Effects of Anti-vasospastic Agents in Japanese Patients with Dilated Cardiomyopathy and Coronary Vasospasm

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SUMMARY

The pathogenesis of dilated cardiomyopathy (DCM) is unknown, but clinical evidence suggests that coronary vasospasm is associated with the development of DCM in some cases. In the present study, we aimed to clarify the prevalence of coronary vasospasm in patients with DCM, the characteristics of patients with DCM and coronary vasospasm, and the effects of anti-vasospastic agents on patients with DCM and coronary vasospasm. This study included 18 consecutive patients with DCM who underwent cardiac catheterization with ergonovine provocation testing. The patient was diagnosed as having coronary vasospasm if ergonovine induced coronary vasoconstriction $\geq 75\%$ diameter narrowing was observed compared to the diameter after nitroglycerin administration. Six (33%) patients were found to have coronary vasospasm and anti-vasospastic agents were added after the cardiac catheterization. The prevalence of atrial fibrillation in the patients with DCM and coronary vasospasm was greater than that in DCM without coronary vasospasm [67% vs 8% ($P < 0.05$)]. The left ventricular end-diastolic dimension decreased from 61 mm (56/64) to 55 mm (53/56) (median, 25th/75th percentile, $P < 0.05$) and the left ventricular ejection fraction increased from 36% (32/40) to 47% (46/48) (median, 25th/75th percentile, $P < 0.05$) after the administration of anti-vasospastic agents and 4 of the 6 patients improved symptomatically. Therefore, ergonovine provocation testing is useful in identifying patients with DCM and coronary vasospasm, in whom cardiac performance is expected to be improved with anti-vasospastic agent therapy. DCM patients with atrial fibrillation may be a clue for identifying patients with coronary vasospasm. (Jpn Heart J 2002; 43: 333-342)

Key words: Coronary vasospasm, Ergonovine, Dilated cardiomyopathy, Anti-vasospastic agents

DILATED cardiomyopathy (DCM) is manifested by marked chamber dilation, diffusely reduced left ventricular wall motion, and congestive heart failure. The pathogenesis of DCM is unknown, but clinical studies have suggested that coronary vasospasm plays a role in the development of DCM.^{1,2)} Shimizu, *et al*¹⁾ and

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Sakata, *et al*²⁾ demonstrated that anti-vasospastic agents are efficacious in the treatment of patients with multi-vessel coronary vasospasm, diffuse left ventricular hypokinesis, and mild left ventricular dilation. The aims of the present study were to clarify the prevalence of coronary vasospasm in patients with DCM, the characteristics of those patients with coronary vasospasm, and the effects of anti-vasospastic agents on those patients with coronary vasospasm.

METHODS

Patients: This study included 18 consecutive patients with DCM who underwent diagnostic cardiac catheterization with ergonovine provocation testing during the period from January 1998 through December 2000. Patients ranged in age from 36 to 78 years (median: 55 years) and included 12 men and 6 women. Left ventriculography showed that each of the 18 patients had left ventricular dilation (left ventricular end-diastolic volume index ≥ 90 mL/m²) and impaired systolic function (left ventricular ejection fraction $\leq 45\%$). No significant organic coronary lesions were detected in any of the patients. Three patients were in New York Heart Association (NYHA) functional class I, 14 patients in class II, and 1 patient in class III. Thirteen patients were in sinus rhythm and 5 had atrial fibrillation. Diuretics were prescribed for 11 patients, angiotensin-converting enzyme (ACE) inhibitors for 9, nitrates for 4, digitalis for 3, and calcium antagonists for 1. Nitrates and calcium antagonists were withdrawn at least 24 hours before cardiac catheterization. Table I summarizes the clinical characteristics of the patients. The study was explained to each patient before obtaining their written informed consent.

