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Abnormal fatty acid metabolism in patients with coronary vasospasm

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Although various noninvasive methods have been used to detect vasospasm, none of them are sensitive enough for patients with sporadic attacks. Since abnormal fatty acid metabolism is observed in ischemic myocardium, ^{123}I-β-methyl-p-iodophenyl pentadecanoic acid (BMIPP), a radiolabeled fatty acid analog, has recently been proposed as a useful tracer for detecting myocardial damage. The aim of this study was to clarify the clinical implications of decreased myocardial BMIPP uptake in patients with vasospastic angina. We evaluated 53 patients with vasospastic angina (32 with clinically documented vasospasm [Group-A] and 21 with vasospasm induced by ergonovine provocation [Group-B]) and 27 control subjects, 20 in Group-A were re-evaluated 6 months after medical treatment. The territorial regions of vasospasm-induced coronary artery, the wall motion by left ventriculography, and BMIPP uptake were compared. Vasospasm was induced in multiple coronary arteries in 29 (55%) patients. Reduced wall motion and decreased BMIPP uptake were observed in 19 (36%) patients and 47 (89%) patients, respectively. The sensitivity and specificity of determination of vasospasm-induced coronary arteries with BMIPP scintigraphy were 71% (69/97 coronary arteries) and 88% (126/143), respectively. Vasospasm was re-induced by ergonovine provocation in 8 patients (Group-I) and not re-induced in 12 (Group-II) after treatment. In Group-I, improvement of decreased BMIPP uptake was lower than in Group-II (19 $\pm$ 11 vs. 59 $\pm$ 22%, mean $\pm$ SD, $p < 0.001$). The regions in which vasospasm was re-provoked exhibited decreased BMIPP uptake.

Abnormal fatty acid metabolism was more often observed than wall motion abnormality in the vasospastic region in patients with vasospastic angina. BMIPP scintigraphy is a highly accurate and non-invasive technique for determining the presence and location of vasospasm.

Key words: ^{123}I-β-methyl-p-iodophenyl pentadecanoic acid (BMIPP) scintigraphy, fatty acids, vasospasm, myocardial stunning

INTRODUCTION

VASOSPASTIC ANGINA is characterized by resting anginal attacks occurring mainly at night and in the early morning, but asymptomatic ischemic attacks are more frequent in patients with vasospastic angina. Some patients may exhibit reduced left ventricular wall motion due to transient myocardial ischemia resulting from vasospastic attacks.[1–4] Although various noninvasive methods have been used to detect vasospasm, none of them is sensitive enough for patients with sporadic attacks.

Long-chain fatty acid is one of the major cardiac energy substrates, and decreased myocardial fatty acid metabolism has been demonstrated in some patients with ischemic heart disease. ^{123}I-β-methyl-p-iodophenyl

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pentadecanoic acid (BMIPP) is a newly developed tracer for assessing myocardial fatty acid metabolism, and BMIPP is appropriate for use with single photon emission computed tomography (SPECT) because of its stable accumulation in the myocardium.[5–8] Some recent studies have demonstrated regional abnormalities in myocardial fatty acid metabolism by visual assessment of BMIPP SPECT in patients with ischemic heart disease.[9–11]

In this study we performed myocardial BMIPP SPECT scintigraphy on patients with vasospastic angina before and after medical treatment. The aim of this study was to clarify the clinical implications of fatty acid metabolic imaging with BMIPP in patients with vasospastic angina.

MATERIALS AND METHODS

Subjects

(1) Study-1

Between January 1994 and June 1997, 156 patients with vasospastic angina were admitted to our institution. Fifty-three patients (46 males and 7 females, age 57 ± 8 years [mean ± SD], range 44 to 69 years) were prospectively selected for this study by using the following criteria. All 53 patients had angiographically normal coronary arteries (defined as < 25% stenotic) and angiographically documented coronary artery vasospasm. Coronary arteriograms were performed by the Judkins technique. Left ventriculography right and left anterior oblique projections were used to evaluate segmental contraction abnormalities. If coronary artery stenosis was more than 99% with ST-segment elevation or depression developing after intracoronary injection of methyl ergometrine maleate (ergonovine), coronary vasospasm was diagnosed as previously reported.[4,12–15] Ambulatory electrocardiogram monitoring (SM-50, Fukuda Denshi Co., Japan) for at least 48 hours demonstrated that 32 patients (clinically documented definite vasospasm group, Group-A) had spontaneous vasospastic attacks (ST-segment elevation with or without chest pain) and 21 (vasospasm induced group, Group-B) did not have signs of spontaneous vasospastic attacks.

