Influence of Blood Substrate Levels on Myocardial Kinetics of Iodine-123-BMIPP

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To evaluate the influence of blood substrate levels on myocardial uptake of ^{123}I-labeled beta-methyl-iodophenyl-pentadecanoic acid (BMIPP), we examined the correlation between myocardial BMIPP uptake and blood levels of free fatty acid (FFA), glucose, insulin, triglyceride and total cholesterol. **Methods:** In 180 patients, venous blood samples were obtained, and the early and late myocardial uptakes (MU15 and MU150) were determined on planar images at 15 and 150 min after injection at rest, respectively, and the clearance rate of BMIPP from the myocardium was calculated. Dynamic SPECT with BMIPP, PET with [^{18}F]fluoro-deoxyglucose and determination of myocardial carnitine contents were performed in 15, 1 and 3 patients, respectively. **Results:** In the 180 patients, MU15 correlated with blood insulin ($r = 0.22$, $p = 0.005$) and FFA ($r = -0.19$, $p = 0.02$) levels, whereas MU150 did not correlate with blood levels of any variables that were measured ($p > 0.05$). The clearance rate correlated with blood insulin ($r = 0.28$, $p < 0.001$), glucose ($r = 0.17$, $p = 0.03$) and FFA ($r = -0.40$; $p < 0.001$) levels. The correlations were, however, weak, and five patients (2.8%) with no myocardial BMIPP uptake, all of whom had anterior myocardial infarction, had no characteristics regarding the blood substrate levels. Although dynamic SPECT demonstrated rapid myocardial extraction of BMIPP in 13 patients with myocardial BMIPP uptake, it demonstrated no myocardial BMIPP extraction in two patients with no myocardial BMIPP uptake. One of the five patients with no myocardial BMIPP uptake showed increased myocardial [^{18}F]fluoro-deoxyglucose uptake and decreased myocardial carnitine content. **Conclusion:** The influence of blood substrate levels on myocardial BMIPP uptake is not very significant, although high serum FFA levels may be associated with slow clearance of BMIPP from the myocardium. The complete absence of myocardial BMIPP uptake is not rare and may not be associated with changes in blood substrate levels or early back diffusion of BMIPP.

Key Words: fatty acid metabolism; Iodine-123-BMIPP; myocardium

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Myocardial fatty acid metabolism can be evaluated with conventional gamma camera imaging systems and a radioiodinated fatty acid such as ^{123}I-labeled 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP). Regional mismatch of myocardial flow tracer and BMIPP uptake have been recognized in cardiomyopathy and ischemic heart disease (*1–4*). Mechanisms for the mismatch have not been elucidated, but reduced BMIPP uptake is likely to represent myocardial metabolic disturbances because BMIPP is metabolized in the myocardium (*5–7*) and because regions with reduced BMIPP uptake frequently show wall motion abnormality (*3,4*).

We have observed several patients who show no significant BMIPP accumulation in the myocardium (*8*). The absence of myocardial BMIPP uptake may be due to changes in blood substrate levels, although some specific myocardial disease may be involved in such a phenomenon. In perfused rat hearts, myocardial BMIPP metabolism has been reported to depend on energy substrate levels in the perfusate (*5*). Levels of blood substrates such as glucose and free fatty acids (FFAs) may therefore influence myocardial BMIPP uptake in humans. Moreover, the absence of myocardial BMIPP uptake may be due to early back diffusion of BMIPP from the myocardium because most SPECT studies involve initiation of acquisition at least 10 min after tracer administration. In this study, therefore, we examined whether blood levels of FFA, glucose, insulin, triglyceride and total cholesterol may influence myocardial BMIPP uptake in various patients with different disorders. In addition, we examined the involvement of early back diffusion, enhanced myocardial glucose metabolism or changes in myocardial content of carnitine (the carrier of FFA from cytosol to mitochondria) in some patients with complete absence of myocardial BMIPP uptake.

MATERIALS AND METHODS

Patients

The study group consisted of 180 consecutive patients who underwent myocardial scintigraphy with BMIPP in our nuclear cardiology laboratory. Their clinical characteristics are summarized in Table 1.