Coronary angiography and ergonovine provocation testing: Standard cardiac catheterization, including measurements of pressure and cardiac output, left ventriculography, and selective coronary angiography were performed. After confirming the absence of luminal narrowing $>50\%$, ergonovine provocation testing was performed. Ergonovine (methylethylergometrine maleate) was injected in incremental doses of 1, 5, and 10 μ g into the right coronary artery and 1, 5, 10, and 30 μ g into the left coronary artery over 1 minute with a 3-minute interval between each injection. A standard 12-lead electrocardiogram was recorded every minute. ST-segment changes were considered significant if a change ≥ 0.1 mV was observed during ergonovine provocation testing. Coronary angiography was performed to measure the diameter of the coronary artery 3 minutes after the injection of each dose of ergonovine or at the time when ischemic electrocardiographic changes were noted. The ergonovine provocation testing was terminated at the time when coronary vasoconstriction $\geq 75\%$ compared with the baseline diameter appeared, with or without ST-segment changes of ≥ 0.1 mV, or

when the patient complained of chest pain. After the ergonovine provocation testing was completed, 100 to 300 μg of nitroglycerin was administered to resolve any coronary spasm. Coronary angiography was performed again after the injection of nitroglycerin to confirm the reversal of coronary vasospasm. The degree of coronary vasoconstriction was calculated as: $[(\text{lumen diameter after nitroglycerin administration} - \text{minimum lumen diameter after ergonovine administration}) / \text{lumen diameter after nitroglycerin administration}] \times 100\%$. Patients were diagnosed as having coronary vasospasm, if ergonovine induced $\geq 75\%$ coronary vasoconstriction. A diffuse decrease of approximately 10 to 20 percent in the caliber of the coronary arteries is almost always seen in response to ergonovine, as shown in earlier studies.³⁻⁵⁾ The occurrence of narrowing exceeding 75 percent (50 percent in some laboratories) is considered to be diagnostic of spasm in epicardial coronary arteries like in the earlier studies.^{3,6-9)}

Administration of anti-vasospastic agents and follow-up echocardiography: We performed echocardiography before and after the administration of calcium antagonists and/or nitrates. In all of the patients with DCM and coronary vasospasm, calcium antagonists and/or nitrates were given after the cardiac catheterization. Echocardiograms were obtained using a Toshiba SSH-160A, SSA-370A, SSA-380A, or SSA-390A Ultrasonoscope (Toshiba Corp. Tokyo, Japan) equipped with a 2.5- or 3.75-MHz transducer. The left ventricular ejection fraction was calculated by the Teichholz method. After initial evaluation, all patients with DCM and coronary vasospasm were followed at Tsukuba University Hospital. The left ventricular end-diastolic dimension and ejection fraction were evaluated by echocardiography. The NYHA functional class was also reassessed at the end of the follow-up period.

Statistical analysis: Data are presented as the median, 25th/75th percentile. Significant differences were determined with the Mann-Whitney U test or Wilcoxon signed-ranks test as appropriate. Differences in frequencies were analyzed with the Fisher exact probability test, chi-squared test, or Mann-Whitney U test. Statistical calculations were performed using Statview software. A *P* value < 0.05 was considered statistically significant.

RESULTS

Our data indicate that 33% of the patients with DCM had coronary vasospasm, and also showed that DCM patients with coronary vasospasm were related to the complication of atrial fibrillation, and their left ventricular dilation and dysfunction were improved after the administration of calcium antagonists and/or nitrates in all of the patients with DCM and coronary vasospasm.

Prevalence of provoked coronary vasospasm in patients with DCM: In 6 of the

Table I. Clinical Characteristics of Patients with DCM

Case No.	Age (yr)	Gender	Chief complaint	NYHA	Smoking	af
1	48	M	Chest pressure	II	-	+
2	58	M	Exertional dyspnea, orthopnea	II	+	-
3	43	M	Hypertension	I	+	-
4	62	M	Exertional dyspnea, nocturnal dyspnea	II	-	+
5	60	M	Dyspnea, chest pain	II	-	+
6	53	M	Exertional dyspnea	II	-	+
7	48	F	Chest pain, loss of consciousness	II	-	-
8	67	M	Premature ventricular contraction	I	-	-
9	57	F	Dyspnea	II	-	-
10	57	F	Dyspnea, orthopnea	III	-	-
11	64	M	Cough	II	+	-
12	48	M	Nocturnal dyspnea	II	+	+
13	47	F	Electrocardiographic abnormalities	II	-	-
14	78	M	Premature ventricular contraction	I	-	-
15	36	M	Cough	II	+	-
16	50	F	Dyspnea	II	+	-
17	41	M	Orthopnea	II	+	-
18	60	F	Exertional dyspnea, ventricular tachycardia	II	-	-

DCM=dilated cardiomyopathy; M=male; F=female; NYHA=New York Heart Association; af=atrial fibrillation.

