# Absent Myocardial Iodine-123-BMIPP Uptake and Platelet/Monocyte CD36 Deficiency

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Global absence of myocardial $^{123}$I-15-(p-iodophenyl)-3-(R,S)-methyl pentadecanoic acid (BMIPP) uptake is occasionally noted, and it reflects myocardial long-chain fatty acid uptake abnormality. CD36, a membrane glycoprotein expressed on platelet, monocyte and endothelial cells, may contribute to myocardial fatty acid transport, and its deficiency has been reported in a small subset of the population. We hypothesized that CD36 deficiency may be related to absent myocardial BMIPP uptake. Thus, we investigated CD36 expression of platelet/monocyte in patients with absent myocardial BMIPP uptake. **Methods:** Peripheral blood of 7 patients with global absence of myocardial BMIPP uptake (3 of 7 patients in one family) and 3 control subjects were examined in flow cytometric analysis. Platelet/monocyte surface CD36 was detected by using OKM5, an anti-CD36 mouse monoclonal antibody. **Results:** There were no apparent relationships between specific clinical symptoms and absent myocardial BMIPP uptake. None of the blood samples of the 7 patients were stained with OKM5 on the platelet/monocyte cell surface, indicating that all of these patients were Type I CD36-deficient subjects. In contrast, all the control subjects showed normal staining. **Conclusion:** The fact that rare Type I CD36 deficiency was observed in all patients with absent myocardial BMIPP uptake suggests that CD36 plays a role in the myocardial long-chain fatty acid uptake process in humans.

**Key Words:** 15-(p-iodophenyl)-3-(R,S)-methyl pentadecanoic acid; family; CD36 deficiency

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Iodine-123-15-(p-iodophenyl)-3-(R,S)-methyl pentadecanoic acid (BMIPP) is an iodinated methyl-branched fatty acid developed for evaluating myocardial long-chain fatty acid uptake using SPECT. A reduced myocardial BMIPP uptake, less than blood flow, has been observed in various disease conditions such as ischemia. These findings were assumed to reflect reduced myocardial long-chain fatty acid utilization (*1–11*).

In some cases, however, globally absent (negative) myocardial BMIPP uptake has been reported (*12–16*). These patients showed markedly reduced global myocardial palmitate uptake (*13*), but the underlying mechanisms accounting for the absent myocardial BMIPP uptake are still unknown.

Recent studies have suggested that myocardial long-chain fatty acid uptake is mediated or facilitated by fatty acid binding proteins (*17–22*), one of which revealed marked homology with CD36 (*21,22*). CD36 has been detected in a wide variety of cell types involving platelet, monocyte and endothelial cells, and platelet/monocyte CD36 deficiency has been reported in a small subset of the population (*23–33*).

In this study, we hypothesized that absent myocardial BMIPP uptake would be associated with long-chain fatty acid transport abnormality. To confirm this, we analyzed platelet/monocyte CD36 in 7 patients with absent myocardial BMIPP uptake.

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## MATERIALS AND METHODS

### Subjects

A total of 432 consecutive patients underwent BMIPP scintigraphy. Nine patients (2.1%) showed absent myocardial BMIPP uptake. Six of these 9 patients and 1 additional patient with absent myocardial BMIPP uptake who is the second son of Patient 1 (Patient 2) were investigated. Table 1 shows the clinical information for these 7 patients at the time of BMIPP scintigraphy. Three of 7 patients (Patients 1–3) were family cases previously described (*12*).

### Scintigraphy Protocol

After at least 5 hr fasting, 111 MBq BMIPP were injected. Twenty minutes after injection, planar and SPECT images were obtained. All 7 patients underwent stress or rest $^{201}$Tl myocardial perfusion imaging on a separate day. Planar and SPECT images were interpreted by nuclear cardiologists, who were unaware of the clinical or other scintigraphic information. No significant uptake of the tracer in any segment of the myocardium was considered to represent absent myocardial uptake.

