Diagnostic Value of ^{123}I -Betamethyl-p-Iodophenyl-Pentadecanoic Acid (BMIPP) Single Photon Emission Computed Tomography (SPECT) in Patients With Chest Pain

— Comparison With Rest-Stress $^{99\text{m}}\text{Tc}$ -Tetrofosmin SPECT and Coronary Angiography —

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Background Basic and clinical studies have indicated that 15-(p-[^{123}I] iodophenyl)-3-(R, S) methylpentadecanoic acid (BMIPP) single photon emission computed tomography (SPECT) can identify ischemic myocardium without evidence of myocardial infarction by the regional decline of tracer uptake. The present study compared BMIPP SPECT with rest-stress myocardial perfusion imaging (MPI) findings and coronary angiography (CAG) in 150 patients with acute chest pain.

Methods and Results Patients with acute chest pain who underwent all of the following tests were selected: MPI at rest-stress, BMIPP SPECT at rest and CAG. Organic coronary artery stenosis ($\geq 75\%$) was observed in 46 patients, 27 patients had total or subtotal coronary occlusion by spasm in the spasm provocation test on CAG and the remaining 77 patients had no significant coronary artery stenosis or spasm. The sensitivity of BMIPP at rest to detect organic stenosis was significantly higher (54%) than that of rest-MPI (33%, $p < 0.005$), but lower than that of stress-MPI (76%, $p = 0.05$). The sensitivity of BMIPP at rest to detect spasm was significantly higher (63%) than that of both rest-MPI (15%; $p < 0.001$) and stress-MPI (19%; $p < 0.001$). Overall, the sensitivity of BMIPP at rest to detect both organic stenosis and spasm was significantly higher (58%) than that of rest-MPI (26%; $p < 0.001$), despite having no significance with that of stress-MPI (55%). The specificity was not significantly different among the three imaging techniques.

Conclusion Resting BMIPP SPECT is an alternative method to stress MPI for identifying patients with not only organic stenosis but also spasm without the need for a stress examination. (Circ J 2004; 68: 547–552)

Key Words: Acute coronary syndrome; Emission computed tomography; Fatty acids; Myocardial ischemia; Rest–stress test

Myocardial perfusion imaging (MPI) is well known as an efficacious tool for evaluating patients with coronary artery disease (CAD). As $^{99\text{m}}\text{Tc}$ labeled perfusion imaging agents are now available for emergency use, MPI has become a cogent method of diagnosis of acute myocardial ischemia in the emergency ward.^{1–4}

On the other hand, MPI at rest has limited value for identifying ischemic disease, particularly when the chest pain has subsided and the imaging shows normal findings.⁴ Under those circumstances, stress MPI may be the next step for identifying coronary patients,⁵ but the stress test is often contraindicated for the patients with unstable angina,

and we hesitate to use it for elderly patients or those with suspected multivessel disease.

The iodinated fatty acid analog, 15-(p-[^{123}I] iodophenyl)-3-(R, S) methylpentadecanoic acid (BMIPP), can assess fatty acid utilization by the myocardium. Basic studies have shown that abnormal BMIPP uptake reflects metabolic alterations because of severe ischemia and therefore BMIPP single photon emission computed tomography (SPECT) can identify previous ischemia as a region(s) of reduced tracer uptake.^{6–9} Clinical studies have also indicated that BMIPP SPECT can identify ischemic myocardium without evidence of myocardial infarction^{10–14} and we have used SPECT for patients with acute coronary syndrome in order to prove its diagnostic value for identifying patients with CAD without evidence of myocardial infarction.¹⁵ The present study compared the evaluation by BMIPP SPECT of patients with acute chest pain with that of rest-stress MPI and coronary angiography (CAG).