18 patients with DCM, ergonovine induced $\geq 75\%$ coronary vasoconstriction. These patients were diagnosed as having coronary vasospasm (Patients 1-6, Table I). Patient 6 did not undergo ergonovine provocation testing of the left coronary artery because the right coronary artery developed subtotal occlusion during intracoronary injection of ergonovine and ventricular fibrillation occurred. The other 5 patients did not have chest pain or significant ST-segment changes during intracoronary injections of ergonovine. Patient 1 did not undergo ergonovine provocation testing of the left coronary artery because the right coronary artery developed total occlusion during intracoronary injection of ergonovine, and the occlusion was immediately relieved by intracoronary injection of nitroglycerin. In the remaining 4 DCM patients with coronary vasospasm (Patients 2-5), coronary vasoconstriction, including the left anterior descending coronary artery, developed (Figure 1, Table II). Patient 2 did not undergo ergonovine provocation testing of the right coronary artery because the right coronary artery had a 75% luminal narrowing. However, the 75% luminal narrowing of the right coronary artery decreased to 25% luminal narrowing with the intracoronary injection of nitroglycerin.

Characteristics of patients with DCM and coronary vasospasm: The prevalence of atrial fibrillation in the DCM patients with coronary vasospasm was greater than that in those without coronary vasospasm [67% vs 8% ($P<0.05$)]. Coronary

Figure 1. Coronary angiograms from a representative patient (patient 4). **A:** After 30 µg of intracoronary infusion of ergonovine, 80% coronary vasoconstriction was induced in segment 8 of the left coronary artery (left). After infusion of 200 µg of intracoronary nitroglycerin, generalized dilation occurred (right). **B:** Right coronary angiogram obtained after intracoronary infusion of 10 µg of ergonovine, showing a generalized reduction in coronary caliber (left). After infusion of 200 µg of intracoronary nitroglycerin, generalized dilation occurred (right). No significantly fixed stenosis was noted in either of the coronary arteries after nitroglycerin injection. **C:** Left ventriculogram showing diffuse hypokinesis.

Table II. Coronary Vasoconstriction Provoked by Ergonovine

Case No.	Right coronary artery	Left anterior descending artery	Left circumflex artery
1	#1: 100%	Not provoked by ergonovine	Not provoked by ergonovine
2	Not provoked by ergonovine	#8: 75%, #9: 71%	IM: 80%, #14: 70%
3	#1: 70%	#7: 76%	
4	#1: 79%, #2: 74%, #3: 87%, 4AV: 75%	#8: 80%, #9: 70%	
5	#3: 79%, 4AV: 79%, 4PD: 70%	#7: 70%	
6	#1: 99%	Not provoked by ergonovine	Not provoked by ergonovine

Severity of coronary vasoconstriction $\geq 70\%$ of the luminal diameter is described. #: Coronary segments are numbered according to the classification of the American Heart Association. IM=intermediate artery; PD=posterior descending artery; AV=atrioventricular node artery.

Table III. Hemodynamic Data from Cardiac Catheterization

	Patients with DCM with coronary vasospasm	Patients with DCM without coronary vasospasm	P value
Number	6	12	
HR (bpm)	79 (65/80)	70 (67/80)	NS
SBP (mm Hg)	128 (120/130)	117 (103/145)	NS
DBP (mm Hg)	75 (70/90)	73 (65/78)	NS
PAWP (mm Hg)	8 (5/8)	9 (6/12)*	NS
LVEDP (mm Hg)	7 (6/8)	9 (7/16)	NS
LVEDVI (mL/m ²)	102 (93/103)	126 (98/169)	NS
LVESVI (mL/m ²)	62 (60/64)	85 (63/122)	NS
LVEF (%)	37 (35/41)	35 (29/39)	NS

Continuous values are median (25th/75th percentile). * Patient 7 did not undergo right heart catheterization; DCM=dilated cardiomyopathy; HR=heart rate; bpm=beats per minute; SBP=systolic blood pressure; DBP=diastolic blood pressure; PAWP=pulmonary artery wedge pressure; LVEDP=left ventricular end-diastolic pressure; LVED (S) VI=left ventricular end-diastolic (end-systolic) volume index; LVEF=left ventricular ejection fraction.

vasospasm tended to be induced at a higher frequency in males (50%) than in females (0%) ($P=0.054$). There were no significant differences in age, NYHA functional class, smoking, or hemodynamic data from cardiac catheterization (Table III) between DCM patients with coronary vasospasm and those without coronary vasospasm.

