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Evaluation of Adjunctive Intracoronary Administration of Acetylcholine Following Intravenous Infusion of Ergonovine to Provoke Coronary Artery Spasm

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Abstract

A dilemma arises in patients with chest pain or other symptoms suggestive of coronary artery disease but without significant coronary artery stenosis or spasm even after the spasm provocation test by either ergonovine or acetylcholine.

Incremental doses of intracoronary acetylcholine (up to 100 μg for left coronary artery and 50 μg for right coronary artery) were administered when intravenous infusion of ergonovine 0.4 mg showed negative results. A total of 39 patients were studied. Provocation test was performed because of chest pain suggestive of coronary artery disease ($n = 19$), atypical chest pain ($n = 6$), post balloon angioplasty status ($n = 6$), silent ischemia ($n = 4$), Adams-Stokes syndrome ($n = 3$), and dead-on-arrival ($n = 1$). Characteristics of chest pain indicated variant angina ($n = 11$), rest angina ($n = 4$), and effort angina ($n = 4$). No electrocardiographic evidence of ischemia was detected before this test in any patient.

Spasm was induced in 23 patients (59.0%) with complete obstruction in 7 (30.4%), diffuse vasoconstriction (90–99%) in 14 (60.9%), and focal spasm in 2 (8.7%). The patients with chest pain showed the highest positive rate of 78.9%. Further, the patients with atypical chest pain and miscellaneous reasons also revealed positive rates of 33.3% and 42.9%, respectively. One ventricular tachycardia and 2 atrial fibrillations occurred but terminated spontaneously.

This test is useful for detecting spasm in a variety of patients in whom intravenous ergonovine infusion fails to induce spasm.

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Key Words
■ Acetylcholine (intracoronary) ■ Angiography ■ Coronary artery disease
■ Coronary vasospasm (ergonovine)

INTRODUCTION

Intravenous administration of ergonovine is a technically simple and established test for inducing coronary artery spasm in patients with variant angina with both high sensitivity and specificity[1-4]. However, the sensitivity is very low[5] and is less likely to be diagnostic for patients with chest pain in whom the clinical syndrome is less clearly defined, except for variant angina pectoris. Thus, even after performing the intravenous ergonovine test, a dilemma arises in patients with chest pain suggestive of coronary artery disease significant enough to warrant angiography but do not have hemodynamically significant coronary spasm at the time of angiography to explain the symptoms. We developed a novel approach to detect coronary artery spasm by using adjunctive intracoronary acetylcholine infusion after intravenous ergonovine and evaluated the spasm provocative rate and safety in patients with chest pain suggestive of angina pectoris or other symptoms or conditions that might be due to spasm.

SUBJECTS AND METHODS

Subjects

A total of 47 patients received intravenous administration of ergonovine (a total of 0.4 mg) to provoke coronary vasospasm at the Bisai City Hospital. The test was positive in 8 patients who had rest angina in the early morning ($n = 4$) and rest angina ($n = 4$). The remaining 39 patients, 22 males and 17 females (mean age 60 ± 9 years) received adjunctive intracoronary acetylcholine infusion after intravenous ergonovine administration. The test was performed for evaluation of chest pain suggestive of coronary artery disease in 19, atypical chest pain in 6, and miscellaneous conditions in 14 such as post balloon angioplasty status ($n = 6$), silent ischemia ($n = 4$), Adams-Stokes syndrome ($n = 3$), and dead-on-arrival in one patient. Mean duration of follow-up after balloon angioplasty was 182 days (12−450 days). Two patients with recent myocardial infarctions who underwent direct balloon angioplasty at the onset were included. Chest pain consisted of typical chest pain (rest angina in the early morning) as variant angina pectoris in 11, rest angina in 4, and effort angina in 4. No electrocardiographic evidence of ischemia was obtained during occurrence of chest pain in patients with chest pain. No patients had severe atherosclerosis with more than 75% angiographical stenosis. The study protocol was approved by the Ethics Committee of the Bisai City Hospital. Informed consent was obtained from all subjects. All antianginal and antihypertensive drugs were withdrawn more than 24 hr before the test.

