ORIGINAL ARTICLE

Annals of Nuclear Medicine Vol. 16, No. 8, 563–568, 2002

Ischemic "memory image" in acute myocardial infarction of ^{123}I-BMIPP after reperfusion therapy: A comparison with ^{99m}Tc-pyrophosphate and ^{201}Tl dual-isotope SPECT

Teruhito MOCHIZUKI,* Kenya MURASE,** Hiroshi HIGASHINO,*** Masao MIYAGAWA,* Yoshifumi SUGAWARA,* Takanori KIKUCHI* and Junpei IKEZOE*

**Department of Radiology, Ehime University School of Medicine*
***Department of Medical Engineering, Division of Allied Health Sciences, Osaka University Medical School*
****Department of Radiology, Ehime Imabari Hospital*

Ischemic "memory image" is a phenomenon of ^{123}I-15-(*p*-iodophenyl)-3-(*R,S*)-methylpentadecanoic acid (BMIPP) in which an area at risk of acute myocardial infarction (AMI), could be detected as a defect in a couple of weeks even after successful reperfusion therapy.

The purpose of this study was to clarify the incidence of the ischemic "memory image" of ^{123}I-BMIPP in patients with AMI by comparing ^{99m}Tc-PYP and ^{201}Tl dual-isotope SPECT.

Materials consisted of 14 patients with successfully reperfused AMI and 20 patients with old myocardial infarction (OMI). All AMI patients underwent PYP/Tl dual-isotope SPECT within 1 week after the onset of AMI, and BMIPP SPECT was performed within 1 week after the PYP/Tl dual-isotope SPECT. The extent and severity of the defect of BMIPP and Tl were visually scored into four grades: 0 = no defect to 3 = large or severe defect. These scores were compared.

PYP positive AMI lesions were concordant with BMIPP defects (13/14). In AMI, both the extent and severity scores of BMIPP were higher than ^{201}Tl ($p < 0.001$). Differences (BMIPP – Tl) of extent and severity scores were greater in AMI than in OMI ($p < 0.001$).

In conclusion, the ischemic "memory image" obtained by means of the BMIPP is a common phenomenon (13/14) in AMI, and helpful in evaluating the area at risk.

Key words: fatty acid metabolism, acute myocardial infarction, ^{99m}Tc-pyrophosphate, ^{201}Tl

INTRODUCTION

IT IS IMPORTANT to assess areas at risk or damaged myocardium for management of patients with acute myocardial infarction (AMI) after reperfusion therapy. A successfully reperfused and viable area may recover function, but is a candidate for a cardiac event in the future. Nevertheless, a myocardial perfusion study (^{201}Tl, ^{99m}Tc-hexakis-2-methoxyisobutylisonitrile (MIBI), ^{99m}Tc-tetrofosmin) often underestimates the area at risk in patients after successful reperfusion therapy, since the reperfused area may be depicted as normal or with slightly reduced perfusion.

^{123}I-labeled 15-(*p*-iodophenyl)-3-(*R,S*)-methylpentadecanoic acid (BMIPP) is an imaging radiopharmaceutical, which reflects fatty acid metabolism.[1–6] Several investigators reported that a combination study of myocardial perfusion (^{201}Tl, ^{99m}Tc-MIBI, or ^{99m}Tc-tetrofosmin) and fatty acid metabolism (^{123}I-BMIPP) is useful to estimate myocardial viability. When a mismatch phenomenon exists in area at risk (less BMIPP accumulation than perfusion), functional recovery is expected.[1–3,7–12] In other words, since the mismatch area of myocardial perfusion and fatty acid metabolism is viable, even jeopardized, cardiac events may occur in this area in the future.[12] These studies suggest that recovery of fatty acid metabolism will lag behind the recovery of myocardial perfusion. We hypothesize that ^{123}I-BMIPP can depict an

