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Resting ^{123}I-BMIPP scintigraphy for detection of organic coronary stenosis and therapeutic outcome in patients with chest pain

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Purpose: Resting ^{123}I-BMIPP scintigraphy can detect coronary artery disease based on persistent abnormality of myocardial fatty acid metabolism after transient ischemia. The present study aimed to determine the value of resting ^{123}I-BMIPP scintigraphy in diagnosing coronary artery disease and predicting the therapeutic outcome in patients with chest pain symptom.
Method: Five hospitals participated in this study, and scintigraphic and angiographic studies were performed in 104 patients without myocardial infarction. Twenty of them had non-coronary artery disease (chest pain syndrome), 26 had stable effort angina, 35 had unstable angina with organic coronary lesions, and 23 had vasospastic angina without significant organic stenosis.
Results: Overall sensitivity for diagnosing angina pectoris (stable, unstable and vasospastic) was 45%, and overall specificity for excluding non-coronary artery disease was 80%. The incidence of positive ^{123}I-BMIPP was 54% among patients with organic coronary stenosis (50% in stable angina and 61% in unstable angina with organic stenosis), but it was low (22%) in vasospastic angina without organic stenosis. Patients with advanced coronary stenosis and multi-vessel disease were found to have a higher incidence of positive ^{123}I-BMIPP. A positive ^{123}I-BMIPP result was correlated with a higher rate of subsequent intervention therapy (catheter intervention or CABG) than a negative result (48% versus 27%, $p = 0.03$ at one month; and 63% versus 35%, $p = 0.008$ at one year).
Conclusion: Resting ^{123}I-BMIPP scintigraphy was valuable in detecting advanced coronary lesions in angina patients associated with a high incidence of subsequent intervention therapy.

Key words: ^{123}I-BMIPP, angina, CABG, PTCA, intervention

INTRODUCTION

^{123}I-BMIPP SCINTIGRAPHY is clinically useful for diagnosing defective accumulation of fatty acid after myocardial ischemia. It is a feasible method for evaluating various types of coronary artery disease.[1–11] This approach is particularly advantageous in patients who are at high risk of myocardial infarction, since a culprit lesion can be detected without stress testing. Positive ^{123}I-BMIPP scintigraphy has been reported to be associated with the following conditions: unstable angina pectoris,[4,5,12–20] severe coronary stenosis,[7,12] multi-vessel disease,[14] the active phase of vasospastic angina,[6] and abnormal ventricular function.[3,12,13,19] This suggests that ^{123}I-BMIPP scintigraphy becomes abnormal in the advanced stage of angina pectoris, and that the above mentioned conditions may be linked to the therapeutic outcome but, therapeutic stratification by ^{123}I-BMIPP scintigraphy has never been established. The present study was undertaken to determine the value of resting ^{123}I-BMIPP scintigraphy in the

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diagnosis of angina pectoris and to predict the outcome of treatment. This is the first report of a multi-center study performed for detecting the therapeutic outcome of angina pectoris in Japan.

MATERIAL AND METHODS

Patient Population

The study group consisted of 104 patients (66 men and 38 women, aged 65 ± 11 years) who had been admitted complaining of chest pain. They were examined at the five hospitals participating in this study. All the patients underwent resting ^{123}I-BMIPP SPECT and coronary angiography. Patients with chest pain associated with increased cardiac enzymes, newly developed Q waves, previous myocardial infarction, those who had undergone coronary angioplasty or coronary-aorta bypass grafting (CABG), and those who had other organic heart diseases were excluded from this study. Anti-angina medication was not discontinued before the examination. Vasospastic angina was predominantly diagnosed by provocative coronary angiography, but in a few cases it was diagnosed on the basis of a spontaneous attack with ST elevation. "Chest pain syndrome" which represents a group of non-coronary artery diseases, was defined as chest pain with normal coronary angiograms and negative provocation for vasospasm on coronary angiography or a spontaneous attack with ST changes.

