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A long-acting calcium antagonist over one year did not improve BMIPP myocardial scintigraphic imagings in patients with pure coronary spastic angina

Shozo SUEDA,* Akira OSHITA,* Yousuke IZOE,* Hiroaki KOHNO,* Hiroshi FUKUDA,* Takaaki OCHI** and Tadao URAOKA***

*Department of Cardiology, Saiseikai Saijo Hospital
**Department of Cardiology, Takanoko Hospital
***Department of Cardiology, Kita Medical Association Hospital

Background: Calcium antagonists (Ca) have been effective in reducing angina attacks in patients with variant angina. However, there are no reports regarding the effectiveness of Ca on myocardial fatty acid metabolic images in patients with pure coronary spastic angina (CSA). ***Objectives:*** This study sought to examine the correlation between myocardial fatty acid metabolic images and the medical treatment of Ca in patients with pure CSA. ***Methods and Results:*** This study included 35 consecutive patients (28 men, mean age of 66 ± 10 years) with angiographically confirmed coronary spasm and no fixed stenosis. Long-acting Ca was administered to all 35 patients. Isosorbide dinitrate / nicorandil / another Ca / beta-bloker were administered when chest pain was not controlled. Using an iodinated fatty acid analogue, 15-(*p*-[iodine-123]iodophenyl)-3-(*R*,*S*)methylpentadecanoic acid (BMIPP), myocardial scintigraphies with intravenous adenosine triphosphate infusion were performed before cardiac catheterization and 12 mo after medical therapy. According to the medical control states, these 35 patients were classified into 3 groups; response (disappearance of angina attacks, 12 pts, 60 ± 11 years), partial response (angina attacks < 4/mo, 12 pts, 67 ± 10 years), and no response to therapy (angina attacks ≥ 4/mo, 11 pts, 71 ± 6 years). Reduced BMIPP uptake was observed in 24 (69%) of 35 patients before the treatment. Reduced BMIPP uptake was also found in 18 patients (51%) after 12 mo. Normal BMIPP uptake after 12 mo therapy was observed in about half (response: 42%, partial response: 58%, no response: 45%) of patients among the 3 groups. There was no difference regarding the value of washout rate (WOR) (response; 10 ± 7 (before), 14 ± 8% (12 mo)), partial response; 11 ± 7, 10 ± 5%, no response; 13 ± 9, 14 ± 8%) among the 3 groups. The defect scores of BMIPP in the three groups were not different during at least one year medical therapy. No difference regarding the distribution of other medical therapies (angiotensin converting enzyme inhibitors / angiotensin receptor blockers / beta-blockers / statins) was found. The administration of Ca and isosorbide dinitrate / nicorandil and 2 Ca was significantly higher in the poor than in the good control patients. ***Conclusions:*** Long-acting Ca over one year did not improve myocardial fatty acid metabolic images in patients with pure CSA. This may be related to silent ischemia.

Key words: fatty acid metabolism, coronary spastic angina, long-acting calcium antagonist

INTRODUCTION

VARIOUS CALCIUM ANTAGONISTS (Ca) were effective in suppressing the number of spontaneous attacks in patients with variant angina or coronary spastic angina (CSA).[1–4] We had already reported that the widespread use of Ca decreased the occurrence of variant angina in Japan.[5]

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For reprint contact: Shozo Sueda, M.D., Department of Cardiology, Saiseikai Saijo Hospital, Tsuitachi 269–1, Saijo, Ehime 793–0027, JAPAN.
E-mail: EZF03146@nifty.com

However, we also reported the limitations of medical therapy in patients with pure CSA. Long-acting Ca suppressed chest pain or chest discomfort in 38% of patients, while 42% showed resistance to medical therapy in patients with pure CSA.[6]