Received May 31, 2002, revision accepted October 24, 2002.
For reprint contact: Teruhito Mochizuki, M.D., Department of Radiology, Ehime University School of Medicine, Shitsukawa, Shigenobu-cho, Onsen-gun, Ehime 791–0295, JAPAN.
E-mail: tmochi@m.ehime-u.ac.jp

area at risk as a lesion of impaired fatty acid metabolism even after successful reperfusion therapy. The ability to memorize the area at risk as an impaired fatty acid metabolism, or as a defect even after successful reperfusion therapy, can be called an ischemic memory imaging of ^{123}I-BMIPP.[6,13,14]

The purpose of this study was to clarify the incidence of the ischemic "memory image" of ^{123}I-BMIPP in a region of acute myocardial infarction (AMI) by comparing ^{99m}Tc-pyrophosphate (PYP) and ^{201}Tl dual-isotope single photon emission computed tomography (SPECT).

MATERIALS AND METHODS

Patients and Study Protocol

Materials consisted of 14 patients with AMI and 20 patients with old myocardial infarction (OMI in this study: more than 3 months from the onset of AMI). There were 7 antero(-septal) AMI and 7 interior AMI (11 males and 3 females). There were 7 antero(-septal) OMI, 11 interior OMI, and 2 lateral OMI (16 males and 4 females). All of the 14 AMI lesions were confirmed with clinical symptoms, EKG changes, increase in creatinine kinase-MB, and positive ^{99m}Tc-PYP and ^{201}Tl dual-isotope SPECT (PYP was positive in all 14 patients). All AMI patients received successful primary reperfusion therapy. All AMI patients underwent PYP/Tl dual-isotope SPECT within 1 week from the onset, and BMIPP SPECT within 1 week after PYP/Tl dual-isotope SPECT. All of the 20 OMI lesions were confirmed with a clinical history of AMI and rest ^{201}Tl SPECT. All OMI patients underwent both BMIPP and rest ^{201}Tl SPECT within two weeks during a stable condition.

All patients received oral and written information about the routine tests performed in this study and gave written informed consent.

^{123}I-BMIPP SPECT

^{123}I-BMIPP (111 MBq) was injected intravenously. Thirty minutes later, the data were acquired by means of a 3-head camera with low-energy high-resolution collimators (GCA-9300A, Toshiba, Inc., Tokyo, Japan). The photopeak was 160 keV with a 20% window for ^{123}I. The data acquisition parameters were 40 sec/step in 20 steps × 3 detectors (13 min, 60 steps in all). The matrix was 64 × 64 and the zooming factor was 1.5. Transaxial slices were reconstructed by filtered back-projection with a Butterworth filter (order = 8, 0.15 cycle/pixel). Transaxial images were reoriented to short and long cardiac axes. The image processor was a GMS-550u (Toshiba, Inc., Tokyo, Japan).

^{99m}Tc-Pyrophosphate/^{201}Tl Dual Isotope SPECT

^{99m}Tc-pyrophosphate (370 MBq) was injected intravenously. Two hours later, ^{201}Tl (111 MBq) was injected intravenously during resting condition. Fifteen minutes after the Tl injection, the data were acquired with a dual-isotope mode. Photopeaks were 140 keV for ^{99m}Tc and 71 keV for ^{201}Tl both with 20% window. The data acquisition

Table 1 Extent and severity scores of BMIPP and Tl

Extent of the defect	Severity of the defect
0 = no defect	0 = no defect
1 = small	1 = mild
2 = intermediate	2 = intermediate
3 = large	3 = severe

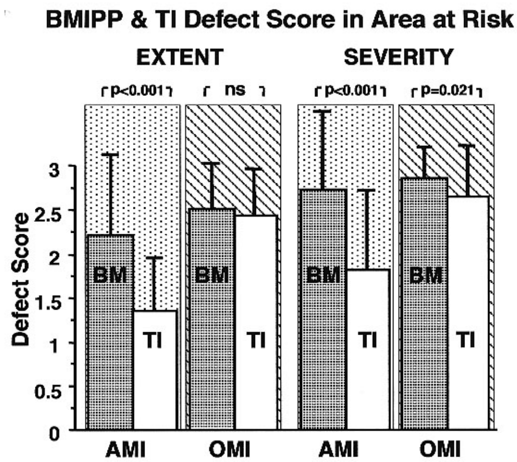

Fig. 1 Comparison of extent and severity scores of ^{123}I-BMIPP and ^{201}Tl in AMI and OMI groups. Both extent and severity scores of BMIPP were significantly higher than those of ^{201}Tl in AMI group ($p < 0.001$). In OMI group, only severity score of BMIPP was higher than that of ^{201}Tl ($p = 0.021$).