Coronary Angiography and Echocardiography

All patients underwent coronary angiography. Stenosis of coronary vessels was coded according to the criteria of the American Heart Association reporting system.[21] Luminal stenosis with 75%, 90%, 99% and 100% occlusion was defined as a significant lesion. Wall motion abnormality was evaluated by echocardiography.

^{123}I-BMIPP SPECT Scintigraphy

All the patients underwent resting ^{123}I-BMIPP scintigraphy under pain-free conditions after a 6-hour fast. A dose of 111 MBq of ^{123}I-BMIPP was injected intravenously with the patients in the sitting posture, and 15 to 30 minutes later data acquisition for single photon emission computed tomography (SPECT) was begun in the routine manner in each hospital. Data acquisition time was 15 to 20 minutes. Tomographic images were constructed with short axis, horizontal axis and vertical axis sections. The ventricular images were divided into 3 territories: region of the left anterior descending artery, right coronary artery, and circumflex artery. The ^{123}I-BMIPP images were interpreted by physicians in each hospital who had no information on the clinical or angiographic features of the patient. Defect of ^{123}I-BMIPP images in the three coronary territories was visually scored from 0 to 2 (0 = normal, 1 = reduced but not significant, 2 = distinctly reduced).

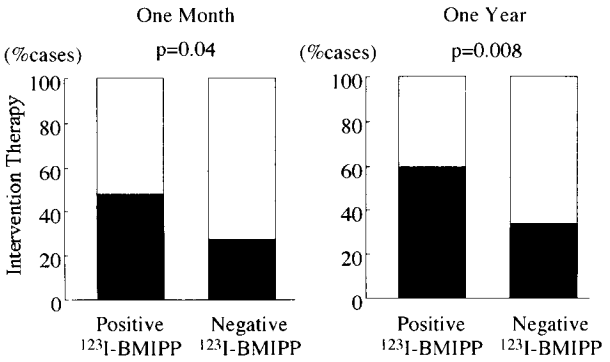

Fig. 1 The incidence of intervention therapy separated by the results of ^{123}I-BMIPP scintigraphy. Patients with positive ^{123}I-BMIPP scintigraphy had undergone intervention therapy one month after the examination more frequently than patients with negative ^{123}I-BMIPP scintigraphy (48% versus 27%; p = 0.04). A year later, this difference between the two groups was more prominent (63% versus 35%; p = 0.008).

Follow-up Study

Patient outcome with respect to catheter intervention therapy and CABG was assessed one month and one year after scintigraphy by mailed a questionnaire and/or a telephone interview. Four patients were lost to follow-up at one year.

Statistics

The chi-square test was used to determine the statistical significance of the distribution of the patients. Fisher's exact probability test was used when there were fewer than 5 cases. ANOVA was also performed to assess differences between mean values. A p-value of less than 0.05 was considered significant.

RESULTS

Clinical Features and ^{123}I-BMIPP SPECT

There were 26 cases of stable effort angina, 31 cases of unstable angina with significant organic stenosis, 27 cases of vasospastic angina without organic stenosis, and 20 cases of chest pain syndrome. Three of 20 cases of chest pain syndrome were characterized by exercise-induced ST depression, so-called "syndrome X." SPECT was positive, defined as a score of 2, in 42 patients, and negative, defined as a score of 1 or 0, in the other 62 patients. Overall sensitivity for the diagnosis of angina pectoris (all types) was 45%, and overall specificity for excluding chest pain syndrome was 80%. Table 1 summarizes the clinical features of the patients according to the results of ^{123}I-BMIPP scintigraphy. No significant differences between the negative group and the positive group were found in regard to age or sex distribution. The incidence of a positive ^{123}I-BMIPP result was higher in stable angina (50%) and in unstable angina with organic stenosis (61%) than in vasospastic angina without organic

Table 1 Patients' profile

	N (cases)	Age (yo)	Male/Female	Chest pain	Spastic	Stable	Unstable	WMA
^{123}I-BMIPP Negative	62	64 ± 11	M: 39, F: 23	16	21	13	12	8 (13%)
^{123}I-BMIPP Positive	42	67 ± 12	M: 27, F: 15	4 (20%)	6 (22%)	13 (50%)	19 (61%)	20 (48%)
Statistics		ns	ns	ref	ns	0.03	0.004	0.00008