BMIPP Imaging and Blood Sampling

BMIPP was obtained from Nihon Medi-Physics Co., Ltd. (Tokyo, Japan). Myocardial images were obtained with a large field of view gamma camera (ZLC 7500; Siemens Gammasonics, Inc., Des Plaines, IL), equipped with a low-energy, all-purpose, parallel-hole collimator and interfaced with a computer system (Scintipac 2400; Shimadzu Corp., Kyoto, Japan). Energy discrimination was provided by a 20% window centered on the 159-keV photopeak.

On the day of BMIPP imaging, patients had no breakfast and continued fasting until the end of the late imaging session. At rest, serial dynamic anterior imaging (64 × 64 matrix) at 1-sec intervals over the whole thorax was commenced just before rapid i.v. injection of BMIPP (111 MBq) and was continued for 60 sec. Anterior images of 180-sec acquisition were obtained in a 64 × 64 matrix over the whole thorax 15 min and 150 min after injection. Immediately after the early and late planar imaging, SPECT was acquired with a three-headed SPECT system (PRISM3000; Picker International, Inc., OH) and low-energy, general-purpose, parallel-hole collimators.

Blood samples were obtained via an indwelling catheter in the forearm vein to measure the blood concentrations of FFA, glucose, insulin, triglyceride and total cholesterol immediately before BMIPP administration, while the patients were lying at rest.

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TABLE 1
Clinical Characteristics of the Study Population

Characteristic	Value
Age (mean ± s.d. years)	64 ± 13 (range, 12–92)
Men/Women	127/53
Major cardiac disorders	
Myocardial infarction	81 (45%)
Angina pectoris	35 (19%)
Cardiomyopathy	30 (17%)
Miscellaneous	34 (19%)
Diabetes mellitus	39 (22%)

TABLE 2
Correlation Coefficients Between Blood Substrate Levels and BMIPP Kinetics

	MU15	MU150	Clearance rate
FFA	−0.17*	0.03	−0.40†
Glucose	0.07	−0.08	0.17*
Insulin	0.22*	−0.02	0.28†
Triglyceride	−0.06	−0.09	0.05
Total cholesterol	−0.04	0.05	0.02

*$p < 0.05$.
†$p < 0.001$.

Analysis of Myocardial BMIPP Accumulation

We measured the total injected dose (T, counts/sec) for BMIPP by applying the Ishii-MacIntyre method (*9,10*) to the above dynamic imaging. In brief, the total injected dose was obtained from the peak counts of the time–activity curve over the whole thorax. On these images, we set a region of interest (ROI) over the heart and another ROI around the heart for background estimation (*11*). We measured the mean counts per pixel over the myocardial ROI (LV, counts/pixel) and over the background ROI (BG, counts/pixel). The mean myocardial uptake per pixel (MU, % uptake/pixel) was used to evaluate the myocardial uptake of BMIPP: $MU = 100 \times (LV - BG)/(T \times 180)$. The early (15-min) and late (150-min) uptakes per pixel were defined as MU15 and MU150 (% uptake/pixel), respectively. The clearance rate (%) was calculated using the following formula: $(MU15 - MU150) \times 100/MU15$.

We assessed the interobserver variability of MU15, MU150 and clearance rate in 25 patients and found excellent correlations ($r = 0.86 \sim 0.98$; $p < 0.001$).

Dynamic SPECT with BMIPP

Using a three-headed SPECT system (PRISM3000) and low-energy, general-purpose, parallel-hole collimators, we performed dynamic SPECT study with BMIPP in 13 patients with and two patients without myocardial BMIPP accumulation. Each patient was injected with 111 MBq of BMIPP, followed by a 20-ml saline flush via an i.v. cannula. Immediately after injection, dynamic data acquisition was performed with continuous rotation. A total of seven series of projection data (2-min data) acquired during a 14-min period was obtained, and transaxial tomograms were reconstructed on a dedicated nuclear medicine computer.

