

Impaired myocardial fatty acid metabolism detected by ^{123}I -BMIPP in patients with unstable angina pectoris: Comparison with perfusion imaging by $^{99\text{m}}\text{Tc}$ -sestamibi

Yasuchika TAKEISHI, Hiroyasu SUKEKAWA, Haruo SATTO, Shozo NISHIMURA, Takayuki SHIBU, Yasuhiko SASAKI and Hitonobu TOMOIKE

*Divisions of Cardiology and Radiology, Ishinomaki Red Cross Hospital
First Department of Internal Medicine, Yamagata University School of Medicine*

The present study was undertaken to determine the potential diagnostic value of ^{123}I -BMIPP scintigraphy for the detection of altered myocardial fatty acid metabolism in patients with unstable angina. Both myocardial metabolic imaging with ^{123}I -BMIPP and perfusion imaging with $^{99\text{m}}\text{Tc}$ -sestamibi were performed at rest in 28 patients with unstable angina in the pain-free state. The regional uptakes of ^{123}I -BMIPP or $^{99\text{m}}\text{Tc}$ -sestamibi were scored semiquantitatively (0 = normal, 4 = no activity) and compared with the coronary arteriographic findings. Decreased uptakes of ^{123}I -BMIPP were observed in 18 patients, and 11 patients had abnormal $^{99\text{m}}\text{Tc}$ -sestamibi images. Defect scores of ^{123}I -BMIPP were larger than those of $^{99\text{m}}\text{Tc}$ -sestamibi (7.8 ± 2.1 vs. 5.2 ± 1.9 , $p < 0.01$). The sensitivity for the detection of patients with unstable angina was higher in ^{123}I -BMIPP than in $^{99\text{m}}\text{Tc}$ -sestamibi (77% vs. 45%, $p < 0.01$). The site of the decreased ^{123}I -BMIPP uptake corresponded to the most stenotic coronary artery lesion in all patients.

Fatty acid metabolic imaging with ^{123}I -BMIPP was more sensitive for detecting myocardial ischemia than perfusion imaging with $^{99\text{m}}\text{Tc}$ -sestamibi. ^{123}I -BMIPP may be a clue to define the culprit lesion in unstable angina and be helpful to decide the best treatment and guide coronary angioplasty.

Key words: ^{123}I -BMIPP, $^{99\text{m}}\text{Tc}$ -sestamibi, unstable angina

INTRODUCTION

IN UNSTABLE ANGINA, there is a significant 1-year mortality rate and a high incidence of myocardial infarction.¹ The diagnosis of the presence and extent of myocardial ischemia in patients with unstable angina is important, because this diagnosis carries with it the imminent danger of acute myocardial infarction or sudden death. A 12-lead electrocardiography is generally used for the detection of myocardial ischemia.² Although electrocardiographic ischemic changes are considered to be the major indicator of myocardial ischemia, these changes are not sensitive enough for the satisfactory diagnosis.³⁻⁶ A noninvasive approach for the assessment of the presence and severity

of myocardial ischemia is desirable, since a provocation test, such as exercise or pharmacologic stress, is usually contraindicated in unstable angina. Recently, myocardial perfusion imaging with thallium-201 (^{201}Tl)^{3,7,8} or technetium-99m methoxy-isobutyl-isonitrile ($^{99\text{m}}\text{Tc}$ -sestamibi)⁴⁻⁶ has been used for the diagnosis of unstable angina. $^{99\text{m}}\text{Tc}$ -sestamibi perfusion imaging is a reliable diagnostic tool for the noninvasive detection of myocardial ischemia and the identification of the involved coronary artery stenoses, but perfusion imaging often yields false negative results when the isotope is injected in the pain-free state.³⁻⁵

In the fasting state, fatty acids account for more than 70% of myocardial energy requirements at rest under normal aerobic conditions. With positron emission tomography, ^{11}C -palmitate has been used for the evaluation of myocardial fatty acid metabolism.^{9,10} For practical purposes, single photon emitting radionuclides that can assess myocardial metabolism have long been desired.¹¹⁻¹⁸

Received February 13, 1995, revision accepted April 20, 1995.

For reprint contact: Yasuchika Takeishi, M.D., First Department of Internal Medicine, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-23, JAPAN.

