analyzed using the Student's t-test, and serial changes using the ANOVA program. A value was expressed in terms of mean ± s.d., and a value of $p < 0.05$ was considered statistically significant.

RESULTS

Surgical preparation was performed on 14 dogs. Two dogs died during surgery in spite of resuscitation and were thus excluded from the study. The remaining 12 dogs completed the protocol. Dogs were divided into the control group (n = 6) and the etomoxir provocation group (n = 6).

Hemodynamics

There was no significant change in either heart rate or mean aortic blood pressure during the protocol.

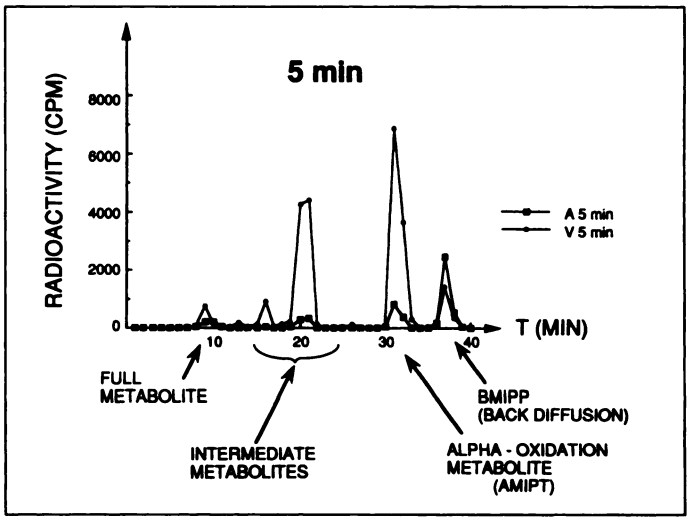

FIGURE 3. A typical elution profile of radioactive metabolites in arterial and GCV plasma samples of normal control 5 min after BMIPP injection. At this time, all the metabolites had been already found in GCV plasma.

BMIPP Extraction and Retention

Extraction, retention and percent washout in the early phase are shown in Table 1. Although extraction (30 sec) and retention (30 min) did not change significantly, the percent washout in the early phase (8 min) increased from 49.6% + 13.3% to 70.5% ± 10.7% with etomoxir provocation; this change was statistically significant ($p < 0.05$).

Metabolism of BMIPP

A typical HPLC chromatogram 5 min after BMIPP injection is shown in Figure 3 and illustrates the identification of four major peaks. The first peak (Fractions 7–11) corresponds to the retention time of 2-(ρ-iodophenyl)acetic acid (PIPA), which is the full metabolite of BMIPP. Fractions 12–29 correspond to 12-(ρ-iodophenyl)dodecanoic acid, and so on, which are intermediate metabolites. Fractions 30–34 correspond to 14-(ρ-iodophenyl)-2(α)-R,S-methyltetradecanoic acid (AMIPT), which is the alpha-oxidation metabolite. Fractions 35–40 correspond to BMIPP.

The washout of each metabolite from the myocardium was calculated from these data, and the results from a typical case are shown in Figure 4. Compared to the control, BMIPP backdiffusion increased in the early phase and full metabolite washout in the late phase decreased with etomoxir provocation.

Table 2 shows the cumulative washout fraction of each metabolite (30 min). The levels of the full metabolite formed by complete beta-oxidation decreased from 21.4%±10.9% to 5.5%±3.5% and backdiffusion of BMIPP increased from 25.1%±8.0% to 41.9%±12.0% with etomoxir provocation, and these changes achieved statistical significance. But the levels of alpha-oxidation metabolite (AMIPT) and intermediate metabolites formed by oxidation of BMIPP did not change significantly.

Regional Myocardial Blood Flow

Absolute myocardial blood flow decreased from 1.04±0.67 ml/min/g to 0.83±0.45 ml/min/g with etomoxir provocation, but this change did not achieve statistical significance.

Regional Myocardial Thickening

Myocardial thickening fraction in the LAD region was expressed as a percent of the control. With etomoxir provocation, the percent myocardial thickening fraction decreased 84.9%±23.5% (time = −30), 73.2%±34.0% (time = −15,

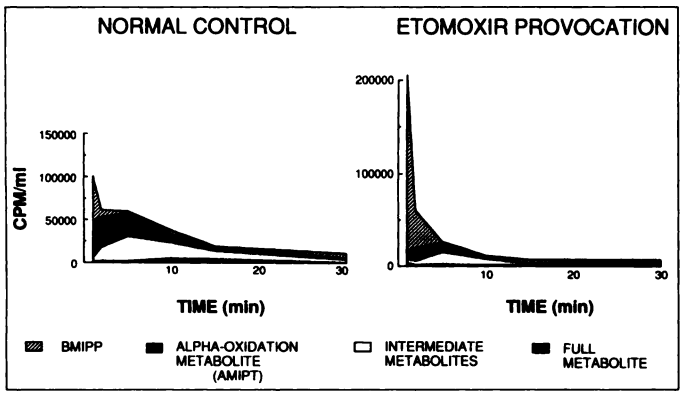

FIGURE 4. Typical cases of myocardial washout of each metabolite. Comparison between a normal control dog and a dog with etomoxir provocation.