Methods

Two sheaths were inserted into the same femoral artery and 2 catheters were engaged in the right and left coronary artery ostium at the same time during the test. A temporary cardiac pacemaker set at 40 − 50 beats/min was positioned into the right ventricle. After ascertaining no significant stenosis in the right and left coronary arteries, ergonovine was given intravenously as 2 sequential identical doses of 0.2 mg at an interval of 90 sec for a total dose of 0.4 mg. Cineangiograms of both coronary arteries were obtained 90 sec after each ergonovine administration. If no spasm was provoked, up to 100 μg of acetylcholine was given into the left coronary artery. Cineangiograms were obtained about 2 min after administration or at any time significant electrocardiographic change or chest pain occurred, and test injections were performed frequently until spasm subsided completely. Awaiting spontaneous resolution of coronary spasm, up to 50 μg of acetylcholine was administered into the right coronary artery. Patients likely to suffer hemodynamic collapse were promptly given nitroglycerin and acetylcholine infusion into the right coronary artery was not performed. Final cineangiograms were obtained after intracoronary infusion of nitroglycerin for both coronary arteries.

The projection was chosen to avoid vessel overlap and kept consistently the same throughout the test, usually using the right anterior oblique view for the left coronary artery and left anterior oblique view for the right coronary artery. The vessel diameter was measured quantitatively using the Cardiovascular Measurement System (MEDIS) at control (C), after ergonovine infusion, after acetylcholine infusion, and after final nitroglycerin infu-

Table 1 Clinical characteristics in patients undergoing adjunctive acetylcholine provocation test

	Overall (n=39)	Positive group (n=20)	Negative group (n=19)	p value
Age (yr, mean±SD)	60±9	59±9	60±9	NS
Male ratio	22(56)	13(65)	9(47)	NS
Hypertension	15(38)	8(40)	7(19)	NS
Hyperlipidemia	6(15)	2(10)	4(21)	NS
Diabetes mellitus	9(23)	4(20)	5(26)	NS
Smoking	10(26)	5(25)	5(26)	NS

( ): %

sion (N) at the proximal angiographically intact segment in the left anterior descending coronary artery and right coronary artery. The severity of focal coronary stenosis was measured and coronary tones were defined as (N − C) × 100/N from diameters measured quantitatively. If coronary spasm of % diameter stenosis > 90% with electrocardiogram change or chest pain was induced after ergonovine or acetylcholine administration, the test was considered positive.

All values are expressed as mean ± SD. Chi-square analysis was used to compare categorical variables. The unpaired t-test was used for comparison of clinical and angiographic parameters between groups with positive and negative results. A probability level of < 0.05 was considered statistically significant.

RESULTS

Acetylcholine could be administered in both left and right coronary arteries in 33 patients (a total of 99 vessels), in only the left coronary artery in 5 patients (a total of 10 vessels), and in only the right coronary artery in one patient (one vessel). As a result, acetylcholine was not administered into the left or right coronary artery in 6 patients because of nitroglycerin delivered to relieve severe spasm elicited by acetylcholine in the right or left coronary artery, respectively. The adjunctive acetylcholine test was positive in 23 patients (59.0%) with complete coronary obstruction in 7 patients (30.4%), diffuse coronary vasoconstriction in 14 patients (60.9%), and focal spasm in 2 patients (8.7%). Adjunctive intracoronary acetylcholine infusion raised the spasm provocation rate from 17.0% (8/47) after intravenous ergonovine to 66.0% (31/47). There were no differences between the adjunctive acetylcholine test positive and negative groups in clinical characteristics (**Table 1**).

The clinical and angiographic results of this test are shown in **Table 2** (positive group) and **Table 3** (negative group). The positive rate was 37.3% (41/110), 55.3% (21/38) for the left anterior descending coronary artery, 31.6% (12/38) for the left circumflex coronary artery, and 23.5% (8/34) for the right coronary artery. Multivessel spasm was recognized in 35.9% (14/39). Patients with chest pain showed the highest positive rate of 78.9% (15/19) among the 3 groups. However, the patients with atypical chest pain and miscellaneous reasons also revealed positive rates of 33.3% (2/6) and 42.9% (6/14), respectively. The relationship between chest pain type and spasm provocation rate is shown in **Table 4**. The provocation rate appeared to be higher in patients with chest pain suggestive of coronary artery disease compared with patients with atypical chest pain or miscellaneous reasons. The patients with chest pain at rest or on effort showed a similar positive rate to that of patients with symptoms suggestive of variant angina.