PET with Fluorine-18-FDG

The PET study was performed using a PET camera (HEADTOME IV; Shimadzu Corp.) in one of the five patients with no myocardial BMIPP uptake. The scanner had an axial resolution of 8 mm, and a transmission scan was obtained using a ^{68}Ga ring source to correct for photon attenuation. Immediately after injection of FDG (285 MBq), dynamic data acquisition was performed for 40 min at rest after 7 hr of fasting. Two BMIPP studies, both of which showed no myocardial uptake, were performed for each patient before and after coronary artery bypass surgery, and the PET study was performed 3 mo after the second BMIPP study.

Five ROIs (5 × 5 pixels) were defined within the basal septum, apical septum, anteroapical wall, apical lateral wall and basal lateral wall. The Patlak graphical analysis was used to calculate the regional metabolic rate of glucose.

Determination of Myocardial Carnitine Concentrations

Two patients with and one patient without myocardial BMIPP uptake gave informed consent to sampling of myocardial tissue at the time of coronary artery bypass surgery, which was scheduled within 9 days after the BMIPP study. Tissue carnitine content was determined with a part of the left ventricular myocardium obtained at the time of coronary artery bypass surgery by radioimmunoassay modified from the method of Cereblad and Linstedt (*12,13*). Carnitine content was expressed as content per mg of noncollagenous protein to avoid contamination with tissue fibrosis.

Statistical Analysis

All measurements were expressed as mean ± s.d. Correlations between two variables were examined by linear regression analysis. A $p < 0.05$ was considered statistically significant.

RESULTS

Correlation Between Blood Substrate Levels and Myocardial BMIPP Kinetics

The correlation coefficients between blood substrate levels and myocardial BMIPP kinetics in the 180 patients are listed in Table 2. The MU15 showed a significant positive correlation with plasma insulin level ($p = 0.005$) and a significant negative correlation with serum FFA level ($p = 0.04$), whereas the MU15 did not correlate significantly with blood concentrations of glucose ($p = 0.40$), triglyceride ($p = 0.48$) and total cholesterol ($p = 0.62$). The MU150 showed no significant correlation with any blood levels ($p = 0.25 \sim 0.81$). The clearance rate of BMIPP from the heart showed a significant positive correlation with plasma glucose ($p = 0.03$) and insulin ($p < 0.001$) levels and a significant negative correlation with serum FFA level ($p < 0.001$; Fig. 1), whereas the clearance rate did not correlate significantly with serum levels of triglyceride ($p = 0.51$) and total cholesterol ($p = 0.80$). However, the highest absolute value of these correlation coefficients ($r = -0.40$) was observed between the clearance rate and serum

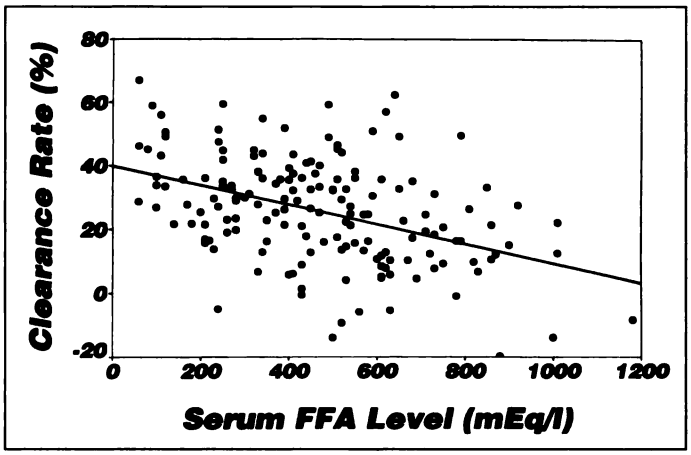

FIGURE 1. Correlation between serum FFA levels and clearance rates of BMIPP from the myocardium. A significant negative correlation is observed ($r = -0.40$).