An iodinated fatty acid analogue, 15-(*p*-[iodine-123] iodophenyl)-3-(*R*,*S*)methylpentadecanoic acid (BMIPP) can be used for ischemic memory imaging in patients with coronary artery disease.[7–9] Because altered fatty acid utilization may be associated with repetitive ischemic episodes, BMIPP single photon emission computed tomography (SPECT) may hold promise for detecting coronary spasms. Myocardial fatty acid metabolism may be decreased in patients with CSA due to frequent angina attacks. Long-acting Ca decrease the number of angina attacks and may improve myocardial fatty acid metabolic findings in patients with pure CSA. In this study, we sought to examine whether the administration of a long-acting Ca improved the myocardial fatty acid metabolic images in patients with pure CSA.

METHODS

Study patients: This study included 35 patients (28 men and 7 women, mean age of 66 ± 10 years) with pure CSA. As shown in Table 1, all 35 patients had normal or near normal coronary arteries and had angiographically confirmed coronary artery spasms by intracoronary injection of acetylcholine or ergonovine. Essential hypertension was observed in 9 patients (26%), 28 (80%) were habitual smokers, 15 (43%) had hyperlipidemia and 8 (23%) had overt diabetes mellitus. The values of serum cholesterol, triglycerides, and high-density-lipoprotein (HDL) cholesterol were 192 ± 29 mg/d*l*, 122 ± 56 mg/d*l*, and 53 ± 16 mg/d*l*, respectively. Three patients had a 10-yr or longer history of hypertension and in all 9 patients with hypertension, blood pressure was well controlled with medication. In addition, the value of mean glycohemoglobin was < 7.0% in all 8 patients with diabetes mellitus.

According to the control state during one year, we classified these 35 patients into three groups, consisting of 12 patients with disappearance of chest pain attacks (response to therapy) for at least 1 year, 12 patients with < 4 attacks/month (partial response to therapy), and 11 patients ≥ 4 attacks/month (no response to therapy). Written informed consent was obtained from all patients before the study, and the protocol was in agreement with the guidelines of our institutional ethics committee.

Medication: All 35 patients were treated with long-acting Ca for at least one year. After hospital discharge, all patients returned for regular visits (once a month) to a special clinic for CSA patients. When angina was not controlled with one Ca, a long-acting nitrate or nicorandil was added. In addition, another Ca or a beta-blocker was added when angina was not controlled with the above therapy. No patients were lost to follow-up. For hospitalized patients, we checked residual drugs at each regular visit and confirmed the number of chest pain attacks per month requiring sublingual administration of nitroglycerin in detail. We excluded chest pain attacks due to failure to take regular medicine. The doses of Ca, isosorbide dinitrates, or nicorandil were not gradually tapered in patients who experienced no angina after the angiogram. The mean duration of chest pain attacks before hospitalization was 4.9 ± 4.8 years (range: 0–12 years). Ca, isosorbide dinitrates, nicorandil and beta-blockers were administered in 100%, 31%, 34%, and 3% of all patients, respectively. Angiotensin converting enzyme inhibitors (ACEI) / angiotensin receptor blockers (ARB) were administered in 9%, while statins were given to 20%.