This study also included 27 control subjects (Group-C) who were suspected of having coronary artery vasospasm because of characteristic chest pain (16 males and 11 females, mean age 56 ± 11 years, range 36 to 69 years). These control subjects underwent diagnostic cardiac catheterization for evaluation of chest pain. They had angiographically normal coronary arteries and did not have coronary artery vasospasm after injection of ergonovine. Ambulatory electrocardiogram monitoring of each subject did not detect any spontaneous vasospastic attacks.

In all 80 subjects, medical treatment, except sublingual nitroglycerin, had not yet been administered, and chest pain attacks had occurred.

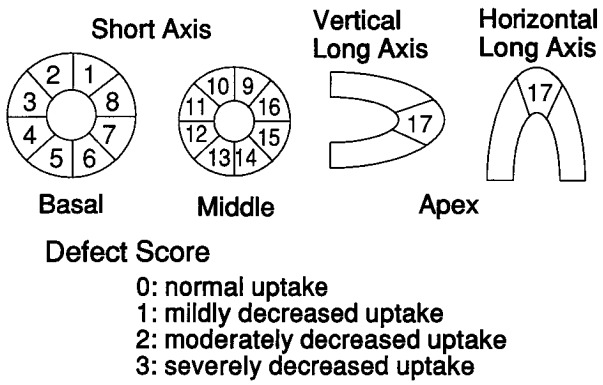

Fig. 1 Schematic representation of the basal short axis, midventricular short axis (middle), vertical long axis and horizontal long axis. BMIPP scintigrams were fractionated into 17 segments. The degree of BMIPP accumulation in each segment was visually graded on a 4-point scale. Scores for all 17 segments in subjects were totaled to yield the BMIPP total defect score for that subject. The segments were classified into the territories of the three major coronary arteries. The territory of the left descending artery = 1, 2, 3, 4, 9, 10, 11, 12, 17. The territory of the right coronary artery = 5, 6, 13, 14. The territory of the left circumflex artery = 7, 8, 15, 16. The coronary artery perfusing 2 overlap area in the apical segment was determined by the methods of Segar et al.[18]

(2) Study-2

Twenty of 32 patients in Group-A underwent a second BMIPP myocardial scintigraphy, left ventriculography and ergonovine-provoked coronary arteriography after 6 months of single or combined administration of nifedipine at 40–120 mg/day, diltiazem at 90–300 mg/day, amlodipine at 5–20 mg/day and isosorbide dinitrate at 40–120 mg/day. Ambulatory electrocardiogram monitoring for at least 48 hours did not detect any cardiac symptoms with ST-segment depression or elevation, comfirming that anginal attacks were completely suppressed by the medical treatment. Dosage and combination of medications were optimized and stabilized on suppression of cardiac symptoms, and all medications were continued during this study.

Although exercise ^{201}TlCl myocardial scintigraphy was performed on all 80 subjects, no persistent abnormalities in ^{201}TlCl uptake were seen. No subject had myocardial infarction, cardiomyopathy, valvular heart disease, left ventricular hypertrophy, congenital heart disease or hypertensive heart disease.

Written informed consent was obtained from each subject before the study. The protocol of this study was in agreement with the guidelines of the ethical committee of our institution.

Myocardial BMIPP SPECT scintigraphy

BMIPP scintigraphy on all 80 subjects in Group-A, B or C was performed within 2 weeks before diagnostic cardiac catheterization. BMIPP scintigraphy was performed

Table 1 Decreased ^{123}I-β-methyl-p-iodophenyl pentadecanoic acid (BMIPP) uptake with coronary territorial regions

(A) Group-A (definite vasospastic angina, n = 32)

patient No.	gender	age (year)	vasospasm induced coronary arteries	reduced wall motion by LVG	decreased BMIPP uptake		
1	male	66	1, 6, 9, 13	2, 3, 4, 6, 7	LAD		RCX
2*	male	63	1, 2, 6, 7	2, 3, 6	LAD		RCX
3	male	46	3, 7, 9, 11	7	LAD		RCX
4	male	56	2, 3, 6, 7, 11	none	LAD		RCX
5	female	60	1, 9, 11	none	LAD		
6	male	50	1, 7, 11	2, 3, 6	LAD		RCX
7	male	62	1, 2, 3, 7, 11, 13	1, 2, 3, 4, 5, 6, 7	LAD		RCX
8	male	59	2, 4, 6, 11, 12, 13	none	LAD		RCX
9	male	64	2, 3, 6, 7, 11, 13	2, 3	LAD		RCX
10	male	47	1, 2, 3, 7, 8, 11	none		LCX	RCX
11	male	47	1, 11	2, 3, 6, 7		LCX	
12	male	69	3, 6, 11	none	LAD		RCX
13	male	64	1, 6, 11	2, 3	LAD		RCX
14*	male	60	1, 7, 9	none	LAD		RCX
15	male	57	1, 11	4, 7		LCX	RCX
16	male	57	2, 7	none	LAD		RCX
17	female	47	2, 3, 7	3	LAD		RCX
18	male	54	2, 7	2, 3, 6	LAD		RCX
19	male	48	1, 2, 3	4	LAD		RCX
20	male	69	1	none	LAD		RCX
21	male	64	1, 2, 3	none	LAD		RCX
22	male	66	1	none			RCX
23	male	68	2, 3	none	LAD		RCX
24	male	57	13	4, 7		LCX	RCX
25	female	50	7	none	LAD		RCX
26	male	66	2	none			RCX
27	male	53	1, 2	none		LCX	RCX
28	female	59	6, 9	none		none	
29	male	69	7	none		none	
30	male	59	1	none	LAD		RCX
31	male	53	6	none		none	
32	male	44	3	none			RCX

