Metabolism and Kinetics of Iodine-123-BMIPP in Canine Myocardium

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The kinetics and metabolic fate of ^{123}I-15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) in canine myocardium were studied in an open-chest dog model. **Methods:** After left anterior descending artery injection of BMIPP, blood samples were collected from the corresponding great coronary vein (V) and femoral artery (A). On the basis of the A-V radioactivity difference as well as the HPLC elution profile at various time points, myocardial extraction, retention and metabolism of BMIPP were evaluated. **Results:** BMIPP was instantly extracted from the plasma into the myocardium (74% of the injected dose) and was then retained (65.3%). Washout of the retained radioactivity was low (8.7%) and most of the washout was as alpha- and beta-oxidation metabolites (2.3 + 2.9 + 1.4%), with little loss of BMIPP itself (2.1%). **Conclusion:** BMIPP is suitable for static SPECT imaging of the myocardium, and its slow washout appears to be due to metabolism through alpha- and beta-oxidation.

Key Words: iodine-123-BMIPP; SPECT; myocardium

J Nucl Med 1996; 37:757–761

BMIPP (15-p-iodophenyl-3-(R,S)-methylpentadecanoic acid) is a radioiodinated fatty acid analog used for myocardial SPECT imaging based on high cardiac fatty acid metabolism (*1*). The beta-methyl branched structure of BMIPP does not affect its conversion to acyl-CoA but reduces its susceptibility to beta-oxidation. As a result, BMIPP shows superior characteristics for clinical SPECT and as a long myocardial retention time as triglycerides (*1,2*). BMIPP accumulation is considered to be an indicator of fatty acid metabolism, especially triglyceride pool turnover. Abnormal accumulation of BMIPP in the myocardium has been reported in various diseases and its clinical applicability has also been discussed (*3–11*). In Japan, ^{123}I-labeled BMIPP is available commercially and has been widely used in myocardial SPECT studies, with more than 30,000 patient studies completed (unpublished data) and various findings reported (*12–15*).

This agent, however, does not show ideal irreversible retention, which has been demonstrated with Te-containing fatty acid (*16*) or beta-dimethyl substituted fatty acid (*1*). It seems possible that some part of BMIPP is metabolized through alpha-oxidation followed by beta-oxidation to smaller metabolites. In fact, Yamamichi et al. (*17*) confirmed the presence of p-iodophenyl-alpha-methyltetradecanoic acid and p-iodophenylacetic acid, alpha- and beta-oxidation metabolites of BMIPP, respectively, in the recirculated perfusate of an isolated Langendorf rat heart model. Basic as well as clinical studies have indicated that washout of BMIPP radioactivity has some correlation with myocardial metabolism and function. It is still unclear, however, whether alpha- to beta-oxidation and/or backdiffusion of BMIPP contributes to radioactivity washout radioactivity in vivo.

Received Apr. 7, 1995; revision accepted Oct. 8, 1995.
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In the present study, myocardial metabolism of BMIPP was investigated in an open-chest dog model using high-performance liquid chromatography (HPLC). Based on the differences of radioactive metabolites in arterial and venous plasma samples after BMIPP injection into the left anterior descending (LAD) artery, myocardial metabolism of BMIPP was evaluated.

MATERIALS AND METHODS

We used BMIPP containing 2 mCi [^{123}I] BMIPP (0.4 mg) dissolved in 1 ml aqueous solution of ursodesoxycholic acid (4 mg). The radiochemical purity was higher than 98%. Iodine 125-bovine serum albumin (^{125}I-BSA) was prepared by the conventional chloramine T method and used as an unextractable reference agent. Standard samples for IPAA (p-iodophenylacetic acid), IBA (p-iodobenzoic acid), IPDA (p-iodophenyldodecanoic acid), AMIPT (α-methyl-p-iodophenyltetradecanoic acid) and BMIPP also underwent HPLC analysis. The other reagents used were of special reagent grade.