Recently, iodine-123 beta-methyl-iodophenyl-pentadecanoic acid (^{123}I -BMIPP) has been developed and used as a tracer for myocardial fatty acid metabolism.^{19,20}

The goal of the present study was to evaluate the potential diagnostic value of ^{123}I -BMIPP at rest in patients with unstable angina. We hypothesized that fatty acid metabolic imaging was more sensitive than perfusion imaging for the detection of myocardial ischemia. To test this hypothesis, myocardial single photon emission computed tomography (SPECT) with both ^{123}I -BMIPP and $^{99\text{m}}\text{Tc}$ -sestamibi were performed at rest during the pain-free period in patients with unstable angina.

MATERIALS AND METHODS

Subjects and study protocol

All patients with suspected unstable angina admitted to the coronary care unit of Ishinomaki Red Cross Hospital from April, 1993 to June, 1994 were enrolled. Chest pain suggestive of myocardial ischemia had to occur within one week before admission. The exclusion criteria consisted of a previous well documented myocardial infarction, known coronary anatomy, previous coronary angioplasty or aortocoronary bypass surgery and refused consent. Blood levels of total creatine kinase and its MB fraction were obtained on admission and every 6 hr for 48 hr. Patients with acute myocardial infarction determined by a doubling of the creatine kinase levels with the presence of MB fraction or the appearance of a new Q wave were also excluded from the present study.

During this period, 39 patients with suspected unstable angina were admitted and satisfied the criteria. All patients were treated with nitroglycerin, heparin, aspirin, beta blockers or calcium antagonists. However, in 11 out of these 39 patients, medical therapy was unsuccessful in controlling chest pain, and angiography was performed without scintigraphy. Therefore, 28 patients were examined in the present study. The subjects consisted of 18 male and 10 female with a mean age of 69 years.

After receiving medication and controlling chest pain, scintigraphy was performed at rest in the pain-free state. Myocardial perfusion imaging with $^{99\text{m}}\text{Tc}$ -sestamibi was performed 1 to 3 days after admission and myocardial fatty acid metabolic imaging with ^{123}I -BMIPP was obtained 2 days after the $^{99\text{m}}\text{Tc}$ -sestamibi imaging, because $^{99\text{m}}\text{Tc}$ was always available in our laboratory. Written informed consent was obtained from all subjects. The study protocol was approved by the Committee of Human Research of Ishinomaki Red Cross Hospital.

Myocardial perfusion imaging with $^{99\text{m}}\text{Tc}$ -sestamibi

A dose of 740 MBq of $^{99\text{m}}\text{Tc}$ -sestamibi was administered intravenously in the resting supine position after an overnight fast. Data acquisition was carried out 1 hr after the $^{99\text{m}}\text{Tc}$ -sestamibi injection. All studies were obtained on a large field-of-view rotating gamma camera (Siemens,

ZLC-7500 DIGITRAC) equipped with a parallel-hole, high-resolution collimator. Energy discrimination was provided by a 20% window centered at 140 keV.²¹ Thirty-two images were obtained over a 180-degree arc from the 30-degree right anterior oblique to the 60-degree left posterior oblique position. Each image was accumulated for 30 seconds. The data were stored on a 64×64 matrix. Data processing was performed on a nuclear medicine computer system (Shimadzu, Scintipac-700). A series of contiguous transaxial images of 6 mm thickness were reconstructed by means of a filtered back-projection algorithm without attenuation correction. These transaxial images were then oriented in the short axis, vertical long axis, and horizontal long axis of the left ventricle.²²

Myocardial metabolic imaging with ^{123}I -BMIPP

After an overnight fast, a dose of 148 MBq of ^{123}I -BMIPP was injected intravenously in the resting supine position. The patients were carefully repositioned by a laser positioning device at the same position as in the $^{99\text{m}}\text{Tc}$ -sestamibi studies. Data acquisition was performed 20 min after the injection of ^{123}I -BMIPP. The process of image acquisition was the same as for $^{99\text{m}}\text{Tc}$ -sestamibi with the following exceptions²³: 1) the imaging time per projection was 40 sec; and 2) a 20% window was centered at the 159 keV photopeak of ^{123}I . The accumulated data were processed in a manner identical to that for the $^{99\text{m}}\text{Tc}$ -sestamibi studies.