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Table 1 Study Group

<i>n</i>	150
<i>M/F</i>	98/52
Age (years)	61±11 (30–84)
History of hypertension/therapy	98 (65%)/81
History of diabetes mellitus/therapy	45 (30%)/40
History of hyperlipidemia/therapy	52 (35%)/46
History of smoking	67 (45%)
Previous medication	45 (30%)
Single episode	79 (53%)
>20 min of chest pain	19 (13%)
Trigger of chest pain	
Effort	62
Rest	45
Not specific	43
ECG abnormality	19 (13%)
Paroxysmal atrial fibrillation	3
ST-T elevation	4
ST-T depression	12
Wall motion abnormality (UCG, LVG)	25 (17%)
LVEF (%) (UCG, LVG)	62±9 (43–85)
>75% of luminal narrowing	46 (31%)
OVD/1VD/2VD/3VD	104/24/15/7
VD involving LAD/LCX/RCA/LMT	36/21/24/2

Data are presented as number (%) or mean's (range), EF, ejection fraction; LVG, left ventriculography; UCG, ultrasonic cardiography; VD, vessel disease.

Methods

Study Population

Of 500 patients admitted to the Emergency Department because of acute chest pain from January 1998 to October 2000, this study included 150 (98 males, 52 females, aged 61±11 years (Table 1)) who underwent rest-stress ^{99m}Tc-tetrofosmin (tetrofosmin) SPECT, BMIPP SPECT and CAG. If the creatine kinase concentration was more than

twice the upper normal limit or there was positive troponin T, if there was evidence of prior myocardial infarction or coronary angioplasty or a coronary artery bypass graft surgery the patients were excluded. The hospital institutional review board approved the study and written informed consent was obtained from each patient.

Study Protocol

All patients underwent tetrofosmin SPECT at rest on admission, which was within 1–48 h after the disappearance of chest pain. Stress tetrofosmin SPECT was performed for 85 patients on the 2nd day and the remaining 65 on the 3rd day because of their unstable condition. BMIPP SPECT was performed after the stress-MPI (85 patients on the 3rd day and 65 patients on the 4th day). Thus, BMIPP results were obtained within 5 days of the last episode of chest pain. All patients underwent CAG within 6 days (mean: 3.8±1.0 days) after the last episode of chest pain. Luminal stenosis of 75% or greater was defined as a significant organic lesion. A spasm provocation test was performed in those patients who did not have significant coronary artery stenosis on CAG. After a control CAG image was obtained, 20 µg ergonovine maleate was injected into the coronary arteries. The provocation test was judged as positive only when all the following criteria were satisfied: total or subtotal coronary occlusion, significant ST-T changes on ECG and onset of chest pain.

Stress Test Protocol

The patients underwent a pharmacologic (n=91) or exercise (n=59) stress protocol based on their clinical condition. The pharmacological stress test was an intravenous infusion of ATP, at a total dose of 0.16 mg/kg per min infused over 5 min. In the exercise protocol, the age-adjusted maximal heart rate was the endpoint on an ergometer, but

Table 2 SPECT Findings

	Rest MPI			Stress MPI		BMIPP	
	<i>n</i>	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Organic stenosis	46	31	15	11	35	21	25
Spasm	27	23	4	22	5	10	17
Normal coronary artery	77	76	1	74	3	74	3
Total	150	130	20	107	43	105	45

MPI, myocardial perfusion imaging.

Fig 1. Comparison of the sensitivity and the specificity of SPECT for detecting organic stenosis or spasm.

Fig 2. (A) CAG showed severe stenosis in the regions of the right coronary artery (arrow). (B) No significant abnormal perfusion is observed on the tetrofosmin images at rest and the reduced uptake in the inferior region of tetrofosmin images on stress with ATP. The BMIPP images show severely reduced uptake in the inferior region.

other endpoints included physical exhaustion, severe angina, uncommon arrhythmia or significant hypotension. At either the endpoint of the symptom-limited bicycle ergometer exercise test or at 3 min after the ATP infusion, 740 MBq of tetrofosmin was injected; exercise was continued for a further 2 min.

Data Acquisition

SPECT images were obtained by using a dual head gamma camera (Optima; General Electric; Milwaukee, WI, USA) equipped with low-energy, general-purpose collimators.

