amine metabolism and might be a clinical aid for diagnosing arrhythmias and determining follow-up treatment.

CONCLUSION

At present, the usefulness of cardiac ^{123}I-MIBG scintigraphy in evaluating patients with Brugada syndrome is uncertain. A large number of patients and long-term follow-up studies are required to address the impact of MIBG SPECT imaging in assessing regional cardiac neuronal function and in determining the denervation and reinnervation of the myocardium.

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Effect of Metabolic Substrate on BMIPP Metabolism in Canine Myocardium

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The lipid tracer 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) is clinically useful, and its basic metabolism is being analyzed. Because the pharmacokinetics of this lipid tracer may be affected by blood concentrations of fatty acid or glucose, this study evaluated the effects of excess levels of lipid or glucose on BMIPP uptake and metabolism. **Methods:** A technique using an open-chest dog model was used. Blood sampling was performed from the left anterior descending coronary artery and great cardiac vein after an injection of ^{123}I-BMIPP either with a glucose infusion (n = 6) or a lipid infusion (n = 5). High performance liquid chromatography and double-tracer kinetic analyses clarified the extraction, retention, backdiffusion and further metabolism of BMIPP. These results were compared with data from control dogs (n = 6). **Results:** In this experiment, a 10-fold increase over the normal lipid blood concentration and twofold increase over the normal blood glucose concentration were evaluated with either intralipid or glucose infusion, respectively. In the lipid infusion studies, the extraction significantly decreased compared with the control values (74% ± 12% to 58% ± 8%; $p < 0.05$), and the washout increased from 50% ± 13% to 68% ± 16% ($p < 0.05$). The BMIPP backdiffusion increased ($p < 0.05$), and the levels of the further metabolites decreased ($p < 0.05$), while the retention level remained constant (normal, 89% ± 9%; lipid infusion, 91% ± 3%; ns). In the glucose infusion studies, the BMIPP extraction, retention and washout showed no statistical differences compared to controls; however, these parameters showed the same tendencies as those in the lipid infusion group. In addition, the BMIPP backdiffusion increased significantly (control, 25.1% ± 8%; glucose infusion, 48.7% ± 25.6%; $p < 0.05$) as it did after the lipid infusion. **Conclusion:** BMIPP metabolism and uptake are affected by excess concentrations of lipid and glucose in the blood. However, the retention of BMIPP was not affected by either type of infusion. The BMIPP backdiffusion and the further metabolite comprising 10% of the tracer extracted were affected both by the lipid and glucose infusions. These results indicate that an excess fat concentration and glucose affect BMIPP uptake, especially the extraction of BMIPP and BMIPP backdiffusion.

Key Words: iodine-123-15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid; lipid metabolism; triglyceride pool; glucose

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As an important tracer of lipid metabolism (*1*), 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) has methyl group introduced into the beta-position and shows a good cardiac image different from that shown by myocardial perfusion (*2,3*). We have already shown that BMIPP uptake is related to the adenosine triphosphate (ATP) contents (*4*) and that both extraction and retention are closely related to the mitochondrial function, which was evaluated using etomoxir (*5*), a carnitine shuttle inhibitor. We also showed that ischemia strongly affects

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the backdiffusion and beta-oxidation of BMIPP in the myocardium (*6*). In addition, our clinical studies have shown that BMIPP imaging provides different images from perfusion imaging (*7*) indicating that BMIPP imaging can provide additional important information not shown by function and perfusion studies. PET studies have already shown that ^{18}F-fluorodeoxyglucose (*8*) and ^{11}C-palmitate uptake (*9*) and metabolism were strongly affected by the blood concentration of metabolic substrates. These data indicate that even a novel tracer such as BMIPP might also be more or less affected by the blood glucose and/or lipid levels. The potential effects of blood glucose and lipids in the clinical use of BMIPP as a tracer require clarification. This study was thus intended to evaluate the effect of blood metabolic substrates on the myocardial uptake and metabolism of BMIPP.

