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Long-Term Outcome of Patients With Ergonovine Induced Coronary Constriction Not Associated With Ischemic Electrocardiographic Changes

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Abstract

Objectives. This study investigated the long-term outcome of patients with coronary artery constriction induced with ergonovine but not associated with ischemic electrocardiographic changes.

Methods. The ergonovine provocation test was performed in 419 patients with suspected but unproven variant angina. Ergonovine maleate was administered into the coronary arteries at 8 μg/min for 5 min during cardiac catheterization. Patients were categorized into three groups according to their response to ergonovine. The positive group contained patients who developed coronary constriction of more than 90% in diameter associated with ischemic electrocardiographic changes and chest pain. The intermediate group contained patients who had coronary constriction of more than 90% but no electrocardiographic changes. The negative group contained patients who had neither significant coronary constriction nor ST segment changes.

Results. There were 305 patients, 49, and 65 in the negative, intermediate, and positive groups, respectively. Death occurred in six patients(2%), one(2%), and one(2%)in the negative, intermediate, and positive groups, respectively. Sudden cardiac death occurred in one patient in the negative group. Recurrence of chest pain with effectiveness of sublingual administration of nitroglycerine was observed in 26 patients (9%), 10(20%), and 11(17%)in the negative, intermediate, and positive groups, respectively.

Conclusions. Some patients in the intermediate group might show " false negative " response to ergonovine so careful treatment with calcium antagonists should be continued in patients in the intermediate group as well as patients with vasospastic angina.

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Key Words

■ **Coronary vasospasm(ergonovine provocation test)** ■ **Electrocardiography**
■ **Prognosis**

INTRODUCTION

Ergonovine maleate has been widely used as a potent drug for the provocation test of coronary artery spasm in patients with suspected but unproven vasospastic angina. Intracoronary administration of ergonovine is highly sensitive and specific for making the diagnosis of variant angina[1,2]. However, the sensitivity of the ergonovine provocation test for patients with variant angina decreases

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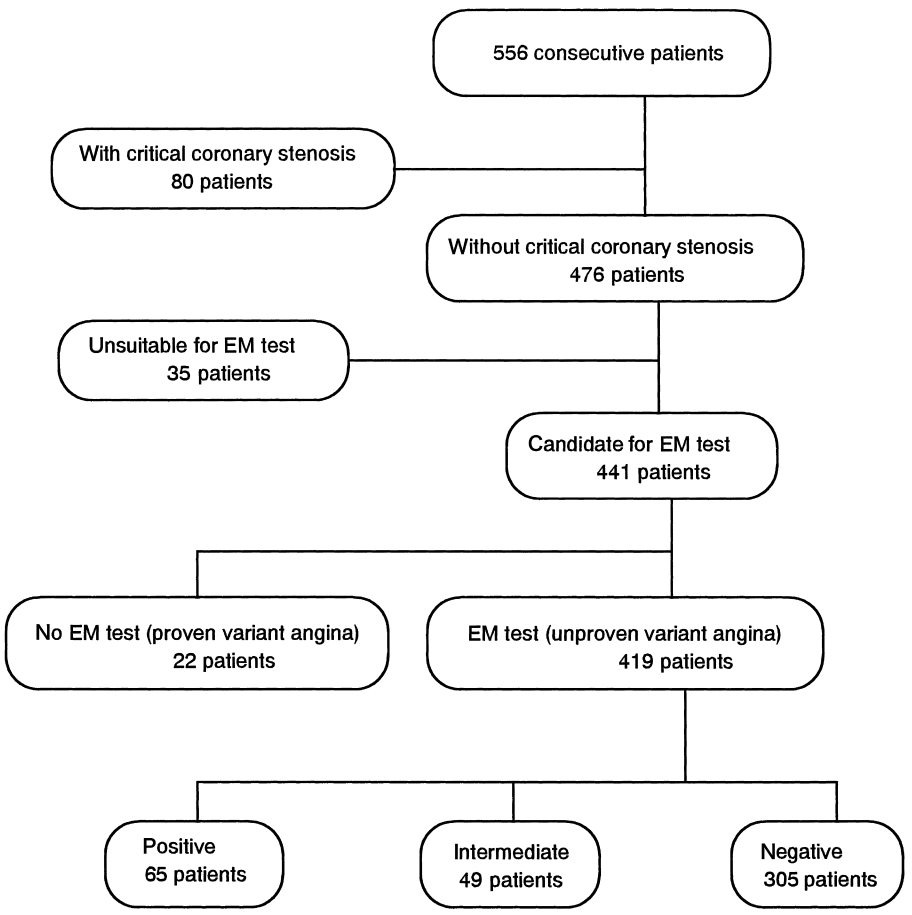

