Resting 123I-BMIPP scintigraphy in diagnosis of effort angina pectoris with reference to subsets of the disease

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This study was undertaken to assess the diagnostic value of resting 123I-BMIPP scintigraphy in patients with effort angina pectoris. One hundred and four patients underwent scintigraphic and angiographic examinations. The subsets of the patients were stable effort angina pectoris (stable type) in 27 cases, new onset of effort angina pectoris (new onset type) in 21 cases, and worsening effort angina pectoris (worsening type) in 35 cases. The remaining 21 cases were subjects without evidences of coronary artery disease (non-CAD). 123I-BMIPP was injected under resting and pain free condition, then data for single photon emission tomography (SPECT) were acquired. The positive regional 123I-BMIPP defects in three coronary territories were visually judged on the tomographic images. The overall sensitivity to diagnose the patients was 62.6% (52/83) and the overall specificity to exclude non-CAD subjects was 95.2% (20/21). The detection rate in each subset of the disease was 48.1% (13/27) in stable type, 47.6% (10/21) in new onset type and 77.1% (27/35) in worsening type (p < 0.05 versus two other types). For detection of stenosed vessels, the overall sensitivity was 41.4% (56/148) and the overall specificity was 93.8% (152/164). The rate of detection of stenosed vessels was 31.7% (13/41) in stable type, 31.4% (11/35) in new onset type, and 55.6% (40/72) in worsening type (p < 0.05 versus two other types). Vessels with 75% stenosis were more sensitively detected in the worsening type (33.3%; 4/12) compared to the remaining two types (8.3%; 1/12) even though the difference was not significant. The resting 123I-BMIPP scintigraphy was therefore valuable in diagnosing patients with effort angina pectoris and involved coronary arteries especially in the subset of patients with worsening type.

Key words: 123I-BMIPP, stable angina pectoris, unstable angina pectoris

INTRODUCTION

Up to 90% of the energy require by the normal myocardium under aerobic conditions derives from the metabolism of free fatty acids (FFA).[1] 11C-palmitate with positron emission tomography clearly demonstrated that FFA imaging enables ischemic myocardium to be identified.[2,3]

Iodine-123-β-methyl iodophenyl-pentadecanoic acid (123I-BMIPP) is a branched FFA analog characterized by its resistance to β-oxidation. The use of this tracer in single photon emission computed tomography (SPECT) offers several advantages, i.e., high myocardial uptake, rapid blood clearance, long retainability in the myocardium and persistent defective accumulation in the ischemic or injured myocardium.[4] Recent clinical studies have shown the usefulness of 123I-BMIPP in the diagnosis of ischemic heart disease,[5] reperfused myocardium in acute infarction,[6] hibernating myocardium,[7] unstable angina pectoris,[8,9] vasospastic angina pectoris[10] and idiopathic cardiomyopathies,[11,12] but patients with effort angina pectoris

	N (cases)	Age (yo)	Male/Female (cases)	Coronary angiography			LVEF (%)	WMA (case) (%)
				Single vd	Double vd	Triple vd		
Chest pain syndrome	21	61 ± 12	M: 11, F: 10	—	—	—	67.8 ± 3.3	4 (19%)
Stable EAP	27	63 ± 11	M: 21, F: 6	16	8	3	62.2 ± 7.3	13 (48%)
New EAP	21	65 ± 8	M: 15, F: 6	11	6	4	72.0 ± 10.6	8 (38%)
Worsening EAP	35	65 ± 8	M: 19, F: 16	10	13	12	60.1 ± 11.3	20 (57%)
Total	104	63 ± 10	M: 66, F: 38	37	27	19	64.3 ± 10.9	45 (43%)

EAP = effect angina pectoris, Single vd = single vessel disease, LVEF = left ventricular ejection fraction, WMA = wall motion abnormality of left ventricle

who did not have myocardial infarction have not been closely examined with resting ^{123}I-BMIPP scintigraphy.[13] The present study was undertaken to determine the diagnostic significance of resting ^{123}I-BMIPP SPECT in effort angina pectoris, with special reference to the subsets of the disease.