For tetrofosmin SPECT imaging, 32 views were collected at 40 min post-injection of the tracer at 15 s/step over 180° from the right anterior oblique to the left posterior oblique projection.

For BMIPP SPECT imaging, 32 views were collected at 20 min post-injection of the tracer at 30 s/step over 180°.¹⁵

Data Analysis

The left ventricular myocardium was divided into 20 segments to visually score the tracer uptake on the SPECT images on a 4-point grading system: 0: normal uptake, 1: slightly reduced, 2: moderately reduced, 3: severely reduced. Scores of 2 and 3 were considered to be significant. Only areas that were perfused by a stenosed coronary artery with an abnormal uptake (score ≥ 2) on the SPECT images were considered as abnormal. The septal and anterior segments corresponded to the left anterior descending coronary artery (LAD), the inferior and posterior segments corresponded to the right coronary artery (RCA) and the lateral segments corresponded to the left circumflex coronary artery (LCX). Luminal stenosis $\geq 75\%$ was defined as a significant lesion. In each patient, the segmental how many people in total without prior knowledge of the clinical data.¹⁵ This was a completely blinded method.

Statistical Analysis

Data were expressed as mean $\pm$ SD. Fisher's test was used to calculate the significance of differences between individual groups. The significance of differences in inci-

dence between the groups was assessed by McNemer's test. In all tests, a p-value < 0.05 was regarded as significant.

Results

Coronary Angiography

Organic coronary artery stenosis ($\geq 75\%$) was observed in 46 patients (31%) on CAG: 24 had single vessel disease and 22 had multivessel disease; 36 patients showed significant stenosis in the LAD, 21 in the LCX, 24 in the right coronary artery (RCA), and 2 in the left main trunk (LMT).

The spasm provocation test was performed in 104 patients who did not show organic artery stenosis: 27 patients showed total or subtotal coronary occlusion with ECG changes and chest pain because of spasm (26%), 9 patients showed spasm in the LAD, 2 in the LCX and 16 in the RCA. No patients showed spasm in 2 or more coronary arteries. The remaining 77 patients (72%) did not show organic stenosis or spasm.

SPECT Findings (Table 2, Fig 1)

There were regional perfusion abnormalities in 20 patients (13%) on MPI at rest, including 15 patients with organic stenosis, 4 with spasm and 1 with a normal coronary vessels. Similarly, on stress MPI, regional perfusion abnormalities were seen in 43 patients (29%) including 35 patients with organic stenosis, 5 with spasm and 3 with normal coronary arteries. Additionally, BMIPP SPECT revealed regional abnormalities in 45 patients (30%) at rest, including 25 with organic stenosis, 17 with spasm, and 3 with normal coronary arteries. In all patients, the areas of the abnormal coronary arteries and the reduced uptake of BMIPP were the same.

The sensitivity of BMIPP at rest to detect organic stenosis (25/46=54%) was significantly higher than that of rest-MPI (15/46=33%; $p < 0.005$), but slightly lower than that of stress-MPI (35/46=76%; $p = 0.05$). The sensitivity of BMIPP at rest to detect spasm was significantly higher (17/27=63%) than that of rest-MPI (4/27=15%; $p < 0.001$) or stress-MPI (5/27=19%; $p < 0.001$). Overall, the sensitivity of BMIPP at rest to detect both organic stenosis and spasm

Fig 3. (A) After injection of ergonovine maleate into the right coronary artery, total spasm was induced (Left). After isosorbide dinitrate was injected, the spasm was completely resolved (Right). (B) No significant abnormal perfusion is observed on the rest and stress tetrofosmin images. BMIPP images show the reduced uptake in the inferior region.

was significantly higher (42/73=58%,) than that of rest MPI (19/73=26%; $p<0.001$), despite having no significance with that of stress MPI (40/73=55%). In contrast, the specificity was not significantly different among the 3 techniques (BMIPP; 74/77=96%, rest-MPI; 76/77=99%, stress-MPI; 74/77=96%).