Myocardial fatty acid metabolic images: In this study, we performed BMIPP myocardial scintigraphy with intravenous administration of adenosine triphosphate over 5 min at a constant rate of 0.16 mg/min per kg body weight with the aid of an accurate computerized infusion pump system.[10] BMIPP cardiac scintigraphy was performed before and 12 mo after the medication in all 35 patients. The BMIPP (Nihon Medi-Physics Co., Nishinomiya, Hyogo, Japan) was injected at a dose of 111 MBq (3 mCi) in the fasting state. Early images (twenty minutes) and delayed images (four hours) after BMIPP injection were acquired using a Toshiba GCA 901A/SB (Toshiba Co., Tokyo) equipped with a low energy, high-resolution collimator and interfaced to a computer (Toshiba GMS-550U). Two 256 × 256 matrix planar images were added in the anterior and left anterior oblique views. The energy discriminator of the camera was set on the 159-keV photopeak of BMIPP with a 20% window. The short-axis tomographic images encompassing the entire left ventricle were reconsructed at 6-mm intervals. Myocardial segments were divided into five-regions: anterior, septal, inferoposterior, lateral, and apical regions. Correspondence between coronary artery territory and regions was anterior and septal to the left anterior descending artery, lateral to left circumflex artery, inferoposterior to right coronary artery and the apex in the principle artery corresponding to the left anterior descending artery. The left ventricular myocardium was divided into 20 segments to visually score the tracer uptake in each SPECT study on a four-point grading system: 0 = normal uptake; 1 = slightly reduced; 2 = moderately reduced; and 3 = severely reduced.[11] The defect scores of early BMIPP uptake were visually assessed by 2 physicians who were unaware of the coronary angiography. The total defect score was calculated as the summation of all counts. Scores of 2 and 3 were considered to be significant reduced uptake. We assessed the improvement with ≥ 2 point decrease in total defect score between the serial BMIPP scintigrams, while we assessed the worsening

with ≥ 2 point increase in the total defect score. We also assessed no change with < 2 points changes in total defect scores. Myocardial BMIPP washout rate (WOR; %) was defined as the percent change in activity from the 20 minute and 4-hour images within the left ventricle.

Echocardiography and left ventriculography: Echocardiography was performed using a Toshiba SSH-160A system with a 3.5-MHz transducer. Left ventricular end-diastolic, end-systolic diameters, intraventricular septum, and posterior wall thickness (LVDd, LVDs, IVST, and PWT, respectively) were measured on the 2-dimensional parasternal long-axis view according to the criteria recommended by the American Society of Echocardiography. The right anterior oblique view of the left ventriculograms before coronary arteriography to avoid the effect of coronary spasm on wall motion, and left ventricular ejection fraction were measured by the area-length method.

Table 1 Patient characteristics

Total number of patients	35
Male/Female	28/7
Age (year)	66 ± 10
Duration of angina (year)	4.9 ± 4.8
Hypertension	9 (26%)
History of smoking	28 (80%)
Curent smoker	15 (43%)
Hyperlipidemia	15 (43%)
Diabetes mellitus	8 (23%)
T. cholesterol (mg/d*l*)	192 ± 29
Triglyceride (mg/d*l*)	122 ± 56
HDL-cholesterol (mg/d*l*)	53 ± 16
Single spasm	11
Multiple spasm	24

Acetylcholine (ACh) and Ergonovine (ER) spasm provocation test: Coronary arteriography was performed in the fasting state with the Sones technique through the brachial artery between 10:00 am and 4:00 pm under no medication for at least 24 hour except nitroglycerine, which was stopped 6 hours before the study. Control coronary arteriographies of the left coronary artery (LCA) in the right anterior oblique with caudal projection and of the right coronary artery (RCA) in the left anterior oblique with cranial projection were obtained by the injection of 8–10 m*l* of Iopamiron (Schering, Bracco, Italy). A bipolar electrode catheter was inserted into the right ventricular apex through the femoral or antecubital vein and was connected to a temporary pacemaker set at the rate of 45 beats/min.

Provocation of coronary artery spasm was initially performed with an intracoronary injection of acetylcholine (ACh).[12–15] ACh chloride (Neucholin-A, 30 mg/2 m*l*) [Zeria Shinyaku; Tokyo, Japan] dissolved in warm 0.9% saline solution was administered over 20 seconds. ACh was injected in incremental doses of 20, 50, and 80 μg into the RCA and 20, 50, and 100 μg into the LCA with at least a 3-minute interval between each injection. Coronary arteriography was performed when ST segment changes, chest pain or both occurred, or 1 minute after the completion of each injection. Intracoronary injection of ACh into the responsible vessel was not performed if coronary artery spasm occurred spontaneously during coronary angiography.