MATERIAL AND METHODS

Patients
The study group consisted of 104 patients (66 men, 38 women; age 63 ± 10 yr.) who had been admitted complaining of effort chest pain. They were examined at the five hospitals participating in this study. All patients underwent coronary angiography and resting ^{123}I-BMIPP SPECT. Patients with previous myocardial infarction, chest pain associated with a high level of creatine kinase or angiographically-proven vasospastic angina, those who had undergone coronary angioplasty or coronary arterial bypass grafting, and those who had idiopathic cardiomyopathy or other organic heart diseases were excluded from this study. Anti-anginal medications were discontinued, in principle, for at least 12 hours just before the examination, but if the medication was considered necessary for a given patient he continued taking it. Subdivision of patients was made according to the WHO classification[14]: stable effort angina pectoris (stable type) in 27 cases defined as effort angina of 1 month's duration or more, de novo effort angina pectoris (new onset type) in 21 cases defined as effort angina of less than 1 month's duration, and worsening effort angina pectoris (worsening type) in 35 cases defined as sudden worsening in frequency, severity, or duration of chest pain caused by the same effort. The remaining 21 cases complained of typical or atypical chest pain with or without exercise-induced ST depression but did not have significant coronary stenosis, vasospasm nor regional perfusion defect on the stress perfusion scintigraphy. They were classified as non-coronary artery disease (non-CAD) subjects.

Coronary angiography and ventriculography
All patients underwent coronary angiography and 98 patients ventriculography. Stenoses of coronary vessels were coded according to the criteria of the American Heart Association reporting system.[15] Luminal stenoses with 75%, 90%, 99% and 100% occlusion were defined as significant lesions. Wall motion abnormality was evaluated from angiographic ventriculography with both right anterior projection and left posterior projection, but it was determined by echocardiography in 3 cases.

^{123}I-BMIPP scintigraphy
All patients underwent resting ^{123}I-BMIPP scintigraphy under pain-free conditions after a 6 hr fast. A dose of 148 MBq of ^{123}I-BMIPP was injected intravenously with patients in the sitting posture. Twenty to thirty minutes after the ^{123}I-BMIPP injection, data for single photon emission computed tomography (SPECT) were acquired at each hospital. The time for data collection was 15 minutes to 20 minutes in each hospital. Tomographic images were then constructed with short axis, horizontal axis and vertical axis sections. The ventricular images were divided into 17 segments. Eight segments in the antero-septal area were interpreted as the territory of the left anterior descending artery, 4 segments of inferior area as the territory of the right coronary artery, and 4 segments in the lateral area as the territory of the circumflex artery. If the defect was present in the apical region conjunct with the other sequential regions, it was interpreted as indicating the territory supplied by the artery corresponding to the sequential region. If the defect was localized within the apical region alone, it was not judged as indicating a coronary lesion. The radio-activity of each segment was visually scored into 0 to 3 (0 = normal, 1 = mildly but definitely reduced, 2 = moderately reduced, 3 = severely reduced). A regional defect was interpreted as significant for coronary lesion if 2 consecutive segments with a total defect score 3 were present along the coronary territories. All scintigraphic interpretations were performed by the same three experienced investigators who had no information about clinical features or the results of angiography.

Statistics
One way variance test and Bonferroni test were used to compare average values. A chi-square test was also used. A p value < 0.05 was considered significant.

RESULTS

Clinical features of patients studied

Table 1 summarizes the clinical features of the patients according to the subsets of the disease. No significant difference among the four groups were found regarding average age. The proportion of females was significantly higher in non-CAD patients and in the worsening type than in the stable type (both p < 0.05). Multiple vessel disease was significantly more prevalent in the worsening type than in the other two groups (both p < 0.05). The average left ventricular ejection fraction was relatively higher in non-CAD patients and the new onset type than in the worsening type, but the difference was not statistically significant. Regional wall motion abnormality was more frequently recognized in the worsening type, but the difference was not significant.