Chest pain = chest pain syndrome, Spastic = vasospastic angina pectoris, Stable = stable effort angina pectoris, Unstable = unstable angina pectoris with organic coronary stenosis, WMA = echographic wall motion abnormality, M = male, F = female, ref = reference for the statistical comparison, ns = not significant

Table 2 Coronary angiographic findings

	Organic stenosis	0 vd	1 vd	2 vd	3 vd/LMT	0–50%	75%	90%	99%	100%
^{123}I-BMIPP Negative	27/62 (43%)	33	17	7	5	33	6	8	12	3
^{123}I-BMIPP Positive	32/42 (76%)	10	11	10	10	10	2	5	13	12
		23%	41%	59%	67%	23%	25%	38%	52%	80%
Statistics	0.0009	ref	ns	0.008	0.002	ref	ns	ns	0.01	0.0004

Organic stenosis = patients with significant organic stenosis, 0 vd = patients without significant organic stenosis, 1 vd = patients with one vessel patients with two vessel disease, 2 vd = patients with two vessel disease, 3 vd/LMT = patients with three vessel disease or left main disease, ref = reference for the statistical comparison, ns = not significant

Table 3 Comparison based on positive criteria

	N	Chest pain	Spastic	Stable	Unstable	WMA	Organic stenosis	0–50%	75%	90%	99%	100%	Collateral (+)
Negative	42	13 (31%)	13 (31%)	7 (10%)	9 (26%)	2 (5%)	16 (38%)	20 (49%)	5 (25%)	3 (7%)	6 (14%)	2 (5%)	2 (5%)
Positive criteria score 1	20	3 (15%)	4 (20%)	6 (30%)	7 (35%)	6 (37%)	13 (65%)	7 (35%)	1 (5%)	5 (25%)	6 (30%)	1 (5%)	6 (30%)
Positive criteria score 2	42	4 (10%)	6 (14%)	13 (31%)	19 (45%)	20 (48%)	32 (76%)	10 (24%)	2 (5%)	5 (12%)	13 (31%)	12 (28%)	20 (48%)
p (negative vs. score 1)		ns				0.02	0.05						0.02
p (negative vs. score 2)		0.03				> 0.001	> 0.001						> 0.001

Abbreviations are as same as Table 1

stenosis (22%, $p < 0.05$ versus unstable angina). Echocardiography revealed regional wall motion abnormalities more frequently in the positive ^{123}I-BMIPP group ($p < 0.001$).

Coronary Angiography and ^{123}I-BMIPP Scintigraphy

Table 2 summarizes the results of coronary angiography based on whether ^{123}I-BMIPP scintigraphy was negative or positive. The positive ^{123}I-BMIPP group included significantly more patients with organic stenosis ($p < 0.001$). Overall sensitivity for the diagnosis of patients with significant organic stenosis was 54%. Zero-vessel disease was positive in 23% of 43 cases. One-vessel disease was positive in 41% of 29 cases, two-vessel disease was positive in 59% of 17 cases and three-vessel or left main disease was positive in 67% of 15 cases, so that the positive rate was increased in proportion to the extent of vessel lesions. The group without significant stenosis (0–50% stenosis) was positive in 23% of the 43 cases. The 75% stenosis group was positive in 25% of the 8 cases. The 90% stenosis group had positive in 38% of 13 cases. The 99% stenosis group was positive in 52% of the 25 cases. The 100% occlusion group was positive in 80% of the 15, so that the positive rate was increased in proportion to the severity of the organic stenosis.