Intracoronary injection of ergonovine (ER) was then administered 10 minutes after the last ACh test.[16–18] ER

Table 2 Comparisons of clinical characteristics among three groups

	Response	Partial response	No response
Number of patients	12	12	11
Male	10	10	8
Age (year)	60 ± 11	67 ± 10*	71 ± 6*
Duration of angina (year)	1.3 ± 2.1	4.8 ± 4.2*	9.0 ± 4.4*
Risk factors			
HT/Smo/HL/DM	2/9/7/3	2/10/3/2	5/9/5/3
T. cholesterol (mg/d*l*)	187 ± 30	199 ± 23	188 ± 37
HDL-cholesterol (mg/d*l*)	55 ± 14	51 ± 10	44 ± 10*
LDL-cholesterol (mg/d*l*)	103 ± 24	137 ± 16*	134 ± 18*
Triglyceride (mg/d*l*)	144 ± 73	94 ± 35	135 ± 19
Single vs. multiple spasm	2 : 9	6 : 6	3 : 8
Mean number of proved spasm	2.1 ± 0.7	1.7 ± 0.8	2.0 ± 0.7
Left ventricular end-diastolic diameter	48.8 ± 3.2	49.1 ± 3.6	50.0 ± 2.5
Left ventricular end-systolic diameter	27.4 ± 3.2	26.2 ± 4.7	30.1 ± 2.8
Intraventricular septum thickness	8.2 ± 1.0	8.5 ± 0.8	8.2 ± 0.9
Posterior wall thickness	7.6 ± 0.8	8.1 ± 0.8	8.1 ± 1.2
Left ventricular ejection fraction (%)	72.6 ± 5.3	69.2 ± 8.4	71.2 ± 6.5

(HT: hypertension, Smo: smoking, HL: hyperlipidemia, DM: diabetes mellittus, HDL: high-density-lipoprotein, LDL: low-density-lipoprotein, *: $p < 0.05$ vs. response group)

(Ergomerine injection F, 0.2 mg/m*l*) [Fuji Seiyaku; Tokyo, Japan] in 0.9% warm saline solution was injected in 10 μg/min for 4 minutes for a maximal dose of 40 μg into the RCA and 16 μg/min over 4 minutes for a total dose of 64 μg into the LCA, with at least a 5-minute interval between each injection. Coronary arteriography was performed when significant ST changes, chest pain, or both developed, or 2 min after the completion of each injection. When coronary artery spasm was provoked and did not spontaneously resolve within 3 min after the completion of ACh and ER injection, or when hemodynamic instability due to coronary artery spasm occurred, 2.5 to 5.0 mg of isosorbide dinitrate was administered into the responsible vessel. In all patients, coronary arteriography after the administration of 2.5 to 5.0 mg of isosorbide dinitrate was performed in multiple projections at the end of the study to estimate atherosclerotic lesions.

Positive coronary spasm was defined as > 99% luminal narrowing. Focal spasm was defined as a discrete transient vessel narrowing localized in the major coronary artery > 99%. Diffuse spasm was diagnosed when a transient vessel narrowing was > 90% compared to the baseline coronary angiography was observed from the proximal to the distal segment in the 3 major coronary arteries. The degree of ST-segment depression was measured 80 m sec after the J point, and we considered at least 1 of the following ischemic electrocardiographic changes was demonstrated during and/or after the ACh or ER test to be an indication of positive coronary spasm: 1) ST-segment elevation of $\geq$ 0.2 mV in at least 2 related leads, 2) ST-segment depression of 0.1 mV of a horizontal or downsloping type, or $\geq$ 0.2 mV of a junctional type. During the study, arterial blood pressure and 1 ECG lead (II) were continuously monitored on an oscilloscope with a polygraph. A standard 12 lead ECG was recorded every 30 seconds with a radiolucent carbon electrode used as the chest lead electrode.