(B) Group-B (vasospasm induced by ergonovine provocation, n = 21)

patient No.	gender	age (year)	vasospasm induced coronary arteries	reduced wall motion by LVG	decreased BMIPP uptake		
33	male	46	2, 7, 11	none	LAD		RCX
34	female	68	3, 13	none			RCX
35	male	62	2, 7, 11	2, 3, 5	LAD		RCX
36	male	46	2, 6	none	LAD		RCX
37	female	67	4, 7, 9, 11, 12, 13	2, 3, 6	LAD		RCX
38	male	64	1, 7, 11	none	LAD		RCX
39	male	64	1, 6	2, 3, 4, 6			RCX
40	male	51	1, 7	2, 3			RCX
41	male	65	1, 2, 13	none		none	
42	male	58	1, 7	none			RCX
43	male	48	1, 7	none		none	
44	female	62	1	none			RCX
45	male	48	2	none	LAD		RCX
46	male	62	1	4			RCX
47	male	45	13	none		none	
48	male	61	6	none	LAD		RCX
49	female	56	7	none	LAD		RCX
50	male	57	6	2, 3	LAD		
51	male	57	11, 13	none		LCX	
52	male	56	11	none		LCX	
53	male	58	1, 2	none			RCX

(C) Group-C (control subjects, n =27)

subject No.	gender	age (year)	vasospasm induced coronary arteries	reduced wall motion by LVG	decreased BMIPP uptake	
1	female	65	none	none	none	
2	female	57	none	none	none	
3	male	40	none	none	none	
4	male	43	none	none	none	
5	male	63	none	none	none	
6	female	60	none	none	none	
7	female	66	none	none	none	
8	male	36	none	none	none	
9	male	51	none	none	none	
10	male	64	none	none	none	
11	male	61	none	none	none	
12	male	43	none	none	none	
13	male	63	none	none		RCX
14	female	50	none	none	none	
15	male	57	none	4		RCX
16	female	55	none	none	none	
17	female	43	none	none	none	
18	male	66	none	2, 3	LAD	
19	female	64	none	none	none	
20	female	39	none	none	none	
21	male	69	none	none	none	
22	male	66	none	none		RCX
23	female	66	none	none	none	
24	female	66	none	none	none	
25	female	57	none	2, 3, 7	LAD	
26	female	59	none	none	none	
27	male	56	none	none	none	

LVG = left ventriculography, LAD = left anterior descending artery (No. 5–10), RCX = right coronary artery (No. 1–4), LCX = left circumflex artery (No. 11–15). Numbers of coronary artery and left ventriculography were expressed according to the American Heart Association classification.[15] *These 2 patients are demonstrated in Figs. 2 and 3.

the morning after an overnight fast. BMIPP (111 or 148 MBq) was intravenously injected into the subjects at rest. The BMIPP scintigram image was obtained 15 minutes after the injection. In 20 patients in Group-A, the second study was performed 6 months after the beginning of the medical treatment.

The SPECT system used consisted of a single head, and a large field digital γ-camera equipped with a general purpose, low energy, parallel hole collimator (ZLC-D-ORBITER, Siemens, German) connected to a microcomputer (Scintipak 24000, Shimadzu Co., Japan), as previously reported.[4,12] Both image sequences consisted of 32 projections with 64 × 64 matrix acquired for 40 seconds (BMIPP) and 30 seconds (^{201}TlCl) over a 180° circular orbit, from 30° right anterior oblique to 60° left posterior oblique.

