Myocardial Kinetics of Iodine-123-BMIPP in Canine Myocardium After Regional Ischemia and Reperfusion: Implications for Clinical SPECT

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To evaluate the clinical utility of ^{123}I-(ρ-iodophenyl)-3-R,S-methylpentadecanoic acid (^{123}I-BMIPP) for ischemic heart disease, we investigated the metabolic fate of ^{123}I-BMIPP in canine models with mild and severe ischemia and evaluated the clinical utility of this tracer. **Methods:** Using open-chest dogs under anesthesia, we assembled a system that would release all the blood from the great cardiac vein without recirculation, if necessary. After injection of BMIPP into the left anterior descending coronary artery, blood samplings from cardiac vein and abdominal aorta were performed for 10-min ischemia (mild ischemia, five dogs) and 30-min ischemia (severe ischemia, six dogs), after reperfusion and for normal controls (six dogs). The catabolites of BMIPP, including backdiffusion of nonmetabolized BMIPP, were evaluated using high-performance liquid chromatography. **Results:** Although the rapid extraction of BMIPP from the plasma into the myocardium and the subsequent retention were unchanged among three groups, the early washout (at 8 min) of radioactivity significantly increased (from 50% ± 13% to 61% ± 8%; $p < 0.05$) in severe ischemia. The metabolites from the myocardium consisted of backdiffusion of nonmetabolized BMIPP and alpha-oxidation, intermediate-oxidation and full-oxidation metabolites. For mild ischemia, these values were not significantly changed from the normal control, although the respective proportions of metabolites showed some variation. Lactate production after reperfusion on mild ischemia, which indicates the severity of ischemia, was closely correlated with the level of backdiffusion of BMIPP ($r = -0.92$) and the full-oxidation metabolite ($r = 0.78$). On the other hand, for severe ischemia, the level of backdiffusion of nonmetabolized BMIPP increased (from 25.1% ± 8.0% to 34.7% ± 8.7%; $p < 0.05$), and the full-oxidation metabolites decreased (from 21.4% ± 10.9% to 14.8% ± 7.3%). **Conclusion:** The metabolism of BMIPP was closely associated with the severity of myocardial ischemia. Thus, ^{123}I-BMIPP might be a promising and sensitive radiopharmaceutical for the evaluation of ischemic heart disease.

Key Words: iodine-123-BMIPP; ischemic heart disease; fatty acids

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Iodine-123-(ρ-iodophenyl)-3-R,S-methylpentadecanoic acid (^{123}I-BMIPP) is a radioiodinated fatty acid analog, into which a methyl group has been introduced in the β-3 position of the fatty acid chain to inhibit rapid myocardial catabolism (*1,2*). Therefore, BMIPP has a long retention in the myocardium because of its incorporation into the triglyceride pool (*3,4*) and performs good clinical SPECT imaging. Clinical protocols using BMIPP have been performed at several institutions in both western Europe (*5–8*) and in Japan (*9–11*) for the evaluation of the impairment of myocardial fatty acid metabolism and of myocardial viability, and several studies have reported that BMIPP has the apparently unique property of "mismatch," often observed on SPECT imaging, between the regional distribution of this agent and flow tracers in patients with ischemic heart disease (*8,9,11,12*). This agent does not show ideal irreversible retention, as do β-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*) or in an open-chest canine model (*14*). Furthermore, the backdiffusion of BMIPP significantly increased in the early phase, and the full metabolite of beta-oxidation in the late phase also decreased after intravenous administrations of etomoxir, which is one of carnitine shuttle inhibitors, and in addition to that, the total backdiffusion of BMIPP was significant (*15*). However, the metabolic fate of BMIPP in the ischemic myocardium and the mechanism of mismatch are still not completely elucidated.

The aims of this study were to investigate the myocardial metabolism of BMIPP in canine models with mild and severe ischemia, try to explain the mechanism of mismatch and evaluate the clinical utility of this tracer for ischemic heart disease.

MATERIALS AND METHODS

Experimental Procedure

This study followed the Guidelines for Animal Experiments of Kyoto University established in 1988.