### Platelet/Monocyte CD36 Analysis

To detect the platelet/monocyte CD36, immunofluorescent flow cytometric analysis was performed by using a mouse monoclonal antibody against CD36, (OKM5; Ortho Diagnostic System, Inc., Raritan, NJ). Twenty milliliters of heparinized peripheral blood were centrifuged, and platelet-rich plasma and buffy coat were isolated. EDTA, 10 mmol, containing phosphate-buffered solution (PBS)-washed platelet and PBS-washed buffy coat, was incubated with fluorescein isothiocyanate-conjugated OKM5, phosphatidylethanolamine-conjugated anti-CD41a (platelet marker) or anti-CD14 (monocyte marker) monoclonal antibody for 30 min at 4°C and assayed on a FACScan (Becton Dickinson and Co., Mountain View, CA) with logarithmic scales using the Consort30 program. Twenty thousand cells were analyzed in each sample after gating the area corresponding to platelet and monocyte.

As a control, platelet/monocyte CD36 analysis was performed in three healthy volunteer subjects.

## RESULTS

### History of Absent Myocardial BMIPP Uptake

Table 1 summarizes the clinical information of the 7 patients with absent myocardial BMIPP uptake. There was 1 patient with an old myocardial infarction, 1 patient with hypertension, 1 patient with Churg-Strauss syndrome, 3 patients with non–insulin-dependent diabetes mellitus and a son of 1 patient with absent BMIPP uptake. The patient with an old myocardial infarction had lateral wall motion and perfusion abnormalities. There were no apparent relationships between present history,

**TABLE 1**
Clinical Information of Patients with Absent Myocardial 15-(p-Iodophenyl)-3-(R,S)-Methyl Pentadecanoic Acid Uptake

| Patient no. | Age (yr) | Sex | Present illness | Wall motions | Perfusion | Other | Medications |
|---|---|---|---|---|---|---|---|
| 1 | 72 | F | HT | No asynergy | Normal perfusion | | Fur, Spi, CeH, PS |
| 2 | 49 | M | – | No asynergy | Normal perfusion | Second son of Patient 1 | – |
| 3 | 66 | F | NIDDM | – | Normal perfusion | Sister of Patient 1 | Ins, PS |
| 4 | 71 | F | NIDDM | – | Normal perfusion | | Ins, Sim |
| 5 | 79 | F | NIDDM | No asynergy | Normal perfusion | | Gli, AB, ArH |
| 6 | 78 | M | OMI (lateral) | Lateral wall hypokinesis | Lateral wall reversible perfusion defect | | ID, Asp, Nif, DD, Nip, Pro |
| 7 | 29 | F | Churg-Strauss syndrome | No asynergy | Normal perfusion | | Pre, Thp, ClH |

HT = hypertension; NIDDM = non-insulin-dependent diabetes mellitus; OMI = old myocardial infarction; Fur = furosemide; Spi = spironolactone; CeH = celiprolol hydrochloride; PS = pravastatin sodium; Ins = insulin; Sim = simvastatin; Gli = glibenclamide; AB = amlodipine besilate; ArH = arotinolol hydrochloride; ID = isosorbide dinitrate; Asp = aspirin; Nif = nifedipine; DD = dilazep dihydrochloride; Nip = nipradilol; Pro = probucol; Pre = prednisolone; Thp = theophylline; ClH = clenbuterol hydrochloride.

medications or past illnesses and absent myocardial BMIPP uptake.

### Blood Substrate Levels

Blood samples were taken early in the morning after an overnight fast. Table 2 lists blood glucose, insulin, free fatty acids, triglyceride and total cholesterol levels of the 7 patients with absent BMIPP uptake. There were no characteristic features regarding blood substrate levels.

### Platelet/Monocyte CD36 Expression

Platelet cells of all subjects were detected by positive staining with anti-CD41, a monoclonal antibody specific for platelet and monocyte cells with anti-CD14 monoclonal antibody specific for monocyte in flow cytometry. Platelet and monocyte cells from control subjects stained positively with OKM5 (Fig. 1C). However, platelet and monocyte cells from patients with absent BMIPP uptake exhibited only background fluorescence (Fig. 1D). These findings indicated that all of the patients with absent myocardial BMIPP uptake were platelet/monocyte (Type I) CD36-deficient subjects.