Fig. 1 Flow chart of patient selection for the ergonovine provocation test
EM = ergonovine maleate.

with time[3–6]. On the other hand, anginal symptoms often recur even in patients in whom coronary constriction was not developed in the ergonovine provocation test. Thus, the reproducibility is not necessarily preserved. The clinical significance of the ergonovine provocation test remains controversial for evaluating patients with vasospastic angina. Therapeutic strategy cannot always be established through the ergonovine provocation test, particularly in patients with dissociation between findings of coronary arteries and electrocardiography (ECG) during the test. This study investigated the long-term outcome of patients who showed coronary artery constriction induced by ergonovine but not associated with ischemic ECG changes.

METHODS

Patient selection

The present study included 556 consecutive patients with chest pain at rest between April 1992 and December 1997. Coronary angiography was performed in all patients (**Fig. 1**). Eighty patients with critical coronary stenosis (more than 75% reduction in diameter) were excluded from this study because those patients were considered to be candidates for coronary angioplasty. Another 35 patients with an anomalous origin of the coronary artery, a marked distortion of the aorta, and/or catheter-induced coronary spasm were also excluded. Transient ST elevation was detected during spontaneous chest pain at rest in 22 patients, who were also excluded. Ergonovine testing was finally performed in 419 patients with suspected but unproven variant angina. Patients with old myocardial infarction, unstable angina, valvular disease, and cardiomyopathy were excluded from enrollment in the present study.

Ergonovine provocation test during coronary angiography

All calcium antagonists were discontinued for at least 48 hr before the catheterization study, with only sublingual nitroglycerin administered as needed. Coronary angiographic examination was carried out by Judkins' method after femoral artery puncture. Control angiograms of the right and left coronary arteries were obtained, then intracoronary ergonovine maleate was administered at 8 μg/min each for 5 min. When ST changes of more than 0.2 mV occurred on ECG during chest pain, loading was discontinued immediately, and angiography was performed to confirm vasospasm. When vasospasm was confirmed, nitrate preparation was administered into the coronary artery until the vasospasm disappeared. Stenotic lesions were classified in accordance with the American Heart Association/American College of Cardiology (AHA/ACC) classification[7]. The coronary arterial diameter was measured using calipers at the site of the most severe narrowing of each segment before and after the administration of ergonovine. Both patients and their family members were fully informed about the angiographic examination and the provocation test, and gave written consent.

Definition of response to provocation test

Patients were divided into three groups according to response of the coronary arteries and ECG findings. The positive group contained patients who had developed coronary constriction of more than 90% in diameter associated with ST elevation (more than 0.2 mV) during chest pain. The intermediate group contained patients who had coronary constriction of more than 90% but no ST elevation (more than 0.2 mV) on ECG. The negative group contained patients who had neither significant coronary constriction nor ECG changes after administration of ergonovine.

Follow-up study

A standardized questionnaire was recorded at each visit to the out-patient clinic of our hospital, or through telephone interview, or by mail.

Statistical analysis

Continuous data are presented as mean ± SD. Group comparisons were performed using the χ^2 test for discrete variables and the unpaired *t*-test for continuous variables. Statistical significance was assumed at $p < 0.05$. Survival analysis used the Kaplan-Meier method, and was tested by the log-rank method.