Comparison of Defect Scores in ^{123}I-BMIPP Scintigraphy

In this study we defined a positive ^{123}I-BMIPP result as a score 2. When we took a score of 1 as positive result, sensitivity for diagnosing angina pectoris (all types) was 65%, and specificity was 65%. Table 3 compares patients' manifestations in the score 1 group and the score 2 group. Chest pain syndrome was significantly less frequently included in the score 2 group than in the negative group ($p < 0.05$), but in the score 1 group and the negative group it was not significantly different. The distribution of the three types of angina was similar in the score 1 group and the score 2 group. Wall motion abnormality, organic coronary lesions and collateral flow were less frequent in the score 1 group than in the score 2 group, but the differences were not statistically significant.

Relation to Therapeutic Outcome

Figure 1 shows the percentages of patients who under-

went intervention therapy separated by the results of ^{123}I-BMIPP scintigraphy. One month after scintigraphy, 37 of the 104 patients had undergone intervention therapy (catheter intervention in 30 cases and CABG in 7 cases). Significantly more patients in the positive ^{123}I-BMIPP group underwent intervention therapy than in the negative ^{123}I-BMIPP group (48% versus 27%, p = 0.04). Four patients were lost to follow-up at one year after scintigraphy. Forty-six of the 100 patients underwent intervention therapy (catheter intervention in 33 cases, CABG in 13 cases). The statistical difference in intervention therapy became more distinct (63% versus 35%, p = 0.008) after one year later. There was no difference between selection for catheter intervention or CABG in the two groups.

DISCUSSION

The present study was a multi-center study, and no such studies have ever been performed with ^{123}I-BMIPP for angina pectoris. We documented two major findings. First, ^{123}I-BMIPP scintigraphy detected patients with organic coronary lesions, especially patients with advanced coronary disease. Second, positive ^{123}I-BMIPP scintigraphy was associated with a higher rate of subsequent coronary intervention than negative scintigraphy.

The reason for using resting ^{123}I-BMIPP scintigraphy to diagnose angina pectoris is the prolonged disturbance of fatty acid metabolism that occurs after myocardial ischemia.[2,22] This allows ^{123}I-BMIPP scintigraphy to detect regions with severe coronary stenosis[7,12,13] or reduced ventricular wall motion.[7,12–14,23] This property of ^{123}I-BMIPP led us to hypothesize that the results of ^{123}I-BMIPP scintigraphy are linked to the outcome of treatment. The purpose of this study was to determine whether resting ^{123}I-BMIPP scintigraphy could predict intervention therapy in patients complaining of chest pain, and five hospitals participated in the study. According to our protocol, the ^{123}I-BMIPP images were interpreted by skilled physicians in each hospital. This had the advantage of preventing misinterpretation caused by differences in image construction. It also has the benefit of preventing hospital-based bias.

A wide range of sensitivity of ^{123}I-BMIPP scintigraphy for the diagnosis of angina pectoris has been reported: 10% to 67% (average 46%) in stable effort angina[7,12,13,16,17] and 46% to 100% (average 76%) in unstable angina.[4,5,12–20] Such wide variations in sensitivity might be attributable to differences in patient selection, preparation before the examination, image construction, and definition of positive criteria. Our sensitivity was 50% for stable effort angina and 61% for unstable angina with organic coronary stenosis. The rate for stable angina was consistent with that in other reports, but the rate in unstable angina was lower than the reported average. The angiographic findings in our patients with unstable angina and organic stenosis were similar to those in stable angina pectoris in terms of the number of diseased vessels and the severity of organic stenosis. This may have caused the low sensitivity in unstable angina patients. We defined a positive ^{123}I-BMIPP result as only a score of 2 excluding a score of 1. When a score of 1 was included as a positive criterion, diagnostic specificity became too low. Even though we defined a score of 2 as positive, specificity was 80%. This was slightly lower than the reported values of 88% to 95% (average 92%).[4,12,23] The non-coronary artery disease group in our study consisted of patients with chest pain syndrome. This group included those with syndrome X, who might have had disturbed microvascular coronary circulation. Such patients characteristic was a cause of the decreased specificity. Actually, the score 1 finding was prevalent in the non-coronary artery disease group. It therefore seemed to be preferable to exclude equivocal ^{123}I-BMIPP findings from the positive criteria for the diagnosis of angina pectoris.