Imaging analysis

Locations where reduced wall motion and vasospasm occurred, as revealed by left ventriculography and coronary angiography, were described according to the American Heart Association classification.[16] The left ventriculogram was analyzed by means of the CAA-10 ELK cine-angio system (Nishimoto Co., Japan) and the region of reduced wall motion was the area that deviated from the lower limit of the normal range as defined by our institution.[4,12] BMIPP scintigrams of the basal short axis, the middle short axis, the vertical long axis and the horizontal long axis patterns were obtained by SPECT and fractionated into 17 segments by coronary arterial territory (Fig. 1).[17] The left ventricle was divided into the three major coronary territories. Coronary arteries perfusing 2 overlapping areas were determined by the methods of Segar et al.[18] The defect score of BMIPP uptake (graded as normal uptake = 0, mildly decreased uptake = 1, moderately decreased uptake = 2, severely decreased uptake or defect pattern = 3) were visually assessed by 2 physicians blinded to the results of the coronary angiogram (Fig. 1). Differences of opinion were resolved by consensus. A summational point of a defect score of more than 3 in the respective coronary territories was defined as decreased BMIPP uptake. The total defect score was calculated as the summation of all counts. We assessed the improvement in the total defect score from initial and second BMIPP scintigrams (initial score – second score/initial score × 100%).

The intraobserver and interobserver variations for determining the defect score were tested in 50 coronary

Table 2 Identification of vasospastic angina and vasospasm-induced coronary arteries with ^{123}I-β-methyl-p-iodophenyl pentadecanoic acid (BMIPP)

(A) vasospastic angina

	vasospasm-positive (Group-A and B, n = 53)		definit vasosopastic angina (Group-A, n = 32)	vasospasm-negative (Group-C, n = 27)
decreased BMIPP uptake	47		29	5
normal BMIPP uptake	6		3	22
sensitivity =	89% (47/53)	or	91% (29/32)	
specificity =				81% (22/27)

(B) vasospasm induced coronary arteries by ergonovine provocation

	vasospam-induced coronary arteries in Group-A and B (n = 97)	non-vasospasm induced arteries in Group-A, B and C (n = 143)	non-vasospasm induced arteries in Group-C (n = 81)
decreased BMIPP uptake	69	17	5
normal BMIPP uptake	28	126	76
sensitivity =	71% (69/97)		
specificity =		88% (126/143) or	94% (76/81)

sensitivity = true-positive/true-positive + false negative
specificity = true-negative/true-negative + false positive

territories, and the correlation coefficients were 0.95 and 0.90, respectively.

Statistical analysis

Fisher's exact probability test and Student's t-test were used to compare the defect score and abnormalities in BMIPP uptake and wall motion in patients with vasospastic angina and the control subjects. A p value < 0.05 was considered significant. Values are presented as mean ± SD.

RESULTS

Provocation of coronary vasospasm at cardiac catheterization

Vasospasm was induced in the right coronary artery (RCX) of 42 patients, in the left anterior descending artery (LAD) of 32, and in the left circumflex artery (LCX) of 23. Multiple coronary artery vasospasm occurred in 29 (55%) patients (18 [56%] in Group-A and 11 [52%] in Group-B). Overall, 97 of 159 coronary arteries in all 53 patients in Groups-A and B developed coronary vasospasm after intracoronary administration of ergonovine (i.e., vasospasm-induced coronary artery) and 62 did not (i.e., non-vasospasm induced coronary artery).

Left ventriculography

Reduced wall motion was observed in 19 (36%) patients in Groups-A and B (13 [41%] patients in Group-A and 6 [29%] in Group-B, $p < 0.05$) by left ventriculography. Location of reduced wall motion coincided with territorial regions of the vasospasm-induced coronary artery (Table 1). Reduced wall motion was more frequently associated with patients having multiple coronary artery vasospasm than with single coronary arterial vasospasm (15 [52%] of 29 patients and 4 [17%] of 24, $p < 0.01$). Reduced wall motion was observed in 3 (11%) subjects in Group-C.

BMIPP SPECT scintigraphy

Decreased BMIPP uptake was observed in 47 (89%) patients in Groups-A and B (29 [91%] patients in Group-A and 18 [86%] in Group-B, NS). The regions with decreased BMIPP uptake were consistent with territorial regions of the vasospasm-induced coronary artery. In most patients, decreased BMIPP uptake was observed in regions where reduced wall motion was indicated by left ventriculography. Decreased BMIPP uptake was also observed in 5 (19%) of 27 control subjects. Based on these results, the sensitivity and specificity for the identification of the vasospastic angina with BMIPP scintigraphy were 89% (47/53) and 81% (22/27), respectively (Table 2).

In 53 patients in Groups-A and B, the regions with decreased BMIPP uptake in each territorial region of the vasospasm-induced coronary artery were 25 (78%) of 32 arteries in LAD, 6 (26%) of 23 arteries in LCX and 38 (90%) of 42 arteries in RCX, as shown in Table 1. In the control subjects, the regions were 2 (7%) of 27 arteries in LAD, 0 (0%) of 27 arteries in LCX and 3 (11%) of 27 arteries in RCX. Overall, decreased BMIPP uptake was detected in 69 (71%) of 97 myocardial regions that were perfused by vasospasm-induced coronary arteries in 53 patients in Groups-A and B. In addition, decreased BMIPP uptake was detected in 17 (27%) of 62 regions that were perfused by non-vasospasm-induced coronary arteries in Groups-A and B, and in 5 (6%) of 81 regions in Group-C. The sensitivity and specificity of BMIPP scintigraphy for the identification of vasospastic coronary artery was 71% (69/97) and 88% (126/143), respectively (Table 2).