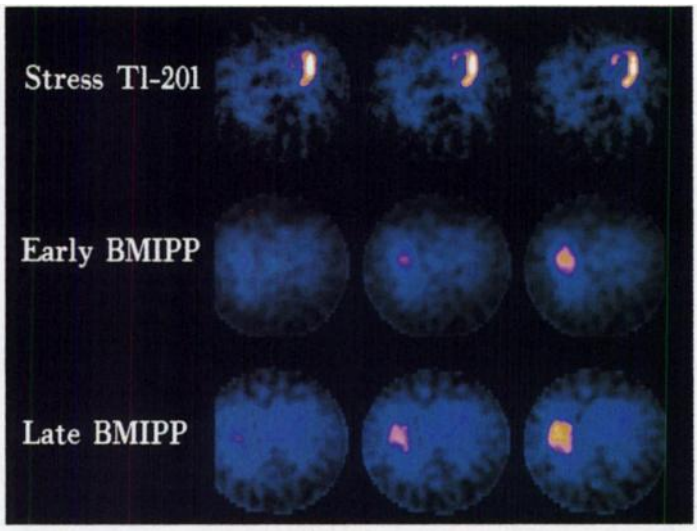

FIGURE 2. Transaxial tomograms of the stress ^{201}Tl and early and late BMIPP imaging in one (M.S.) of the five patients with no myocardial BMIPP uptake. Decreased ^{201}Tl uptake is observed in the septal and apical regions. In both the early and late studies, there is no significant BMIPP accumulation in the left ventricular myocardium. Faint ventricular uptake in the late BMIPP study is likely to correspond to the blood activity in the left and right ventricular cavities.

FFA level. These statistically significant correlations were thus all weak ($R^2 < 0.2$).

Also, in 81 patients with myocardial infarction, the serum concentration of FFA showed significant negative correlations with MU15 ($r = -0.35$, $p = 0.004$) and clearance rate ($r = -0.37$, $p = 0.002$) but no significant correlation with MU150 ($r = -0.17$, $p = 0.18$). On the other hand, there were no significant correlations between myocardial BMIPP kinetics (MU15, MU150 and clearance rate) and blood levels of other substrates, other than a borderline significance of positive correlation between MU15 and plasma insulin levels ($r = 0.24$, $p = 0.051$).

In all 180 patients, we examined the correlations between blood levels of glucose, insulin and FFA, all of which significantly correlated with myocardial BMIPP kinetics. The blood level of insulin correlated significantly with those of glucose ($r = 0.42$, $p < 0.001$) and FFA ($r = -0.25$, $p = 0.001$), whereas there was no significant correlation between those of glucose and FFA ($r = -0.10$, $p = 0.18$).

Patients without Myocardial BMIPP Uptake

There were five patients (2.8% of 180 patients) who showed no myocardial BMIPP uptake on the early and late planar images. In all of these patients, no significant accumulation of BMIPP could be recognized in the myocardium, even on both transaxial tomograms acquired immediately after the early and late planar imaging (Fig. 2). Table 3 shows clinical characteristics and blood substrate levels of the five patients, all of whom were male, had significant stenosis of the left anterior descending artery and suffered from anterior wall infarction. These clinical characteristics, however, were not significantly different between the five patients without and 175 with myocardial BMIPP uptake ($p > 0.05$), and there were no characteristic features regarding blood substrate levels.

Dynamic SPECT

Dynamic SPECT demonstrated that BMIPP did not accumulate in the left ventricular myocardium, even immediately after injection, in two patients with no myocardial BMIPP uptake on the early and late planar images (Fig. 3A). On the other hand, dynamic SPECT demonstrated the rapid accumulation of BMIPP immediately after injection in all 13 patients with myocardial BMIPP uptake on the planar images (Fig. 3B). The ratio of activity in the myocardium to that in the left ventricular cavity increased gradually during dynamic SPECT in the 13 patients with BMIPP uptake, whereas it neither increased nor decreased in the two patients without BMIPP uptake (Fig. 4). These observations indicated that the lack of myocardial BMIPP accumulation on the planar image obtained 15 min after injection was not due to the early back diffusion of BMIPP from the myocardium.