Image interpretation

The distribution of $^{99\text{m}}\text{Tc}$ -sestamibi and ^{123}I -BMIPP in the myocardium was analyzed in the three standard orthogonal tomographic imaging planes as follows: the anterior, septal, inferior, and lateral regions in the short axis view; the anterior, apical, and inferior regions in the vertical long axis view; and the septal, apical, and lateral regions in the horizontal long axis view.²⁴ The left ventricular myocardium was divided into 9 segments by splitting the anterior, septal, inferior, and lateral walls into a basal and apical segment, including an extra segment for the apex.^{25,26} The anterior, septal and apical walls were assumed to represent the territory of the left anterior descending artery; the inferior wall, the territory of the right coronary artery; and the lateral wall, the left circumflex artery territory. The images were interpreted by two independent observers who were unaware of the clinical history and the angiographic findings of the patients. A 5-point scoring system was used for evaluating the myocardial uptakes of the tracer^{25,26}: 0 = normal, 1 = slightly reduced, 2 = moderately reduced, 3 = severely reduced, 4 = no activity. Scores of ≥ 2 were considered to be significant. The grading was settled by consensus between the two observers. When they disagreed on the results, the third observer reviewed the images, and his judgment was chosen.

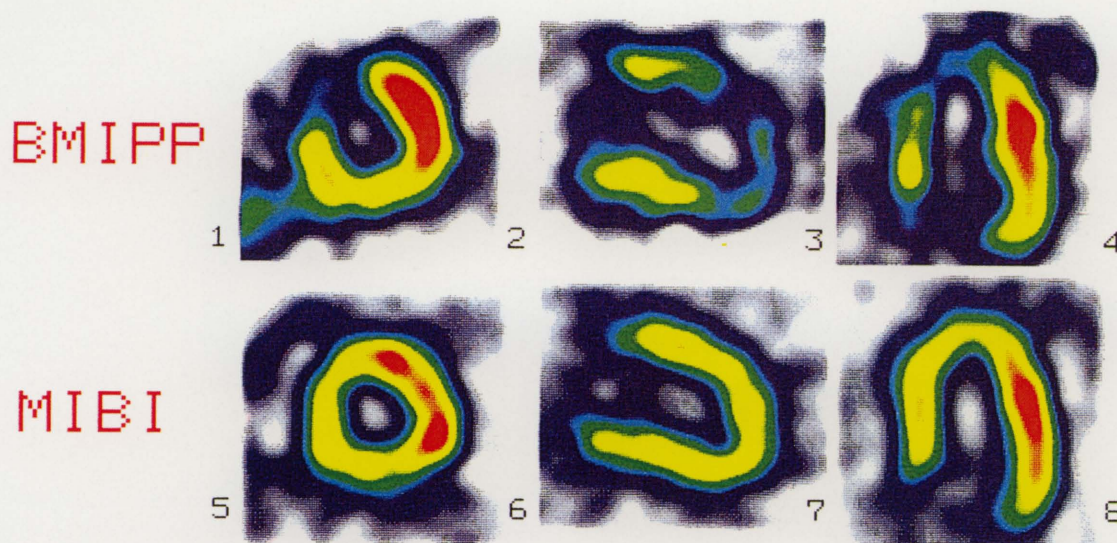


Fig. 1 A 69-year-old male with unstable angina pectoris who had a coronary stenosis of 90% in the proximal left anterior descending artery. Left, middle and right images are short axis, vertical long axis and horizontal long axis planes of the left ventricular myocardium, respectively. ^{123}I -BMIPP uptake was markedly reduced in the anterior, septal, and apical regions of the left ventricle. In $^{99\text{m}}\text{Tc}$ -sestamibi images, the decreased perfusion was not observed.