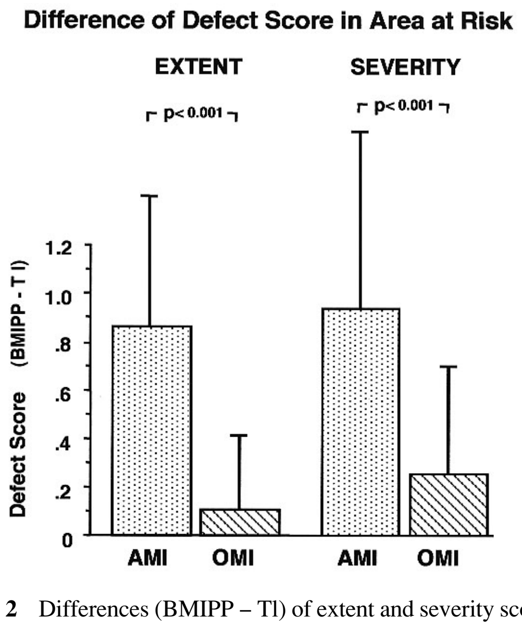

Fig. 2 Differences (BMIPP – Tl) of extent and severity scores in AMI group and OMI groups. Both differences of extent and severity scores (BMIPP – Tl) were greater in AMI patients, than those in OMI patients.

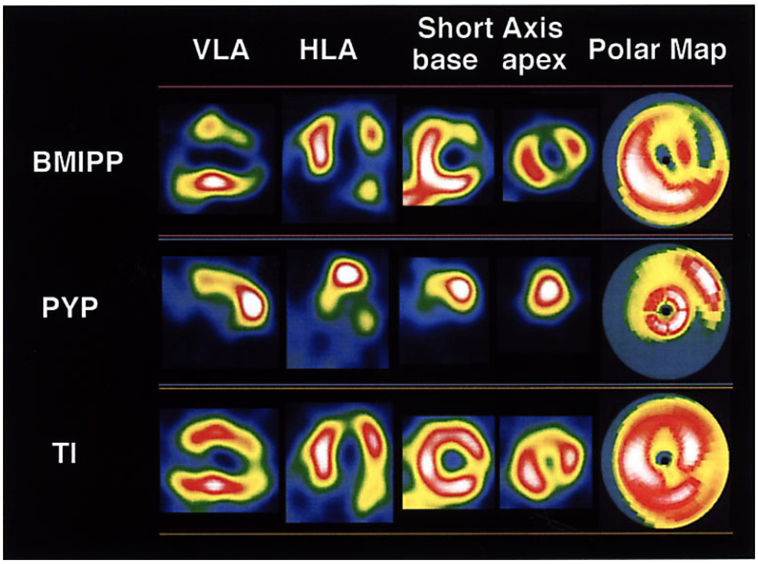

Fig. 3 Representative antero-lateral AMI patient (62-year-old man). ^{99m}Tc-pyrophosphate accumulation (middle row: 3 days after onset) is concordant with the defect of ^{123}I-BMIPP (*upper row:* 9 days after onset). Defect area (extent) and severity of BMIPP (score 2 and 3, respectively) are larger and greater than those of Tl (*lower row:* 3 days after onset) (score 1 and 1, respectively).
Abbreviations: PYP, ^{99m}Tc-pyrophosphate; VLA, vertical long axis; HLA, horizontal long axis; SA, short axis.