PET with FDG

In one of the five patients with no myocardial BMIPP uptake, PET with FDG during fasting demonstrated that the metabolic rate of glucose was similar between the normal and ischemic regions (0.65–1.17 μmol/min/g in the anteroseptal region versus 0.97–1.14 μmol/min/g in the lateral region). These metabolic rates were comparable to those recorded after glucose loading in healthy volunteers (0.94–1.15 μmol/min/g in the anteroseptal region and 0.89–1.16 μmol/min/g in the lateral region). This observation suggested enhanced glucose metabolism in the myocardium, which could not accumulate BMIPP.

Myocardial Carnitine Content

Carnitine contents of viable myocardium were measured within 9 days after BMIPP study in a patient without and two patients with myocardial BMIPP uptake. Table 4 shows clinical characteristics and myocardial carnitine contents of the three patients. Myocardial content of total carnitine was lower in the

TABLE 3
Clinical Characteristics, Blood Substrate Levels and Myocardial Carnitine Levels in Five Patients without Myocardial BMIPP Uptake

	Patient				
	S.M.	I.A.	M.H.	S.K.	I.Y.
Age, sex	56, male	65, male	56, male	81, male	52, male
Cardiac disease	ant-MI, angina	ant-MI	ant-MI	ant-MI	ant-MI
Diseased vessel	LAD	LAD, CX, RCA	LAD	LAD, CX	LAD
Diabetes mellitus	+	−	+	+	−
Blood levels					
FFA (mEq/liter)	350	370	550	970	430
Insulin (microunits/ml)	7	9	7	5	6
Glucose (mg/dl)	84	98	249	155	99
Triglyceride (mg/dl)	157	237	135	91	92
Total cholesterol (mg/dl)	161	215	203	181	219

ant-MI = anterior myocardial infarction; CX = circumflex artery; LAD = left anterior descending artery; RCA = right coronary artery.

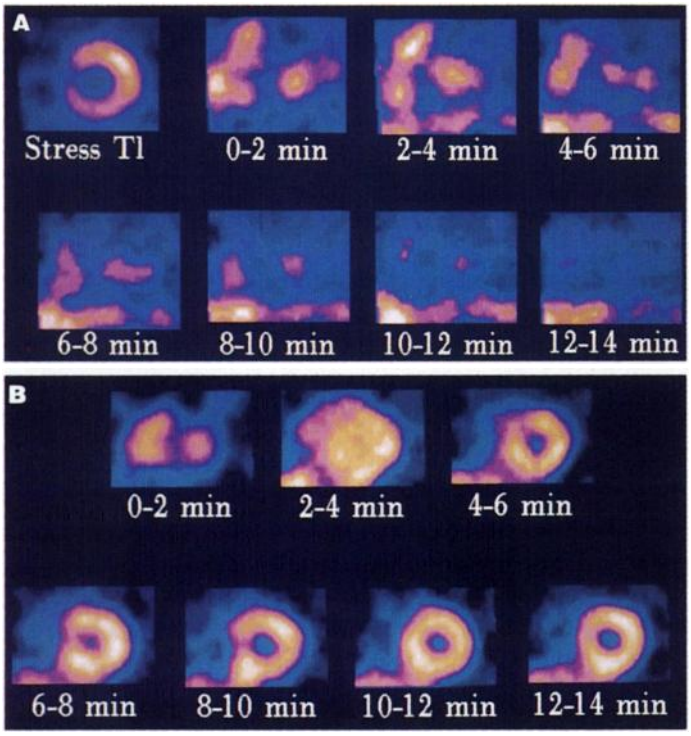

FIGURE 3. Serial short-axis tomograms in the dynamic SPECT studies with BMIPP (seven series of 2-min acquisitions). (A) A patient (M.S.) with absence of myocardial BMIPP uptake in both the early and late imaging shows no myocardial uptake in all of seven images acquired during the 14 min after injection. A ^{201}Tl short-axis tomogram obtained immediately after exercise testing is also shown. The blood activity in the right and left ventricular cavities gradually decreases in the BMIPP images. (B) Another patient with myocardial BMIPP uptake in both the early and late imaging shows a significant uptake in the left ventricular myocardium from 4 min after injection.

patient without BMIPP uptake, compared with the two patients with BMIPP uptake.