RESULTS

The 419 patients were divided into three groups containing 65, 49, and 305 in the positive, intermediate, and negative groups, respectively (**Fig. 2**). The clinical variables of the three groups are shown in **Table 1**. There was no statistically significant difference between the three groups with respect to age, follow-up period, history of hypertension, serum lipid, free blood sugar, and left ventricular ejection fraction. The ratio of males and cigarette smokers was significantly lower in the negative group than in the other two groups. All patients were observed during a mean follow-up period of 3.9 ± 1.5 years. Patients treated with at least one kind of calcium antagonists on discharge were 53%, 90%, and 94% in the negative, intermediate, and positive groups, respectively.

Death occurred in six patients (2%), one (2%), and one (2%) in the negative, intermediate, and positive groups, respectively. Sudden cardiac death occurred in one patient of the negative group (**Table 2**). Neither non-fatal myocardial infarction nor unstable angina was observed in any group. The diagnosis of vasospastic angina was made in 87 patients, including patients with spontaneous vasospastic angina (22 patients, 58 ± 9 years) and all patients in the positive group (65 patients, 59 ± 10 years). Two cardiac deaths occurred only in this population, which included significantly more males and cigarette smokers. Relief of chest pain was observed immediately following the administration of sublingual nitroglycerine in 26 patients (9%), 10 (20%), and 11 (17%) in the negative, intermediate, and positive groups, respectively. There was a significant difference between the negative group and the other two groups. The survival rate free from both cardiac death and recurrent chest pain was significantly lower in the intermediate group and positive group than the negative group (**Fig. 3**). Chest pain recurrence in the intermediate group and positive group was not different with respect to the ST changes during ergonovine testing, presence of chest pain during effort, results of exercise stress electrocardiography, and calcium antagonist medication (**Table 3**).