MATERIALS AND METHODS

In 19 adult mongrel dogs (body weight, 16–25 kg), anesthesia was induced by intramuscular injection of Ketaral (2.5 mg/kg) and was maintained by intravenous injection of Nembutal (25 mg/kg). The animals were intubated and respiration was controlled with a Harvard respirator (Harvard Apparatus, South Natick, MA). Catheters were inserted into both femoral arteries, one for monitoring blood pressure and the other for taking blood samples by continuous withdrawal for calculating the myocardial blood flow. Another catheter was inserted into a femoral vein for fluid and drug infusion. A thoracotomy was performed at the fifth intercostal space and the pericardium was suspended in a cradle. Another catheter was inserted into the left atrial appendage and was used for the infusion of colored microspheres. The great cardiac vein (GCV) was dissected free and cannulated and a three-way valve was attached to switch the GCV blood flow to the left atrial appendage for recirculation or to the open port for venous blood sampling. The left anterior descending coronary artery (LAD) was also dissected free for the radioisotope administration and a sensor of Doppler flow meter was attached to the LAD for flow monitoring.

Extraction Study

Our study method is similar to our previous studies (*1,4–6*), which involved collecting the GCV blood samples for 60 sec immediately 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 weighed blood samples were counted using a well scintillation counter. The actual radioactive contents of ^{123}I and ^{125}I in the samples were calculated using the crosstalk ratio obtained from a ^{123}I standard sample. The 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 fractions were calculated as follows (*1,4–6*):

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

Retention and Metabolite Study

Similar to our previous studies (*1,4–6*), after the extraction study, ^{123}I-BMIPP (2 mCi, 0.2 ml) was injected directly into the LAD and both blood from GCV and the simultaneously collected 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 the BMIPP injection). Plasma samples were separated by centrifugation at 3000 rpm for 10 min and the radioactivity of a 0.1 ml aliquot was measured using a well scintillation counter as soon thereafter as possible. The remainder of the plasma was extracted twice with a 2:1 mixture of chloroform and methanol. The organic layer was collected and evaporated and the residue was dissolved in 500 μl of methanol for high-performance liquid chromatography (HPLC) analysis, as we described previously (*1,4–6*). 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.

Data Calculation

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

Percent washout in the early phase (8 min) = [washout dose (8 min)/washout dose (30 min)] × 100.

Percent cumulative metabolite washout fraction (1–30 min).

The plasma metabolite levels were calculated from the total radioactivity in plasma and the fraction of each metabolite obtained by HPLC. The washout of each metabolite from the myocardium was then estimated from the differences in the metabolite levels of arterial and GCV plasma. The extraction of BMIPP from the arterial plasma was calculated as follows:

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

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

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

Study Protocols

Six healthy dogs were used for the controls and the other 13 dogs were used for the metabolic substrate study. In these 13 dogs, 5 dogs were used for the lipid infusion study and 8 dogs were used for the glucose infusion group. Among the 8 dogs in the glucose infusion group, 2 dogs expired intraoperatively because of technical failure. One had severely reduced venous flow and the other fell in ventricular fibrillation. Thus, 6 dogs were used in the final glucose infusion study group. Glucose was infused intravenously (50 g glucose, 100 IU regular insulin and 20 mmol KCl in 100 ml sterile H_2O per hour); this infusion was designed to increase the plasma glucose and to decrease the plasma fatty acid concentrations. In the lipid infusion study group, Intralipid was infused intravenously (0.6 mg lipid/kg/60 min of a 20% solution of neutral triglycerides consisting predominantly of linoleic, oleic, palmitic and linolenic acids; Otsuka Pharmaceutical Co., Tokyo, Japan) to raise the plasma fatty acid concentrations. These protocols followed the report by Brown et al. (*10*). Because the metabolic effects of these glucose or Intralipid infusions are prolonged and because the study length was limited by the radioisotope half-life, the tracer kinetic study was performed separately for each protocol.