DISCUSSION

This study demonstrated the following findings:

1. The early myocardial BMIPP uptake correlated positively with plasma insulin levels and negatively with serum FFA levels.
2. The clearance rate of BMIPP from the myocardium correlated positively with plasma insulin and glucose levels and negatively with serum FFA levels.

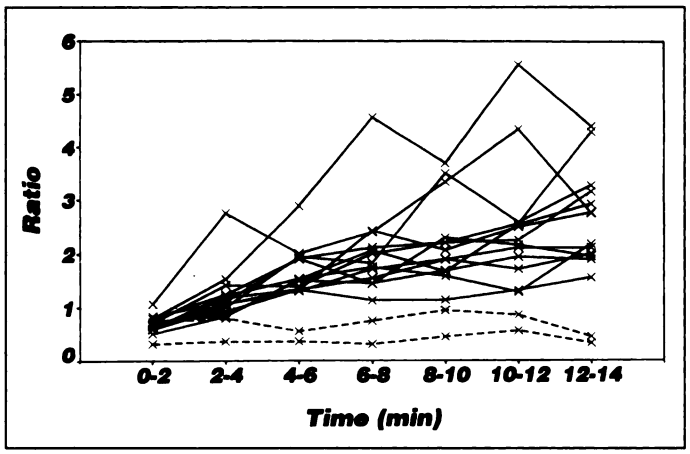

FIGURE 4. Time courses of ratios of BMIPP activity in the lateral wall to that in the left ventricular cavity. Solid lines indicate the ratios in 13 patients with myocardial BMIPP uptake, and dashed lines indicate the ratios in two patients with no myocardial BMIPP uptake. The ratios of the patients with no BMIPP uptake never exceeded unity.

TABLE 4
Clinical Characteristics, Blood Substrate Levels and Myocardial Carnitine Levels in Three Patients with Measurable Carnitine Contents After BMIPP Imaging

	Patient		
	S.M.	K.T.	K.N.
Myocardial BMIPP uptake	−	+	+
Age, sex	56, male	74, male	68, female
Cardiac disease	MI, angina	MI, angina	angina
Diseased vessel	LAD	LMT, LAD, CX	LAD, CX, RCA
Diabetes mellitus	+	−	+
Blood levels			
FFA (mEq/l)	350	410	570
Insulin (microunits/ml)	7	2	13
Glucose (mg/dl)	84	89	123
Triglyceride (mg/dl)	157	68	64
Total cholesterol (mg/dl)	161	170	169
Myocardial content			
Total carnitine*	2.15	7.37	8.12

CX = circumflex artery; LAD = left anterior descending artery; LMT = left main trunk; MI = myocardial infarction; RCA = right coronary artery.
*nmole/mg noncollagenous protein.

3. The late myocardial BMIPP uptake did not correlate with any blood levels that were measured.
4. The highest absolute value of correlation coefficients was observed between the clearance rate of BMIPP and FFA level ($R^2 = 0.16$). The above correlations were thus weak.
5. Five of 180 patients (2.8%) showed no myocardial BMIPP uptake.
6. These five patients did not have any unique characteristics regarding blood substrate levels.
7. In two of the five patients, dynamic SPECT showed no extraction of BMIPP to the myocardium, suggesting that early back diffusion of BMIPP from the myocardium may not be involved in the absence of myocardial BMIPP uptake.
8. One of the five patients showed increased myocardial FDG uptake and decreased myocardial carnitine content.

High blood FFA levels may be therefore associated with slow clearance of BMIPP from the myocardium, but the influence of blood substrate levels on myocardial BMIPP uptake is not so significant. Thus, the complete absence of myocardial BMIPP uptake is not rare and may not be due to either changes in blood substrate levels or to early back diffusion of BMIPP from the myocardium.