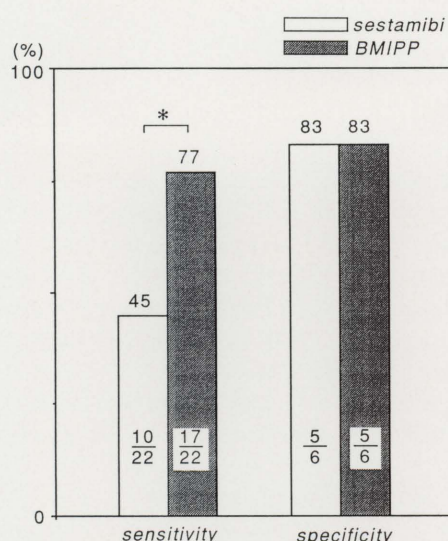


Fig. 2 The sensitivity and specificity for the detection of patients with unstable angina. * $p < 0.01$.

Echocardiography

Two-dimensional echocardiography was performed on admission for the assessment of left ventricular wall motion by an experienced cardiologist. Standard parasternal short- and long-axis views and an apical four-chamber view were recorded. The echocardiograms were analyzed by two independent observers who had no knowledge of the patients' clinical data. The left ventricle was divided into 5 segments in each view, and the level of segmental wall motion was scored as follows: 0 = normal, 1 = hypokinesis, 2 = akinesis, 3 = dyskinesis.

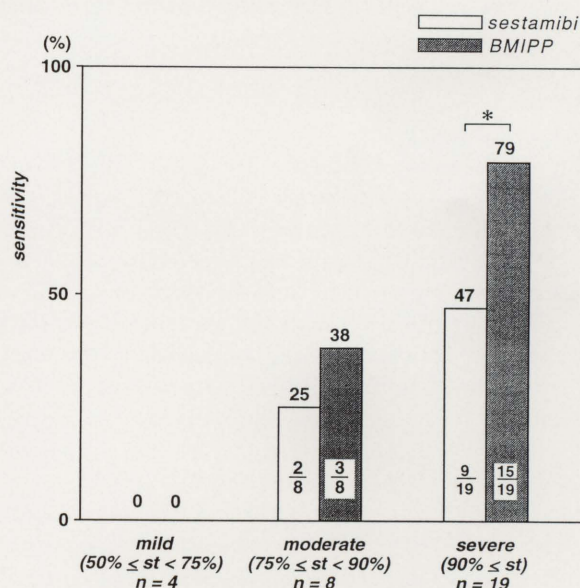


Fig. 3 Comparison of sensitivity for the detection of individual coronary artery lesion between the coronary stenoses of graded severity. * $p < 0.01$.

Coronary arteriography

Coronary arteriography was performed in multiple projections with the standard Judkins' technique. Coronary arteriograms were interpreted by 3 experienced observers unaware of the clinical conditions and scintigraphic data of the patients. Stenoses of large diagonal or marginal branches were considered as lesions of the left anterior descending artery or circumflex artery, respectively. Stenoses with $\geq 50\%$ luminal diameter reduction was considered significant.

		¹²³ I-BMIPP				
		0	1	2	3	4
^{99m} Tc-sestamibi	0	112	26	10	3	
	1	12	43	12	5	1
	2		1	9	2	2
	3			1	5	3
	4				2	3

Fig. 4 Comparison of regional defect scores between ^{99m}Tc-sestamibi and ¹²³I-BMIPP.

Statistics

Data were reported in mean \pm SD. Continuous variables were compared by Students' t-test, and the differences in proportion (categorical variables) were examined by a chi-square test. A p value < 0.05 was considered significant.

RESULTS

Case presentation

Figure 1 shows myocardial images with ¹²³I-BMIPP and ^{99m}Tc-sestamibi in a patient with unstable angina. The patient was a 69-year-old male who was admitted with worsening effort angina. In the ¹²³I-BMIPP images, decreased uptake was observed in the anterior, septal and apical regions of the left ventricle. However, myocardial uptake of ^{99m}Tc-sestamibi was homogeneous. Coronary arteriography demonstrated 90% coronary stenosis in the proximal left anterior descending artery.