Effects of anti-vasospastic agents in patients with DCM and coronary vasospasm: In the DCM patients with coronary vasospasm, the left ventricular end-diastolic dimension decreased from 61 mm (56/64) to 55 mm (53/56) (median, 25th/75th percentile, $P<0.05$) and the left ventricular ejection fraction increased from 36% (32/40) to 47% (46/48) (median, 25th/75th percentile, $P<0.05$) after the administration of anti-vasospastic agents [Case 1, isosorbide mononitrate 40 mg/day,

Table IV. Echocardiographic Measurements and NYHA Functional Class before and after Calcium Antagonist and/or Nitrate Therapy

Case No.	B-LVDd (mm)	A-LVDd (mm)	B-LVEF (%)	A-LVEF (%)	B-NYHA class	A-NYHA class	Follow-up (months)	Drugs
1	61	58	40	47	II	I	5	diu+MN, nis, dig
2	64	55	29	53	II	I	11	diu, ACEi, DN+nis
3	64	56	32	46	I	I	9	+DN, nis
4	55	51	34	40	II	II	5	diu, ACEi, DN+dil
5	61	55	40	47	II	I	3	dig, diu, ACEi+nif
6	56	53	37	48	II	I	2	dig, diu, ACEi+nis
	61 (56/64)	55 (53/56)*	36 (32/40)	47 (46/48)*			5 (3/9)	

Continuous values are median (25th/75th percentile). NYHA=New York Heart Association; B=before; LVDd=left ventricular end-diastolic dimension; A=after; LVEF=left ventricular ejection fraction; diu=diuretic; MN=isosorbide mononitrate; nis=nisoldipine; dig=digitalis; ACEi=angiotensin-converting enzyme inhibitor; DN=isosorbide dinitrate time release; dil=diltiazem hydrochloride; nif=nifedipine coat core;

*: $P < 0.05$ vs before calcium antagonist and/or nitrate administration.

nisoldipine 10 mg/day; Case 2, nisoldipine 10 mg/day; Case 3, isosorbide dinitrate time release 40 mg/day, nisoldipine 10 mg/day; Case 4, diltiazem hydrochloride 100 mg/day; Case 5, nifedipine coat core 40 mg/day, Case 6, nisoldipine 5 mg/day] (Table IV). The heart rate [77 bpm (69/89); 83 bpm (58/87)] and systolic blood pressure [136 mmHg (115/146); 122 mmHg (118/135)] did not change between the baseline values and the values at the end of the follow-up period in patients with DCM and coronary vasospasm. Four of the 6 patients with DCM and coronary vasospasm improved symptomatically: their NYHA class II ($n=4$) improved to class I (Table IV).

DISCUSSION

Our results demonstrate that 6 of the 18 patients (33%) with DCM had coronary vasospasm. The prevalence of atrial fibrillation in the DCM patients with coronary vasospasm was greater than in those without coronary vasospasm. In all of the DCM patients with coronary vasospasm, the left ventricular end-diastolic dimension decreased and the left ventricular ejection fraction increased $\geq 5\%$ after treatment with anti-vasospastic agents. We suggest that ergonovine provocation testing is useful in identifying patients with DCM and coronary vasospasm, in whom atrial fibrillation is frequently associated and cardiac performance is improved by anti-vasospastic agents.

Prevalence of provoked coronary vasospasm in patients with DCM: The prevalence of coronary vasospasm in patients with DCM reported by Bertrand, *et al*⁽¹⁰⁾ is lower than that in our study (0% vs 33%). However, differences in coronary vasospastic responses after recent myocardial infarction in Japanese and Caucasian patients has been described by Pristipino, *et al*.⁽¹¹⁾ They reported that the