The effects of blood substrate levels on myocardial uptake of BMIPP or other beta-methyl fatty acids have been previously evaluated in only a few studies (*7,14,15*). Bianco et al. (*14*) demonstrated that glucose and insulin infusion resulted in increased first-pass extraction fraction of radioiodinated beta-methyl tetradecanoic acid unaccompanied by changes in coronary flow or hemodynamics and suggested an insulin-mediated augmented transport of the fatty acid analog. In contrast, Elmaleh et al. (*7*) demonstrated that glucose and insulin infusion decreased the net extraction fraction of 1-beta-R,S-[^{11}C]methylheptadecanoic acid and concluded that the beta-methyl fatty acid is a useful metabolic tracer for quantifying fatty acid metabolism. Thus, kinetics of radiolabeled beta fatty acids in the heart can reflect alterations of energy substrate preference induced by glucose and insulin infusion, although the above two studies reported different changes in kinetics of beta-methyl fatty acids. On the other hand, Sakuma et al. (*15*)

reported that plasma levels of FFA or glucose/insulin hardly influenced myocardial uptake of BMIPP. Thus, it has not been conclusively established in animal experiments whether (or how) blood substrate levels influence myocardial kinetics of beta-methyl fatty acids.

A recent clinical study by Tsuchimochi et al. (*16*) concluded that the myocardial uptake of BMIPP was not influenced by the plasma substrate level under the fasting state, which is not consistent with our results. In their study, however, the number of patients (n = 26) was small compared to our study (n = 180), and they did not measure the clearance rate of BMIPP from the myocardium. Moreover, methodological differences, such as estimation of total injected doses, background subtraction and uptake/organ versus uptake/pixel, might explain the discrepancy between these results.

Our study demonstrated significant but weak correlations between blood substrate levels and myocardial BMIPP kinetics. It may be difficult to reason about underlying mechanisms for the correlations because the weak correlations suggest that blood substrate levels may not be directly associated with BMIPP kinetics. In our study, the correlation coefficient between blood FFA level and clearance rate of BMIPP had the highest absolute value ($R^2 = 0.16$). If FFAs including BMIPP move from the myocardial cells to circulating blood by passive diffusion, the high blood level of FFA may prevent BMIPP in the myocardium from diffusing back to circulating blood. If high blood FFA levels interfere with myocardial BMIPP extraction, the interference may explain the negative correlation between the early BMIPP uptake and blood FFA levels in our study. It may also explain the negative clearance rates of BMIPP shown in Figure 1 because myocardial BMIPP extraction may persist after the early imaging when a blood FFA level is high. Moreover, high blood FFA levels are likely to be associated with low plasma insulin and glucose levels, which may result in lower myocardial BMIPP uptake in the early imaging (*14*).

Myocardial distribution of BMIPP may be influenced by regional perfusion, fatty acid uptake, the turnover rate of endogenous lipid pool and alpha- and beta-oxidation of fatty acids (*5*). Therefore, BMIPP may provide information on myocardial metabolism independent from myocardial perfusion (*6*), although BMIPP distribution often seems to be similar to the distribution of perfusion tracers, such as ^{201}Tl (*17*). In fact, previous studies have reported that a regional defect of BMIPP with preserved uptake of perfusion tracers is often seen in patients with hypertrophic cardiomyopathy and coronary artery disease (*2–4*). Mechanisms for decreased BMIPP uptake without reduction in regional perfusion have not been elucidated, but the discordantly decreased BMIPP uptake may reflect increased glucose utilization, which is recognized as glucose–perfusion mismatch on PET studies (*6*). In addition, a discordant decrease in BMIPP is frequently associated with mild to moderate abnormality of regional wall motion (*3,4*). Discordant BMIPP uptake, thus, may represent ischemic but viable myocardium in patients with coronary artery disease (*18,19*).

