Annals of Nuclear Medicine Vol. 12, No. 1, 43–46, 1998

Absent myocardial accumulation of two different radioiodinated pentadecanoic acids

Jun HASHIMOTO,* Seiichiro KOSEKI,** Fumio KINOSHITA,** Atsushi KUBO,* Shiro IWANAGA,*** Hideo MITAMURA*** and Satoshi OGAWA***

*Department of Radiology, and ***Department of Internal Medicine, School of Medicine, Keio University
**Department of Internal Medicine, Tokyo Fussa Hospital

This article presents two cases with preserved myocardial ^{201}Tl uptake and absent uptake of two kinds of radioiodinated fatty acids: iodine-123-labeled 15-(p-iodophenyl)-3-(R,S)-methyl-pentadecanoic acid (BMIPP) and iodine-123-labeled 15-(p-iodophenyl)-9-(R,S)-methyl-pentadecanoic acid (9MPA). Although coronary angiography showed no stenotic lesion and left ventriculography revealed no wall motion abnormality, no myocardial uptake of BMIPP and 9MPA was observed in the first case. In the second case, no myocardial accumulation was recognized even in the initial phase of dynamic SPECT acquired soon after the injection of 9MPA. The results suggest that the non-visualized myocardium was not specific for BMIPP imaging and that rather than the early back diffusion of the tracers from the myocardium, abnormality of the myocardial cell membrane was a possible mechanism accounting for the phenomenon.

Key words: myocardial SPECT, fatty acid metabolism, I-123-BMIPP, I-123-9MPA

INTRODUCTION

NORMAL MYOCARDIUM GENERATES ENERGY for contraction mainly by the oxidation of free fatty acids under the fasting condition, so that radionuclide imaging of the myocardial fatty acid metabolism is expected to be a sensitive indicator of myocardial ischemia. Iodine-123-labeled 15-(p-iodophenyl)-3-(R,S)-methyl-pentadecanoic acid (BMIPP, Fig. 1) has been used for myocardial imaging, and was designed to be eliminated slowly from the myocardium. Some authors have reported cases without myocardial uptake of BMIPP.[1-8] Some of these cases did not show signs of significant coronary stenosis, wall motion abnormality or decreased uptake of ^{201}Tl. We had the opportunity to conduct a clinical trial of another iodinated branched fatty acid, iodine-123-labeled 15-(p-iodophenyl)-9-(R,S)-methyl-pentadecanoic acid (9MPA, Fig. 1), which is washed out faster than BMIPP. In this article, we present two cases with absent myocardial uptake of both of these two iodinated fatty acids.

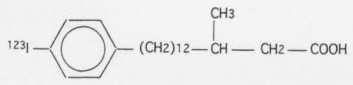
The study was approved by the institutional review board of Keio Univ. Hospital. Written informed consent was obtained from each subject after detailed explanation of the study. No side effects were observed in any of the subjects after administration of BMIPP and 9MPA.

CASE REPORT

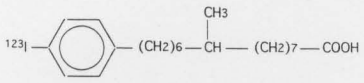
The first case was a 53-year-old man. He had felt occasional chest pain at rest or during exercise since 1989. Treadmill exercise testing revealed 2 mm asymptomatic ST segment depression. He was admitted to our hospital to undergo coronary angiography in September, 1995. His past history was unremarkable and he did not have any risk factors. In laboratory tests, the counts of blood cells, the levels of serum enzymes, electrolytes, free fatty acids and insulin were within the normal ranges. Mild and transient increase in the blood glucose level was documented (maximum value: 119 mg/d*l*). Coronary angiography showed no stenotic lesion and left ventriculography revealed no wall motion abnormality. He was referred for imaging with ^{201}Tl, BMIPP and 9MPA in September, 1995. As

Received September 3, 1997, revision accepted September 3, 1997.

For reprint contact: Atsushi Kubo, M.D., Department of Radiology, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160–8582, JAPAN.