Open-Chest Dog Model Preparation

The open-chest dog model was prepared according to a previously reported method (*18*) with some modifications. Five male mongrel dogs weighing 21–32 kg were anesthetized with ketaral (i.m.) and pentobarbital (i.v.). For respiratory management, an endotracheal tube was connected to a dual-phase ventilator, and 100% oxygen was supplied at 2 liters/min. Thoracotomy was performed in the fifth intercostal space and the heart was immobilized in a cradle. The great cardiac vein (GCV) was dissected out, cannulated, and a three-way valve was attached to switch blood flow to the left auricle for recirculation or to the open port for venous blood sampling. A catheter to monitor blood pressure was introduced into one femoral artery and another catheter for arterial blood sampling was inserted into the abdominal aorta through the opposite femoral artery. A catheter was introduced into the femoral vein for maintenance fluid infusion and injection of maintenance anesthesia.

Extraction Study

A mixture of BMIPP (^{123}I, 0.5 μCi) and ^{125}I-BSA (0.5 μCi) in 100 μl saline was injected into the left anterior descending artery. To stabilize the flow rate, a three-way valve was opened 20–30 sec before injection. Immediately after injection, all of the blood from the GCV was collected through the three-way valve into preweighed tubes at 10-sec intervals for 60 sec. The collected blood samples were weighed and the radioactivity was measured at an energy range of 120–180 keV (^{123}I) and 15–70 keV (^{125}I) with a well-type scintillation counter. Twenty microliters of the injection solution were collected and used for the 1/5 control. The actual radioactivity 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, so no correction was needed. The average flow rate of the GCV was calculated from the weight of the

collected blood samples and the extraction fraction was calculated as follows:

Extraction fraction

$$= 1 - \frac{[^{123}\text{I in the blood (0–30 or 60 scc)}]/[^{123}\text{I injected}]}{[^{125}\text{I in the blood (0–30 or 60 sec)}]/[^{125}\text{I injected}]}.$$

Retention and Metabolism Studies

Immediately after the extraction study, the same dog was used for retention and metabolism analyses. BMIPP (^{123}I: 2 mCi, 0.2 ml) was injected into the LAD artery. All of the blood from the GCV was collected from 0 to 30 sec after injection to minimize leakage of untrapped BMIPP into the systemic circulation. Blood samples (5 ml) from the GCV were collected at various time intervals (30 sec, 1 min, 2 min, 5 min, 10 min, 15 min and 30 min postinjection) into heparinized tubes. Simultaneously, arterial blood was obtained from the abdominal aorta. Plasma was separated by centrifugation at 3000 rpm for 10 min and a 0.1-ml aliquot was placed into a counting tube so that the radioactivity could be measured with a well-type scintillation counter. The rest of the plasma was extracted twice with a 2:1 mixture of chloroform and methanol (*19*). Then, the organic layer was collected, evaporated and the residue was dissolved in 500 μl of methanol for HPLC analysis. The injected dose of BMIPP was determined using 1000-fold diluted samples.

HPLC

Radioactive metabolites of BMIPP were determined by HPLC as reported previously (*17*). A YMC-Pack ODS column (20 × 150 + 20 × 50 mm, YMC Co. Ltd., Kyoto, Japan) was attached to the chromatographic system. The mobile phase consisted of methanol: water:acetic acid (96:4:1) and the flow rate was 6 ml/min. Samples (400 μl) were injected and the eluate was collected into 1-min fractions with a fraction collector. The radioactivity of each fraction then was measured with the well-type scintillation counter. To identify each peak, nonradioactive standard samples were injected and the retention time was determined by detecting the UV absorbance at 254 nm.

Data Calculation

Time-activity data were fitted to a three-exponential curve to calculate the area under the curve (AUC). The following parameters also were calculated:

Cumulative dose = Injected dose × Extraction fraction

Washout dose (0.5–30 min)

= AUC of (radioactivity in GCV plasma

− radioactivity in arterial plasma)

× Average flow rate × (100 − hematocrit)/100

Retention fraction at 30 min

= 1 − Washout dose/Cumulative dose

% 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 differences in the metabolite levels of arterial and GCV plasma. The extraction of BMIPP from arterial plasma was considered as follows:

Washout of BMIPP = GCV content − arterial content

× (1 − Extraction fraction).