Figure 1 shows the ^{123}I-BMIPP SPECT images in a patient with the worsening type who had 99% stenosis on the left anterior descending artery. There were large defects in the anterior wall and apex.
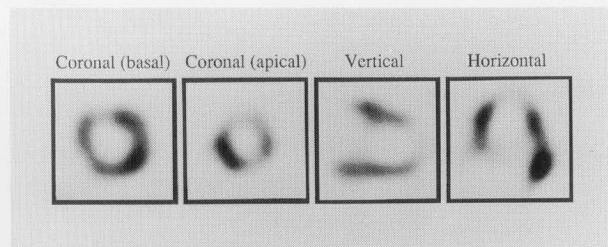
Diagnosis of effort angina pectoris by ^{123}I-BMIPP SPECT

For the diagnosis of angina patients, including the stable type, new onset type and worsening type, the overall sensitivity was 62.6% (52/83) and the overall specificity to exclude non-CAD subjects was 95.2% (20/21). The detection rate of the patients depended on the subsets of the disease (Figure 2). It was 48.1% (13/27) in the stable type and 47.6% (10/21) in the new onset type, but it was significantly better (77.1%; 27/35) in the worsening type (p < 0.05 versus the other two groups). The detection rate also tended to be different for single and multiple vessel disease, being 54.1% (20/37) in those with single vessel disease, 59.2% (16/27) in those with double vessel disease and 73.7% (14/19) in those with triple vessel disease. However, the difference between groups divided by the number of involved vessels was not statistically significant.

In the Figure 3, the left panel shows the incidence of patients with none, single, double and triple vessel disease diagnosed by angiography. The right panel shows the incidence of patients diagnosed by scintigraphy. The ^{123}I-BMIPP SPECT tended to underestimate the number of vessels involved.

Detection of the stenosed coronary artery by ^{123}I-BMIPP SPECT

In the whole study population there were 148 stenosed coronary arteries and 164 normal arteries. As for the detection of each stenosed coronary artery, the overall sensitivity was 41.4% and the overall specificity was 91.9%. There were 12 false positive regions and 96 false negative regions. Of these 12 false positive regions, 9 were misinterpretation between the right coronary artery and circumflex coronary artery, 2 were misinterpretation


Fig. 1 The ^{123}I-BMIPP SPECT images. In a patient with effort angina pectoris associated with 99% stenosis of the left anterior descending artery. Tomographic images show regional defect in the anterior wall and apex.
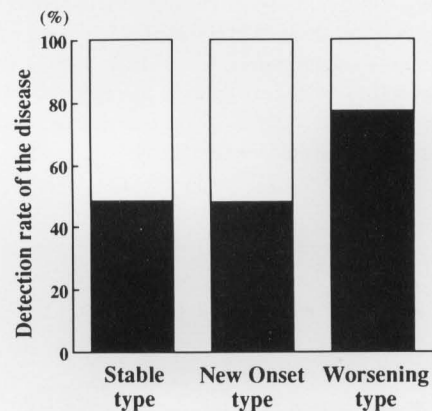

Fig. 2 Rate of detection of ^{123}I-BMIPP SPECT in patients. The detection rate differed among subsets of effort angina pectoris. It was 48.1% in the stable type and 47.6% in the new effort type, but it was better (77.1%) in the worsening type (p < 0.05 versus the other two types).

of the single vessel region into the double vessel region, and only 1 region was observed in a non-CAD patient. The ability of ^{123}I-BMIPP to detect the stenosed vessels was related to the degree of luminal stenosis. The detection rate was 52.0% (13/25) in the case of 100% occlusion, 46.9% (23/49) in that of 99% stenosis, 42.0% (21/50) in that of 90% stenosis, and 20.8% (5/24) in that of 75% stenosis. The detection rate for 75% stenosis was significantly lower than for other stenosed vessels (p < 0.01 versus 100% occlusion or 99% stenosis, p < 0.05 versus 90% stenosis).