Angiographic analysis: The percent luminal diameter narrowing of coronary arteries was measured by an automatic edge-contour detection computer analysis system (CARDIO 500, Kontron Instrument, Tokyo). The size of the coronary catheter was used to calibrate the image in millimeters and the measurement was performed in the same projection of coronary angiography at each stage. Patients with catheter-induced spasms were excluded from this study. Significant organic stenosis was defined as $\geq$ 50% luminal narrowing. Coronary arteries were measured after intracoronary administration of isosorbide dinitrate (2.5–5.0 mg) to evaluate coronary atherosclerosis according to the AHA classification system.[19]

Statistical analysis: Values are expressed as means ± SD. Differences among proportions were analyzed by the chi-square test with correction or the analysis of variance test. A p value < 0.05 was considered significant.

RESULTS

Neither chest pain nor ischemic electrocardiographic changes were recognized on any 70 of the BMIPP myocardial scintigraphic examinations with intravenous adenosine triphosphate infusion.

Comparisons of clinical characteristics among the 3 groups

As shown in Table 2, patients in the partial response and no response groups were significantly older than those in the response group. The duration of angina before admission in patients in the no response group was significantly longer than the other 2 groups, and partial response group had a longer duration of angina before admission than the

Table 3 Abnormal BMIPP SPECT findings and spasm site among three groups

	No.	before	12 mo	Spasm site
Response	1	inf		#1(d), #6(d), #11(d)
	2	ant	ant	#2(f), #7(f)
	3	inf	apex	#2(f), #8(d)
	4			#4(f)
	5			#1(d), #6(d), #11(d)
	6	inf		#1(d), #6(d)
	7	apex	inf	#3(f), #6(f)
	8	ant	apex	#2(f), #6(f)
	9	ant/inf	ant	#1(d), #6(d), #11(d)
	10		sep/inf	#2(f), #7(f)
	11	inf	sep/inf	#3(d), #7(d)
	12			#7(d)
Partial response	1		sep	#4(d), #7(d)
	2	ant/inf		#7(f)
	3	ant	ant/lat	#7(f), #11(d)
	4			#2(f), #7(f)
	5			#2(d)
	6	inf		#1(d)
	7	ant/apex		#2(d), #6(f)
	8	inf	inf	#3(d)
	9	inf/ant	inf	#1(d), #6(d), #11(d)
	10			#4(d), #7(d)
	11	inf		#2(d)
	12		inf	#3(d)
No response	1	ant/lat	ant/lat	#2(d), #6(d), #11(d)
	2	inf/ant	inf	#3(f), #7(f)
	3	inf		#1(d)
	4			#7(d)
	5	inf	inf	#3(d)
	6	inf	inf	#2(f), #7(d)
	7	inf	inf	#1(f), #6(f)
	8	inf	inf	#2(f), #7(f)
	9	inf		#4(d), #6(d), #11(d)
	10			#2(d), #8(d)
	11	apex		#6(d), #11(d)

(d: diffuse spasm, f: focal spasm, inf: inferior, ant: anterior, lat: lateral, sep: septal)

response group. Risk factors, such as hypertension, history of smoking, hyperlipidemia, and diabetes mellitus were not different among the 3 groups. The values of total cholesterol, HDL cholesterol, and triglycerides were not different among the 3 groups. The value of HDL cholesterol in patients in the no response group was significantly lower than the other 2 groups, while the value of low-density-lipoprotein (LDL) cholesterol in patients in the response group was significantly lower than the other two groups. The mean number of spasm-provoked vessels was not different among the 3 groups, while single spasm was frequently observed in the partial response group. The left ventricular ejection fraction and echocardiographic parameters were not different among the 3 groups and no patients had left ventricular thickness > 10 mm, as shown in Table 2.