Table 3 Defect score with ^{123}I-β-methyl-p-iodophenyl pentadecanoic acid (BMIPP)

Patient No.	before treatment			treat-ment	after treatment			improvement of total defect score
	vasospasm induced arteries	reduced wall motion by LVG	total defect score		vasospasm induced arteries	reduced wall motion by LVG	total defect score	
Group-I (re-induced vasospasm, n = 8)								
1	1, 6, 9, 13	2, 3, 4, 6, 7	14	N, A	2, 6, 13	none	10	29
3	3, 7, 9, 11	7	17	D	3, 7, 11	none	16	6
6	1, 7, 11	2, 3, 6	10	N, D	2	none	8	20
7	1, 2, 3, 7, 11, 13	1, 2, 3, 4, 5, 6, 7	25	N, A, I	7	2, 3, 6	20	20
8	2, 4, 6, 11, 12, 13	none	8	A	2	none	5	38
10	1, 2, 3, 7, 8, 11	none	13	N, D	7	none	11	15
11	1, 11	2, 3, 6, 7	27	N, A, I	1	none	21	22
24	13	4, 7	18	N	13	7	16	11
			17 ± 6				13 ± 6	20 ± 11 (%)
Group-II (non re-induced vasospasm, n = 12)								
2	1, 2, 6, 7	2, 3, 6	27	N, A, I	none	none	4	85
4	2, 3, 6, 7, 11	none	8	N, D	none	none	6	25
5	1, 9, 11	none	11	N, A	none	none	3	73
9	2, 3, 6, 7, 11, 13	2, 3	20	N, A, I	none	none	7	65
19	1, 2,3	4	14	N, A	none	none	4	71
20	1	none	12	N	none	none	9	25
21	1, 2, 3	none	7	D	none	none	2	71
22	1	none	8	A	none	none	3	63
23	2, 3	none	3	N	none	none	0	100
25	7	none	14	N, A	none	none	0	100
26	2	none	8	D	none	none	1	88
27	1, 2	none	13	N	none	none	7	46
			12 ± 6				4 ± 3*	68 ± 25 (%)*

LVG = left ventriculography, A = amlodipine, D = diltiazem, I = isosorbide dinitrate, N = nifedipine.
*$p < 0.01$, Group-I vs. II.

Re-evaluation by left ventriculography, coronary arteriography and BMIPP scintigraphy

Twenty patients in Group-A were re-evaluated 6 months after medical treatment. Vasospasm was re-induced by ergonovine provocation in 8 patients (Group-I) and not re-induced in 12 (Group-II) (Table 3). Medications were continued during this study, and the dosage and combination of medications did not differ significantly in the two groups. In all 8 patients in Group-I, higher dosages of ergonovine were required to induce vasospasm as compared with pre-treatment provocation (31 ± 5 and 16 ± 6 μg for each coronary artery, $p < 0.01$). Although there were many patients with multiple coronary artery vasospasm and reduced wall motion in Group-I, the total defect score for Group-I was not higher than that of Group-II (17 ± 7 vs. 12 ± 6, respectively, NS) before medical treatment.

After medical treatment, reduced wall motion was observed in 2 patients in Group-I and in 0 in Group-II by left ventriculography, and the region of its occurrence corresponded to the region in which vasospasm was re-induced and in which decreased BMIPP uptake was observed. Table 3 shows that decreased BMIPP uptake still remained in 8 (100%) of 8 patients in Group-I and in 4 (33%) of 12 patients in Group-II. In Group-I, the total defect score (13 ± 6 vs. 4 ± 3, $p < 0.01$) was higher, and improvement in the total defect score was poorer than in Group-II (19 ± 11% vs. 59 ± 22%, $p < 0.01$).

DISCUSSION

Although vasospasm can be induced by various kinds of stress in daily life, attacks usually occur at night or in the early morning and can often be suppressed by calcium antagonists.[19] However, as in case 14 in Group-A (Fig. 3), some patients experience a recurrence of chest pain, acute myocardial infarction or sudden death despite receiving treatment.[1,12] Provocation tests of coronary vasospasm are consequently important in the diagnosis and treatment of this disease. Infusion of ergonovine into the coronary arteries can safely induce vasospasm with a high degree of probability and good reproducibility.[4,12–15] It is expected that administration of drugs which can suppress ergonovine-provoked vasospasm can eliminate attacks and prevent sudden death during treatment.