$p < 0.05$ versus control), 40.7%±11.6% (time = 0, $p < 0.001$), and 44.8%±7.7% (the end of protocol, $p < 0.001$).

Metabolic Parameters

Arteriovenous difference (A-V difference) for oxygen saturation (O_2-SAT), blood sugar and NEFA values and lactate production are shown in Table 3. Etomoxir increased A-V difference of O_2-SAT, which represents ischemia or flow reduction. These changes, however, did not achieve statistical significance except 15 min after etomoxir injection (time = −15). The A-V difference of values for NEFA reduced with etomoxir provocation, and this reduction represents the decrease of free fatty acid utilization. The difference in A-V values for blood sugar and lactate production did not significantly change with etomoxir, implying that glycolysis could not compensate for reduced free fatty acid utilization.

DISCUSSION

A recent study (*13*) demonstrated that a fraction of the BMIPP pool was catabolized through alpha-oxidation followed by beta-oxidation to PIPA in a recirculating isolated rat heart. Results from our current study indicated that BMIPP was well retained in the canine myocardium and showed the same metabolic fate as observed in an isolated rat heart (*13*) and that backdiffusion of nonmetabolized BMIPP was rather low (*12*). It is still unknown, however, how BMIPP is metabolized, that is, how alpha-oxidation and beta-oxidation and/or backdiffusion of BMIPP contribute to the washout of radioactivity from dysfunctional myocardium such as ischemic myocardium after BMIPP administration.

This study demonstrates that BMIPP is well retained in the myocardium despite etomoxir intervention, but that the percent washout in the early phase (8 min) is significantly increased with etomoxir. Given the difference in heart rate between dogs and humans, one can estimate that an 8-min period after BMIPP injection in canine models corresponds to 15–20 min in humans, which corresponds to the usual time period for initiation of early SPECT imaging. It is expected that the change of washout with etomoxir would be detected if dynamic SPECT or early and delayed SPECT imaging is performed. In fact, the current study demonstrates that early clearance of BMIPP from the ischemic region of the myocardium could be observed with dynamic SPECT (*19*).

According to the cumulative washout fraction of each metabolite (Table 2), full metabolite of beta-oxidation significantly decreased and backdiffusion of BMIPP increased with etomoxir provocation, although AMIPT and intermediate metabolites did not change significantly. It has been reported that BMIPP is catabolized through alpha-oxidation followed by beta-oxidation to PIPA (*13,14*) and, moreover, etomoxir inhibits the import of long-chain lipids to mitochondria. Therefore, these changes in metabolites with etomoxir intervention might indicate that alpha-oxidation and some part of beta-oxidation are mainly performed outside the mitochondria in the myocardial cell.

There have been many recent studies of myocardial metabolism using radioisotopes such as ^{11}C-palmitate or [^{18}F]-FDG, and these studies have elucidated myocardial metabolism. In fact, Rosamond et al. (*20*) reported that increased backdiffusion of nonmetabolized radiolabeled palmitate greatly influenced the radioactivity clearance during ischemia. The results from our study demonstrated that backdiffusion of BMIPP increased significantly in the early phase and the full metabolite of beta-oxidation in the late phase decreased after etomoxir administration, creating a condition similar to ischemia and resulting in significant total backdiffusion of BMIPP. These results suggest that the increased washout of radioactivity in the early phase might be due mainly to increased BMIPP backdiffusion. This metabolic change due to an ischemic-like condition might influence BMIPP distribution on SPECT images.

TABLE 2
Comparison between Control and Etomoxir Provocation of Percent Cumulative Washout Values of Radioactive Metabolites from the Myocardium

	Control	Etomoxir provocation
Full metabolite	21.4% ± 10.9%	5.5% ± 3.5%**
Intermediate metabolites	26.8% ± 10.5%	32.2% ± 8.5%
Alpha-oxidation metabolite (AMIPT)	26.7% ± 4.3%	20.3% ± 6.2%
BMIPP (backdiffusion)	25.1% ± 8.0%	41.9% ± 12.0%*

*$p < 0.05$ versus control; **$p < 0.01$ versus control.