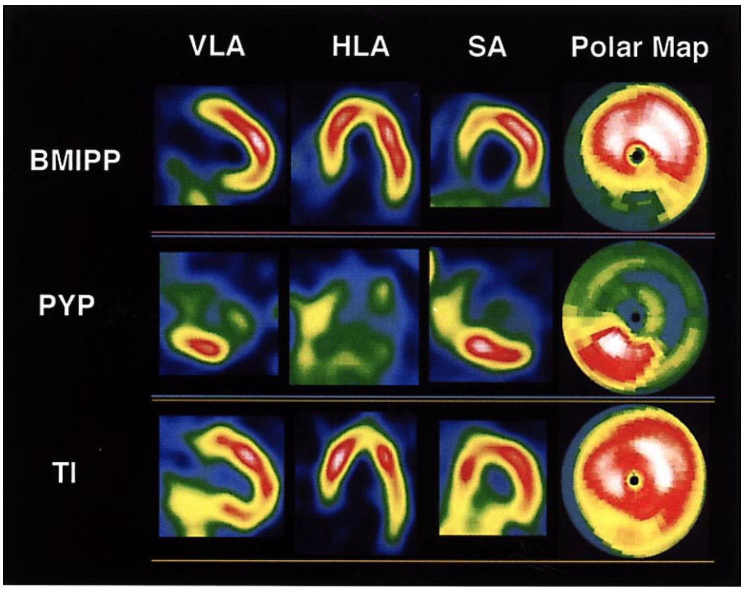

Fig. 4 Representative inferior AMI patient (49-year-old man). ^{99m}Tc-pyrophosphate accumulation (*middle row:* 4 days after onset) is concordant with the defect of ^{123}I-BMIPP (10 days after onset). Defect area (extent) and severity of BMIPP (*upper row*) (score 2 and 3, respectively) are larger and greater than those of Tl (*lower row*) (score 1 and 2, respectively).
Abbreviations: PYP, ^{99m}Tc-pyrophosphate; VLA, vertical long axis; HLA, horizontal long axis; SA, short axis.

parameters were 30 sec/step in 20 steps × 3 detectors (10 min, 60 steps in all). The matrix was 64 × 64 and the zooming factor was 1.5. Transaxial slices were reconstructed by filtered back-projection with a Butterworth filter (order = 8, 0.15 cycle/pixel). Transaxial images were reoriented to short and long cardiac axes. The SPECT system and the processor were the same as in the BMIPP study.

Data Analysis

In each AMI lesion, accumulation of ^{99m}Tc-PYP and defect of BMIPP were visually evaluated, by agreement between two experienced nuclear medicine physicians, as to whether they are concordant.

In AMI patients, we evaluated the area at risk, where ^{99m}Tc-PYP SPECT was positive. In OMI patients, we evaluated the OMI lesion, where Tl SPECT depicted a perfusion defect. To simplify the interpretation of the results, we did not analyze the remote (non-AMI or non-OMI) area in this study. The extent and severity of the defect of BMIPP and Tl were visually scored into four grades; 0 = no defect, 1 = small or mild defect, 2 = intermediate defect and 3 = large or severe defect (Table 1). The extent and severity scores for Tl and BMIPP in AMI and OMI groups were compared.

Differences (BMIPP – Tl) between AMI and OMI groups in extent and severity scores were also compared.

Statistical Analysis

Values were expressed as the mean ± SD. The mean extent and severity scores for Tl and BMIPP were analyzed by two-tailed Student's t-test. Mean differences in extent and severity scores (BMIPP – Tl) in AMI and OMI groups were also compared by means of the two-tailed Student's t-test. $P < 0.05$ was considered as significant.