Comparison with coronary arteriographic findings

Out of 28 patients, 10 patients had normal ^{99m}Tc-sestamibi and normal ¹²³I-BMIPP images, 11 patients had abnormal ^{99m}Tc-sestamibi and abnormal ¹²³I-BMIPP images, and 7 patients had normal ^{99m}Tc-sestamibi and abnormal ¹²³I-BMIPP images. Coronary arteriography revealed that significant coronary stenosis of $\geq 50\%$ was observed in 22 out of 28 patients. The sites of coronary stenosis were left anterior descending artery in 15 patients, right coronary artery in 12 patients and left circumflex artery in 4 patients. The sensitivity and specificity for the detection of patients with significant coronary stenosis are shown in Figure 2. The sensitivity of ¹²³I-BMIPP was higher than that of ^{99m}Tc-sestamibi (77% vs. 45%, $p < 0.01$), although specificity was comparable (83% vs. 83%). The regions of decreased ¹²³I-BMIPP uptake coincided topologically well with those of most severe coronary stenosis in all patients.

The sensitivity for the detection of individual coronary

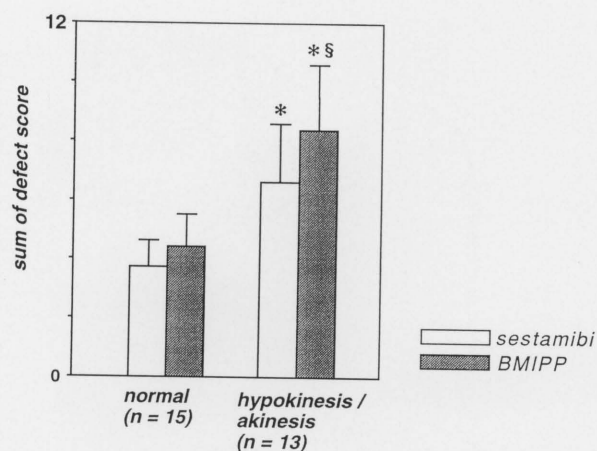


Fig. 5 Comparison of defect scores between the patients with and without a wall motion abnormality. * $p < 0.01$ vs. patients with normal wall motion. § $p < 0.01$ vs. ^{99m}Tc-sestamibi in patients with a wall motion abnormality.

stenosis was compared between the coronary stenoses of graded severity (Fig. 3). The sensitivities of ¹²³I-BMIPP and ^{99m}Tc-sestamibi were 0% and 0% with mild stenosis, 38% and 25% with moderate stenosis, and 79% and 47% with severe stenosis ($p < 0.01$, ¹²³I-BMIPP vs. ^{99m}Tc-sestamibi), respectively.

Comparison of regional ¹²³I-BMIPP and ^{99m}Tc-sestamibi uptakes

Regional ¹²³I-BMIPP uptakes in each segment were compared with those of ^{99m}Tc-sestamibi (Fig. 4). Defect scores of ¹²³I-BMIPP were concordant with those of ^{99m}Tc-sestamibi in 172 segments (69%). In 64 segments (25%), defect scores of ¹²³I-BMIPP were higher than those of ^{99m}Tc-sestamibi. ^{99m}Tc-sestamibi had higher defect scores than ¹²³I-BMIPP in only 16 segments (6%). The sum of defect scores in each patient was greater in ¹²³I-BMIPP than in ^{99m}Tc-sestamibi (7.8 ± 2.1 vs. 5.2 ± 1.9 , $p < 0.01$).

Relationship to the presence of a wall motion abnormality

Hypokinetic or akinetic wall motion abnormality was observed in 13 of 28 patients. In patients with normal wall motion, the sum of defect scores of ^{99m}Tc-sestamibi and ¹²³I-BMIPP was 3.7 ± 0.9 and 4.4 ± 1.1 , respectively (Fig. 5). In patients with a wall motion abnormality, the sum of defect scores was 6.6 ± 2.0 in ^{99m}Tc-sestamibi ($p < 0.01$, vs. normal motion) and 8.4 ± 2.2 in ¹²³I-BMIPP ($p < 0.01$, vs. normal wall motion). The sum of defect scores of ¹²³I-BMIPP was higher than that of ^{99m}Tc-sestamibi in patients with a wall motion abnormality ($p < 0.01$). The sensitivity for detecting the presence of a wall motion abnormality was 85% by ¹²³I-BMIPP and 62% by ^{99m}Tc-sestamibi ($p = \text{ns}$).