Case Reports

Case 1 A 62-year-old man with severe effort angina was admitted to the Emergency Department. Neither cardiomegaly nor pulmonary congestion were apparent on the chest X-ray, there was ST-segment horizontal depression in leads II, III, aVF, and V₄₋₆ of the ECG and coronary arteriography (Fig 2A) showed severe stenosis in the regions of the RCA. The LCA was intact. No significant abnormal perfusion was observed on the tetrofosmin images at rest, but there was reduced uptake in the inferior region of the tetrofosmin images on stress imaging with ATP. The BMIPP images showed severely reduced uptake in the inferior region (Fig 2B).

Case 2 A 64-year-old man was referred because of anterior chest oppression with rest in the early morning. The medical history included hyperlipidemia. Blood pressure was 148/84 mmHg, heart rate was 64/min, the chest X-ray showed a cardiothoracic ratio of 53% without pulmonary congestion and the ECG demonstrated no specific ST-segment abnormalities. Coronary angiography (Fig 3A) showed no significant stenosis in either artery. After injection of ergonovine maleate into the RCA, there was total spasm with severe chest pain and ST-T elevation on ECG. After isosorbide dinitrate was injected, the spasm completely resolved. No significant abnormal perfusion was observed on the rest or stress tetrofosmin images, but the BMIPP images showed reduced uptake in the inferior region (Fig 3B).

Discussion

The results of the present study indicate that abnormal findings at rest were more often observed with BMIPP than with resting MPI in the patients with CAD and acute chest pain but no evidence of acute myocardial infarction.

BMIPP SPECT at rest had higher sensitivity for detecting CAD than resting MPI though it had slightly lower sensitivity than stress MPI. Therefore, BMIPP, performed immediately after the onset of acute chest pain (within 5 days) may be useful for detecting CAD, particularly when patients are not suitable for the stress test or have suspected coronary spasm.

Advantages of BMIPP for Identifying Myocardial Insult

Free fatty acids are the major energy source in the well-perfused normal myocardium, but fatty acid oxidation is easily suppressed in the ischemic heart.^{16,17} It is well known that the metabolic abnormality may be prolonged, with persistent wall motion abnormalities shortly after ischemia,¹⁸ and therefore alterations of fatty acid oxidation are considered to be a sensitive marker of ischemia and myocardial damage.

Basic studies have shown that abnormal uptake of the iodinated analog, BMIPP, reflects metabolic alteration caused by severe ischemia^{19,20} and BMIPP SPECT can identify prior ischemia as areas of reduced tracer uptake. We previously reported that BMIPP uptake is reduced in risk areas with recovered perfusion several days after reperfusion therapy in patients with acute myocardial infarction, indicating that BMIPP SPECT may estimate both areas at risk and salvaged myocardium.²¹ Based on the concept that BMIPP may identify not only ischemia but also a history of ischemia, BMIPP SPECT can also identify ischemic disease without myocardial infarction (ie, stunned areas) as areas of reduced tracer uptake.¹⁰⁻¹⁴

In the present study, we evaluated the sensitivity of BMIPP and rest-stress MPI to detect both organic coronary stenosis and spasm. In the emergency department it is not easy to distinguish whether the patient with chest pain has an organic stenosis or spasm and if BMIPP shows abnormal uptake, CAG may be the next step.