Anesthesia was induced by intramuscular injection of ketalar (2.5 mg/kg) in adult male mongrel dogs weighing 20.0 kg–33.0 kg after an overnight fasting, followed by intravenous injection of pentobarbital (25 mg/kg). For respiratory management, an endotracheal tube was connected to a dual-phase control respirator (Harvard Apparatus, Southnatick, MA), through which 2 liters/min 100% oxygen were supplied. 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 fluid infusion and the injection of anesthetic drugs. 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 a Doppler flow probe and snare were implanted around the proximal part of the LAD. The great cardiac vein (GCV) was also dissected free and 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 (Fig. 1). The colored microspheres were injected through the catheter, which was inserted into the left appendage, for use in determining the absolute value of regional blood flow. The catheter was later used for the injection of Evans blue for the calculation of ischemic region. The wall tracker module using ultrasonography

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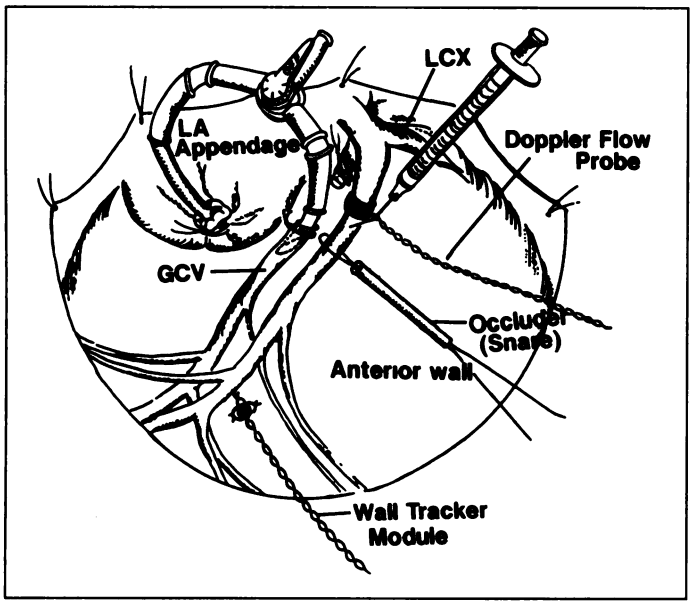

FIGURE 1. Heart instrumentation. The wall tracker module was attached to the wall of the myocardium of the left ventricle, where the LAD dominated. The Doppler flow probe and snare were implanted around the proximal part of the LAD. LCX = left circumflex artery; LA = left atrium.

(WT-10; Crystal Biotech, Hopkinton, MA) was attached to the LAD region of the left ventricle for measurement of regional myocardial thickening (Fig. 1).

Experimental Protocol

The experimental protocol is summarized in Figure 2. Surgical preparation was performed on 33 dogs. Ten dogs died during surgery or procedure of protocols in spite of resuscitation and were excluded from the study. Another six dogs were excluded from this study, four dogs because of acute myocardial infarction and two dogs because of inadequately decreased myocardial blood flow (MBF) during ischemia.

The remaining 17 dogs completed the protocol. Dogs were divided into a control group (n = 6), a group with mild ischemia (n = 5) and a group with severe ischemia (n = 6). For mild ischemia, 10-min LAD occlusion followed by 20-min reperfusion was performed, and then the extraction, retention and metabolism studies were conducted in the same way as they were for the controls. For severe ischemia, 30-min LAD occlusion followed by 20-min reperfusion was performed, and then the above-mentioned three studies were also completed, in the same manner.

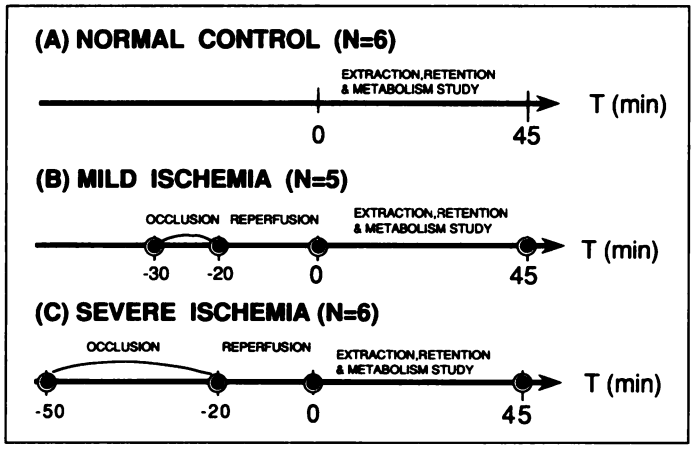

FIGURE 2. Experimental time schedule. The starting times of extraction, retention and metabolism studies were defined as zero (min). ◉ = the measurement of microsphere flow, wall thickening, oxygen saturation, NEFA, blood sugar and lactate.