DISCUSSION

Impaired fatty acid metabolism in patients with unstable angina was detected as a decrease of myocardial uptake of ^{123}I -BMIPP. The sensitivity of ^{123}I -BMIPP for the detection of unstable angina was 77%, that is higher than that of $^{99\text{m}}\text{Tc}$ -sestamibi (45%). The site of decreased ^{123}I -BMIPP uptake corresponded to the most stenotic coronary artery in all cases, and ^{123}I -BMIPP imaging identified the left ventricular wall motion abnormality in 85% of patients.

In the present study, 6 patients without significant coronary artery stenosis were included. The presence of a coronary artery spasm might be related to the occurrence of chest pain in these patients. Induction of a coronary artery spasm by intracoronary injection of acetylcholine was performed in only 2 of 6 patients, and a spasm was not induced in these patients.

A noninvasive evaluation of myocardial metabolism in addition to perfusion has long been desired. ^{123}I -BMIPP has been applied to clinical as well as experimental studies for the assessment of myocardial fatty acid metabolism.^{23,27-30} ^{123}I -BMIPP has the following favorable biological properties for myocardial SPECT imaging^{19,20}: 1) high uptake and prolonged retention in the myocardium; 2) relatively higher heart-to-background count ratio; and 3) rapid blood clearance. ^{123}I -BMIPP is not metabolized by beta-oxidation but is trapped into the triglyceride fraction in the myocardium. Although, ^{123}I -BMIPP is not an ideal tracer for myocardial fatty acid metabolism, the myocardial accumulation of ^{123}I -BMIPP is associated with triglyceride synthesis, which in part reflects fatty acid utilization and depends on the level of adenosine triphosphate concentration in the myocardium.²⁸ The safety and potential usefulness of this isotope have now been confirmed clinically in patients with myocardial infarction,²⁹ stable angina pectoris,³⁰ and cardiomyopathy,²³ but not in those with unstable angina.

Two radiopharmaceutical agents, ^{201}Tl and $^{99\text{m}}\text{Tc}$ -sestamibi, are currently available for myocardial perfusion imaging. The characteristics of $^{99\text{m}}\text{Tc}$ -sestamibi make this agent more appropriate than ^{201}Tl for emergency use. $^{99\text{m}}\text{Tc}$ is produced with a generator and is more readily available than ^{201}Tl . Furthermore, $^{99\text{m}}\text{Tc}$ -sestamibi shows minimal redistribution and its properties allow the delayed imaging acquisition after tracer administration. Scintigraphic acquisition does not prevent any delay in the initiation of medical treatment. This has important implications in patients with unstable angina in whom immediate medical therapy is required. Gregoire and Theroux have reported high accuracy of $^{99\text{m}}\text{Tc}$ -sestamibi studies for the detection of coronary artery disease in patients with unstable angina.⁴ $^{99\text{m}}\text{Tc}$ -sestamibi SPECT has a sensitivity of 96% during a episode of chest pain, that is much higher than that of electrocardiography (35%). $^{99\text{m}}\text{Tc}$ -sestamibi is also useful to rule out acute

myocardial ischemic events in patients with nondiagnostic electrocardiograms.⁶ However, sensitivity of $^{99\text{m}}\text{Tc}$ -sestamibi in unstable angina decreased to 65% in the pain-free state.^{4,5}

Extensive reports have shown that fatty acid metabolism is altered in the ischemic myocardium.^{9-18,29,30} In patients with unstable angina, repeated episodes of transient ischemia may result in the depletion of fatty acid metabolism. However, metabolic state of the diseased myocardium in patients with unstable angina has not been rigorously examined. We showed that decreased uptakes of ^{123}I -BMIPP were more frequently observed than those of $^{99\text{m}}\text{Tc}$ -sestamibi, and the reduction of ^{123}I -BMIPP uptake was more extensive in most patients. The sensitivity for unstable angina was higher in ^{123}I -BMIPP than in $^{99\text{m}}\text{Tc}$ -sestamibi, although $^{99\text{m}}\text{Tc}$ -sestamibi studies were performed before ^{123}I -BMIPP scans. These findings suggest that in patients with unstable angina impaired fatty acid metabolism, which is independent of myocardial perfusion, is present in the pain-free period, and that can be detected by ^{123}I -BMIPP SPECT at rest. Because patients in whom medical therapy was unsuccessful in controlling chest pain were excluded from the present study, it was considered that the sensitivity of 77% by ^{123}I -BMIPP was good enough. The mechanisms for the decreased ^{123}I -BMIPP uptake in the presence of normal $^{99\text{m}}\text{Tc}$ -sestamibi uptake are still controversial. The following two possible mechanisms might be suggested: 1) the repeated transient reduction of coronary blood flow lead to the depletion of fatty acid metabolism, and this post ischemic metabolic disturbance may be prolonged after the recovery of myocardial perfusion; 2) mild ischemia due to coronary artery narrowing, which is sufficient to alter myocardial metabolism, is present during the pain-free period, but this is not detected by perfusion scintigraphy with $^{99\text{m}}\text{Tc}$ -sestamibi.