After recording the control value of heart rate, blood pressure, microsphere flow and Doppler flow velocity, the infusion drip of glucose or Intralipid was initiated with an infusion pump. At 45 min after initiation of the infusion, heart rate, blood pressure and Doppler flow value were again recorded without stopping the infusion, followed by extraction and retention studies as previously reported (*1,4–6*). After the completion of these studies, the heart rate, blood pressure and Doppler flow were also recalculated. The dogs were killed by injection of saturated KCl solution, just after

TABLE 1
Effect of Glucose or Lipid Infusion on Hemodynamics and Myocardial Blood Flow

Study	Heart rate (bpm)	Systolic blood pressure (mm Hg)	Rate-pressure products ($\times 10^4$)	Myocardial blood flow (ml/g)
Glucose study (n = 6)				
Baseline	176 ± 14	141 ± 12	2.48 ± 0.29	1.66 ± 0.36
Glucose infusion	178 ± 14	145 ± 19	2.58 ± 0.40	1.61 ± 0.32
Intralipid study (n = 5)				
Baseline	180 ± 6.5	137 ± 14	2.47 ± 0.23	1.43 ± 0.76
Intralipid infusion	186 ± 10	140 ± 31	2.60 ± 0.60	0.95 ± 0.45

injection of Nembutal. The heart was then removed, and four pieces of the myocardium (1–2 g each) were dissected as cubes and were then separated into endo- and epicardium to calculate the microsphere flow values.

Statistics

The data are presented as the mean ± s.d. The significance of differences between groups was calculated by the paired Student's t-test, corrected for the number of comparisons by Bonferroni's method.

RESULTS

Hemodynamics

The infusions of glucose and Intralipid did not produce any significant changes in the heart rate, blood pressure or double products compared to the baseline values (Table 1). Myocardial blood flow calculated by colored microsphere also showed no statistical differences after infusion of either substrate (Table 1).

Substrate Utilization

In the glucose study, 75 g of glucose had been infused when the BMIPP extraction study was begun. At this time, the arterial glucose levels had increased twofold and the myocardial glucose extraction fraction also increased (Table 2). The fatty acid concentration, myocardial fatty acid extraction and arteriovenous difference were all decreased and only very small differences were found in the arterial levels and the arteriovenous extraction of lactate.

The dogs in the lipid infusion group received a mean of 18 mg of lipid. The arterial concentration of fatty acids increased by approximately 10-fold and the myocardial anteriovenous extraction decreased markedly. In contrast, the arterial concentration and the myocardial extraction of glucose showed little change, as did lactate after the infusion of lipid.

Extraction, Retention and Metabolite Data

The BMIPP extraction, retention, washout and metabolite data during the infusion of glucose or Intralipid are summarized in Figures 1 and 2. The extraction (30 sec) of BMIPP was significantly decreased (78.4% of control) during the lipid infusion, although it showed minimal (not significant [ns]) change during the glucose infusion. Little change was observed in BMIPP retention during infusion of either substrate. The percent washout (8 min) increased significantly from the control value of 50% ± 13% to 68% ± 16% ($p < 0.05$) during the lipid infusion and increased to 60% ± 12% during the glucose infusion, although difference in the latter did not reach statistical significance.

Detected metabolites after BMIPP infusion by HPLC were summarized in the scheme in Figure 3.

The metabolite studies showed that the backdiffusion of BMIPP was significantly increased ($p < 0.05$) and the αMIPT and partial metabolite levels were significantly suppressed during the lipid infusion. During the glucose infusion, it also showed a similar tendency or increased backdiffusion of BMIPP and suppressed further metabolites.