There was no significant difference in basal coronary tone between the adjunctive acetylcholine test positive and negative coronary arteries (8.1 ± 10.2% vs 6.1 ± 9.9%). Diffuse vasoconstriction of over 50% stenosis was recognized after ergonovine infusion at the site of coronary spasm that was induced after acetylcholine infusion in 50.0% (11/22 patients) of acetylcholine positive group and in 17.6% (3/17) of acetylcholine negative group (p = 0.0367). The site of diffuse vasoconstriction after ergonovine in the acetylcholine positive group coincided with that of spasm induced after acetylcholine infusion in all patients. There was no change in systemic hemodynamics after ergonovine infusion in all patients. All patients complained of chest pain during the provocation test in the acetyl-

Table 2 Clinical and angiographic characteristics in patients with positive results by the adjunctive acetylcholine provocation test

Case No.	Age(yr) /sex	Type of chest pain	Severity of CAD(%DS)	Site(μg)	Spasm(%DS)†	
					ERG	Ach
1	41/M	Rest	0	L 100, R 50	25 in 3 vessels	LAD 99, LCX 99/RCA 99
2	73/F	Rest	0	R 20	#3-4	RCA subtotal
3	72/F	Typical	0	L 40, R 20	LAD 25	LAD 99, LCX 90/RCA 50
4	81/M	Atypical	#7 bridge	L 60, R 10	#7: 75	LAD total
5	45/M	Rest	0	L 100, R 20	0	LAD 99(tandem)
6	62/M	Atypical	0	L 50, R 20	0	LAD 99, LCX 99/RCA 99
7	64/F	Typical	0	L 100, R 50	0	LAD 90 focal
8	58/M	Silent ischemia	#7: 41	L 100, R 50	#7: 50 #4: AV25	LAD 99, LCX 99/RCA 75 focal
9	80/F	Effort	0	L 50, R 50	0	LAD 99, LCX 50 4AV, 4PD 90
10	57/M	Effort	#1: 32	L 100, R 50	#7-8: 50 #1: 50 focal	LAD 50, LCX 50 RCA #1: 90 focal
11	64/M	No pain(SSS)	0	L 50, R 20	#7: 50, #13: 50	LAD total, LCX total
12	59/M	Silent ischemia	#2, #9: 25	L 50, R 20	0	LAD 90 tandem LCX 90 tandem
13	46/F	Typical	#3: 25	L 50	0	LAD 99, LCX 99
14	73/F	Typical	#6: 25	L 100, R 50	LAD 50, #4: 50	LAD 90
15	44/F	No pain (post PTCA)	#6: 50	L 50	LAD 50	LAD total
16	60/M	Typical	0	L 50, R 50	0	LAD 99, LCX 99/RCA 99
17	39/M	Typical	0	L 50	0	LAD total, LCA total
18	59/M	No pain (post PTCA)	#1: 45 #7: 34	L 50, R 20	50 in 3 vessels	LAD 99, LCA 99/RCA 90
19	56/M	Typical	0	L 100, R 50	#7: 50, #4: AV50	LAD 99, LCX 99/RCA 75
20	62/F	Effort	#1: 37 #7: 54	L 50	LAD 25	LAD total, LCA 99
21	60/M	No pain (post PTCA)	#1: 29 #7: 52	L 50, R 20	#7: 75	LAD 99/RCA 90 tandem
22	52/M	Typical	#1: 25	L 50	LAD, RCA 50	LAD total, LCX total
23	50/F	Rest	0	L 100, R 30	0	LAD 90

† Spasm was diffuse in the entire coronary or segment except for the cases described as focal or tandem.
# Segment number is according to the American Heart Association classification.
M=male; F=female; SSS=sick sinus syndrome; PTCA=percutaneous transluminal coronary angioplasty; CAD=coronary artery disease; L=left; R=right; ERG=ergonovine; DS=diameter stenosis; LAD=left anterior descending coronary artery; AV=arteriovenous; Ach=acetylcholine; LCX=left circumflex artery; RCA=right coronary artery; PD=posterior descending artery.

choline positive groups, whereas only 2 patients had chest pain in the acetylcholine negative group.

Electrocardiographic ischemic changes included ST segment elevation recognized in 12 patients and ST segment depression in 16 patients in the acetylcholine positive group. ST elevation was due to 99% diffuse stenosis or 100% complete occlusion. On the other hand, no significant electrocardiographic change was observed in the acetylcholine negative group. The patients without chest pain (post percutaneous transluminal coronary angioplasty) showed positive results, with spasm provoked in all 3 previously dilated sites. One ventricular tachycardia and 2 atrial fibrillations occurred but regressed spontaneously in the acetylcholine positive group. No complications occurred in the acetylcholine negative group. All clinical characteristics were similar between the adjunctive acetylcholine test positive and negative patients.