Measurement of Regional Myocardial Blood Flow

MBF was measured four times with colored microspheres: at baseline, during the LAD occlusion, after 20 min of reperfusion and at the end of the protocol (Fig. 2). Red, yellow, blue and black microspheres were chosen in this study. The colored microspheres were nonradioactive (E-Z Co. Ltd., Los Angeles, CA), and 7 million–10 million microspheres were injected into the left atrium with a syringe after sufficient manual mixing with another connected syringe. Simultaneously, blood samples were collected from the femoral artery at a rate of 10 ml/min by 90 sec of aspiration. After the dogs were sacrificed, myocardial tissue samples (each piece weighing 0.5 g–1.0 g) were collected from 20 sites in the epicardial and endocardial layers of each ischemic and normal area. Each sample was then treated by routine methods as previously reported (*16*). Microspheres were counted under a microscope at ×100–400 magnification, and regional MBF was quantitated. Evans blue and triphenyl tetrazolium chloride stains did not affect this measurement.

Measurement of Myocardial Thickening

Myocardial thickening was assessed with a wall tracker module (WT-10) as described previously (*17*). 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 in the difference between venous blood and arterial blood values was considered to represent ischemia or flow reduction. The blood sampling from the GCV and the abdominal aorta were performed to measure lactate, blood sugar and nonesterified fatty acids (NEFAs). Lactate production was calculated as follows:

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

Evaluation of Ischemic Area

Just before sacrifice of the dogs, 10% Evans blue dye (100 ml) was injected through the left appendage after the complete occlusion of the LAD with a snare, and the stained left ventricle was then sectioned into four or five short-axis slices (about 10 mm in thickness) to evaluate the ischemic area. The apparent ischemic areas in the LAD region were certified with all dogs used for the experiments.

Evaluation of Infarct Area

All slices were stained with 1% triphenyl tetrazolium chloride (37°C) for 20 min to detect the infarct area. Dogs that showed apparent infarction were excluded from the study.

Extraction of BMIPP

This study followed our previous protocol (*14*) and involved collection of all the blood from the GCV for 60 sec, just after the injection of a mixture of ^{123}I-BMIPP (0.5 μCi) and ^{125}I-bovine serum albumin (0.5 μCi) in 100 μl of saline. The collected blood samples were weighed, and the radioactivity was measured by a well scintillation counter (ARC-350; ALOKA, Tokyo, Japan) with decay correction. The actual radioactive content of ^{123}I and ^{125}I in the samples was calculated using the cross-talk ratio obtained from the ^{123}I standard sample (crosstalk from ^{125}I to ^{123}I was negligible).

TABLE 1
Regional Myocardial Blood Flow Comparisons between Ischemic Area and Normal Control

	Flow (ml/min · g)				Flow (% baseline control)			
	Baseline	Occlusion	Reperfusion	End of protocol	Baseline	Occlusion	Reperfusion	End of protocol
Ischemic area of 10 min								
LAD occlusion	0.88 ± 0.22	0.18 ± 0.18*	0.75 ± 0.25	0.75 ± 0.19	100	21.3 ± 23.9*	87.7 ± 34.3	88.2 ± 20.0
Normal control	0.96 ± 0.16	0.97 ± 0.22	0.92 ± 0.31	0.88 ± 0.20	100	103.3 ± 22.7	94.8 ± 26.7	92.8 ± 18.4
Ischemic area of 30 min								
LAD occlusion	0.87 ± 0.27	0.22 ± 0.10*	0.76 ± 0.11	0.87 ± 0.32	100	28.0 ± 17.5*	89.6 ± 25.6	96.4 ± 30.9
Normal control	0.82 ± 0.20	0.99 ± 0.31	0.86 ± 0.33	0.92 ± 0.44	100	123.1 ± 34.2	103.9 ± 27.9	105.5 ± 37.5

*$p < 0.001$ compared to baseline.

The average flow rate of the GCV was calculated from the weight of the blood samples and the extraction fraction as follows:

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

Retention and Metabolism of BMIPP

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 scintillation counter as soon as possible. The remainder of the plasma was extracted twice with a 2:1 mixture of chloroform:methanol (*18*). The organic layer was then collected and evaporated, and the residue dissolved in 500 μl of methanol for high-performance liquid chromatography (HPLC) analysis. An LC-6A chromatographic system (Shimadzu Co. Ltd., Kyoto, Japan) with a YMC-Pack ODS column (20 × 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 scintillation counter with decay correction.