Myocardial BMIPP accumulation was not detected in 2.8% of our 180 patients. Our study could not elucidate mechanisms for the complete absence of myocardial BMIPP uptake, but our observations examined several possible mechanisms. First, marked changes in blood substrate levels may prevent myocardial uptake of BMIPP because the interaction between carbohydrate and fatty acid use in the heart depends to a large extent on the concentration of these substrates in the blood. Our patients with absence of myocardial BMIPP uptake, however, did not show any characteristic changes in blood substrate levels, compared to the remaining 175 patients with myocardial BMIPP uptake. Second, early back diffusion of BMIPP from the heart may result in no myocardial accumulation of BMIPP in the early imaging (*20,21*). In our patients with absence of myocardial BMIPP uptake, however, dynamic SPECT showed no accumulation of BMIPP in the myocardium, even immediately after BMIPP injection. Third, some medication may influence myocardial extraction of BMIPP. In our study, however, there were no characteristic medications that were administered only to the patients with no myocardial BMIPP uptake. Fourth, specific disorders may be involved in the absence of myocardial BMIPP accumulation. All five patients with no myocardial BMIPP uptake had a significant stenosis of the left anterior descending artery with prior anterior infarction. It was not, however, specific to those with no myocardial BMIPP accumulation. Fifth, some impairment of myocardial fatty acid metabolism may result in predominance of glucose metabolism and may prevent BMIPP extraction in the heart. In fact, one of our patients with no myocardial BMIPP uptake showed enhanced glucose metabolism on the PET study with FDG and decreased myocardial carnitine content. There may be underlying factors of unknown origin that must result in the absence of myocardial extraction of BMIPP in some patients. Possible involvement of impairment of myocardial fatty acid metabolism, such as abnormalities of fatty acid binding protein or long-chain acyl-CoA synthetase, as well as carnitine (*22–24*), need to be examined in several patients.

There were several limitations in this study. First, we measured blood substrate levels only once, that is, immediately before injection of BMIPP. A blood FFA level, for example, may show marked variation between the early and late imaging. Integration of multiple measurements during BMIPP study might provide a stronger correlation with clearance rate of BMIPP, compared to a single measurement. Second, our study population included patients with various disorders because the purpose of our study was to examine the influence of blood substrate levels on myocardial BMIPP kinetics over various disorders. Myocardial BMIPP kinetics may be influenced by blood FFA levels in patients with one disorder, whereas it may not in those with another disorder. At last, similar correlations between myocardial BMIPP kinetics and serum FFA levels were observed in our patients with myocardial infarction. Future studies will focus on the influence in healthy subjects or in patients with a single disorder. Third, we evaluated BMIPP kinetics on the whole left ventricular myocardium. In patients with myocardial infarction, for example, BMIPP kinetics may differ from normal regions to infarct regions (*25*). If a region, for instance, shows a rapid clearance of BMIPP and another shows a slow clearance in a patient, our global assessment might conclude a moderate clearance in the whole heart. Fourth, we did not compare myocardial uptake of BMIPP with that of flow tracer. The ratio of BMIPP to flow tracer uptake may reflect myocardial metabolism, which is not dependent on myocardial perfusion. However, both BMIPP and flow tracer imaging could not be performed in a large number of patients.

Our study demonstrated that myocardial BMIPP kinetics may be slightly influenced by blood FFA levels and that a total absence of myocardial BMIPP accumulation is not as uncommon as previously indicated. On the other hand, our results demonstrated that changes in blood levels of glucose, insulin, FFA, triglyceride and total cholesterol may not be involved in the absence of myocardial BMIPP accumulation. Understanding mechanisms for the absence of myocardial BMIPP accumulation, as well as effects of blood substrate levels on myocardial BMIPP kinetics, is indispensable to verifying the

clinical significance of uncoupling between myocardial uptake of BMIPP and flow tracer. If a decrease in BMIPP uptake predicts a poor prognosis (*26,27*), patients with no myocardial BMIPP accumulation must have a markedly poor prognosis. So far, however, all of our patients with absence of myocardial BMIPP uptake have never experienced major cardiac events. That is, we may have failed to recognize a factor that significantly influences myocardial BMIPP uptake but is not associated with myocardial dysfunction. Further experimental and clinical studies are necessary to establish myocardial BMIPP imaging as a routine examination for patients with cardiac disorders.

CONCLUSION

The influence of blood substrate levels on myocardial BMIPP uptake is not so significant, although high serum FFA levels may be associated with slow washout of BMIPP from the myocardium. The complete absence of myocardial BMIPP uptake is not rare and may not be associated with changes in blood substrate levels or early back diffusion of BMIPP.

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