Clinical Implications

The apparently unique, yet not well-understood property of BMIPP, is the mismatch often observed on SPECT images between regional distribution of this agent and flow tracers in patients with ischemic heart disease (*9,11,21*) or hypertrophic cardiomyopathy (*22*). Animal studies with BMIPP have evaluated regional myocardial distribution of this tracer in various cardiac disease models such as hypertensive rats (*23,24*) or cardiomyopathic hamsters (*25*). The results of this study demonstrate that increased backdiffusion of nonmetabolized BMIPP by etomoxir might contribute to this mismatch and that this metabolic change of BMIPP could be detected on SPECT images.

Tamaki et al. (*9*) also demonstrated that mismatch areas are highly likely to include stunned myocardium. Our recently published study (*26*) found that myocardial ATP content and BMIPP accumulation showed a strong positive correlation. Moreover, our latest study demonstrated that myocardial uptake of BMIPP did not decrease in the viable region but in the infarcted region in an acute ischemic model, and myocardial accumulation of BMIPP in the viable ischemic region showed a strong correlation with the ATP content (*27*). The ATP content in the tissue was reported to be significantly decreased in relation to postischemic dysfunction (*28,29*). These results suggest that BMIPP might keenly reflect mitochondrial dysfunction.

TABLE 3
Changes of Metabolic Parameters During Experiments with Etomoxir Provocation

Parameter	Time course of experiments (min)				
	−50 (Control)	−30	−15	0	End
Oxygen saturation (A-V) (%)	59.2 ± 6.7	66.2 ± 12.9	69.8 ± 8.6	63.2 ± 8.8	66.2 ± 14.7
NEFA (A-V) (mEq/liter)	0.11 ± 0.08	0.02 ± 0.18	−0.01 ± 0.08*	−0.07 ± 0.18*	−0.07 ± 0.12*
Blood sugar (A-V) (mg/dl)	4.5 ± 4.0	6.2 ± 5.7	2.2 ± 5.1	2.3 ± 4.9	1.5 ± 2.7
Lactate production (%)	24.2 ± 19.8	36.2 ± 13.4	42.8 ± 22.2	40.0 ± 20.0	40.8 ± 8.3

*$p < 0.05$ versus control.

CONCLUSION

BMIPP is very sensitive to etomoxir, which can create a condition similar to ischemia, although BMIPP is well retained in the myocardium despite etomoxir provocation. Metabolic changes in BMIPP with etomoxir might be detected by dynamic SPECT or early and delayed SPECT imaging. These results suggest that BMIPP is a suitable free fatty acid analog for SPECT imaging to assess mitochondrial dysfunction such as ischemic heart disease, cardiomyopathy and mitochondrial encephalomyopathy.