Data Calculation

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

1. Cumulative dose = injected dose × extraction fraction.
2. Washout dose (0.5 min–30 min) = AUC of {(radioactivity in GCV plasma − radioactivity in arterial plasma) × average flow rate of GCV × [(100 − hematocrit)/100]}.
3. Retention fraction (at 30 min) = 1 − (washout dose/cumulative dose).
4. Percentage washout in the early phase (8 min) = [washout dose (8 min)/washout dose (30 min)] × 100.

Also calculated was the percentage cumulative metabolite washout fraction (0.5 min–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. The extraction of BMIPP from the arterial plasma was taken into consideration as follows:

$$\text{Washout of BMIPP} = \text{GCV content} - \text{Arterial content} \times (1 - \text{Extraction fraction}).$$

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

$$\text{Cumulative metabolite washout fraction} = \frac{\text{AUC of metabolite}}{\text{Sum of each metabolite AUC}}.$$

Statistical Analysis

All measured values were analyzed using Student's t-test, and serial changes were analyzed 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

Hemodynamics

There was no significant change in either heart rate or aortic blood pressure during the experiments with both mild and severe ischemia.

Regional Myocardial Blood Flow

MBF during the experiments with ischemia is summarized in Table 1. MBF in the ischemic region was expressed as an absolute value and a percentage of the baseline control. The percent MBF decreased to 21.3% ± 23.9% during 10-min occlusion of the LAD and decreased to 28.0% ± 17.5% during 30-min occlusion, and these changes achieved statistical significance ($p < 0.001$). However, the percentage MBF after 20 min reperfusion and at the end of the protocol did not change significantly.

Regional Myocardial Thickening

The changes in the thickening fraction during the experimental protocols are shown in Figure 3. Myocardial thickening in the LAD region was expressed as a percentage of the baseline control. The percent myocardial thickening significantly decreased during occlusion for both mild and severe ischemia (mild, −60.8% ± 23.6%; severe, −34.6% ± 13.1%; $p < 0.001$), and these changes showed dyskinesis. The percentage myocardial thickening also significantly decreased after reperfusion (mild, −6.4% ± 8.9%; severe, 9.8% ± 8.4%; $p < 0.001$) for both mild and severe ischemia, and these changes indicated stunning.

Metabolic Parameters

Arterial–venous difference (A–V difference) for oxygen saturation, blood sugar and NEFA values and the lactate production are summarized in Table 2. Arterial–venous difference of oxygen saturation significantly increased during occlu-

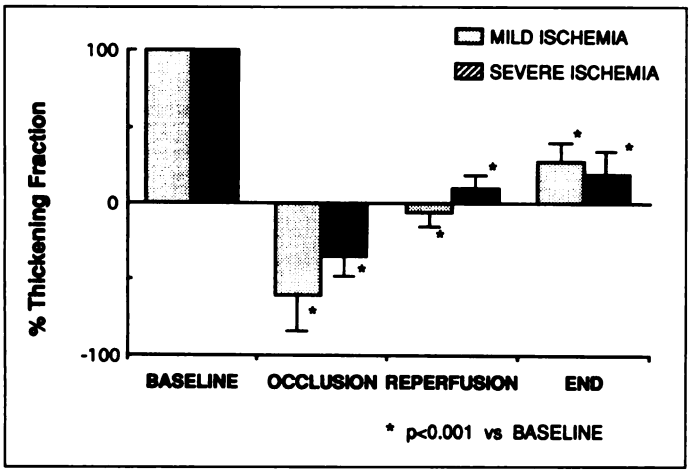

FIGURE 3. Percentage thickening fraction during the experimental protocols. These values were expressed as the percentage of the baseline control. During the LAD occlusion, wall thickening showed hibernation, and after reperfusion, it showed stunning.

sion for both mild and severe ischemia, which represents ischemia or flow reduction because hemoglobin levels did not change during experimental protocols.

The values for NEFA and blood sugar are shown as the (absolute blood flow) × (arterial blood concentration − GCV blood concentration). The A–V difference of values for NEFA decreased during LAD occlusion in both protocols, and the value of severe ischemia achieved statistical significance ($p < 0.05$); however, these values recovered after reperfusion in both protocols. The difference in A–V values for blood sugar increased during occlusion, after reperfusion and at the end of the protocol for both mild and severe ischemia, but these changes did not achieve statistical significance because of wide variation of s.d. Lactate production changed during occlusion and after reperfusion, and the values during occlusion significantly changed for both mild and severe ischemia; however, it did not change at the end of protocol for either mild or severe ischemia.