Comparisons of myocardial fatty acid metabolic images

As shown in Table 3, reduced BMIPP uptake was observed in 24 (69%) of 35 patients, with complete or partial agreement between the BMIPP abnormality and coronary territory observed in all 24 patients before the treatment, while it was also found in 18 patients (51%) after 12 mo. Normal BMIPP uptake after 12 months' medical therapy was observed in 42%, 58%, and 45% of patients in the 3 groups. The washout rate before starting medication and 12 mo after medical therapy were not different among the 3 groups, as shown in Table 4. The defect scores of BMIPP in the 3 groups were decreased but not significantly so over one year medical therapy.

Table 4 Comparisons of I-123 BMIPP data among three groups

	Response	Partial response	No response
Washout rate (%)			
before	10.0 ± 7.4	11.0 ± 7.2	12.9 ± 8.9
12 mo	13.6 ± 7.7	10.2 ± 5.1	13.8 ± 7.8
Defect score			
before (early)	5.1 ± 2.3	6.0 ± 4.3	9.1 ± 5.6*
before (delay)	5.0 ± 3.7	5.5 ± 4.2	8.9 ± 6.0*
12 mo (early)	4.0 ± 2.4	5.0 ± 2.9	7.8 ± 6.0
12 mo (delay)	4.3 ± 4.2	5.7 ± 3.3	9.6 ± 6.9*

(*: $p < 0.05$ vs. response)

Serial changes of BMIPP defect scores

As shown in Figure 1, in all 35 patients, the defect scores of BMIPP early images showed no changes in 51%, 34% of patients had improvement of BMIPP scintigraphic findings, while worsening of BMIPP images was observed in 14% of patients. In contrast, the defect scores of BMIPP delayed images showed no changes in 29%, improvement in 37%, and worsening in 34% of patients. Among the 3 groups, the distribution of the defect scores in serial BMIPP scintigraphic findings, such as improvement, no change, and worsening, was different but not significantly so.

The interval from the last angina attack to the first BMIPP SPECT study

The intervals from the last angina attack to the first BMIPP SPECT study were analyzed. In patients in the response group, the intervals were 86 ± 224 days, while in patients in the partial response group, the intervals were 30 ± 14 days. In contrast, in patients in the no response group, the intervals were 7 ± 4 days.

Comparisons of medical therapy among the 3 groups

Long-acting Ca was administered in all 35 patients after cardiac catheterization procedures. The distribution of amlodipine, benidipine, nifedipine CR, diltiazem R, and cilnidipine was not different among the 3 groups, as shown in Table 5. Short-acting Ca was administered in 2 patients in the partial response group and one patient in the no response group. The administration of isosorbide dinitrate and nicorandil in patients with no response group was higher than the other 2 groups, but not significantly so. ACEI or ARB was administered in one patient in the response group and 2 patients in the no response group. A beta-blocker was administered in only one patient in the

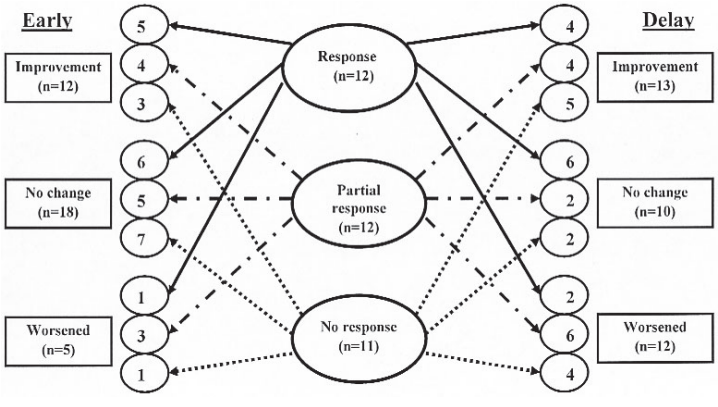

Fig. 1 Serial change of defect score between early and delayed images.