DISCUSSION

In our approach, we expected to observe the

Table 3 Clinical and angiographic characteristics in patients with negative results by the adjunctive acetylcholine provocation test

Case No.	Age(yr) /sex	Type of chest pain	Severity of CAD(%DS)	Site(μg)	Spasm(%DS) ERG	Spasm(%DS) Ach
1	76/F	Typical	#1: 25 #7: 25	L 100, R 50	0	0
2	71/F	Silent ischemia	0	L 100, R 50	0	0
3	57/F	Atypical	0	L 100, R 50	0	0
4	50/M	Typical	#2: 50 #7: 50	L 100, R 50	#2: 40 #7: 50	0
5	50/F	Atypical	0	L 100, R 50	LAD 25	LAD 25
6	37/M	No pain(SSS)	0	L 100, R 50	0	0
7	58/M	Atypical	#2: 50 #7: 50	L 100, R 50	0	0
8	64/M	No pain (post PTCA)	#8: 75 tandem	L 100, R 50	0	0
9	68/M	Atypical	#1: 23	L 100, R 50	0	#1: 44 focal
10	70/M	No pain (post PTCA)	#12: 50	L 100, R 50	0	0
11	68/F	Effort	#7: 47 #13: 25	L 100, R 50	0	0
12	65/F	No pain (post PTCA)	#7: 45	L 100, R 50	0	0
13	61/M	No pain(SSS)	0	L 100, R 50	#2: 75	LAD and LCX 75 tandem
14	73/F	Silent ischemia	#6: 25 #13: 75	L 100, R 30	0	0
15	38/M	Typical	0	L 50, R 20	0	0
16	63/F	Dead-on-arrival	0	L 100, R 50	0	#1: 75

Abbreviations as in Table 2.

Table 4 Relationship between chest pain types and results of the adjunctive acetylcholine provocation test

Chest pain type	Provocation test	
	Positive	Negative
Rest in the early morning (n=11)	8	3
Rest (n=4)	4	0
Effort (n=4)	3	1
Atypical (n=6)	2	4
Miscellaneous reasons (n=14)	6	8

No patients showed electrocardiographic evidence of variant angina (ST segment elevation) before the test.

combined action of ergonovine and acetylcholine, which are the most established agents to provoke coronary artery spasm during coronary angiography in patients with vasospastic angina, especially with Prinzmetal's variant angina. Several groups evaluated the use of ergonovine as a provocative test for coronary artery spasm. The sensitivity was between 93% and 99% and specificity was between 95% and 100%. Similarly, Okumura *et al.*[6] showed high sensitivity (90%) and specificity (99%) of the intracoronary acetylcholine infusion test for detecting variant angina pectoris. However, there is a discrepancy between the coronary artery responses to ergonovine and acetylcholine in the same patients, possibly because of the difference in the spasm provoking mechanism. The combination provocation test with acetylcholine administration followed by ergonovine has been used in Japan, where vasospastic angina is more common compared with Western countries[7,8].

This protocol was used to evaluate each drug separately, because the blood half life of acetylcholine is remarkably short and induced coronary spasm subsides spontaneously within 2 to 3 min in most patients without administration of nitro-

glycerin[6]. Consequently, acetylcholine is not acting when the ergonovine is injected. In contrast, the blood half life of ergonovine is 30−120 min, much longer than that of acetylcholine[9,10]. Therefore, the effect of acetylcholine will be superimposed on ergonovine by using them in the reverse order.

The possible mechanisms to explain coronary artery spasm are complex and include the involvement of autonomic nerve tone[11], basal coronary tone[12,13], vascular endothelial cell dysfunction[14,15], etc. Therefore, the 2 agents adopted in this study may be ideal because of their mechanisms. Acetylcholine is a neurotransmitter that stimulates the muscarinic receptor of the parasympathetic nerve directly, whereas ergonovine is an ergot alkaloid that stimulates the alpha receptor of the sympathetic nerve and the serotonin receptor and causes vasoconstriction by the direct effect on arterial smooth muscle. According to Yoshio *et al.*[11], parasympathetic activity increases during the 10-minute period before attacks of nocturnal angina, which is indicated by ST-segment elevation, whereas sympathetic activity with vagal modulation increases from 5 min before each attack. This change in autonomic nervous tone is a definite cause of coronary spasm in patients with variant angina. The 2 types of stimulation by ergonovine and acetylcholine might create conditions similar to the physiological change of the autonomic nervous system dominance in the early morning[11].