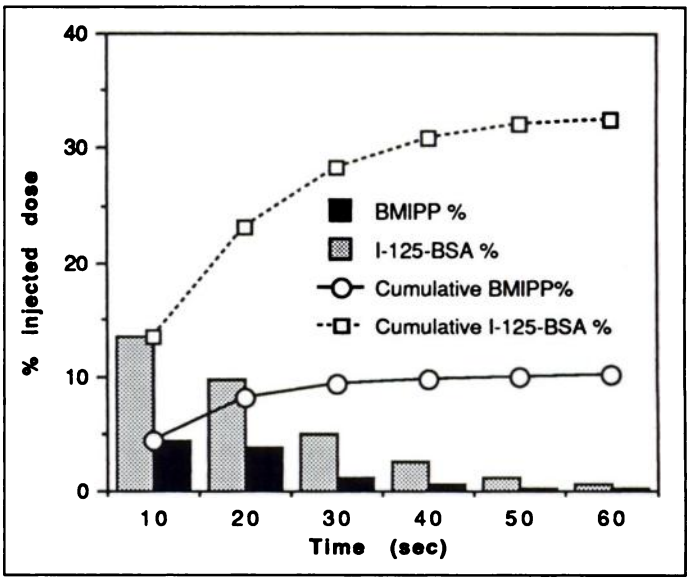

FIGURE 1. Typical elution profile and cumulative washout of BMIPP and ^{125}I-BSA from the GCV (extraction study). First-pass elution of both BMIPP and ^{125}I-BSA was completed within 30 sec after injection.

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

Cumulative metabolite washout fraction

= AUC of metabolite/Sum of each metabolite AUC.

RESULTS

Extraction study

A typical elution profile of BMIPP and ^{125}I-BSA from the GCV is shown in Figure 1. In this dog, first-pass elution of BMIPP was completed within 60 sec after injection and more than 90% was finished by 30 sec. Thus, 30 sec was long enough for nearly complete first-pass extraction. The extraction fraction values calculated from 0 to 30 sec and 0 to 60 sec were also constant: 67.1% and 68.9%, respectively. From these preliminary data, 30 sec was selected as the extraction interval. The percent average extraction fraction also was calculated and is shown in Table 1.

Retention Study

Figure 2 shows typical time-radioactivity curves for arterial plasma (A) and GCV plasma (V) as well as the A-V difference from 0.5 to 30 min after BMIPP injection. The lower radioactivity concentration in arterial than in GCV plasma indicated the selective supply of BMIPP to the myocardium and not to the systemic circulation. The retention fraction was calculated from the AUC of the A-V difference, the average GCV flow rate and the cumulative dose (Table 1). The rather high variation in

TABLE 1
Flow Rate from GCV Cannula and BMIPP Extraction and Retention: Retention Study

Dog no.	Flow rate (ml/min)	Extraction fraction (%)	Retention fraction (%)
1	4.95	67.1	90.6
2	1.03	60.6	71.6
3	1.87	88.4	92.0
4	7.01	78.8	92.5
5	6.91	75.0	94.4
Average (1 s.d.)	4.4 (2.8)	74.0 (10.7)	88.2 (9.4)