Extraction and Retention of BMIPP

Extraction, retention and percentage washout in the early phase are shown in Table 3. Although extraction (30 sec) and retention (30 min) did not change significantly among these three groups, the percentage washout in the early phase (8 min) increased from 50% ± 13% to 61% ± 8% for severe ischemia, and this change was statistically significant ($p < 0.05$). In addition, the percentage washout in the early phase on mild ischemia was correlated with lactate production after 20 min of reperfusion, which indicates the severity of ischemia (if x = lactate production and y = % washout (8 min), $y = 59.641 - 0.100x$; $r = 0.48$).

TABLE 3
Extraction and Retention Studies

	Normal control (%)	Mild ischemia (%)	Severe ischemia (%)
Extraction (30 sec)	74 ± 12	69 ± 7	77 ± 6
Retention (30 min)	89 ± 9	87 ± 5	90 ± 5
% Washout (8 min)	50 ± 13	56 ± 12	61 ± 8*

*$p < 0.05$ compared to normal control.

Metabolism of BMIPP

A typical HPLC, 10 min after BMIPP injection, is shown in Figure 4 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, which is the full-oxidation 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, which is the alpha-oxidation metabolite. And Fractions 35–40 correspond to backdiffusion of nonmetabolized BMIPP.

The washout of each metabolite from the myocardium was calculated from these data, and the cumulative washout fraction of each metabolite (30 min) is shown in Table 4. For severe ischemia, the level of the full-oxidation metabolite formed by the complete beta-oxidation decreased from 21.4% ± 10.9% to 14.8% ± 7.3%, and the level of backdiffusion of nonmetabolized BMIPP increased from 25.1% ± 8.0% to 34.7% ± 8.7%; the latter achieved statistical significance ($p < 0.05$). For mild ischemia, these values did not significantly change from the control, although the respective proportions of metabolites showed some variation. Then, the correlation between lactate production after reperfusion and the level of backdiffusion of BMIPP or the full-oxidation metabolite formed by the complete beta-oxidation in mild ischemia are shown in Figure 5. Lactate production after reperfusion on mild ischemia, which indicates the severity of ischemia, was closely correlated with the level of backdiffusion of nonmetabolized BMIPP ($r = -0.92$) and the full-oxidation metabolite formed by complete beta-oxidation ($r = 0.78$).

TABLE 2
Changes in Metabolic Parameters During the Experimental Protocols

	Baseline	Occlusion	Reperfusion	End
Oxygen saturation (%)				
Mild ischemia	59.6 ± 24.8	66.8 ± 29.4	66.8 ± 28.5	77.0 ± 3.8
Severe ischemia	77.0 ± 3.8	82.2 ± 4.5*	75.3 ± 7.2	72.3 ± 8.0
NEFA (mEq/min·g × 10^{-3})				
Mild ischemia	0.08 ± 0.11	0.02 ± 0.04	0.12 ± 0.07	0.07 ± 0.06
Severe ischemia	0.11 ± 0.10	0.07 ± 0.02	0.16 ± 0.12	0.17 ± 0.15
Blood sugar (1/min × 10^{-5})				
Mild ischemia	7.6 ± 4.3	10.4 ± 5.1	7.3 ± 5.0	8.7 ± 5.9
Severe ischemia	4.9 ± 3.3	6.2 ± 3.6	8.8 ± 4.8	8.6 ± 3.1
Lactate production (%)				
Mild ischemia	26.9 ± 21.4	−68.4 ± 44.3†	−11.8 ± 56.0	33.5 ± 10.1
Severe ischemia	33.5 ± 10.1	−16.5 ± 40.8†	16.3 ± 26.2	34.6 ± 16.7

*$p < 0.05$ compared to baseline control.
†$p < 0.01$ compared to baseline control.