Table 5 Comparisons of medical therapy among three groups

	Response	Partial response	No response
Long-acting Ca antagonist	12 (100)	12 (100)	11 (100)
Amlodipine	2	6	3
Benidipine	5	5	8
Nifedipine CR	2	0	2
Diltiazem R	1	1	2
Cilnidipine	2	0	0
Short-acting Ca antagonist	0	2 (17)	1 (9)
ISDN	2 (17)	2 (17)	7 (64)
Nicorandil	3 (25)	4 (33)	5 (45)
ACEI/ARB	1 (8)	0	2 (18)
Beta-blocker	0	0	1 (9)
Statin	2 (17)	2 (17)	3 (27)
Ca & ISDN/Nicorandil	3 (25)	5 (42)	7 (64)
2 Ca antagonists	0	2 (17)	4 (36)

(Ca: calcium, ISDN: isosorbide dinitrate, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, ( ): %)

Table 6 The correlation of serial changes between BMIPP SPECT findings and WOR

	No.	R/PR/NR	WOR (before)	WOR (12 mo)	WOR improvement	WOR worsened
Abnormal SPECT continuation	15	6/3/6	13.2 ± 7.6	14.1 ± 7.2	7 (47%)	8 (53%)
New abnormal SPECT appearance	3	1/2/0	15.0 ± 1.8	14.9 ± 9.1	2 (67%)	1 (33%)
	18	7/5/6	13.5 ± 6.9	14.3 ± 7.2	9 (50%)	9 (50%)
Abnormal SPECT disappearance	9	2/4/3	10.5 ± 7.9	10.8 ± 5.0	5 (56%)	4 (44%)
Normal SPECT	8	3/3/2	7.1 ± 7.3	10.4 ± 7.9	5 (63%)	3 (37%)
	17	5/7/5	8.9 ± 8.0	10.7 ± 6.3	7 (41%)	10 (59%)

(SPECT: single photon emission computed tomography, R: response, PR: partial response, NR: no response, WOR: washout ratio)

no response group. Statins were administered in 2 in the response, 2 in the partial response, and 3 patients in the no response group.

Correlations of serial changes between BMIPP SPECT findings and WOR

As shown in Table 6, 18 patients with abnormal BMIPP SPECT findings after 12 month's therapy showed abnormal continuation in 15 and new abnormal appearance in 3, while there were 17 normal SPECT findings on 12 month's therapy, consisting of 9 disappearance of abnormal up take and 8 normal up take on both tests. There was no change concerning the BMIPP WOR in any of the four groups on either test. No difference in the improvement of the value of BMIPP WOR was observed in any of the 4 groups. There were no correlations between the improvement on BMIPP SPECT findings and the normalization of value of BMIPP washout rate.

DISCUSSION

Medical therapy including a long-acting Ca did not improve the myocardial fatty acid metabolic images in patients with pure CSA in this study. Washout rate of BMIPP was not different during at least one year medical therapy. Moreover, the BMIPP defect scores did not decrease even in patients with pure CSA in the response and partial response groups over one year medical treatment.

Spontaneous remission or continuous spasmodicity

In this study, chest pain or chest discomfort was eliminated in only 34% of patients and the remaining 66% of patients had continuous vasospasmodicity, irrespective of the administration of long acting Ca.[5] Ca is not a fundamental drug to repair the injured endothelium or damaged smooth muscle. In some patients with CSA and high disease activity, only one omission of regular medicine might lead to a severe angina attack. Ca had no effect to recover the abnormal endothelium or damaged smooth muscle and only decreased the coronary tone. In the near future, if a new epochal drug is developed, coronary spasmodicity may be reduced in the longer term.