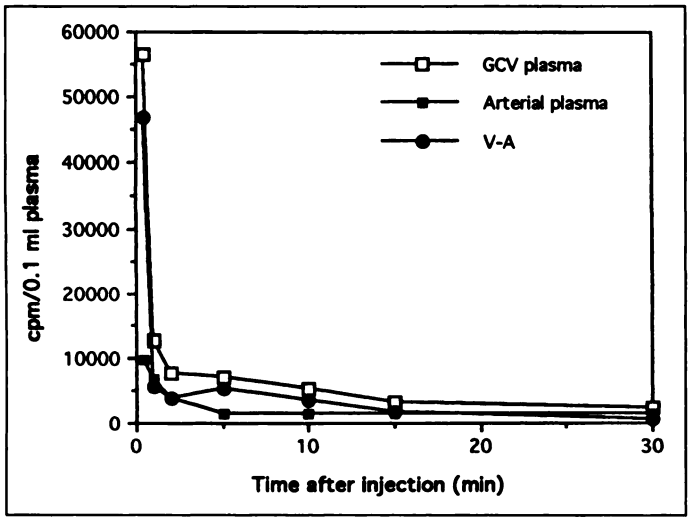

FIGURE 2. Typical time-radioactivity curves for arterial plasma (A) and GCV plasma (V), and the AV difference from 0.5 to 30 min after BMIPP injection (retention study). At every time tested, GCV plasma contained more radioactivity than arterial plasma.

flow rate is considered to be a result of variance in body weight and/or cannulation site of the vessel as mongrel dogs were used.

Metabolism Study

Figure 3 shows typical elution profiles of the radioactive metabolites in arterial and GCV plasma from 1 to 30 min after BMIPP injection. Based on the elution times of nonradioactive standard samples, the radioactivity found in fraction numbers 7–11, 12–29, 30–34 and 35–40 were assigned as full metabolites (IPAA and IBA), intermediate metabolites (IPDA, etc.), an alpha-oxidation metabolite (AMIPT) and BMIPP itself, respectively.

From these findings, the washout of each metabolite from the myocardium was calculated as described in Materials and Methods (Fig. 4). At 1 min postinjection, BMIPP was the major component of the radioactivity washout from the myocardium, but its alpha-oxidation metabolite already showed a high content. Subsequently, BMIPP washout diminished quickly, while the alpha-oxidation metabolite had high levels until 5 min after injection. As washout of the alpha-oxidation metabolite decreased, intermediate metabolites gradually increased and peaked at 5 min postinjection. The levels of the full metabolites were rather low during the experimental period, but they appeared to be constant.

Table 2 shows the cumulative washout fraction of each metabolite (1–30 min). During the experimental period, the cumulative washout fractions of BMIPP, the alpha-oxidation metabolite and the intermediate metabolites were similar, while the full metabolites showed lower washout fractions.