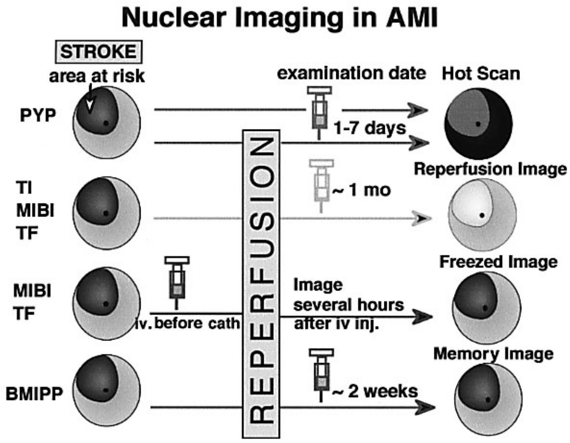

Fig. 5 Concepts of various kinds of nuclear imaging techniques in acute phase were summarized in relation to reperfusion therapy. ^{99m}Tc-pyrophosphate (PYP) can image AMI lesion up to 7 (or 10) days after onset regardless to reperfusion therapy (*upper row*). Myocardial perfusion scintigraphy using ^{201}Tl, ^{99m}Tc-MIBI or ^{99m}Tc-tetrofosmin after reperfusion (reperfusion image) reflects myocardial perfusion at injection (not the status before reperfusion). The ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin can depict area at risk when injected before reperfusion therapy and scanned after reperfusion therapy. This phenomenon is called "frozen image." ^{123}I-BMIPP can depict area at risk as a defect even after successful reperfusion therapy. This phenomenon is called "Memory Image."

RESULTS

Positive PYP lesions and defects in the BMIPP were concordant in 13/14 patients. In 1 patient, the area at risk (positive PYP lesion) was so small that neither BMIPP nor Tl could depict the lesion. Therefore, in AMI, an ischemic memory image was observed in 13/14 (93%) lesions (= patients). Whereas in OMI, the extent of Tl and BMIPP defects were visually concordant in all lesions, so that the incidence of the ischemic memory image was 0/20 (0%).

In the AMI group, the extent score of BMIPP (2.21 ± 0.89) was higher than that of ^{201}Tl (1.36 ± 0.63) ($p < 0.001$); and the severity score of BMIPP (2.71 ± 0.83) was also higher than that of ^{201}Tl (1.79 ± 0.89) ($p < 0.001$) (Fig. 1).

In the OMI group, the extent scores of BMIPP (2.50 ± 0.51) and ^{201}Tl (2.40 ± 0.50) were not significantly different, but the severity score of BMIPP (2.85 ± 0.37) was slightly higher than that of ^{201}Tl (2.60 ± 0.60) ($p = 0.021$) (Fig. 1).

Difference in the extent score (BMIPP – Tl) in the AMI group was greater (0.86 ± 0.54) than that in the OMI group (0.10 ± 0.31, $p < 0.001$) (Fig. 2). Difference in the severity score (BMIPP – Tl) in the AMI group was also greater (0.93 ± 0.73) than that in the OMI group (0.25 ± 0.44, $p < 0.001$) (Fig. 2).

Among the 13 available AMI lesions, wall motion improved in 9 lesions on follow up for about 6 months.

Two typical cases of antero-lateral and inferior AMI are shown in Figures 3 and 4, respectively.

DISCUSSION

The ^{123}I-BMIPP depicted 13 out of 14 AMI lesions when compared to a PYP hot scan. The results indicate that the ischemic "memory image" was observed in 93% (13/14). Because BMIPP missed only one small successfully reperfused AMI lesion, the ischemic "memory image" can reliably be used in the evaluation of an area at risk after successful reperfusion therapy for up to two weeks, when patients become stable.

^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin can depict areas at risk when injected intravenously before reperfusion therapy and imaged after the reperfusion therapy. Since washout of ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin is negligible in most of practical cases, the image after reperfusion still reflects the perfusion at the time of injection. This phenomenon is called "frozen image." Kawai, et al.[15] investigated 65 patients with AMI, who underwent both ^{99m}Tc-tetrofosmin ("frozen image") before revascularization therapy and ^{123}I-BMIPP ("memory image") 1 week after the therapy. Among a total of 1,300 segments (20 segments × 65 patients), the BMIPP defect score was identical to the tetrofosmin score in 1,156 segments (88.9%), using a 4-point grading system. They concluded that BMIPP imaging at 1 week post AMI can identify areas at risk similarly to tetrofosmin perfusion imaging in the acute phase. Their report supports our hypothesis that ^{123}I-BMIPP can depict an area at risk as a lesion of impaired fatty acid metabolism even after successful reperfusion therapy.