Comparisons with a previous study

Nakajima et al.[7] reported some clinical applications of BMIPP imaging in patients with CSA; (1) screening test to determine the necessity for coronary arteriography

accompanied by provocation testing, (2) coronary artery selection when performing provocative testing, (3) estimating present and past history of myocardial injury caused by spasms, (4) monitoring medical treatment. Moreover, they also reported that a discrepancy between BMIPP scintigraphic improvement and course of chest pain was observed in 5 (22%) of 23 patients who had initial BMIPP abnormalities. In this study, we followed the BMIPP imaging for more than one year and analyzed the WOR on BMIPP myocardial scintigraphy. Some patients showed BMIPP improvement despite persistent angina attacks, whereas others showed improved symptoms without improved BMIPP findings. This may be due to the various thresholds of angina attacks and silent ischemia. Detailed analysis of spasmodicity on an average day under medical therapy may be possible when adding the analysis of WOR to the BMIPP SPECT imaging.

Myocardial fatty acid metabolic images

The administration of long-acting Ca did not improve myocardial fatty acid metabolic images in patients with pure CSA; however, it did suppress chest pain attacks. In patients with acute myocardial infarction and chronic heart failure, ACEI therapy affects myocardial fatty acid metabolism.[20,21] In our study, only 3 patients received ACEI or ARB. Medical therapy, including Ca and isosorbide dinitrate / nicorandil had clinical limitations for improvement of myocardial fatty acid metabolism in patients with pure CSA. This may be why silent ischemia was often observed in patients with disappearance or decrease of angina attacks (response and partial response groups), and that medical therapy decreased the severity of angina attacks in patients with continuous symptoms (no response group). The administration of ACEI and ARB may potentially improve myocardial fatty acid metabolic images in pure CSA patients, as well as chronic heart failure and acute myocardial infarction. Long-term treatment with ACEI prevented coronary microvascular remodeling in an animal model of microvascular angina.[22] Sun et al. reported that myocardial ischemia, most probably due to coronary microvascular spasms, was demonstrated in a sizable number of patients with epicardial vasospasms.[23] The combination of Ca and ACEI/ARB may improve microvascular remodeling, and lead to an improvement in myocardial fatty acid metabolic images in patients with pure CSA.

Clinical implications

Spontaneous remission is a frequent outcome in Western people with variant angina.[24,25] Some authors reported that medical therapy can probably be discontinued at some point in most patients with a history of variant angina and, moreover, it is acceptable to begin to taper and discontinue treatment 6 to 12 months after angina disappears. However, persistent chest pains have been observed over many years in Japanese patients with pure CSA.[26,27] Coronary spasmodicity may continue because no improvement in myocardial fatty acid metabolic images is found in patients with pure CSA, irrespective of the administration of long-acting Ca. Longer term therapy, including improvements in the endothelium and smooth muscle, is necessary to decrease coronary spasmodicity in Japanese patients with pure CSA.

This study showed that the disappearance of angina attacks did not always indicate an improvement in vasospasmodicity. Myocardial fatty acid metabolic improvement may lead to clinical improvement. We recommend that medical therapy be reduced or stopped when myocardial fatty acid metabolic images and WOR of BMIPP reach the normal range and, moreover, angina attacks have disappeared.

Study limitations

This study had some limitations. One was that some patients had hypertension and were treated with antihypertensive drugs. Hypertensive heart disease may also influence fatty acid uptake. However, in this series, no patients had severe left ventricular hypertrophy on echocardiography and all patients had left ventricular and posterior wall thickness less than 10 mm, while the left ventricular ejection fraction was within the normal range. Second, was that we defined an angina attack as requiring sublingual nitroglycerine. Subclinical angina attacks without administration of sublingual nitroglycerine were ignored. The angina threshold and sensitivity were variable in each patient. Therefore, we could not detect all silent ischemia. Moreover, we could not detect the sum of total ischemic damage to the left ventricular muscle from the patients' anamnesis. Third, instead of rest BMIPP myocardial scintigraphies, we employed BMIPP myocardial scintigraphies with intravenous adenosine triphosphate infusion. However, neither ischemic changes nor any chest discomfort was observed in any of the 70 examinations. Further study is necessary to investigate the contribution of Ca to myocardial fatty acid metabolism in patients with CSA.

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