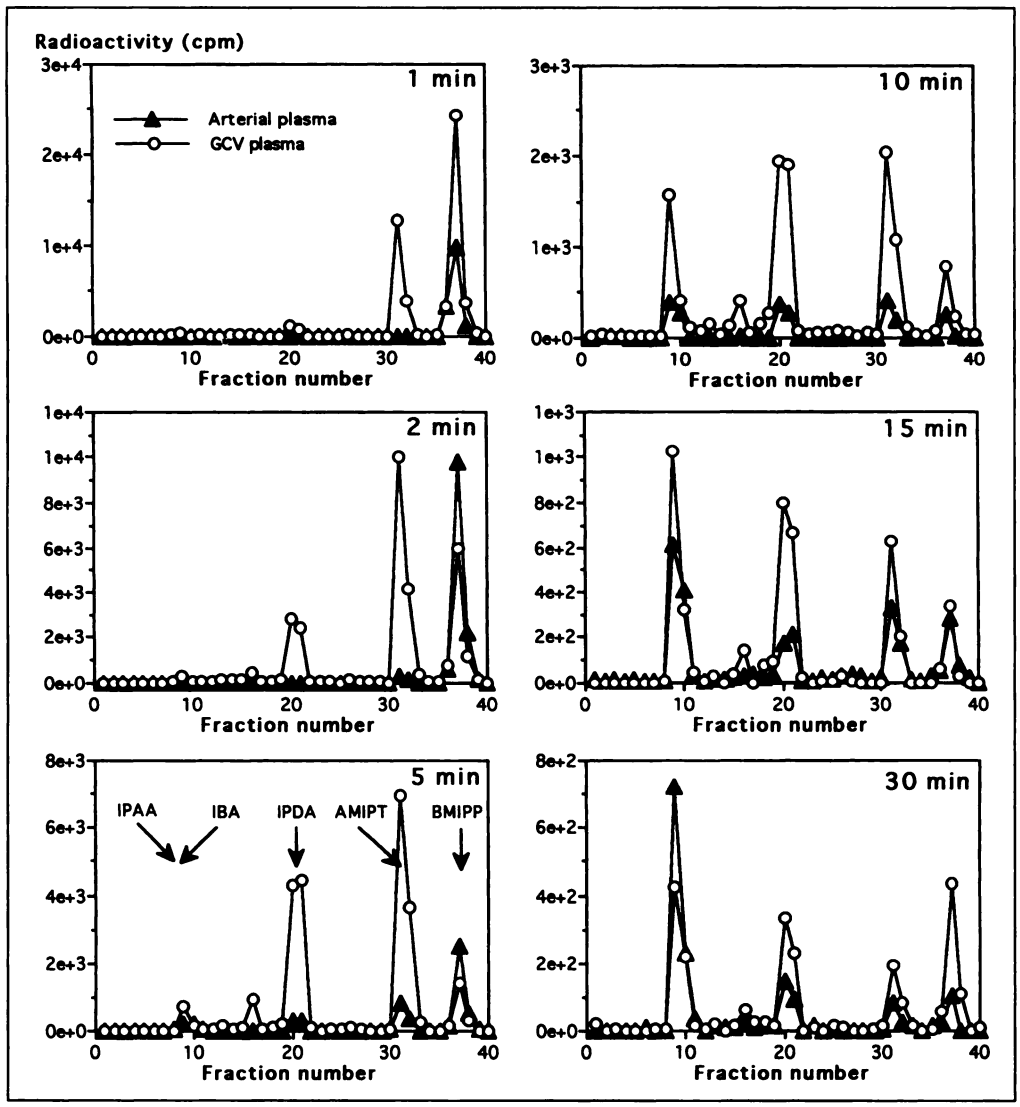

FIGURE 3. Typical elution profiles of radioactive metabolites in arterial and GCV plasma from 1 to 30 min after BMIPP injection. At 1 min postinjection, the alpha-oxidation metabolite was already found in GCV plasma and further catabolism had also begun.

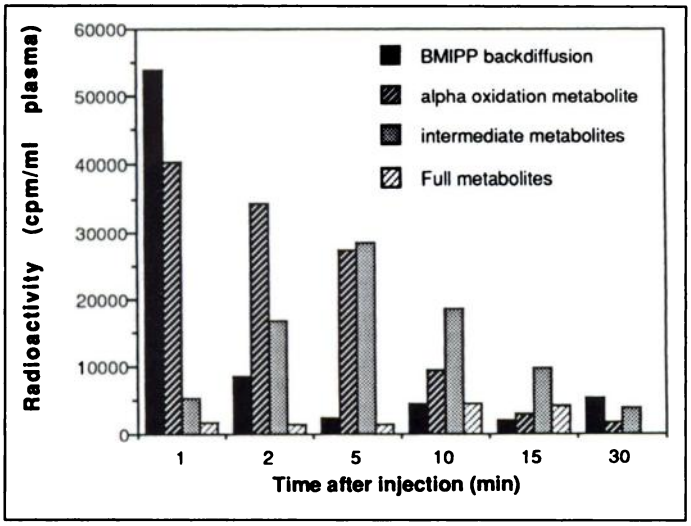

FIGURE 4. Washout of BMIPP and related radioactive metabolites from the myocardium at various time points after BMIPP injection. Backdiffusion of BMIPP diminished quickly, after which the alpha-oxidation metabolite decreased slowly. The peak level of intermediate metabolites was found at 5 min after injection. Continuous but low washout of the full metabolites was observed throughout the experimental period.