Iodine-123-labeled 15-(p-iodophenyl)-3-(R,S)-methyl-pentadecanoic acid (BMIPP)



Iodine-123-labeled 15-(p-iodophenyl)-9-(R,S)-methyl-pantadecanoic acid (9MPA)

Fig. 1 Chemical structures of ^{123}I-BMIPP and ^{123}I-9MPA.

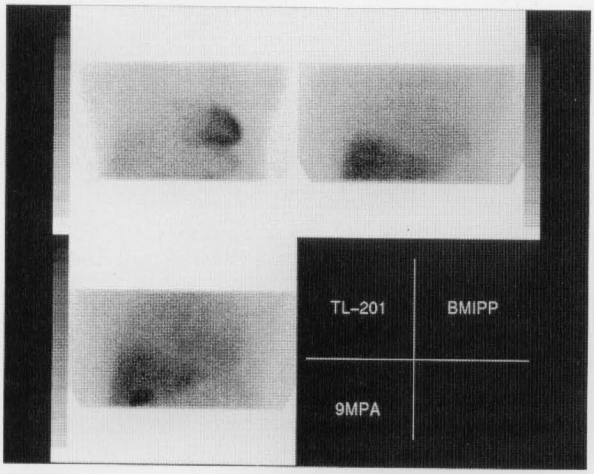
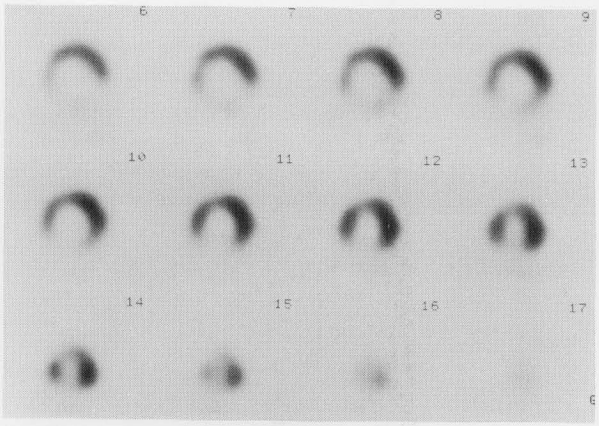


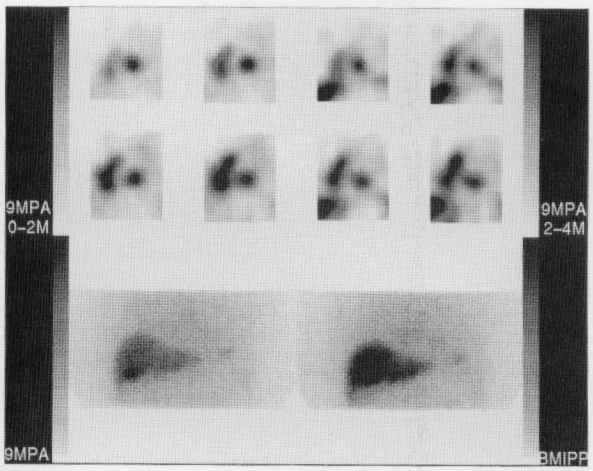
Fig. 2 Myocardial planar images of the first case. Myocardial tracer uptake was recognized in ^{201}Tl study (upper left), meanwhile, BMIPP (upper right) and 9MPA (lower left) images showed absent uptake.

indicated in Fig. 2, fatty acid scintigrams showed no myocardial uptake of the tracers in spite of intact myocardial accumulation of ^{201}Tl.