In the present study, the location of decreased ^{123}I -BMIPP uptake coincided with the region of the most stenotic coronary artery. It is often difficult to determine the culprit coronary artery lesion by coronary arteriography alone in some patients with multi-vessel coronary involvement. Myocardial metabolic imaging with ^{123}I -BMIPP may be a clue to define culprit lesion, because it can provide functional information concerning the severity of myocardial ischemia. This can help to decide the best treatment and guide coronary angioplasty. Metabolic imaging with ^{123}I -BMIPP may provide a new approach for better understanding of myocardial ischemia.

REFERENCES

1. Brown K. Prognostic value of thallium-201 myocardial perfusion imaging in patients with unstable angina who respond to medical treatment. *J Am Coll Cardiol* 17: 1053-1057, 1991.
2. Oliva P. Unstable rest angina with ST-segment depression. Pathophysiologic considerations and therapeutic implica-

- tions. *Ann Int Med* 100: 424–440, 1984.
3. Wackers F, Lie K, Liem K, et al. Thallium-201 scintigraphy in unstable angina pectoris. *Circulation* 57: 738–742, 1978.
 4. Gregoire J, Theroux P. Detection and assessment of unstable angina using myocardial perfusion imaging: Comparison between technetium-99m sestamibi SPECT and 12-lead electrocardiogram. *Am J Cardiol* 66: 42E–46E, 1990.
 5. Bilodeau L, Theroux P, Gregoire J, Gagnon D, Arsenault A. Technetium-99m sestamibi tomography in patients with spontaneous chest pain: Correlations with clinical, electrocardiographic and angiographic findings. *J Am Coll Cardiol* 18: 1684–1691, 1991.
 6. Varetto T, Cantalupi D, Altieri A, Orlandi C. Emergency room technetium-99m sestamibi imaging to rule out acute myocardial ischemic events in patients with nondiagnostic electrocardiograms. *J Am Coll Cardiol* 22: 1804–1808, 1993.
 7. Gewirtz H, Beller G, Strauss H, et al. Transient defects of resting thallium scans in patients with coronary artery disease. *Circulation* 59: 707–713, 1979.
 8. Berger B, Watson D, Burwell L, et al. Redistribution of thallium at rest in patients with stable and unstable angina and the effect of coronary artery bypass surgery. *Circulation* 60: 1114–1125, 1979.
 9. Schelbert H, Phelps M, Hoffman E, Huang S, Kuhl D. Regional myocardial blood flow, metabolism and function assessed noninvasively with positron emission tomography. *Am J Cardiol* 46: 1269–1277, 1980.
 10. Lerch R, Ambos H, Bergmann S, Welch M, Ter-Pogossian M, Sobel B. Localization of viable, ischemic myocardium by positron-emission tomography with ¹¹C-palmitate. *Circulation* 64: 689–699, 1981.
 11. Van der Wall E, Heidendal G, Hollander W, Westera G, Roos J. I-123 labeled hexadecanoic acid in comparison with thallium-201 for myocardial imaging in coronary heart disease. *Eur J Nucl Med* 5: 401–405, 1980.
 12. Van der Wall E, Heidendal G, Hollander W, Westera G, Roos J. Metabolic myocardial imaging with ¹²³I-labeled heptadecanoic acid in patients with angina pectoris. *Eur J Nucl Med* 6: 391–396, 1981.
 13. Kennedy P, Corbett J, Kulkarni P, et al. Iodine 123-phenylpentadecanoic acid myocardial scintigraphy: usefulness in the identification of myocardial ischemia. *Circulation* 74: 1007–1015, 1986.
 14. Hansen C, Corbett J, Pippin J, et al. Iodine-123 phenylpentadecanoic acid and single photon emission computed tomography in identifying left ventricular regional metabolic abnormalities in patients with coronary heart disease: Comparison with thallium-201 myocardial tomography. *J Am Coll Cardiol* 12: 78–87, 1988.