## DISCUSSION

Our study demonstrated that the patients with absent myocardial BMIPP uptake have CD36 deficiency on both their platelets and monocytes.

### Causes of Absent Myocardial BMIPP Uptake

BMIPP is an iodinated beta-methyl-branched fatty acid analog, which has been proposed as a probe for myocardial fatty acid utilization. BMIPP in plasma is transported into myocytes and enzymatically converted into BMIPP-CoA (*34–36*). The majority of converted BMIPP-CoA is stored in the lipid pool, and a small part is washed out after alpha- and beta-oxidation (*34,35*). Myocardial BMIPP accumulation appeared to be associated mostly with triglyceride synthesis (*34–36*). Enzymatic conversion of BMIPP to BMIPP-CoA requires adenosine triphosphate (ATP), and myocardial BMIPP accumulation parallels the ATP concentration (*34,36*). Reduction of myocardial BMIPP accumulation, which is discordant with perfusion tracer, has been observed in certain disease conditions such as ischemia and hypertrophic cardiomyopathy (*1–11*). Most of these reductions were regional and were assumed to reflect some myocardial metabolic abnormality.

Global absence of myocardial BMIPP accumulation has been observed in about 0.9%–2.8% of the Japanese population (*13,14*). The incidence of absent myocardial BMIPP uptake in this study was 2.1%, which was consistent with previous studies. The relationships between specific disease conditions and absent myocardial BMIPP uptake are still unclear. We

**TABLE 2**
Blood Substrate Levels of Patients with Absent Myocardial 15-(p-Iodophenyl)-3-(R,S)-Methyl Pentadecanoic Acid Uptake

| Patient no. | Blood glucose (mg/dl) | Insulin (μU/ml) | Free fatty acid (μEq/liter) | Triglyceride (mg/dl) | Total cholesterol (mg/dl) |
|---|---|---|---|---|---|
| 1 | 93 | 4.2 | 0.56 | 100 | 220 |
| 2 | 89 | 3.4 | 0.83 | 94 | 220 |
| 3 | 158 | 3.6 | 1.27 | 263 | 241 |
| 4 | 94 | 39.4 | 0.65 | 111 | 132 |
| 5 | 195 | 7.1 | 0.75 | 101 | 232 |
| 6 | 106 | 5.4 | 0.49 | 68 | 131 |
| 7 | 82 | 18 | 0.65 | 130 | 203 |
| Average, s.d. | 116, 42.8 | 11.6, 13.3 | 0.742, 0.258 | 124, 64.1 | 197, 46.3 |

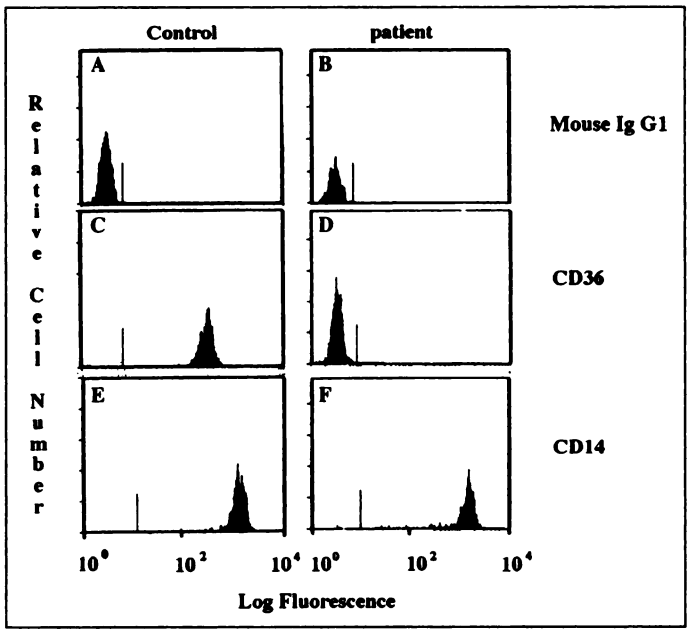


**FIGURE 1.** Flow cytometry of control subject and patient with absent myocardial BMIPP uptake. Mononuclear cells were incubated with control mouse IgG1 (A,B), OKM5 (anti-CD36 monoclonal antibody; C,D), anti-CD14 monoclonal antibody (monocyte marker; E,F). Monocytes of control subject exhibited positive shift of CD36 staining, whereas patient did not show significant staining.

previously observed absent myocardial BMIPP uptake in a family, suggesting that the phenomenon may be related to hereditary factors (*12*). The clinical and pathophysiological implications of absent myocardial BMIPP uptake remain, however, unknown.