The second patient was a 64-year-old man with a past history of inferior myocardial infarction in 1994. The counts of blood cells, the levels of serum enzymes, electrolytes and free fatty acids were within the normal ranges. Increased concentrations of blood glucose (136 mg/d*l*) and insulin (30 μU/m*l*) were found in November, 1995. No sign of ischemia was observed in Treadmill testing, and coronary angiography revealed 50% stenosis in the left anterior descending artery and total occlusion in the left circumflex artery. Left ventriculography demonstrated hypokinesis in the posterolateral segment. Thallium-201 scintigraphy performed in 1994 showed a defect in the inferoposterior wall (Fig. 3). No myocardial uptake was observed in BMIPP and 9MPA images obtained in November, 1995 (Fig. 3). Sequential short-axis images obtained with dynamic SPECT acquisition showed non-visualized myocardium in all frames (Fig. 3).



A



B

Fig. 3 Myocardial planar and SPECT images of the second case. (A) Thallium-201 SPECT images revealed inferoposterior myocardial infarction. (B) BMIPP (lower right) and 9MPA (lower left) planar images presented non-visualized myocardium. Myocardial accumulation of 9MPA was not seen even in the initial phases of dynamic short axial SPECT images (upper). 0–2M: from 0 min to 2 min postinjection; 2–4M: from 2 min to 4 min

DISCUSSION

Although BMIPP is metabolized in part by alpha- and subsequent beta-oxidation, it is slowly washed out of the myocardium because the methyl-branch inhibits beta-oxidization.[9] On the other hand, 9MPA is converted to 3MNA (p-iodophenyl-3-methyl-nanoic acid) after three cycles of beta-oxidation and it is washed out of the myocardium faster. But as it stands, the kinetics of 9MPA have not been reported in detail. Myocardial accumulation of BMIPP was reported to be well correlated with cardiac wall motion and ATP content.[3,10,11] Clinically, BMIPP images have been thought to reflect regional myocardial fatty acid metabolism.

Many clinical studies reported discrepancies between

BMIPP findings and those of ^{201}Tl images in patients with myocardial ischemia, infarction or cardiomyopathy.[1,2,12–20] In these articles, most cases presented impaired myocardial fatty acid metabolism with relatively preserved myocardial perfusion. In contrast, there are not so many reports of no myocardial uptake of BMIPP, and the incidence was reported to be 0.3–2.7%.[1,2,6–8] It is reported that increased FDG uptake was observed in most of the patients with non-visualized myocardium, suggesting a switch in energy utilization.[4,6,7] We could not find any articles mentioning no uptake of other iodinated fatty acids. In the present study, however, both of the two patients had non-visualized myocardium in both BMIPP and 9MPA studies. The results indicated that the phenomenon is not specific to BMIPP imaging.

A mild increase in fasting blood glucose was observed in the two patients in our study. Some authors pointed out decreased myocardial uptake of BMIPP in diabetic patients without overt ischemic heart disease[19] but abnormality of blood glucose cannot completely explain the non-visualized myocardium, because a lack of uptake was not observed even in patients with advanced diabetes.[19] Kurata et al. pointed out that the early myocardial BMIPP uptake correlated positively with plasma insulin levels and negatively with serum free fatty acid levels[7] but decreased insulin levels or increased free fatty acid levels were not documented in any patients with the non-visualized myocardium in their studies or ours.

Another report suggested underlying hereditary factors in this phenomenon by presenting three cases with no BMIPP uptake in one family.[3] Electrocardiography showed QT prolongation in two of the three cases and one patient suffered from non-insulin-dependent diabetes mellitus.

Some articles on dynamic BMIPP SPECT acquisition showed that the findings of early images acquired in a few minutes post-injection were well correlated to those of ^{201}Tl images and that discrepancies between BMIPP and ^{201}Tl images were noted in later phases.[17,18] These studies concluded that BMIPP was taken up to the myocardium in proportion to myocardial blood flow soon after the administration and that the back diffusion in the later phase resulted in the discrepancies in findings. On the other hand, even in the early phase of the dynamic study with 9MPA, the second patient in our study had a non-visualized myocardium which proved to be viable and well perfused in ^{201}Tl imaging. It is also reported that dynamic BMIPP SPECT images revealed no myocardial uptake in any phase.[7] These observations suggest that negative myocardial uptake was mainly due to abnormalities of the myocardial cell membrane rather than the early back diffusion of the tracers from the myocardium. It is probable that 9MPA was taken up into myocardial cells not by passive diffusion but by some transportation mechanisms which also contribute to the uptake of BMIPP.