Patients with vasospastic angina had less positive ^{123}I-BMIPP results than angina patients with organic coronary stenosis. Sensitivity for vasospastic angina has previously been reported to be 70% to 78% (average 73%),[6,23,24] which is very different from our results. Our data were unaffected by a laboratory-based bias, because the patients with vasospastic angina were evenly distributed among the five hospitals. The large difference between other reports and our own was surprising. One of the reasons for this may have been patient selection. The baseline coronary angiogram was normal in our vasospastic angina group. Another reason may be related to disease activity. Nakajima et al.[6] reported that ^{123}I-BMIPP defects disappeared in vasospastic angina patients who responded to drug therapy. Unfortunately the present study did not assess the incidence of attacks immediately prior to examination. The other reason may be the positive criteria: ours excluded equivocal findings. One third of our patients with vasospastic angina had ^{123}I-BMIPP finding that received a score of 1, but in some of the cases the ^{123}I-BMIPP images several hours after a vasospastic attack were normal, suggesting that the angina attack alone was insufficient to produce ^{123}I-BMIPP defect. Positive ^{123}I-BMIPP scintigraphy is associated with advanced coronary stenosis, multi-vessel disease and wall motion abnormality.[7,12–14,25] Our study showed that 80% of patients who had chronic total occlusion with collateral flow had ^{123}I-BMIPP defects. These findings suggest that myocardial ischemia followed by vulnerable coronary flow involves fatty acid metabolism. Back diffusion of non-metabolized BMIPP has been suggested to be a mechanism of ^{123}I-BMIPP defect after myocardial ischemia. This is caused by shortness of myocardial ATP.[26] Vasospastic angina without organic stenosis causes a transient reduction in coronary blood flow during the attack, but blood flow completely recovers after the attack. The myocardial ATP concentration recovers soon after release of the vasospasm. Moreover, wall motion

abnormality was rarely observed (4 out of 27 cases) in the vasospastic angina patients in our study. These factors may account for the low incidence of ^{123}I-BMIPP defects in vasospastic angina without organic stenosis in our study.

The therapeutic strategy for coronary artery disease is an important issue, but no strategy has ever been established in relation to ^{123}I-BMIPP scintigraphy. A few studies[14,25] have examined the validity of ^{123}I-BMIPP scintigraphy for determining the choice of treatment. Takeishi et al.[25] examined a small number of patients and reported that CABG therapy was related to positive ^{123}I-BMIPP. We investigated whether positive ^{123}I-BMIPP scintigraphy was associated with intervention therapy. At one month and one year after ^{123}I-BMIPP scintigraphy, patients with positive ^{123}I-BMIPP findings had been more frequently treated by intervention therapy. This result is thought to be a consequence of the association between ^{123}I-BMIPP defects and advanced organic coronary disease. Our findings suggested that positive ^{123}I-BMIPP scintigraphy is useful for diagnosing advanced coronary disease in patients with angina pectoris and for use in a choosing intervention therapy.

Study Limitation

Our protocol was designed as a retrospective study. The actual choice of intervention therapy might depend on the symptoms, angiographic findings or ^{123}I-BMIPP findings in individual hospitals. It would therefore be difficult to propose that ^{123}I-BMIPP can serve as a basis for treatment selection in individual patients based on the results of this study. Our study did not employ the dual tracer technique or quantitative analysis. Although perfusion-metabolism mismatch may be a sensitive marker for differentiating ischemic myocardium from myocardial scar,[3–6] we aimed to assess the diagnostic ability of ^{123}I-BMIPP scintigraphy alone, because patients with myocardial infarction were excluded from our subjects, and because the dual tracer technique is more expensive than ^{123}I-BMIPP alone.

Conclusion

The present study showed that resting ^{123}I-BMIPP scintigraphy was useful as a diagnostic tool for patients with angina pectoris, and positive ^{123}I-BMIPP was associated with intervention therapy.

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