Some patients with vasospastic angina develop abnormal left ventricular wall motion resulting from repeated vasospastic attacks. This suggests that metabolic disorders occur in these patients.[20,21] Fatty acid is one of the major substrates for normal myocardial energy metabolism. It is therefore important to determine the state of

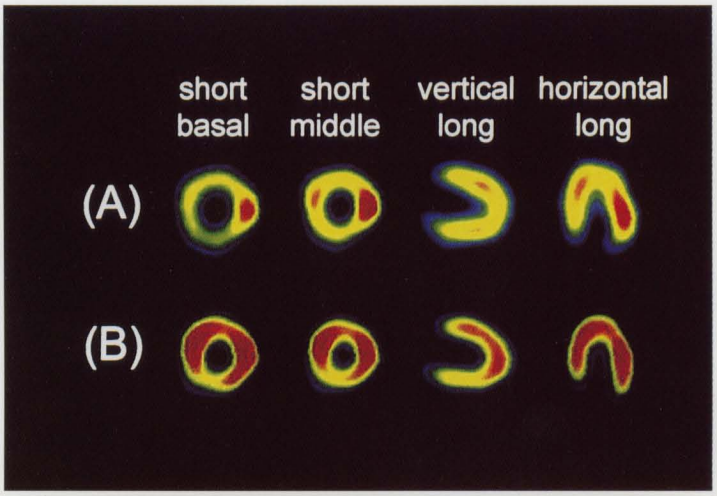

Fig. 2 BMIPP scintigrams of vasospastic angina before and after medical treatment (Case 2 in Group-A). (A) He had spontaneous vasospastic attacks and coronary vasospasm was induced in the left descending and right coronary arteries by ergonovine provocation. Decreased BMIPP uptake was shown in anterior, interventricular septum, inferior and apex regions. The total defect score was 27. (B) After 6 months of medical treatment, anginal attacks were completely suppressed and vasospasm was not re-induced by ergonovine provocation. The total defect score was 4 and the improvement of total defect score was 85%.

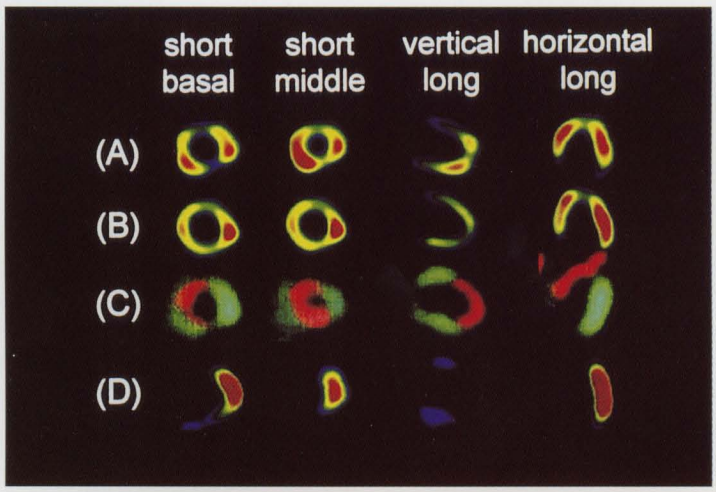

Fig. 3 BMIPP scintigrams of vasospastic angina before and after medical treatment (Case 14 in Group-A). (A) He had spontaneous vasospastic attacks and coronary vasospasm was induced in the left descending and right coronary arteries by ergonovine provocation. Decreased BMIPP uptake was shown in anterior, inferior and apex regions. The total defect score was 27. (B) Although anginal attacks were completely suppressed 6 months after medical treatment, the total defect score was 27 and the improvement of total defect score was 0%. He did not agree to re-study with coronary angiography and additional treatment. (C) Three months after a second BMIPP scintigraphy, he had an anterior myocardial infarction. Figures show dual SPECT of ^{201}TlCl (green) and ^{99m}Tc-pyrophosphate (red). (D) Figures show BMIPP scintigram at 2 weeks after the acute myocardial infarction

myocardial fatty acid metabolism in order to determine the viability and ischemic condition of the myocardium. Although positron computed tomography has been useful for evaluating fatty acid metabolism in the myocardium, BMIPP, a recently developed ^{123}I-labeled fatty acid with side chains, has been employed to clarify stunned myocardium and pathological conditions related to the viability of the myocardium during acute myocardial infarction.[5–8] As decreased BMIPP uptake can be detected for about 1–3 months, it is expected to be utilized in the diagnosis of vasospastic angina.[5–10] We therefore performed BMIPP scintigraphy within 2 weeks before car-

diac catheterization in this study.