DISCUSSION

Lipids are the major energy source in stable cardiac metabolism (50%–80%); however, in case of ischemia this major energy source will be shifted toward glucose (*11*). These differences or shifts in substrate use can help evaluate ischemia and detect viable muscle. Our serial dog experiments (*1,4–6*) and clinical studies have demonstrated the clinical usefulness of ^{123}I-BMIPP in ischemic heart disease (*3*) and cardiomyopathy. A significant fraction of the extracted BMIPP is incorporated into the triglyceride (TG) pool (*4,12*) and the free BMIPP will be backdiffused or fully metabolized (*6*). However, further information about these phenomena is lacking including the effects of excess blood substrates such as lipid and glucose on the uptake and metabolism of BMIPP.

The results of this study clarified the effects of these two substrates on BMIPP uptake and metabolism for extreme conditions of blood concentrations. The lipid infusion causes the BMIPP extraction to decrease and washout to increase. The glucose infusion did not significantly change the BMIPP extraction and washout, but it caused changes similar to those of the lipid infusion. The retention of BMIPP did not show a statistical difference in comparison with the controls, either by lipid or glucose infusion. Changes in the other labeled forms of metabolized substrates other than TG were statistically significant. In other words, BMIPP backdiffusion increased and the presence of BMIPP metabolites, including alpha and partial metabolite, decreased significantly.

Once free fatty acids reach the cytosol, they may follow one of several pathways. The proportional distribution into these pathways depends on the myocardial metabolic status. Free fatty acids may simply backdiffuse into the plasma unaltered. Alternatively, after thioesterification to fatty acyl-CoA, these species may be incorporated into triglycerides or phospholipids. Under most conditions, a substantial proportion of the free acid acyl-CoA is transported across the mitochondrial membrane to the mitochondrial matrix, where beta-oxidation occurs. Our preliminary data show that BMIPP is taken up (or extracted) in proportion to the ATP content (*4,12*) and is stored mainly in the form of TG (*6,12*). About 10% of extracted BMIPP will be further metabolized after alpha- and beta-oxidation to the final metabolite (*1*) (Fig. 3).

Bergman et al. (*9*) used ^{11}C-palmitate PET to quantitate lipid metabolism and found that glucose infusion was accompanied by a marked decrease in arterial fatty acid content and an enhanced myocardial use of glucose and that extracted fatty acids, during glucose infusion, exhibited increased backdiffusion as well as increased shunting to storage forms. Our glucose infusion results are similar; however, retention of BMIPP did not show any statistical differences in comparison with the

TABLE 2
Effect of Glucose or Lipid Infusion on Arterial Plasma Substrate Concentration, Myocardial Extraction Fraction and Arterial-Coronary Sinus Difference

Substrate	Glucose study (n = 6)			Intralipid study (n = 5)		
	Artery concentration	Extraction fraction (%)	Arteriovenous difference	Artery concentration	Extraction fraction (%)	Arteriovenous difference
Glucose (mg/dl)						
Baseline	122 ± 12*	4.59 ± 5.5†	5.8 ± 7.6†	105 ± 17	3.24 ± 2.98	3.6 ± 3.3
Infusion	206 ± 58	5.63 ± 3.9	10.1 ± 5.8	118 ± 7.9	3.10 ± 1.62	3.6 ± 1.7
Fatty acid (mg/dl)						
Baseline	0.64 ± 0.13*	11.4 ± 10.6†	0.07 ± 0.06†	0.46 ± 0.11*	20.9 ± 13.9†	0.10 ± 0.06†
Infusion	0.35 ± 0.10	2.4 ± 3.8	0.008 ± 0.013	4.2 ± 0.98	−0.52 ± 3.5	−0.04 ± 0.15
Lactate (mg/dl)						
Baseline	28.5 ± 12.8	33.7 ± 15.5	9.73 ± 5.57	25.6 ± 8.5	45.4 ± 11.1†	11.5 ± 4.13
Infusion	33.2 ± 11.2	37.1 ± 10.4	12.0 ± 3.90	27.8 ± 4.59	28.3 ± 11.4	8.14 ± 4.11

*$p < 0.01$.
†$p < 0.05$ (baseline vs. infusion).