The detection rate for the stenosed vessel by ^{123}I-BMIPP SPECT differed among the three subsets of the disease (Figure 4). It was 31.7% (13/41) for the stable type, 31.4% (11/35) for the new onset type and 55.6% (40/72) for the worsening type. That of worsening type was significantly higher than for the other types (both p < 0.05). In addition, coronary arteries with 75% stenosis were more sensitively detected in the worsening type (33.3%; 4/12) than in both the stable type and the new onset type together (8.3%; 1/12), although the difference did not attain statistical significance. The average %stenosis in the coronary lesions did not differ among the three
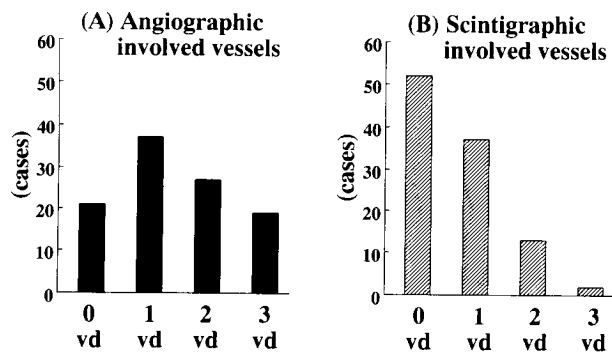
Fig. 3 Distribution of patients with none, single, double and triple vessel coronary disease as detected by angiography and scintigraphy. The figure shows the incidence of patients divided by involved vessels diagnosed by angiography (left panel) and by scintigraphy (right panel). ^{123}I-BMIPP SPECT tended to underestimate the number of vessels involved. (0 vd; normal coronary angiography, 1 vd; single vessel disease, 2 vd; double vessel disease, 3 vd; triple vessel disease)
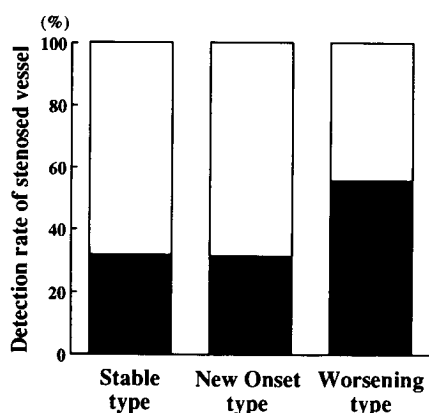
Fig. 4 Detection rate for stenosed coronary artery. Detection rate for the vessel involved by ^{123}I-BMIPP SPECT in three types of effort angina pectoris. The detection rate was 31.7% for the stable type and 31.4% for the new onset type, but was 55.6% for the worsening type. There were significant differences between the former two types and the worsening type (both p < 0.05).

subsets of the disease (92.5 ± 9.1% in the stable type, 93.4 ± 8.6% in the new onset type and 91.5 ± 8.6% in the worsening type).

Relation to abnormal left ventricular wall motion
Abnormal wall motion in the left ventricle was found in 45 (43%) of the 104 patients. Of them 33 patients (73.3%) had positive ^{123}I-BMIPP defects, whereas only 19 (32.2%) of the 59 patients with normal wall motion had ^{123}I-BMIPP defects (p < 0.001).

DISCUSSION

The present study documents the usefulness and feasibility of resting ^{123}I-BMIPP SPECT for diagnosis of the

patients with effort angina pectoris. The overall sensitivity for diagnosis of the disease was 62.6% and the overall specificity was 95.2%. The detection rate was significantly higher in patients with the worsening type than the stable type and the new onset type.

BMIPP is a branched fatty acid analog that is taken up by diffusion, then trapped in the myocardial cells.[4] The degradation pathway is thought to involve alpha-oxidation followed by beta-oxidation,[16] thus showing slower disappearance than endogenous fatty acids. Consequently, ^{123}I-BMIPP is suitable for SPECT imaging. The precise mechanisms of defective ^{123}I-BMIPP accumulation have not been clarified as yet. Since BMIPP is esterified to triglycerides, decreased accumulation can reflect impaired initial activation of fatty acids to acyl-CoA by using adenosine triphosphate[17] or decreased triglyceride synthesis leading to a reduced cellular lipid pool.[18] It is well known that myocardial ischemia easily alters the metabolism of fatty acid.[19,20] Resting ^{123}I-BMIPP SPECT is more useful for the diagnosis of coronary artery disease than resting perfusion scintigraphy; that is, defective accumulation can be detected not only during ischemia[21,22] but also during recovery from ischemia[8-10] such as post-angioplasty[7] or vasospastic angina.[10] The ^{123}I-BMIPP defect after myocardial ischemia but during the ischemic free condition is called "memory of myocardial ischemia" which suggests persistent suppression of FFA metabolism. This characteristic of ^{123}I-BMIPP facilitates the diagnosis of effort angina pectoris patients in whom a stress test is contraindicated. The goal of our study was to determine the diagnostic value of ^{123}I-BMIPP SPECT in patients with effort angina pectoris, focusing on the subsets of the disease.