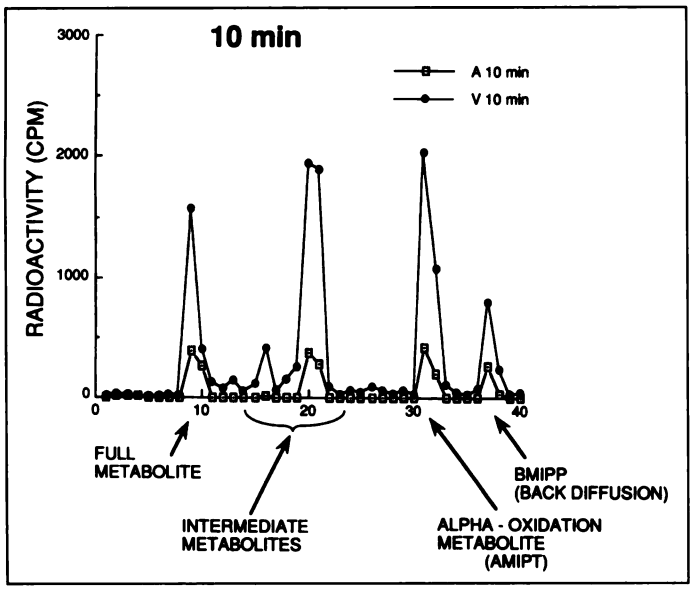

FIGURE 4. A typical elution profile of radioactive metabolites in arterial and GCV plasma samples of normal control after 10 min of BMIPP injection. At this time, all the metabolites had been already found in GCV plasma.

DISCUSSION

The results of our previous studies demonstrated that a fraction of the BMIPP pool was catabolized through alpha-oxidation followed by beta-oxidation to 2-(*p*-iodophenyl)acetic acid in the canine myocardium (*14,15*). We also showed that the backdiffusion of nonmetabolized BMIPP significantly increased in the early phase and that the full-metabolite of beta-oxidation also decreased after intravenous administration of etomoxir, which is one of carnitine shuttle inhibitors that creates a condition similar to ischemia. In addition, this metabolic change could be detectable if dynamic SPECT or early and delayed SPECT imaging are performed (*15*). The results from this study indicated that BMIPP is well-retained in the myocardium in an acute model of both mild and severe ischemia; however, the percentage washout in the early phase (8 min) increased in proportion to the severity of ischemia. Considering 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 min–20 min in humans, which corresponds to the usual time period for the initiation of early SPECT imaging. Thus, the change of washout of ^{123}I-BMIPP from the ischemic myocardium might be detectable on SPECT images. In fact, Matsunari et al. (*19*) demonstrated that the early clearance of BMIPP from the ischemic myocardium could be observed using dynamic SPECT.

Many studies have recently elucidated myocardial metabolism using radioisotopes, such as [^{11}C]palmitate, [^{18}F]fluorodeoxyglucose, [^{11}C]acetate or [^{123}I]iodophenyl-pentadecanoic acid (IPPA). Rosamond et al. (*20*) reported that the increased backdiffusion of nonmetabolized radiolabeled palmitate markedly influenced the clearance of radioactivity during ischemia and, in addition, that externally detected clearance rate could not be used as a direct measure of fatty acid metabolism during ischemia. On the other hand, the results from this study indicated that the backdiffusion of nonmetabolized BMIPP increased and the full metabolite of beta-oxidation decreased in proportion to the severity of ischemia. Backdiffusion of nonmetabolized BMIPP significantly increased in the early phase on severe ischemia (Fig. 6), and the percentage washout of radioactivity in the early phase was strongly correlated with backdiffusion of BMIPP for mild ischemia (if x = % washout (8 min) and y = % backdiffusion of BMIPP, $y = -9.414 + 0.521x$; $r = 0.62$), although backdiffusion of BMIPP did not significantly increase in the early phase. These results demonstrate that the increased washout of radioactivity in the early phase on ischemia is due to the increased backdiffusion of nonmetabolized BMIPP; however, the decreased washout of radioactivity in the late phase of ischemia might be due mainly to the decrease of beta-oxidation of BMIPP.

TABLE 4
Percentage Cumulative Washout Values of Radioactive Metabolites from the Myocardium

	Normal control (%)	Mild ischemia (%)	Severe ischemia (%)
Full metabolite	21.4 ± 10.9	16.7 ± 13.2	14.8 ± 7.3
Intermediate metabolites	26.8 ± 10.5	40.8 ± 12.6	30.5 ± 11.7
Alpha-oxidation metabolite	26.7 ± 4.3	20.2 ± 7.8	20.0 ± 2.6*
BMIPP (backdiffusion)	25.1 ± 8.0	22.3 ± 11.1	34.7 ± 8.7†

*$p < 0.01$ compared to normal control.
†$p < 0.05$ compared to normal control.

Iodine-123-IPPA is a straight-chain fatty acid analog, and recent studies have demonstrated that IPPA is a useful marker of ischemic viable myocardium. Shi et al. (*21*) reported that the retention of [^{123}I]IPPA correlated with the accumulation of [^{18}F]fluorodeoxyglucose during low-flow ischemia of a canine model. Further examination, such as comparison between IPPA and BMIPP, might be necessary.