In the AMI group, both the extent and severity scores of BMIPP were greater than those of Tl. On the other hand, in the OMI group, the extent scores of BMIPP and Tl were not significantly different. Only the severity score of BMIPP was slightly greater than that of Tl. This suggests that impairment of fatty metabolism compared to the perfusion may be prolonged in the jeopardized myocardium in OMI. Nevertheless, the magnitude of differences both in extent and severity scores (BMIPP – Tl) was much greater in the AMI group than in the OMI group. This means that "memory image" is a mismatch phenomenon between rescued perfusion and impaired fatty metabolism, which can be enhanced in the acute phase of myocardial infarction. The mismatch between BMIPP and Tl in patients after reperfusion therapy is reported by several investigators as a predictor of functional improvement of the stunned myocardium.[7–12]

Although ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin can depict an area at risk by utilizing the "frozen image," it is annoying and difficult to schedule the study in the acute phase. On the other hand, fatty acid metabolism by BMIPP can depict an area at risk at least for 2 weeks, even after successful reperfusion therapy. Therefore, the ischemic "memory image" is more practical for assessing the area at risk in the clinical setting. Tanaka et al. investigated the time course of myocardial perfusion after primary reperfusion therapy for AMI with ^{99m}Tc-tetrofosmin, comparing the BMIPP study.[16] In their study, the risk areas depicted by ^{99m}Tc-tetrofosmin before the reperfusion therapy were very close to that by BMIPP. Further study is necessary to clarify the duration that the ischemic "memory image" is document. Concepts of various kinds of nuclear imaging techniques in the acute phase were summarized in relation to reperfusion therapy (Fig. 5).

The ischemic "memory image" observes the same phenomenon of mismatch between myocardial perfusion and fatty acid metabolism from a different standpoint. Nevertheless, the term ischemic "memory image," is easier to memorize than the "frozen image" of the technetium agents (MIBI and tetrofosmin), and it is easy to understand the mechanism by which the recovery of fatty acid metabolism will lag behind the recovery of myocardial perfusion in patients with AMI.

In most reports, the usefulness of the mismatch in the assessment of the area at risk has been investigated by comparing BMIPP with Tl (MIBI or tetrofosmin). In this study, we investigated the incidence of the ischemic "memory image" of BMIPP by comparing BMIPP with ^{99m}Tc-PYP, a positive agent for AMI lesions, as matched areas.

Recovery of BIMPP uptake in the chronic phase (3 to 12 months) was not evaluated in this study, since only 3 patients received BMIPP study during the period. Ito et al. investigated the time course of BMIPP uptake in 10 patients with stunned myocardium.[17] They reported that the BMIPP accumulation dynamically changes over the acute, subacute, and chronic phases. The term ischemic memory image can be used for impaired myocardium in patients with AMI within 2 weeks from the onset, and can also be used for an ischemic episode without myocardial infarction[18]; but should not be used for perfusion/metabolism matched defects in OMI.

CONCLUSION

The ischemic "memory image" is the ability of ^{123}I-BMIPP to memorize the area at risk for a couple of weeks, even after reperfusion therapy. The ischemic "memory image" obtained by BMIPP is a common phenomenon (93%) in patients with AMI after reperfusion therapy and helpful in evaluating the area of damaged myocardium in the acute phase even after normalized or successful reperfusion therapy.

ACKNOWLEDGMENT

We acknowledge the clinical cooperation in patient management of the cardiologists in the Department of Cardiology and technical assistance of the nuclear medicine technologists in Ehime Imabari Hospital and Ehime University Hospital.