In the present study, regional wall motion was reduced in 19 (36%) of 53 patients with vasospastic angina. This suggests that the so-called stunned myocardium resulted from vasospasm, though no coronary stenosis was observed in the coronary arteriography, and the ^{201}TlCl myocardial scintigram was normal. In 7 of the 9 patients who could be re-examined during treatment, reduced left ventricular wall motion was alleviated 6 months after starting treatment in the initially exhibited region. These results also support the above hypothesis.

On the other hand, BMIPP uptake decreased in 47 (89%) of the 53 patients. In addition, the territorial region of vasospasm-induced coronary artery was consistent with the region with decreased BMIPP uptake, and BMIPP uptake was decreased in the region where left ventricular wall motion was reduced in most patients. Reduced wall motion was more frequently associated with patients having multiple artery vasospasm than patients having single vasospasm, and more frequently found in Group-A than in Group-B. Abnormalities were more frequently revealed by BMIPP scintigraphy than by left ventriculography. In some patients who had a long interval after the chest pain attack, wall motion was normal despite decreased BMIPP uptake. Two reasons are suggested for these results. Although moderate or severe ischemic attacks cause abnormal left ventricular wall motion and decreased BMIPP uptake, mild ischemic attacks may cause only decreased BMIPP uptake. Secondly, abnormal BMIPP uptake may last longer than abnormal ventricular wall motion.

Although non-invasive diagnosis of vasospastic angina has been performed by defect pattern identification or redistribution with ^{201}TlCl during a vasospastic attack induced by exercise or hyperventilation, Koyanagi et al.[22] reported that the sensitivity for the diagnosis of vasospasm with exercise ^{201}TlCl scintigraphy was 44%.[21,22] In this study, the sensitivity and specificity for detecting vasospasm-induced coronary artery with BMIPP scintigraphy (determined by analyzing the location of the decreased BMIPP uptake region, and coronary vasospasm induced by ergonovine provocation as a reliable standard) were 71% and 88%, respectively. Our results are therefore comparable to those obtained with invasive techniques.[12–14] This strongly suggests that BMIPP reflects myocardial damage resulting from vasospasm more accurately than ^{201}TlCl scintigraphy or left ventriculography.

In the 12 (Group-II) of 20 patients re-examined by BMIPP scintigraphy 6 months after starting medical treatment, the decreased BMIPP uptake regions improved. This suggests that myocardial damage involving fatty acid metabolism might recover within 6 months. If decreased BMIPP uptake is not alleviated after 6 months of treatment, patients with vasospastic angina should be given additional treatment irrespective of cardiac symptoms.

Decreased BMIPP uptake was observed in some of our control subjects, especially in conjunction with reduced wall motion, as indicated by left ventriculography. We suspect that these patients had coronary vasospasm and were false-negative for ergonovine provocation. In all 5 subjects in Group-C who had decreased BMIPP uptake and could be re-examined during medical treatment, decreased BMIPP uptake was alleviated 6 months after treatment, supporting our hypothesis.

We had previously encountered patients with vasospastic angina which appeared to be completely suppressed, but some of them subsequently experienced sudden death or myocardial infarction (Fig. 3), and those incidences prompted this study. It is extremely difficult to frequently repeat invasive tests such as left ventriculography or coronary angiography. The effects of treatment can be more effectively judged, therefore, by observing the regions with decreased uptake in non-invasive BMIPP myocardial imaging. Non-invasive BMIPP scintigraphy should be remarkably useful. We now judge the effect of medical treatment for vasospasm by using ambulatory electrocardiogram monitoring and BMIPP scintigraphy before and after 6 months of treatment.

In conclusion, the territorial regions in which vasospasm was induced by ergonovine provocation, regions with abnormal left ventricular wall motion, and BMIPP myocardial scintigrams were compared in patients with vasospastic angina before and after medical treatment. Fatty acid metabolic imaging with BMIPP SPECT permitted the evaluation of vasospastic regions and non-invasive judgement of the effects of medical treatment.

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REFERENCES

1. Braunwald E, Kloner EA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation* 60: 1146–1149, 1982.
2. Kloner RA, DeBoer LWV, Darsee JR, Ingwall JS, Brounwald E. Prolonged metabolic, functional, ultrastructural abnormalities following transient myocardial ischemia without infarction. *Clin Res* 28: 615A, 1980.
3. Fournier C, Boujon B, Hebert JL, Zamani K, Grimon G, Blondeau M. Stunned myocardium following coronary spasm. *Am Heart J* 121: 593–595, 1991.
4. Watanabe K, Izumi T, Inomata T, Miyakita Y, Takahashi M, Suzuki M, et al. Vasospastic angina and regional left ventricular hypokinesis. *Matsushita Med J* 33: 105–115, 1994.
5. Goodman MM, Kirsch G, Knapp FF Jr. Synthesis and evaluation of radioiodinated terminal p-iodophenyl-substituted α- and β-methyl branched fatty acids. *J Med Chem* 27:

390–397, 1984.
6. Knapp FF Jr, Ambrose KR, Goodman MM. New radioiodinated methyl-branched fatty acids for cardiac studies. *Eur J Nucl Med* 12: S39–S44, 1986.
7. Tamaki N, Kawamoto M, Yonekura Y, Fujibayashi Y, Takahashi N, Konishi J, 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.
8. Nishimura T, Sago M, Kihara K, Oka H, Shimonagata T, Katabuchi T, et al. Fatty acid myocardial imaging using ^{123}I-β-methyl-iodophenyl pentadecanoic acid (BMIPP): Comparison of myocardial perfusion and fatty acid utilization in canine myocardial infarction (Occlusion and reperfusion model). *Eur J Nucl Med* 15: 341–345, 1989.
9. Tamaki N, Kawamoto M, Yonekura Y, Takahashi R, Nohara H, Kambara J, et al. Combined imaging using iodine-123 branched fatty acid analogue and thallium for assessing ischemic but viable myocardium. *J Nucl Med* 33: 885–886, 1992.
10. Fujiwara S, Takeishi Y, Atsumi H, Takahashi K, Tomoike H. Fatty acid metabolic imaging with iodine-123-BMIPP for the diagnosis of coronary artery disease. *J Nucl Med* 38: 175–180, 1997.
11. Yamabe H, Abe H, Yokoyama M, Shiotani H, Kajiya S, Mori T, et al. Resting ^{123}I-BMIPP scintigraphy in diagnosis of effort angina pectoris with reference to subsets of the disease. *Ann Nucl Med* 12: 139–144, 1998.
12. Watanabe K, Inomata T, Miyakita Y, Takahashi M, Suzuki T, Koyama S, et al. Electrophysiologic study and ergonovine provocation of coronary spasm in unexplained syncope. *Jpn Heart J* 34: 171–182, 1993.
13. Schroeder JS, Bolen JL, Quint RA, Clark DA, Hyden WG, Higgins CB, et al. Provocation of coronary spasm with ergonovine maleate: new test with results in 57 patients undergoing coronary arteriography. *Am J Cardiol* 40: 487–491, 1977.
14. Curry RC, Pepine CJ, Sabom MB, Feldman RL, Christie LG, Conti CR. Effects of ergonovine in patients with and without coronary artery disease. *Circulation* 56: 803–809, 1977.
15. Heupler FA, Proudfit WL, Razavi M, Shirey EK, Greenstreet R, Sheldon WC. Ergonovine maleate provocative test for coronary arterial spasm. *Am J Cardiol* 41: 631–640, 1978.
16. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LSC, et al. AHA Comittee Report: A reporting system on patient evaluated for coronary artery disease. *Circulation* 51: 5–40, 1975.
17. Sakata K, Shirotani M, Yoshida H, Kurata C. Iodine-123 metaiodobenzylguanidine cardiac imaging to identify and localize vasospastic angina without significant coronary artery narrowing. *J Am Coll Cardiol* 30: 370–376, 1997.
18. Segar DS, Brown SE, Sawada SG, Ryan T, Feigenbaum H. Dobutamine stress echocardiography: correlation with coronary lesion severity as determined by quantitative angiography. *J Am Coll Cardiol* 19: 1197–1202, 1992.
19. Watanabe K, Izumi T, Miyakita Y, Koyama S, Ohshima M, Inomata T, et al. Efficacy of amlodipine besilate therapy for variant angina: evaluation by 24-hour Holter monitoring. *Cardiovasc Drugs Ther* 7: 923–928, 1993.
20. Yamamichi Y, Kusuoka H, Morishita K, Shirakami Y, Ito O, Nishimura T, et al. Metabolism of iodine-123-BMIPP in perfused rat hearts. *J Nucl Med* 36: 1043–1050, 1995.
21. Van der Vuss GJ, Glatz JFC, Stam HCG, Reneman RS. Fatty acid homeostasis in the normoxic and ischemic heart. *Physiological Review* 72: 906–918, 1992.
22. Koyanagi S, Sakai K, Irie T, Takeshita A, Nakamura M, Nakagaki O. Exercise-induced silent myocardial ischemia in patients with vasospastic angina. *Am Heart J* 119: 551–556, 1990.
23. Imamura T, Nagatomo Y, Nakagawa S, Koiwaya Y, Hoshi H, Watanabe K, et al. Hyperventilation thallium-201 myocardial imaging for the diagnosis of vasospastic angina. *Clin Nucl Med* 12: 729–734, 1987.