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REFERENCES

1. Knapp Jr FF, Kropp J. Iodine-123-labeled fatty acids for myocardial SPECT: current status and future perspectives. *Eur J Nucl Med* 1995;22:361–381.
2. Knapp Jr FF, 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. Knapp FF Jr, Goodman MM, Ambrose KR, et al. The development of radioiodinated 3-methyl-branched fatty acids for evaluation of myocardial disease by single photon techniques. In: van der Wall EE, ed. *Noninvasive imaging of cardiac metabolism.* Dordrecht, The Netherlands: Martius Nijhoff Publishers; 1987:159–201.
4. Fujibayashi, Y, Yonekura Y, Kawai K, et al. Basic studies on I-123-beta-methyl-r-iodophenylpentadecanoic acid (BMIPP) for myocardial functional diagnosis: effect of beta-oxidation inhibitor. *Jpn J Nucl Med* 1988;25:1131–1135.
5. Kropp J, Kohler U, Knapp Jr FF, Biersack HJ. 15-(ρ-[I-123]iodophenyl)-3-R, S-methylpentadecanoic acid to evaluate ischemia in patients with coronary artery disease [Abstract]. *Eur J Nucl Med* 1991;18(suppl):650.
6. Kropp J, Juergans M, Glaenzer K, et al. Evaluation of ischemia and myocardial viability in patients with coronary artery disease (CAD) with iodine-123-labeled (15-(ρ-iodophenyl)-3-R, S-methylpentadecanoic acid (BMIPP). *Ann Nucl Med* 1993; 7:93–100.
7. De Geeter F, Franken PR, Knapp Jr FF, Bossuyt A. Relationship between blood flow and fatty acid metabolism in subacute myocardial infarction: a study by means of technetium-99m-sestamibi and iodine-123-beta-methyl iodophenyl-pentadecanoic acid. *Eur J Nucl Med* 1994;21:283–291.
8. Franken PR, De Geeter F, Dendale P, et al. 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.
9. 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 iodinated branched fatty acid analogue. *J Nucl Med* 1992;33:659–667.
10. Tamaki N, Kawamoto M, Yonekura Y, et al. Assessment of fatty acid metabolism using ^{123}I branched fatty acid: comparison with positron emission tomography. *Ann Nucl Med* 1993;7:41–48.
11. 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.
12. Goodman MM, Knapp FF Jr, Callahan AP, Ferren LA. A new, well-retained myocardial imaging agent: radioiodinated 15-(ρ-iodophenyl)-6-tellurapentadecanoic acid. *J Nucl Med* 1982;23:904–908.
13. Yamamichi Y, Kusuoka H, Morishita K, et al. Metabolism of ^{123}I-BMIPP in perfused rat hearts. *J Nucl Med* 1995;36:1043–1050.
14. Fujibayashi Y, Nohara R, Hosokawa R, et al. Metabolism and kinetics of ^{123}I-BMIPP in canine myocardium. *J Nucl Med* 1996;37:757–761.
15. Okuda K, Nohara R, Fujita M, et al. Technetium-99m-pyrophosphate uptake as an indicator of myocardial injury without infarct. *J Nucl Med* 1994;35:1366–1370.
16. Folch J, Lees M. Proteolipides, a new type of tissue lipoproteins. *J Biol Chem* 1951;191:807–817.
17. Hale SL, Alker KJ, Kloner RA. Evaluation of nonradioactive, colored microspheres for measurement of regional myocardial blood flow in dogs. *Circulation* 1988;78:428–434.
18. Hartley CJ, Laston LA, Michael LH, et al. Doppler measurement of myocardial thickening with a single epicardial transducer. *Am J Physiol* 1983;245:H1066–H1072.
19. Matsunari I, Saga T, Taki J, et al. Kinetics of I-123-BMIPP in patients with prior myocardial infarction: assessment with dynamic rest and stress images. Compared with stress ^{201}Tl SPECT. *J Nucl Med* 1994;35:1279–1285.
20. Rosamond TL, Abenschein DR, Sobel BE, et al. Metabolic fate of radiolabeled palmitate in ischemic canine myocardium: implications for PET. *J Nucl Med* 1987;28:1322–1329.
21. Takeishi Y, Sukekawa H, Saito H, et al. Impaired myocardial fatty acid metabolism detected by ^{123}I-BMIPP in patients with unstable angina pectoris: comparison with perfusion imaging by ^{99m}Tc-sestamibi. *Ann Nucl Med* 1995;9:125–130.
22. Kurata C, Tawarahara K, Taguchi T, et al. Myocardial emission computed tomography with ^{123}I-labeled beta-methyl-branched fatty acid in patients with hypertrophic cardiomyopathy. *J Nucl Med* 1992;33:6–13.
23. Yonekura Y, Brill AM, Som P, et al. Quantitative autoradiographic measurement of regional myocardial substrate utilization in hypertensive rats. *Science* 1985;227:1494–1496.
24. Yamamoto K, Som P, Brill AB, et al. Dual tracer autoradiographic acid study of β-methyl (1-^{14}C) heptadecanoic acid and 15-ρ-(^{131}I)-iodophenyl-β-methylpentadecanoic acid in normotensive and hypertensive rats. *J Nucl Med* 1986;27:1178–1183.
25. Kurata C, Kobayashi A, Yamazaki N. Dual tracer autoradiographic study with ^{201}Tl and radioiodinated fatty acid in cardiomyopathic hamsters. *J Nucl Med* 1989;30:80–87.
26. Fujibayashi Y, Yonekura Y, Takemura Y, et al. Myocardial accumulation of iodinated beta-methyl-branched fatty acid analogue, ^{125}I-15-(ρ-iodophenyl)-3-(R, S)-methylpentadecanoic acid (BMIPP), in relation to ATP concentration. *J Nucl Med* 1990;31: 1818–1822.
27. Nohara R, Okuda K, Ogino M, et al. Evaluation of myocardial viability with ^{123}I-BMIPP in a canine model. *J Nucl Med* 1996;37:1403–1407.
28. Taegtmeyer H, Roberts AFC, Raine AEG. Energy metabolism in perfused heart muscle: metabolic correlates to return of function. *J Am Coll Cardiol* 1985;6:864–870.
29. Neely JR, Grotyohann LW. Role of glycolytic products in damage to ischemic myocardium: dissociation of adenosine triphosphate levels and recovery of function of reperfused ischemic heart. *Circ Res* 1984;55:816–824.