REFERENCES

1. Nishimura T, Sago M, Kihara K, Oka H, Shimonagata T, Katabuchi T, et al. Fatty acid myocardial imaging using ^{123}I-beta-methyl-iodophenyl pentadecanoic acid (BMIPP): comparison of myocardial perfusion and fatty acid utilization in canine myocardial infarction (occlusion and reperfusion model). *Eur J Nucl Med* 1989; 15: 341–345.
2. Nishimura T, Nishimura S, Kajiya T, Sugihara H, Kitahara K, Imai K, et al. Prediction of functional recovery and prognosis in patients with acute myocardial infarction by ^{123}I-BMIPP and ^{201}Tl myocardial single photon emission computed tomography: a multicenter trial. *Ann Nucl Med* 1998; 12: 237–248.
3. Hasegawa S, Kusuoka H, Fukuchi K, Hori M, Nishimura T. Estimation of the area at risk in myocardial infarction of rats by means of I-123 beta-methyliodophenyl pentadecanoic acid imaging. *Ann Nucl Med* 2000; 14: 347–352.
4. Knapp FF Jr, Kropp J. BMIPP-design and development. *Int J Card Imaging* 1999; 15: 1–9.
5. Kropp J, Eisenhut M, Ambrose KR, Knapp FF Jr, Franke WG. Pharmacokinetics and metabolism of the methyl-branched fatty acid (BMIPP) in animals and humans. *J Nucl Med* 1999; 40: 1484–1491.
6. Tamaki N, Morita K, Tsukamoto E, Kawai Y. Future aspects of BMIPP. *Int J Card Imaging* 1999; 15: 79–89.
7. Franken PR, De Geeter F, Dendale P, Demoor D, Block P,

Bossuyt A. Abnormal free fatty acid uptake in subacute myocardial infarction after coronary thrombolysis: correlation with wall motion and inotropic reserve. *J Nucl Med* 1994; 35: 1758–1765.
8. Knapp FF Jr, Franken P, Kropp J. Cardiac SPECT with iodine-123-labeled fatty acids: evaluation of myocardial viability with BMIPP. *J Nucl Med* 1995; 36: 1022–1030.
9. Hashimoto A, Nakata T, Tsuchihashi K, Tanaka S, Fujimori K, Iimura O. Postischemic functional recovery and BMIPP uptake after primary percutaneous transluminal coronary angioplasty in acute myocardial infarction. *Am J Cardiol* 1996; 77: 25–30.
10. Franken PR, Dendale P, De Geeter F, Demoor D, Bossuyt A, Block P. Prediction of functional outcome after myocardial infarction using BMIPP and sestamibi scintigraphy. *J Nucl Med* 1996; 37: 718–722.
11. Nakata T, Hashimoto A, Eguchi M. Cardiac BMIPP imaging in acute myocardial infarction. *Int J Card Imaging* 1999; 15: 21–26.
12. Tamaki N, Tadamura E, Kudoh T, Hattori N, Yonekura Y, Nohara R, et al. Prognostic value of iodine-123 labelled BMIPP fatty acid analogue imaging in patients with myocardial infarction. *Eur J Nucl Med* 1996; 23: 272–279.
13. Tamaki N, Tadamura E, Kudou T, Hattori N, Inubushi M, Konishi J. Recent advances in nuclear cardiology in the study of coronary artery disease. *Ann Nucl Med* 1997; 11: 55–66.
14. Tamaki N, Kuge Y, Tsukamoto E. Clinical roles of perfusion and metabolic imaging. *J Cardiol;* 2001; 37 (Suppl 1): 57–64.
15. Kawai Y, Tsukamoto E, Nozaki Y, Kishino K, Kohya T, Tamaki N. Use of ^{123}I-BMIPP single-photon emission tomography to estimate areas at risk following successful revascularization in patients with acute myocardial infarction. *Eur J Nucl Med* 1998; 25: 1390–1395.
16. Tanaka R, Nakamura T. Time course evaluation of myocardial perfusion after reperfusion therapy by ^{99m}Tc-tetrofosmin SPECT in patients with acute myocardial infarction. *J Nucl Med* 2001; 42: 1351–1358.
17. Ito K, Sugihara H, Kawasaki T, Katoh S, Azuma A, Nakagawa M. Dynamic changes in cardiac fatty acid metabolism in the stunned human myocardium. *Ann Nucl Med* 2001; 15: 343–350.
18. Kawai Y, Tsukamoto E, Nozaki Y, Morita K, Sakurai M, Tamaki N. Significance of reduced uptake of iodinated fatty acid analogue for the evaluation of patients with acute chest pain. *J Am Coll Cardiol* 2001; 38: 1888–1894.