Some investigators described carrier-mediated fatty acid transportation of myocardial cells, which is compatible with the results of our study.[21,22] In addition, recent reports showed that negative myocardial uptake of BMIPP was observed in seven patients with deficiency of CD36 (type I) which is homologous with the myocardial long-chain fatty acid transporter.[5,8,23] Further studies are required to elucidate the relationship between CD36 deficiency and the lack of 9MPA accumulation.

REFERENCES

1. Torizuka K, Yonekura Y, Nishimura T, Tamaki N, Uehara T. Phase 2 study of beta-methyl-p-(I-123)-iodophenyl-pentadecanoic acid, a myocardial imaging agent for evaluating fatty acid metabolism. *KAKU IGAKU (Jpn J Nucl Med)* 29: 305–317, 1992.
2. Torizuka K, Yonekura Y, Nishimura T, Ohtake T, Bunko H, Tamaki N, et al. Phase 3 study of beta-methyl-p-(I-123)-iodophenyl-pentadecanoic acid, a myocardial imaging agent for evaluating fatty acid metabolism—a multi-center trial. *KAKU IGAKU (Jpn J Nucl Med)* 29: 413–433, 1992.
3. Hwang EH, Yamashita A, Takemori H, Taki J, Nakajima K, Bunko H, et al. Absent myocardial I-123 BMIPP uptake in a family. *Ann Nucl Med* 10: 445–448, 1996.
4. Inoue F, Hashimoto T, Nishida Y, Dohi K, Matsushima A, Sakakibara H, et al. Absence of myocardial I-123-BMIPP uptake in the presence of a normal coronary angiogram and normokinetics on a left ventriculogram. *Jpn Circ J* 61: 263–267, 1997.
5. Tanaka T, Sohmiya K, Kawamura K. Is CD36 deficiency an etiology of hereditary hypertrophic cardiomyopathy? *J Mol Cell Cardiol* 29: 121–127, 1997.
6. Kudoh T, Tamaki N, Magata Y, Konishi J, Nohara R, Iwasaki A, et al. Metabolism substrate with negative myocardial uptake of iodine-123-BMIPP. *J Nucl Med* 38: 548–553, 1997.
7. Kurata C, Wakabayashi Y, Shouda S, Mikami T, Takei Y, Tawarahara K. Influence of blood substrate level on myocardial kinetics of iodine-123-BMIPP. *J Nucl Med* 38: 1079–1084, 1997.
8. Watanabe K, Miyajima S, Kusano Y, Tanabe N, Hirokawa Y. Hypertrophic cardiomyopathy showing no ^{123}I-BMIPP myocardial accumulation with type I CD36 deficiency. *KAKU IGAKU (Jpn J Nucl Med)* 34: 481–486, 1997.
9. Yamamichi Y, Kusuoka H, Morishita K, Shirakami Y, Kurami M, Okano K, et al. Metabolism of Iodine-123-BMIPP in perfused rat hearts. *J Nucl Med* 36: 1043–1050, 1995.
10. Fujibayashi Y, Yonekura Y, Takemura Y, Wada K, Matsumoto K, Tamaki N, et al. Myocardial accumulation of iodinated beta-methyl-branched fatty acid analogue, iodine-125-15-(p-iodophenyl)-3-(R,S)-methyl pentadecanoic acid (BMIPP), in relation to ATP concentration. *J Nucl Med* 31: 1818–1822, 1990.
11. Nohara R, Okuda K, Ogino M, Hosokawa R, Tamaki N, Konishi J, et al. Evaluation of myocardial viability with iodine-123-BMIPP in a Canine Model. *J Nucl Med* 37: 1403–1407, 1996.
12. Hashimoto J, Kubo A, Nakamura K, Hemmi H, Toya K, Hashimoto S, et al. Evaluation of beta-methyl-p-(I-123)-iodophenyl pentadecanoic acid (I-123-BMIPP) for imaging