Clinical Implications

The unique yet not well-elucidated character of BMIPP in patients with ischemic heart disease is the mismatch often observed on SPECT imaging between the regional distribution of this agent and flow tracers (*8,9,11,12*). Reinhardt et al. (*22*) reported that the myocardial concentration of BMIPP activity correlated with coronary blood flow and compared favorably with ^{201}Tl using animal models and that differences in the myocardial distribution of BMIPP and ^{201}Tl, that is, the mismatch in clinical studies, may be related to cellular fatty metabolism as opposed to differences in regional blood flow. The results from this study indicated that the increased backdiffusion of nonmetabolized BMIPP from the ischemic myocardium might contribute to this mismatch, and this metabolic change of BMIPP could be detectable on SPECT imaging. The metabolite rate of ^{123}I-BMIPP in efflux is different from that of radiolabeled palmitate from ischemic myocardium, and backdiffusion of nonmetabolized BMIPP mainly contributes to the clearance of radioactivity in the early phase. One can safely say that ^{123}I-BMIPP can be an index of cellular fatty acid metabolism; however, it can hardly be an index of beta-oxidation, especially when early SPECT imaging is used.

Franken et al. (*8*) reported that segments with more reduced BMIPP uptake than ^{99m}Tc-sestamibi, that is, the mismatch segments, may correspond to either stunned or hibernating myocardium in patients with subacute myocardial infarction, and Tamaki et al. (*9*) also demonstrated that mismatch areas are highly likely to include stunned myocardium. Fujibayashi et al. (*23*) demonstrated that the myocardial ATP content and the BMIPP accumulation showed a strong positive correlation in a murine model with the intervention of dinitrophenol. Also, Nohara et al. (*24*) indicated that the myocardial accumulation of BMIPP in the viable ischemic region showed a strong correlation with the ATP content using a canine model with ischemia. Furthermore, the previous reports demonstrated that the ATP content in the tissue significantly decreased in relation to

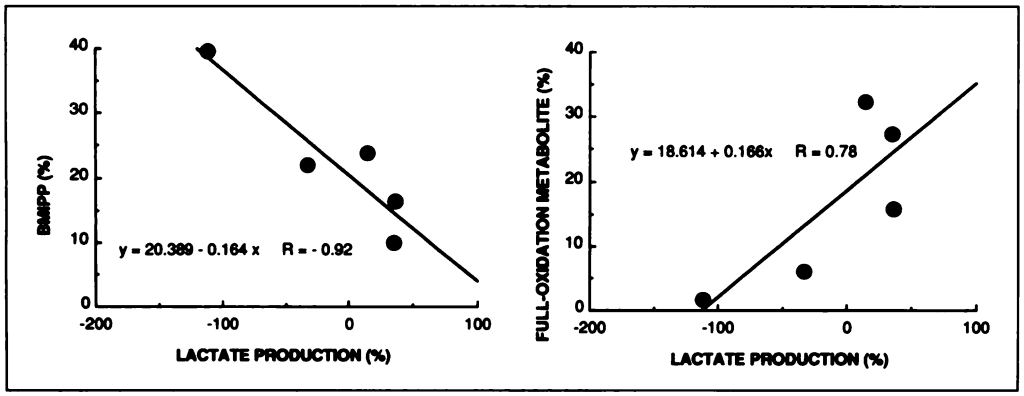

FIGURE 5. The correlation between the lactate production after 20 min of reperfusion and the level of backdiffusion of BMIPP or the full-oxidation metabolite for mild ischemia. Lactate production was expressed as (arterial lactate − GCV lactate/arterial lactate) × 100. Thus, the lesser the value, the more severe the ischemic condition is. The levels of both metabolites showed strong correlation with the lactate production, one of the indices of the severity of ischemia.

postischemic function (*25,26*). From the results of this study, the early washout of radioactivity increased in proportion to the severity of ischemia, when the MBF had already improved and the wall motion of left ventricle still showed stunning (Table 1 and Fig. 3), and in addition, this metabolic change might be detectable on SPECT images. These results suggest that ^{123}I-BMIPP is very sensitive to mitochondrial dysfunction, such as myocardial ischemia.