DISCUSSION

In nuclear medicine, changes in radioactivity in the target tissue are the only information obtainable from patients. Therefore, input/output of radioactivity into/from the target tissue is essential for interpreting radioactivity data as metabolic information. To evaluate the myocardial metabolism of BMIPP in vivo, the present protocol of selective injection into the coronary artery followed by continuous venous blood sampling from the corresponding GCV is considered to be effective. An isolated perfused heart model is one alternative, but our open-chest dog model is more physiologically relevant.

The extraction fraction shown in the present study was higher than that in a previous study using 14-(*p*-iodophenyl)betamethyltetradecanoic acid (*20*), possibly due to the difference in the radiotracer used or differences in chain length. Otto et al. (*21*) found that shortening of chain length induced significant decreases in myocardial extraction, especially if the chain length was between 16 and 13. Thus, BMIPP's longer chain length may have resulted in higher myocardial extraction than 14-(*p*-iodophenyl)betamethyltetradecanoic acid.

From the retention fraction at 30 min postinjection, the mean half-life was calculated to be 138 min. This value was similar to that previously reported in a canine model after intravenous injection of BMIPP (*22*). Cardiac work was unchanged during and after BMIPP injection.

Recent studies have shown that some BMIPP in the myocardium is catabolized through alpha- followed by beta-oxidation to IPAA (*17*). It is, however, still unknown which metabolite(s) form the major part of myocardial radioactivity washout, and this was one focus of the present study. Some other studies have suggested that early washout was due to the backdiffusion of BMIPP. In fact, we also found backdiffusion of BMIPP at a very early stage, but other metabolites also were detected. Thus, metabolism was very rapid and the metabolites produced at each step went back into the circulation. As a result, backdiffusion of unmetabolized BMIPP was rather low.

The fate of intracoronary BMIPP 30 min postinjection is summarized in Figure 5. BMIPP was extensively extracted from the plasma into the myocardium (74% of the injected dose) and was then substantially retained (65.3%). Washout of the retained radioactivity was rather low (8.7%) and most of the washout was as alpha- and beta-oxidation metabolites (2.3% + 2.9% + 1.4%), with little as BMIPP itself (2.1%).

Although BMIPP was designed as a radioiodinated fatty acid analog with a long myocardial retention time, oxidative degradation through alpha- followed by beta-oxidation was observed in the present study and the contribution of unmetabolized BMIPP to the backdiffusion of radioactivity was low. Considering the presence of catabolic washout, BMIPP is not an ideal SPECT imaging agent. Such degradation, however, is considered to be negligible in SPECT protocols. As Knapp et al. mentioned (*1*), this metabolism might make BMIPP useful in delineating patients with heart disease. In fact, some clinical studies have indicated that the difference between early and late BMIPP images, (i.e., the washout of radioactivity) provides useful diagnostic information in cardiomyopathy, acute infarction, angina and other diseases (*23,24*). We are now performing similar metabolic studies in combination with various myocar-