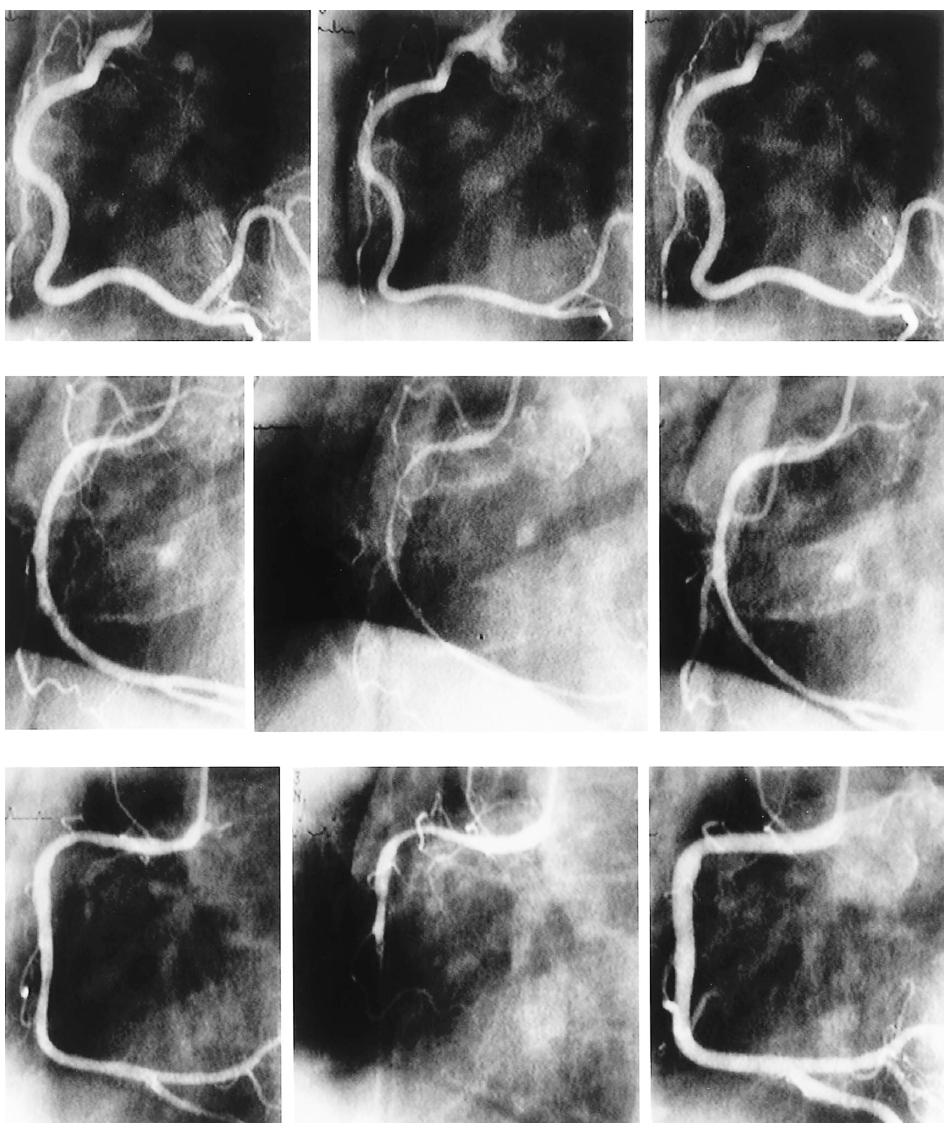

Fig. 2 Right coronary arteriograms in representative cases (left anterior oblique view)
Upper row: More than 90% vasoconstriction was not shown after ergonovine maleate injection (negative response). *Middle row*: More than 90% vasoconstriction was shown but was not associated with ischemic electrocardiographic changes (intermediate response). *Lower row*: Total occlusion was observed and associated with ischemic electrocardiographic changes (positive response). *Left column*: Before ergonovine maleate injection. *Middle column*: After ergonovine maleate injection. *Right column*: After nitrate injection.

DISCUSSION

The present study provides no clear answer to the question of whether treatment should be initiated or not when development of coronary narrowing is not accompanied by ischemic ECG changes during administration of ergonovine. This study tried to clarify the long-term outcome of such patients with only angiographic findings. Such patients are included in the intermediate group in the present study. Criteria for a positive response in the ergonovine provocation test have not been clearly defined, and this was based only on angiographic observation in previous studies[1,2,8,9], so may not necessarily reflect true cardiac ischemia. One of the criteria of vasospastic angina is chest pain at rest associated with ST segment elevation of at least 2 mm on the ECG. Therefore, we considered a positive response for provocation testing only when both coronary constriction and ST elevation of

Table 1 Clinical characteristics of the negative, intermediate and positive groups

	Negative (n=305)	Intermediate (n=49)	p value*	Positive (n=65)	p value†
Age (yr)	59±10	60±9	NS	59±10	NS
Sex (male/female)	147/158 (48)	33/16 (67)	0.01	54/11 (83)	0.0001
Follow-up period (yr)	3.8±1.5	3.9±1.5	NS	3.9±1.5	NS
Coronary risk factor					
Hypertension	105 (34)	22 (45)	NS	24 (37)	NS
Smoking	66 (22)	18 (37)	0.02	25 (39)	0.004
Total cholesterol (mg/dl)	192.5±34.5	188.4±36.8	NS	189.7±35.3	NS
Triglyceride (mg/dl)	135.7±75.9	118.0±57.2	NS	145.8±82.9	NS
High-density lipoprotein (mg/dl)	49.5±14.4	50.4±19.0	NS	49.8±17.6	NS
Low-density lipoprotein (mg/dl)	116.0±33.1	114.3±38.6	NS	110.8±34.7	NS
Fasting blood sugar (mg/dl)	97.3±24.9	96.3±29.7	NS	95.6±21.0	NS
Left ventricular ejection fraction (%)	68.3±8.9	67.3±8.7	NS	66.3±7.9	NS
Ca antagonist on discharge	162 (53)	44 (90)	0.0001	61 (94)	0.0001
Nitrate on discharge	61 (20)	24 (49)	0.0001	45 (69)	0.0001
Ca antagonist during follow-up	143 (47)	37 (76)	0.0006	48 (74)	0.0003

Continuous values are mean±SD. ( ): %. *p values between the negative and intermediate groups. †p values between the negative and positive groups.