In human studies, Nakata et al. (*27*) indicated that the assessment of the degree and improvement of perfusion–metabolism mismatch by ^{201}Tl- and ^{123}I-BMIPP SPECT at an acute stage of myocardial infarction contributes to identifying a future recovery of postischemic myocardial dysfunction. And Nakajima et al. (*28*) reported that ^{123}I-BMIPP might be useful for detecting myocardial injury and for assessing the effect of treatment in patients with vasospastic angina (*28*). These studies indicated ^{123}I-BMIPP could be useful for the prediction of myocardial viability and functional recovery.

Study Limitations

In general, fatty acid utilization decreases in ischemic myocardium, and the uptake of ^{123}I-BMIPP on SPECT imaging often decreased in the region of ischemia in human studies, although MBF did not significantly decrease on SPECT images (*8,9,11,12,27,28*). The results from this study, however, demonstrated that the rapid extraction from plasma into myocardium and the subsequent retention did not change with either mild or severe ischemia. We consider that the reason for this discrepancy may be underground masked conditions, preceded by ischemic events such as acute myocardial infarction or severe recurrent angina attacks in humans. In this animal model, there was no ischemia before our single intervention. A further investigation using a canine model with chronic ischemia might be necessary to assess this discrepancy.

Using a canine model, the respective proportions of metabolites washed out from the myocardium showed some variation. One reason for this variation might be that the same degree of ischemia cannot be induced in all dogs, and each dog has his own arterial and venous circulation, including collaterals. However, small animals are unsuitable for this experiment because of the difficulty in blood sampling from the GCV. Further examination for different types of ischemia such as low-flow ischemia might be necessary to investigate the metabolic fate of BMIPP in detail.

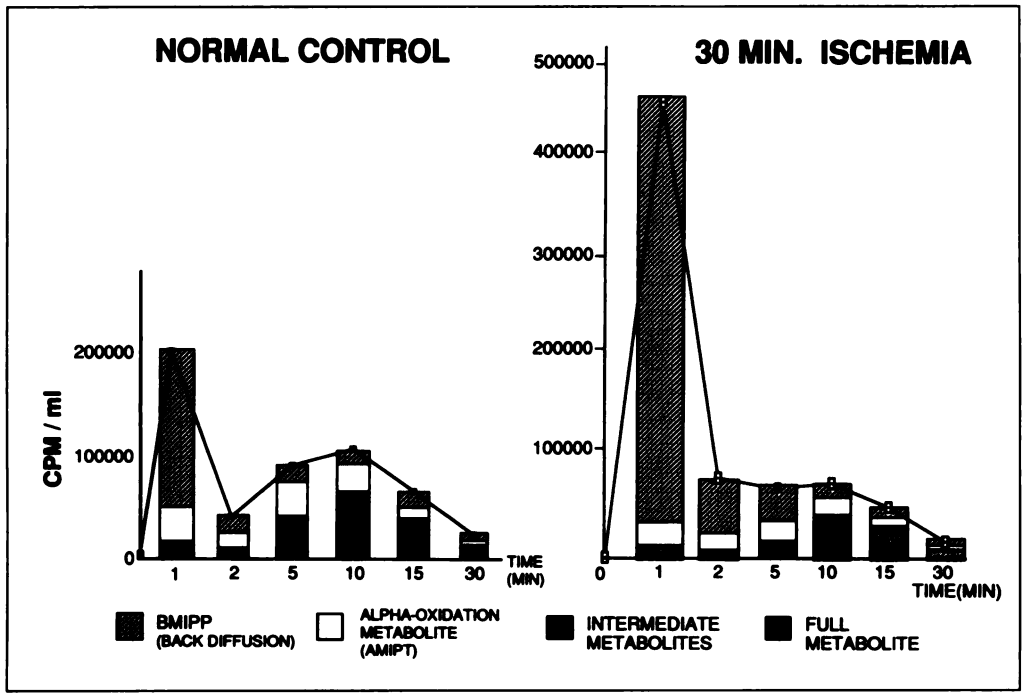

FIGURE 6. The mean washout of each metabolite from the myocardium. A comparison between the normal control and the severe ischemia.

CONCLUSION

The backdiffusion of nonmetabolized BMIPP increased and full metabolites of beta-oxidation decreased in proportion to the severity of myocardial ischemia, and increased backdiffusion of nonmetabolized BMIPP from the ischemic myocardium might contribute to perfusion–metabolism mismatch on SPECT images. Iodine-123-BMIPP might be a promising and sensitive radiopharmaceutical for the evaluation of ischemic heart disease.

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