prevalence of coronary vasospasm after acetylcholine provocation testing was 3 times higher in Japanese patients for both infarct-related and non-infarct-related arteries; furthermore, Japanese patients have a higher prevalence of multiple coronary vasospasms than Caucasian patients. We hypothesize that the differences in the reported frequency of coronary vasospasm between the study by Bertrand, *et al* and our study are related to racial differences, as well as differences in the method of induction of coronary vasospasm (i.e., intravenous vs. intracoronary infusion). Nosaka, *et al*¹²⁾ reported that the prevalence of coronary vasospasm in Japanese patients with DCM is 2.4%. They defined coronary vasospasm as the induction of total or subtotal coronary occlusion with ST-segment changes after the bolus injection of ergonovine maleate into the aorta. We hypothesize that if the patients in the study by Nosaka, *et al* underwent the 75% ergonovine provocation testing protocol used in the present study, the prevalence of coronary vasospasm might be higher. On the other hand, the differences in the drug for induction of coronary vasospasm (i.e., ergonovine vs. acetylcholine) may be another cause, as Sakata, *et al*²⁾ reported that the prevalence of coronary vasospasm in patients with DCM is 35%.

Characteristics of patients with DCM and coronary vasospasm: The prevalence of atrial fibrillation in the DCM patients with coronary vasospasm was greater than in those without coronary vasospasm. Coronary vasospasm was induced at a slightly higher frequency in males than in females. Shimizu, *et al*¹⁾ also reported that 2 of 7 DCM patients with coronary vasospasm had atrial fibrillation and 1 of 7 DCM patients with coronary vasospasm had atrial flutter. Although Sakata, *et al*²⁾ reported that only acetylcholine provocation testing can identify patients with DCM and coronary vasospasm, the present study suggests that male DCM patients with atrial arrhythmia, especially atrial fibrillation, may be related to the complication of coronary vasospasm. The possibility remains that ischemia and/or a change in hemodynamics due to repetitive coronary vasospasms may induce atrial fibrillation.

Effects of anti-vasospastic agents in patients with DCM and coronary vasospasm: We conclude that epicardial coronary artery spasms play a role in the development of left ventricular dysfunction. Because of the possible link between DCM and coronary vasospasm, the use of anti-vasospastic agents, especially calcium antagonists, has been proposed. The use of calcium antagonists in patients with chronic heart failure caused by nonischemic cardiomyopathy is not a first-line therapy at the present time.¹³⁾ However, if patients with DCM and coronary vasospasm are appropriately selected by ergonovine provocation testing, the use of calcium antagonists which do not show tachyphylaxis might be beneficial. Since calcium antagonists also reduce heart rate and afterload, the possibility remains that the reduction in heart rate or afterload by calcium antagonists may

improve hemodynamics. However, we do not believe that the effect of reduced heart rate or afterload was primarily responsible for our beneficial results because all DCM patients with coronary vasospasm, except one, were administered dihydropyridine calcium antagonists and no significant differences were observed in heart rate or systolic blood pressure between baseline and the end of follow-up.

Nitrates are also effective in preventing coronary vasospasm. A major problem with the use of nitrates is the development of nitrate tolerance. Two of 6 patients with DCM and coronary vasospasm had already receive nitrates treatment before cardiac catheterization. In 2 of 6 patients with DCM and coronary vasospasm, the left ventricular ejection fraction increased after treatment with calcium antagonists in addition to nitrates. This result raises the possibility that these patients might have been nitrate tolerant.

Clinical trials have demonstrated that beta-blocker therapy can produce hemodynamic, symptomatic, and prognostic improvement in patients with DCM.¹⁴⁻¹⁶⁾ However, in patients with coronary vasospasm, non-selective beta-adrenoreceptor blockers may actually be detrimental, because blockade of the beta-2 receptors antagonizes beta-2 mediated coronary vasodilation and allows alpha receptor-mediated coronary vasoconstriction. Furthermore, beta-blocker therapy must be initiated with small doses to prevent the worsening of heart failure. Even though full doses of beta-blocker can be administered to these patients, it would take several months to confirm which patients responded to the therapy.

Study limitations: The number of patients included in the study was small, so this can only be considered as a pilot study. Our findings need to be confirmed in a larger cohort of patients. Since the use of calcium antagonists in patients with DCM is not a first-line therapy,¹³⁾ we did not initiate calcium antagonist therapy in patients with DCM but without coronary vasospasm.

Conclusions: Ergonovine provocation testing is useful in selecting patients with DCM and coronary vasospasm whose cardiac performance is improved by anti-vasospastic agent therapy. Male DCM patients with atrial arrhythmia, especially atrial fibrillation, may be a clue for identifying patients with coronary vasospasm.

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