On the other hand, cardiac metabolic conditions, as measured by PET, appear to be unique in such patients . For example, Kudoh et al. (*13*) demonstrated that patients with absent BMIPP uptake showed very low myocardial $^{11}$C-palmitate uptake on PET. Oxidative metabolism or ATP synthesis of these patients was normal, and the majority showed compensatory increased myocardial glucose utilization in the fasting condition. These observations suggest that absent BMIPP uptake may reflect a myocardial abnormality in long-chain fatty acid uptake and/or utilization, but it may not be associated with disturbance of ATP synthesis.

Although the underlying mechanisms that account for the absent BMIPP uptake are unclear, there are two possible explanations that may contribute to this phenomenon: plasma-cytosol long-chain fatty acid transport abnormality and early backdiffusion that was observed in ischemic myocardium (*10,11*). Kurata et al. (*14*) demonstrated that absent BMIPP patients did not show myocardial BMIPP extraction on dynamic SPECT, suggesting that the absent BMIPP uptake may be related to long-chain fatty acid transport abnormality.

Myocardial fatty acid uptake is hypothesized to be mediated or facilitated by multiple fatty acid binding proteins. A 15-kD protein inside the myocyte, termed cytoplasmic fatty acid binding protein (H-FABP), has been linked to intracellular fatty acid transport (*17*). A 40-kD membrane-bound protein, termed FABPPM, similar to that in the liver, adipose tissue and gut was speculated to mediate myocardial fatty acid uptake (*18–20*). Recently, a 88-kD protein (CD36) has been detected in rat adipose tissue, heart and skeletal muscles. This protein is termed fatty acid translocase (FAT) for its postulated function and is thought to contribute to sequestration and uptake of fatty acid (*21,22*). Myocardial FAT expression is closely related to H-FABP expression (*23*), and these proteins might interact with each other.

### CD36 and Its Deficiency

CD36 is a receptor for collagen (*24*), thrombospondine (*25*) and oxidized low-density lipoprotein (*26*), etc., and has been detected in several cells, including platelets, monocytes and capillary endothelial cells. Myocytes themselves were CD36 negative in rat (*27*). High levels of capillary endothelial CD36 expression were found in rat adipose tissue, cardiac and skeletal muscles but not in liver tissue (*27*). CD36 tissue distribution is contrary to the BMIPP distribution of patients with absent myocardial BMIPP uptake, since patients revealed overt hepatic BMIPP accumulation. These observations suggest that the fatty acid uptake process in the myocardium is somewhat different from that in the liver, and CD36 may have some association with this discrepancy.

Platelet membrane CD36 is also referred to as platelet glycoprotein IV, and its deficiency has been reported in about 3%–4% of the Japanese and 0.3% of the U.S. population (*28–30*). Platelet CD36-deficient subjects showed no specific clinical symptoms, but a few have exhibited refractoriness to human leukocyte antigen-matched platelet transfusions (*28*). Tanaka et al. (*15*) suggested that platelet CD36 deficiency may be associated with hypertrophic cardiomyopathy (HCM) and demonstrated a case of monocyte/platelet (Type I) CD36 deficiency with absent myocardial BMIPP uptake. Watanabe et al. (*16*) also reported a case of HCM with Type I CD36 deficiency and absent myocardial BMIPP uptake . However, in our study, no patients with HCM were included. The association between absent myocardial BMIPP uptake/Type I CD36 deficiency and HCM was not demonstrated in our study.