In addition, we found that BMIPP SPECT provided higher sensitivity than resting perfusion imaging, but slightly lower sensitivity than stress perfusion imaging, which concurs with our previous study of another population.¹⁵ The sensitivity of the present study was slightly lower (58%) than the previous one (74%), because the

present study excluded severe and unstable patients who could not tolerate stress perfusion imaging. The data indicated that rest followed by stress perfusion imaging is the method of choice to identify coronary patients who come to an emergency department because of acute chest pain. However, for those patients who cannot undergo a stress study, BMIPP imaging at rest is the method of choice. Furthermore, perfusion abnormalities may not be identified even during stress study in patients with vasospastic angina and in such cases, BMIPP imaging can identify a prior ischemic insult.^{15,22}

Comparison With Myocardial Perfusion Imaging

Acute chest pain is often associated with either organic stenosis or occlusion of the coronary arteries. In the evaluation of these patients without diagnostic ECG, resting MPI is often required to select high-risk coronary patients who may be required to be hospitalized.¹⁻⁴ A resting MPI study is the method of choice to identify lesions in patients with acute myocardial infarction or ongoing ischemia, but it has limited value in identifying ischemic disease when the chest pain has subsided.⁴ Exercise or pharmacological stress MPI may be the next step in identifying such coronary patients.⁵ Ischemic areas are identified as areas of stress-induced hypoperfusion caused by reduced coronary flow reserve and on BMIPP imaging at rest such areas may be identified as areas of altered fatty acid utilization, particularly in cases of severe or repetitive ischemia. On the other hand, in the case of mild or stable ischemia, such organic lesions are less likely to be identified as areas of altered metabolism. Yamabe et al in their coronary study of patients without myocardial infarction attested that the cases with unstable angina tended to show less BMIPP uptake than those with stable angina¹⁴ and our previous study also showed that BMIPP abnormalities were observed more often in patients with changes on ECG or with reduced wall motion.¹⁵ Therefore, the sensitivity of detecting organic coronary stenosis on resting BMIPP imaging was higher than that of resting MPI, but was slightly less than rest-stress myocardial imaging. BMIPP imaging is particularly valuable when stress studies are contraindicated or declined by the patient.

Coronary spasm is an important causes of acute chest pain and is often associated with ST segment elevation and left ventricular dysfunction caused by the recurrent ischemia, even in the absence of coronary stenosis.²³ Although the prognosis of such patients is generally good, severe coronary spasm may cause cardiac death²⁴ so accurate diagnosis and prompt therapy are required. An exercise or dipyridamole stress may not identify regional perfusion abnormalities in these patients unless spasm is induced by the stress tests.²⁵ As repetitive ischemic episodes may cause altered fatty acid utilization, BMIPP is considered to be a useful method of detecting coronary spasm.^{10,14,26} Both of our studies have confirmed the diagnosis value of BMIPP imaging for identifying patients with vasospastic angina.

Methodological Consideration

Tetrofosmin for MPI was used for the current study instead of ^{99m}Tc-sestamibi or ²⁰¹Tl because of its advantages. The half-life of ^{99m}Tc- is shorter than that of ²⁰¹Tl and has a higher emission energy and less scattered radiation. It is easily provided as a cold kit at room temperature, and is rapidly taken into myocardium well after washing out from the liver and lungs.²⁷ Clinical studies have shown that tetro-

fosmin SPECT gives an extremely accurate diagnosis of CAD.²⁸⁻³²

A BMIPP SPECT study cannot be performed at the time of admission and the following day is the earliest. Accordingly, the appearance of abnormal BMIPP findings may be quite limited. Fatty acid utilization may improve to a certain degree after myocardial ischemia even after myocardial infarction,^{33,34} and in patients with less severe ischemia, the altered fatty acid metabolism may improve to a certain degree in the first few days after myocardial ischemia. However, we found this was helpful for detecting and classifying the severity of the myocardial ischemia despite normal perfusion. The frequency of abnormal BMIPP uptake (30%) was relatively low and may depend on the time at which the imaging was performed. We were not investigating the localization of individual stenosed vessels, so the diagnostic accuracy seems more than satisfactory when considering the coronary territories.

Conclusion

BMIPP SPECT is more useful and feasible than tetrofosmin rest imaging alone for those patients who are unable to undergo a stress test in order to detect an abnormal CAG finding. An MPI study combining rest and stress has the best sensitivity in detecting CAD. Resting BMIPP SPECT is an alternative method, particularly for patients suspected of having either unstable angina or coronary spasm.

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