controls. Our previous data obtained by myocardial biopsy specimen indicated that a major part of BMIPP retained in the myocardium was in the TG pool (*6*). These BMIPP results suggest that the exact change of shunt storage of fatty acids will not directly reflect the true conversions using BMIPP. Bergman et al. (*9*) also pointed out that the infusion of a potent inhibitor of carnitine palmitoyltransferase impaired fatty acid oxidation and was accompanied by enhanced esterification and deposition into neutral lipid pools, as well as backdiffusion. Our previous study using etomoxir (*5*), a carnitine shuttle inhibitor, increased backdiffusion but did not alter the retention. Regarding fatty acid infusions, increased arterial concentration was reported to be associated with decreased extraction of fatty acid and no change of glucose and lactate extraction. These results were similar to our data. The decreased extraction and increased washout of BMIPP reflected the present result. However, retention of BMIPP again showed no change compared to controls in spite of severely decreased extraction of fatty acids. These results indicate that BMIPP extraction and retention in the myocardium, which may represent mainly the TG store, show fairly constant values probably because of a rapid and significant shunt mechanism to storage of BMIPP in the TG pool. This result seems to be different from data of Bergman et al. (*9*), but at least 50% of ^{11}C-palmitate will be extracted and used for beta-oxidation. The difference between BMIPP and ^{11}C-palmitate metabolism is reflected in the different patterns of metabolism.

Groot et al. (*13*) pointed out that lactate enhances triglycerol turnover through increased glycerol 3-phosphate levels. Although our results did not show a significant increase in lactate extraction by either of the substrates, the TG pool turnover might have changed. In other words, the estimated increased esterification of fatty acid (*9*) may show increased turnover. Once incorporated in the form of acyl-CoA, BMIPP may show the fairly constant value even if the turnover rate increases and dynamic change may proceed because of a large equilibrium of the TG pool. It is also possible that the presence of two different TG pools, as DeGella and Light (*14*) pointed out, might explain this result. De Gella and Light (*14*) proposed the existence of a small early saturable TG pool and a large nonsaturable pool. The BMIPP TG pool might thus have become saturated in a very early phase of the present experiments.

In the case of ischemia, beta-oxidation decreases and shunt

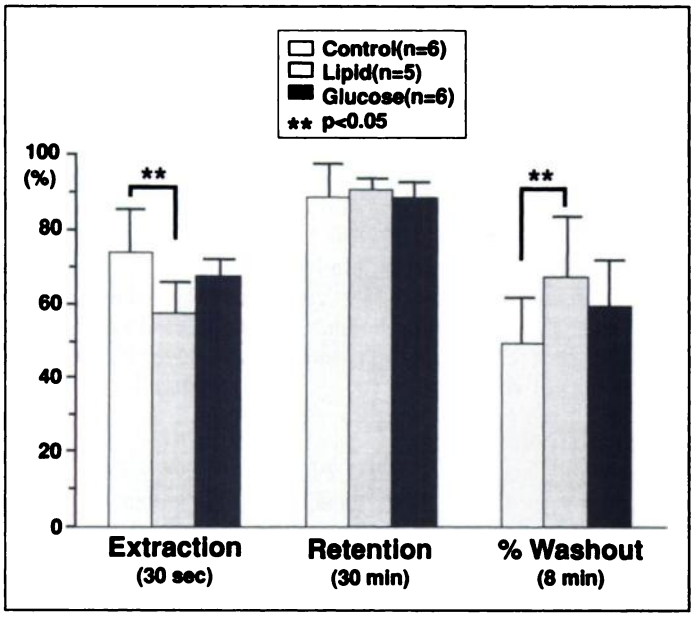

FIGURE 1. Effects of blood lipid and glucose concentrations on BMIPP. Control, lipid (gray bars) and glucose (black bars) data are shown. Extraction and percentage washout showed statistical difference between control and lipid infusion.