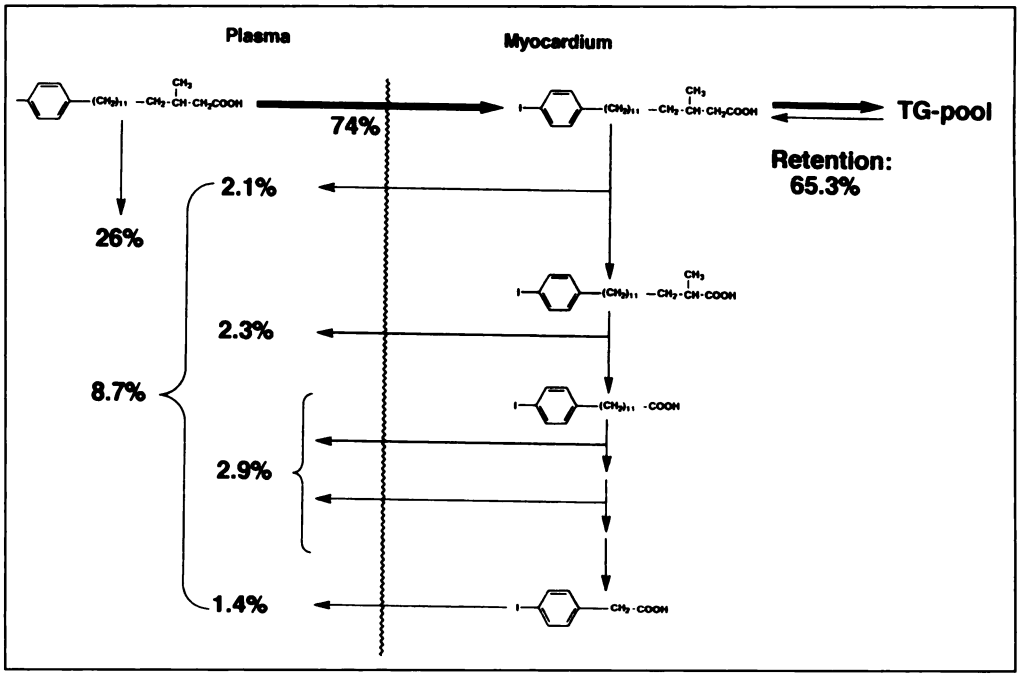

FIGURE 5. Total fate of intracoronary BMIPP at 30 min postinjection.

TABLE 2
Cumulative Washout of Myocardial Radioactive Metabolites

Dog no.	BMIPP (Backdiffusion)	Alpha-oxidation metabolite	Intermediate metabolites	Full metabolites
1	17.9	33.5	40.6	8.0
2	21.3	29.9	39.2	9.6
3	21.6	20.5	21.5	36.4
4	36.7	25.7	36.2	1.4
5	24.4	23.2	26.5	25.9
Average (1 s.d.)	24.4 (7.3)	26.6 (5.2)	32.8 (8.4)	16.3 (14.4)

dial interventions to clarify clinical usefulness of BMIPP as an agent for assessing myocardial fatty acid metabolism.

ACKNOWLEDGMENT

We thank Nihon Medi-Physics Co. Ltd. (Tokyo, Japan) for its generous donations of BMIPP, IPPA, IPDA and AMIPT.

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Ischemic and Reperfused Myocardium Detected with Technetium-99m-Nitroimidazole

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To evaluate the utility of ^{99m}Tc-labeled nitroimidazole (BMS) in the detection of ischemic or reperfused myocardium, we performed dual-tracer autoradiography with BMS and [^{125}I]iodoantipyrine (IAP). **Methods:** In open-chest rats, the left coronary artery was ligated to produce 15- or 60-min ischemia followed by reperfusion or 60-min ischemia without reperfusion. BMS was injected just before ligation, 1 min before reperfusion or 15 min after reperfusion. **Results:** In the area at risk, regional myocardial blood flow (rMBF) evaluated by IAP recovered to the level in the nonischemic septum in all hearts, except in 60-min occlusion without reperfusion. In myocardium reperfused after 15-min ischemia (stunned), normalized BMS uptake (%BMS) in the area at risk was significantly increased only when BMS was injected before ischemia. When BMS was injected before 60-min ischemia or just before reperfusion, %BMS was significantly higher at the marginal zone of infarction than in the infarcted area. In contrast, %BMS was significantly lower in the infarcted area when BMS was injected during reperfusion. After 60 min of occlusion without reperfusion (permanent occlusion), rMBF in the area at risk was significantly decreased as was %BMS. In the peripheral zone of the area at risk, rMBF was significantly reduced, but %BMS was significantly increased. **Conclusion:** BMS images stunned myocardium only when it is injected before ischemia, while it images the area at risk subjected to prolonged ischemia when it is injected up to the time of reperfusion. The infarcted area can be negatively visualized when BMS is injected after reperfusion.

Key Words: technetium-99m-nitroimidazole; ischemia; reperfusion

J Nucl Med 1996; 37:761–766

Received Apr. 3, 1995; revision accepted Sept. 20, 1995.

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Preservation of ischemic but viable myocardium is one of the major goals of therapy for myocardial infarction and unstable