Platelet CD36 deficiency is divided into two subtypes. In Type I, neither platelet nor monocyte cells express CD36; in Type II, the monocyte expresses CD36, but the platelet does not (*30*). The incidence of Type I CD36 deficiency might be ≦10% of that of Type II CD36 deficiency, making it very rare (*31*). Since this rare Type I CD36 deficiency was observed in all patients with absent myocardial BMIPP uptake, it is likely that there is a relationship between Type I CD36 deficiency and global BMIPP uptake abnormality. However, there are no data concerning myocardial CD36 expression. To clarify myocardial CD36 expression, myocardial biopsy is warranted.

Regarding the nature of the CD36 deficiency, some mutations have been reported (*31–33*). CD36 deficiency is a hereditary abnormality, and it is compatible with our observations of family cases.

## CONCLUSION

All 7 patients with absent myocardial BMIPP uptake demonstrated Type I CD36 deficiency. These findings strongly suggest that CD36 is associated with the myocardial long-chain fatty acid uptake process in humans.


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# Comparison of Fatty Acid Tracers FTHA and BMIPP During Myocardial Ischemia and Hypoxia

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To study the sensitivity of two fatty acid tracers to changes in beta-oxidation, the myocardial retention kinetics of $^{125}$I-iodine-15-(p-iodophenyl)-3(R,S)-methylpentadecanoic acid (BMIPP) and 14-$^{18}$F-fluoro-6-thia-heptadecanoic acid (FTHA) were compared in states of oxygen deprivation due to ischemia and hypoxia. **Methods:** Nineteen swine were studied by extracorporeal perfusion of the three coronary arteries. Fatty acid beta-oxidation rates were determined by infusion of tritiated palmitate into the left anterior descending artery (LAD) and by measurement of labeled water production in the LAD perfusion bed. After a baseline period of 30 min, animals were divided into three groups and subjected to a 50-min intervention period. For the control group, there was no change in perfusion; for the ischemia group, there was a 60% decrease in LAD perfusion; and for the hypoxia group, the perfusion rate was unchanged, but venous blood was used as the LAD perfusate. Continuous infusion of FTHA and BMIPP into the LAD started 10 min into the intervention period and continued until the end of the intervention period. Retention rates of the two tracers were compared between the LAD and circumflex perfusion beds. **Results:** No difference in beta-oxidation rate occurred from the baseline to the intervention period in the control group. A 50% reduction in beta-oxidation occurred in the ischemia group, and an 80% reduction occurred in the hypoxia group. No difference in retention of BMIPP or FTHA occurred in the control group. In the ischemia group, reduction in retention of both tracers occurred. However, in the hypoxia group, FTHA uptake was unchanged, whereas BMIPP retention increased compared to the circumflex arterial bed. **Conclusion:** Decreased retention of both BMIPP and FTHA occurred with ischemia, despite the known differences in metabolism of the two tracers. This difference in metabolism was further highlighted in the setting of hypoxia with increased BMIPP uptake. Thus, these results suggest that uptake of both FTHA and BMIPP tracks reduction of fatty acid utilization in myocardial ischemia but fails in tracking reduction of fatty acid oxidation during hypoxia.

**Key Words:** fatty acid tracer; FTHA; BMIPP; myocardial ischemia; myocardial hypoxia

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Long-chain fatty acids are the main energy source for the heart and are rapidly metabolized by beta-oxidation under normal conditions. However, in settings of reduced oxygen delivery such as ischemia and hypoxia, it is well known that fatty acid oxidation is vastly decreased and accompanied by a decline in mechanical function. To noninvasively assess changes in fatty acid metabolism, several fatty acid tracers have been developed over the last decade for imaging with standard gamma cameras or PET. Among the widely investigated tracers has been the 15-carbon methyl-branched fatty acid analog $^{125}$I-iodine-15-(p-iodophenyl)-3(R,S)-methylpentadecanoic acid (BMIPP). Most of the tracer is rapidly incorporated into triacylglycerols in the cytosol, but a portion undergoes alpha-oxidation (*1–3*). BMIPP has also been shown in cultured cell (*4*) and isolated organ (*5*) preparations to be insensitive to changes in beta-oxidation. Extensive clinical trials, however, have reported a mismatch between BMIPP uptake and blood flow distribution (*6–8*).

Recently, a sulfur-substituted fatty acid tracer analog 14-$^{18}$F-

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