Table 2 Long-term outcome of the negative, intermediate and positive groups

	Negative (n=305)	Intermediate (n=49)	p value*	Positive (n=65)	p value†
Death‡	6 (2)	1 (2)	NS	1 (2)	NS
Cardiac death	1 (0.3)	0	NS	0	NS
Angina pectoris	26 (9)	10 (20)	0.01	11 (17)	0.04
Non-fatal AMI	0	0	NS	0	NS
Cardiac events§	28 (9)	11 (23)	0.006	11 (17)	0.06

( ): %. *p values between the negative and intermediate groups. †p values between the negative and positive groups. ‡Including cardiac death. §Cardiac events include cardiac death, acute myocardial infarction, unstable angina, and stable angina.
AMI=acute myocardial infarction.

more than 0.2 mV on the ECG were demonstrated at the same time.

Calcium antagonists were administered to 90% of patients in the intermediate group, which is nearly identical to the 94% of patients in the positive group, but only 53% of patients in the negative group because 34% of them had hypertension. There was no significant differences in mortality between the three groups[10,11]. However, there was a significant difference in the recurrence of chest pain, at 20% in the intermediate group, which was higher than in the negative group (9%), but similar to that of the positive group (17%). Therefore, some patients in the intermediate group may have a "false negative" response to ergonovine administration. The most likely explanation of such "false negative" findings is that the provocation test was performed when disease activity of the coronary vessels was reduced. The activity of coronary vasospasm is considered to be fluctuating. Reduced sensitivity of the coronary vessels to ergonovine is correlated with a decrease in angina attacks in patients with angina pectoris in whom calcium antagonist is effective[3–6]. The ergonovine test was not performed in the patients in whom transient ST elevation had been detected during spontaneous resting angina because of the increased risk of infarction. In the present study, two cardiac deaths

Table 3 Episodes of recurrent chest pain during the follow-up period in the intermediate and positive groups

	Intermediate			Positive		
	Recurrence of chest pain(+) (n=10)	Recurrence of chest pain(−) (n=39)	p value*	Recurrence of chest pain(+) (n=11)	Recurrence of chest pain(−) (n=54)	p value†
Ergonovine provocation test						
ST elevation≧2mm	0	0	NS	11(100)	54(100)	NS
ST elevation＜2mm	0	2(5)	NS	0	0	NS
ST depression≧1mm	1(10)	3(8)	NS	0	0	
Chest pain during effort	1(10)	5(13)	NS	0	17(32)	0.07
Positive on exercise stress ECG	3/7(43)	5/27(19)	0.18	0/6	14/47(30)	0.1
Ca antagonist during follow-up	10(100)	34(87)	NS	10(91)	51(94)	NS
Administration of Ca antagonist (times/day)	2.5	2.2	NS	2.4	2.9	NS

( ): %. *p values between patients with and without recurrence of chest pain. †p values between patients with and without recurrence of chest pain.
ECG＝electrocardiography.