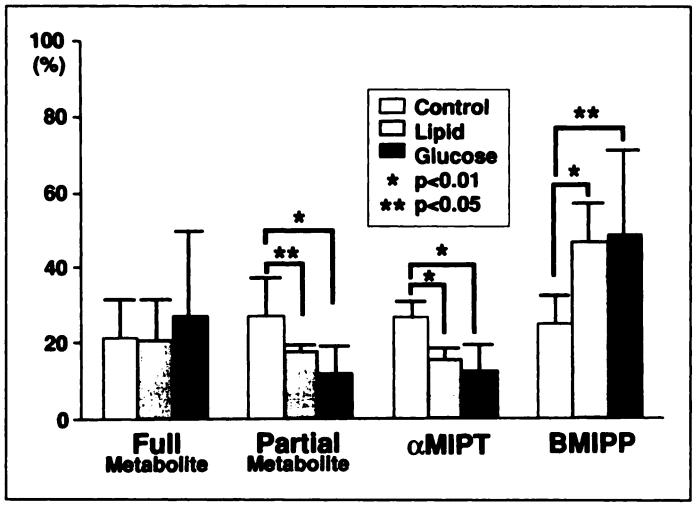

FIGURE 2. Effect of blood lipid and glucose concentrations on BMIPP backdiffusion, αMIPT, partial metabolite and full metabolite are shown. There were significant differences in each parameter except for full metabolite between the glucose and lipid infusion groups.

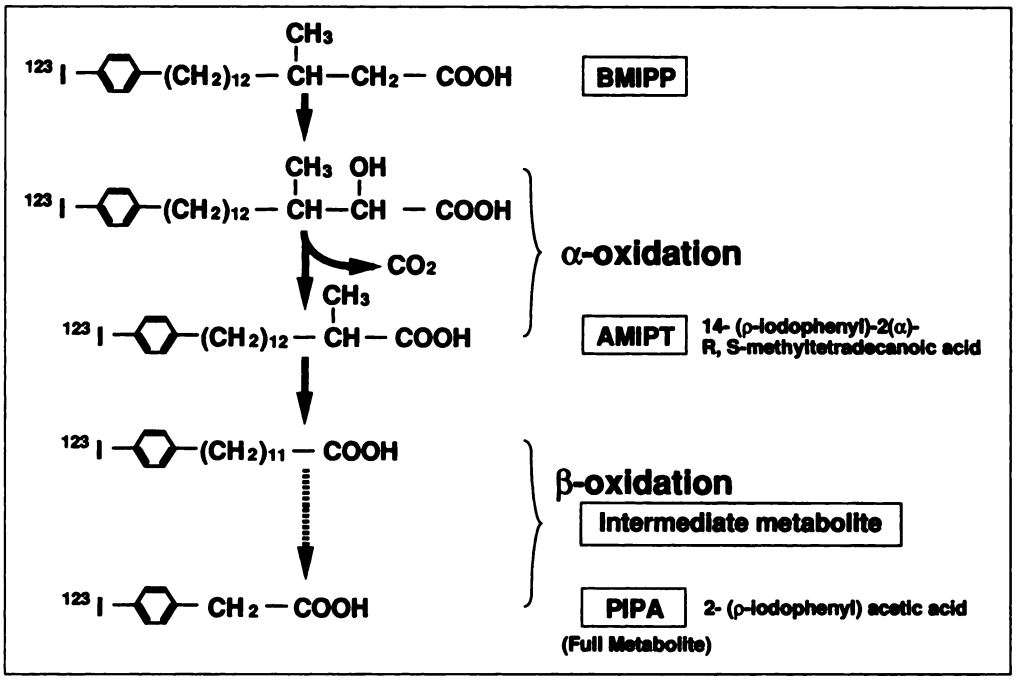

FIGURE 3. Metabolites of BMIPP detected in this study were summarized.