of acute myocardial infarction. *Jpn J Clin Radiol* 36: 1659–1663, 1991.
13. Kurata C, Taniguchi T, Aoshima S, Kobayashi A, Yamazaki N, Kawa H, et al. Myocardial emission computed tomography with iodine-123-labeled beta methyl branched fatty acid in patients with hypertrophic cardiomyopathy. *J Nucl Med* 33: 6–13, 1992.
14. Tamaki N, Kawamoto M, Yonekura Y, Fujibayashi Y, Takahashi N, Konishi J, et al. Regional metabolic abnormality in relation to perfusion and wall motion in patients with myocardial infarction: assessment with emission tomography using an iodinated branched fatty acid. *J Nucl Med* 33: 659–667, 1992.
15. Takeishi Y, Chiba J, Abe S, Tonooka I, Komatani A, Tomoike H. Heterogeneous myocardial distribution of iodine-123 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) in patients with hypertrophic cardiomyopathy. *Eur J Nucl Med* 19: 775–782, 1992.
16. Knapp Jr FF, Kropp J, Goodman MM, Franken P, Reske SN, Ambrose KR, et al. The development of iodine-123-methyl-branched fatty acids and their applications in nuclear cardiology. *Ann Nucl Med* 7: 1–14, 1993.
17. Matsunari I, Ichiyanagi K, Taki J, Nakajima K, Tonami N, Hisada K. Evaluation of early kinetics of I-123-BMIPP in patients with ischemic heart disease. *KAKU IGAKU (Jpn J Nucl Med)* 30: 1445–1450, 1993.
18. Kobayashi H, Asano R, Oka T, Inoue S, Momose M, Ikkatai Y, et al. Simultaneous evaluation of myocardial perfusion and fatty acid metabolism using dynamic SPECT with single injection of I-123-15-(p-iodophenyl)-3-methyl pentadecanoic acid (BMIPP). *KAKU IGAKU (Jpn J Nucl Med)* 32: 19–29, 1995.
19. Shinmura K, Tani M, Suganuma Y, Hasegawa H, Kawamura M, Nakamura Y, et al. I-123-beta-methyl-iodophenyl-pentadecanoic acid myocardial scintigraphy in diabetic patients without overt ischemic heart disease. *J Cardiol* 26: 23–32, 1995.
20. Nakajima K, Shimizu K, Taki J, Uetami Y, Konishi S, Tonami N, et al. Utility of iodine-123-BMIPP in the diagnosis and follow up of vasospastic angina. *J Nucl Med* 36: 1934–1940, 1995.
21. Sorrentino D, Stump D, Potter DJ, Robinson RB, White R, Kiang CL, et al. Oleate uptake by cardiac myocites is carrier mediated and involves a 40-kD plasma membrane fatty acid binding protein similar to that in liver, adipose tissue, and gut. *J Clin Invest* 82: 928–935, 1988.
22. Tanaka T, Kawamura K. Isolation of myocardial membrane long-chain fatty acid-binding protein: homology with a rat membrane protein implicated in the binding or transport of long-chain fatty acids. *J Mol Cell Cardiol* 27: 1613–1622, 1995.
23. Abumrad NA, El-Maghrabi MR, Amri EZ, Lopez E, Grimaldi PA. Cloning of a rat adipocyte membrane protein implicated in binding or transport of long-chain fatty acids that is induced during preadipocyte differentiation. *J Bio Chem* 268: 17665–17668, 1993.