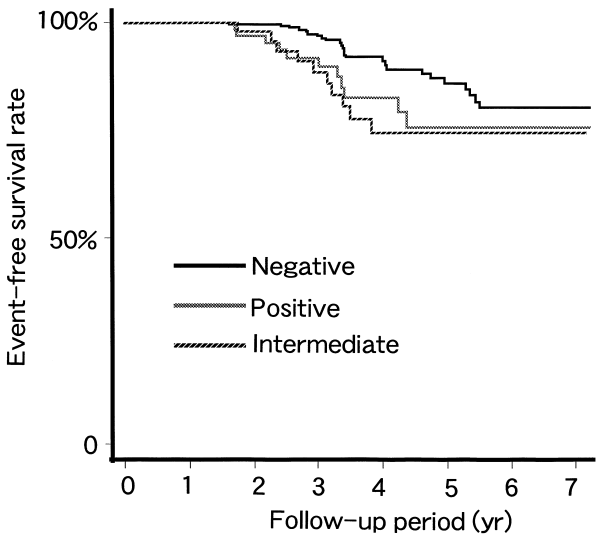

Fig. 3 Cardiac event-free rate throughout the follow-up period by Kaplan-Meier analysis
Cardiac event-free rate was significantly lower in the intermediate and positive groups than in the negative group(74.0%, 75.3%, 80.0%, respectively; $p < 0.03$). Cardiac events include cardiac death, acute myocardial infarction, unstable angina, and stable angina.

occurred in the population of patients with proved spontaneous attack. The ratio of smokers was also higher in the patients with spontaneous angina than in the positive group, indicating that the activity of coronary spasm remains higher in such patients with frequent spontaneous attack[12−19]. Why the disease activity of variant angina changes remains unclear, although change in the endothelium-dependent responsiveness of vascular smooth muscle is very important in the pathogenesis of coronary spasm in experimental studies[20−22]. In medical practice, prophylactic coronary medication may be needed even in patients with the intermediate response to ergonovine testing.

Study limitations

Our conclusions with respect to the prognosis are limited in the present study. The study was designed in a retrospective fashion and the ergonovine test was not performed in all patients. Patients were not randomly allocated to initial treatment after the provocation test. However, it is impractical to assign patients randomly to either calcium antagonists or placebo in a prospective manner. Therefore, evaluation of the prognosis of patients with chest pain should be attempted by discontinuing calcium antagonists, Holter ECG, and/or a second ergonovine test. Further analysis or accumulation of clinical experience concerning recurrences of chest pain are also needed.

CONCLUSIONS

The long-term prognosis was excellent in the patients in whom the ergonovine provocation test was performed. There was no significant difference in mortality between the three patient groups. Chest pain recurrence was more frequent in the intermediate group and positive group than in the negative

group. Some patients of the intermediate group may show " false negative " findings in the ergonovine provocation test and careful treatment with calcium antagonists should be continued in patients in this group as well as in patients with vasospastic angina.

要　　約

エルゴノビン負荷後に虚血性心電図変化を伴わない高度冠動脈収縮例の長期予後

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目　的: 本研究の目的は，エルゴノビン負荷試験で虚血性の心電図変化を伴わず高度な冠動脈収縮が誘発された患者の長期予後を明らかにすることである．

方　法: 発作時の心電図で異型狭心症を証明できなかった419例にエルゴノビン負荷試験を施行した．心臓カテーテル検査時にエルゴノビンを8μg/minで5分間，冠動脈内に持続注入した．患者は負荷試験結果で3群に分類した．陽性群は胸痛時に虚血性の心電図変化を伴い，冠動脈収縮が90%以上認められた群とし，中間群は90%以上の冠動脈収縮のみ認め心電図変化がなかった群，陰性群は90%以上の冠動脈収縮も心電図変化もみられなかった群とした．

結　果: 陰性群，中間群，陽性群はそれぞれ305例，49例，65例であった．総死亡は陰性群6例(2%)，中間群1例(2%)，陽性群1例(2%)にみられた．心臓死は陰性群の突然死1例のみであった．ニトログリセリンの舌下服用が有効な胸痛発作の再燃は陰性群，中間群，陽性群で，それぞれ26例(9%)，10例(20%)，11例(17%)にみられた．

結　論: 中間群の中にはエルゴノビン負荷試験 " 偽陰性 " が含まれる可能性があり，冠攣縮性狭心症患者と同様の注意深い治療を継続する必要があると思われる．

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