Our study showed that resting ^{123}I-BMIPP SPECT performed under pain free condition had a modest sensitivity in detection of the patient with effort angina pectoris without myocardial infarction and good specificity to exclude non-CAD subjects. If the study population had included myocardial infarction, the sensitivity should have been increased. Indeed, several ^{123}I-BMIPP studies reported almost 100% of abnormal findings in cases of myocardial infarction.[6,23-25] In patients with unstable angina pectoris excluding myocardial infarction, Takeishi et al.[7] reported 77% sensitivity of resting ^{123}I-BMIPP SPECT. Similar sensitivity (78%) was also reported in vasospastic angina pectoris.[10] These values are consistent with our results (77.1%) obtained in cases of the worsening type. There have been limited data concerning stable effort angina pectoris and new onset effort angina pectoris. Takeishi et al.[13] reported 43% sensitivity in the case of stable effort angina pectoris, which was consistent with our results (48.1%). Although there has been no study available in the case of the new onset type, our detection rate (47.6%) was very similar to that of the stable type. These values were significantly lower than that for the worsening type. The lower detection rate is considered to

reflect less frequent and less severe ischemic episodes from which patients had suffered compared to those with the worsening type. The prevalent multiple vessel disease in the worsening type might be one of the factors accounting for the high detection rate, but each stenosed vessel was more sensitively detected in the worsening type. In addition, 75% stenosis, a less severe organic lesion, was more frequently detected in the worsening type than in the other two types. It has been reported that the complex configuration and blood clotting were found in the coronary lesions in unstable angina pectoris.[26] Such instability of stenotic lesions should have caused transient reduction in coronary flow, and causes serious ischemic episodes. In addition, the myocardium of patients with the worsening type might suffer metabolical damage owing to repeated and serious ischemia. These reasons may be important for the high detection rate seen in the worsening type. ^{123}I-BMIPP SPECT is therefore considered to diagnose the culprit coronary lesions responsible for recent and severe ischemic episodes. This consideration is compatible with the correlation between ^{123}I-BMIPP defect and wall motion abnormality shown in our study and as reported as other studies.[6,7] The coincidence of ^{123}I-BMIPP defect and wall motion abnormality may indicate an effct of prolonged or repeated ischemia on both metabolism and mechanical function.

In this study we did not examine resting perfusion scintigraphy together with ^{123}I-BMIPP SPECT. The ^{123}I-BMIPP defects are commonly observed in the area with normal perfusion examined by resting ^{201}Tl or ^{99m}Tc-Sestamibi scintigraphy in ischemic heart disease.[7-10] As reported in the past, most angina patients show signs of the perfusion defect only during chest pain,[27,28] and a few during the pain free period.[27-29] Consequently mismatched defects of ^{123}I-BMIPP with normal perfusion is a sensitive marker for detecting abnormal myocardium.[6,23,24] It might be indispensable to perform the dual tracer technique if one attempted to diagnose viable but metabolically impaired myocardium in patients with myocardial infarction,[6] but we consider that perfusion imaging can be omitted in patients without myocardial infarction.

^{123}I-BMIPP SPECT has been reported to be as specific as 90%[8] or 94%[23] in distinguishing normal coronary subjects from patients with coronary artery disease. Our results were consistent with these values. The definition of positive ^{123}I-BMIPP defect was somewhat strict in our study. For example, small defects within a single segment were excluded because they were not considered to be sufficient for interpreting regional defects along the coronary territory. This criterion increased specificity but somewhat decreased the sensitivity. As is well known, diagnostic specificity depends on the population of control subjects. For example, positive ^{123}I-BMIPP defects were reported in patients with idiopathic cardiomyopathies.[11,12] The clinical aspects of our non-CAD subjects were characterized by excluding transient stress perfu-

sion defect and known organic diseases. This might be one of reasons for the good specificity in our study.

CONCLUSION

The present study documents the usefulness and feasibility of resting ^{123}I-BMIPP SPECT as a diagnostic tool for patients with effort angina pectoris, especially in the subset of the worsening type.

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