 15. Vyska K, Machulla H, Stremmel W, et al. Regional myocardial free fatty acid extraction in normal and ischemic myocardium. *Circulation* 78: 1218–1233, 1988.
 16. Kropp J, Likungu J, Kirchhoff P, et al. Single photon emission tomography imaging of myocardial oxidative metabolism with 15-(p-(¹²³I)iodophenyl)pentadecanoic acid in patients with coronary artery disease and aorto-coronary bypass graft surgery. *Eur J Nucl Med* 18: 467–474, 1991.
 17. Chouraqui P, Maddahi J, Henkin R, Karesh S, Galie E, Berman D. Comparison of myocardial imaging with iodine-123-iodophenyl-9-methyl pentadecanoic acid and thallium-201-chloride for assessment of patients with exercise-induced myocardial ischemia. *J Nucl Med* 32: 447–452, 1991.
 18. Walamies M, Turjanmaa V, Koskinen M, Uusitalo A. Diagnostic value of ¹²³I-phenylpentadecanoic acid (IPPA) metabolic and thallium 201 perfusion imaging in stable coronary artery disease. *Eur Heart J* 14: 1079–1087, 1993.
 19. Knapp F, Goodman M, Ambrose K, et al. The development of radioiodinated 3-methyl-branched fatty acids for evaluation of myocardial disease by single photon techniques. In *Noninvasive imaging of cardiac metabolism*, Van der Wall EE (ed.), Dordrecht, Martinus Nijhoff Publishers, pp. 159–201, 1987.
 20. Knapp FF Jr, 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: S11–1–14, 1993.
 21. Takeishi Y, Tonooka I, Chiba J, et al. Simultaneous assessment of left ventricular wall motion and myocardial perfusion at rest and during exercise by technetium-99m methoxy isobutyl isonitrile. *Jpn Circ J* 55: 1192–1199, 1991.
 22. Takeishi Y, Chiba J, Abe S, Yamaki M, Tomoike H. Adenosine-induced heterogeneous perfusion accompanies myocardial ischemia in the presence of advanced coronary artery disease. *Am Heart J* 127: 1262–1268, 1994.
 23. 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.
 24. Dilsizian V, Arrighi J, Diodati J, et al. Myocardial viability in patients with chronic coronary artery disease. Comparison of ^{99m}Tc-sestamibi with thallium reinjection and (¹⁸F)fluorodeoxyglucose. *Circulation* 89: 578–587, 1994.
 25. Coma-Canella I, Martinez M, Rodrigo F, Beiras J. The dobutamine stress test with thallium-201 single-photon emission computed tomography and radionuclide angiography: Postinfarction study. *J Am Coll Cardiol* 22: 399–406, 1993.
 26. Takeishi Y, Abe S, Chiba J, Komatani A, Nakagawa Y, Tomoike H. Organ distribution of thallium-201 during intravenous adenosine infusion: Comparison with exercise. *Am Heart J* 127: 1268–1274, 1994.
 27. Kurata C, Kobayashi A, Yamazaki N. Dual tracer autoradiographic study with thallium-201 and radioiodinated fatty acid in cardiomyopathic hamsters. *J Nucl Med* 30: 80–87, 1989.
 28. Fujibayashi Y, Yonekura Y, Takemura Y, et al. Myocardial accumulation of iodinated beta-methyl-branched fatty acid analogue, iodine-125-15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP), in relation to ATP concentration. *J Nucl Med* 31: 1818–1822, 1990.
 29. Tamaki N, Kawamoto M, Yonekura Y, 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 analog. *J Nucl Med* 33: 659–667, 1992.
 30. Tawarahara K, Kurata C, Taguchi T, et al. Simultaneous dual myocardial imaging with iodine-123-beta-methyl iodophenyl-pentadecanoic acid (BMIPP) and thallium-201 in patients with coronary heart disease. *Jpn Circ J* 58: 107–115, 1994.