storage such as that of TG and phospholipids increases. Studies by Rosamond et al. (*15*) using ^{11}C-palmitate clarified the lipid metabolism in ischemia and reported that the majority of exogeneously administered free fatty acids (traced with ^{11}C-palmitate) entered beta-oxidation with more than 45% of the initially extracted tracer evolved as $^{11}CO_2$ over the initial 10 min after injection in the fasted state during normoxic condition. Over the 40-min observation period, only 8.9% of the initially extracted tracer backdiffused as unaltered ^{11}C-palmitate. In contrast, during myocardial ischemia, only 16.9% of the initially extracted tracer evolved to $^{11}CO_2$ during the initial 10 min, and a total of 40.6% of the tracer extracted backdiffused. The percentage of extracted tracer that is stored as TG increased from 2.9% under the control condition to 18% during ischemia. Our ischemic study using BMIPP showed similar results, indicating that the severity of ischemia would be correlated with the backdiffusion and negatively related to the production of the final BMIPP metabolite. However, this proportion of the tracer initially extracted was only 10%. Most of the tracer extracted will be converted to TG and stored in the myocardium. The mean value of retention of the tracer in ischemia (occlusion and reperfusion) showed almost no statistical change from the control values, which may be due to an augmented shunting mechanism of free fatty acid as TG or phospholipid using high-energy phosphate or lactate stimulation of TG turnover (*13*) in ischemia or the subsequent suppressed left ventricular function despite decreased BMIPP extraction. However, other possibilities should be considered such as the possibility that the early saturable pool might have modified the result.

Taken together, our prior and present results suggest that 10% of the extracted BMIPP seems to be followed by physiological metabolic regulation as ^{11}C-palmitate, which is also true in extreme conditions such as a high concentrations of blood glucose or lipid. However, the chemical form of the BMIPP that is initially extracted will be mostly stored in one shunt, although the dynamic changes may not be accurately reflected.

The initial extraction of BMIPP was reduced significantly reduced by the infusion of free fatty acids in this study. The initial uptake of free fatty acid was reported to take place through an albumin-dependent sarcolemmal transport system and this nondiffusional uptake process was mediated by the initial interaction of fatty acids with the 40-kDa membrane fatty acid binding protein of cardiac endothelial cells according to Vyska et al. (*16*). However, other investigators have proposed two mechanisms, one involving a readily saturable process and the other resembling passive diffusion (*17*). Rose et al. (*18*) found that simple diffusion is regulated by the fatty acid-to-albumin ratio and is also limited by the velocity of acyl-CoA formation. These studies may indicate that BMIPP uptake is also affected to some degree by other free fatty acids through a saturable process or acyl-CoA formed in the myocardium. Unfortunately, this study did not answer this question.

When PET was performed using the lipid tracer ^{11}C-palmitate, the distribution of this tracer was found to be homogeneous in normal subjects. The locus and characteristics of the metabolic defects were shown to match the locus and type of infarctions and the size of metabolic defects correlated closely with the infarct size determined enzymatically (*19*). BMIPP imaging also shows homogeneous distribution in the normal heart and is reduced in uptake depending on the energy level (*4*). It has been suggested that BMIPP imaging represents ischemic memory well (*7*), especially in cases of unstable angina, although the precise mechanism is unknown. We postulate that a higher washout and limited energy production decrease the BMIPP storage. Clinical studies have also revealed that early and late images of BMIPP differ. Our present experimental model deals mainly with the early phase of BMIPP metabolism. In another experimental model, TG was reported to accumulate later than 6 hr in ischemic dogs (*20*). These differences should be considered in analyses of the total metabolism of BMIPP.

CONCLUSION

This study clarifies that BMIPP metabolism is affected by high glucose or lipid blood concentrations in the normal heart. Most of the tracer extracted showed a similar retention rate, although the BMIPP extraction was decreased by about 15% by the lipid infusion. However, the extraction rate remained at 58% after the lipid infusion and at 68% after the glucose infusion. Further evaluation is necessary to clarify the clinical effects of BMIPP metabolism in early and late images of BMIPP. In addition, studies of the effects of high concentrations of

metabolic substrates such as lipids in case of low flow ischemia or infarction should be performed.

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