This protocol may be beneficial for detecting spasm or hyperconstriction in a variety of patients with high sensitivity. In contrast to the high sensitivity in detecting variant angina, the ergonovine test has not been so sensitive in patients with other clinical entities. For example, Harding *et al.*[5] reported that the utility of ergonovine for coronary artery spasm was assessed in 3,447 patients who did not have Prinzmetals' variant angina. Overall, only 4% had a positive ergonovine test result, defined by spasm causing more than 75% focal spasm. Bertrand *et al.*[16] also established the incidence of coronary artery spasm provoked by 0.4 mg of methergine in 1,089 consecutive patients undergoing coronary angiography. Focal spasm was recognized in 38.0% with angina at rest, in 13.8% with angina both at rest and induced by exercise, in 1.2% with atypical precordial chest pain, in 6.2% with old myocardial infarction, and 1.95% with valvular disease. In our series, the provocation rate was as high as 56.4% even after the exclusion of most variant angina patients by intravenous ergonovine administration. This rate is much higher than that of the intracoronary acetylcholine infusion test for nonvariant angina pectoris, at about 10% according to Okumura *et al.*[6] or the 2 studies mentioned above. As a result, in all patients who received intravenous ergonovine, adjunctive intracoronary acetylcholine infusion led to the dramatical increase of spasm provocation rate from 17% after intravenous ergonovine to 66%.

Although recent studies clearly suggest that increased vasoconstriction contributes to a various coronary syndromes and that the difference between hyperconstriction and true coronary spasm is gradual with no definitive evidence for different pathogenetic mechanisms[17], chest pain in patients with positive provocation test in this study were different from typical vasospastic angina in several aspects. First, although coronary artery tone is said to be higher in patients with vasospastic angina than in normal subjects[13], it was almost same as that of the negative test group. Second, our study revealed that even patients with no chest pain or atypical chest pain showed positive reaction in 46.2% and 33.3% of the cases, respectively. Third, in general, intravenous ergonovine bathes all of the coronary arteries simultaneously and produces focal severe coronary artery narrowing on a background of diffuse mild narrowing of the entire coronary tree in patients susceptible to coronary spasm[18]. In contrast, the angiographic features during provocation in our positive cases seemed to be hyperconstriction rather than critical focal stenosis. In addition, even in the cases of total occlusion, the total occlusion seemed to be in the same spectrum as hyperconstriction because the proximal segment was also severely constricted. These findings suggest that adjunctive acetylcholine injection could reveal only endothelial dysfunction or mild atherosclerosis rather than typical vasospastic angina.

The patients with chest pain at rest or on effort also showed similar or even higher positive rates compared with that of patients with symptom suggestive of variant angina (**Table 4**). Although the classification of angina type in this study did not include electrocardiographic evidence, our approach might have raised the sensitivity for detecting vasospastic angina pectoris except variant angina.

No lethal complications occurred during the study period, however, an increasing number of

tests may cause further complications. Thus, meticulous attention should be paid during this test by experienced operators with adequate skill in the spasm provocation test.

This pharmacological intervention might be useful for detecting spasm or hyperconstriction in vasospastic angina pectoris as well as in patients without typical symptoms suggestive of coronary vasospasm. The underlying pathogenesis in provocation test positive group is not clear, but we might see a clinical entity with endothelial dysfunction or mild atheroscrelosis but with less susceptibility to acetycholine and ergonovine compared with variant angina pectoris.

There are several limitations to this study. First, in this study only a small number of patients were included. A larger number of patients is necessary to evaluate this protocol compared to previous studies. Second, to evaluate the benefit of our method for provoking vasospasm strictly, it may be better to compare our data with the provocation rate of spasm by only acetylcholine in a similar population as included in this study or to perform only acetylcholine infusion before adjunctive acetylcholine following ergonovine infusion in the same patient. However, because intravenous infusion of a total of 0.4 mg of ergonovine has been recognized as adequate to provoke spasm with a sensitivity of between 93% and 99%[1-4], we believe that at least the majority of the patients with typical vasospastic angina were excluded before perfoming adjunctive acetylcholine infusion. Thus, this test may be beneficial for detecting spasm even in patients without variant angina pectoris. On the other hand, 50% of positive patients showed over 50% coronary vasoconstriction after ergonovine infusion. Although a higher dose of ergonovine might induce spasm with a higher rate in our patients, we did not use an additional dose of ergonovine to avoid the serious refractory spasm that often causes hemodynamic collapse.

要　約

冠動脈攣縮誘発におけるエルゴノビン静注負荷後アセチルコリン冠動脈内投与法の評価

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胸痛や冠動脈疾患を示唆する症状を有しながら，冠動脈造影において有意な動脈硬化性狭窄を示さず，かつ現行のアセチルコリンやエルゴノビンによる冠動脈攣縮誘発試験が陰性な例に遭遇することがまれならずある．

本研究では，総量0.4 mgのエルゴノビン静注負荷が陰性であった例に引き続き，アセチルコリンを左冠動脈内に最大100 μg，右冠動脈内に最大50 μg追加投与し，攣縮誘発率向上に寄与するかを検討した．対象は冠動脈疾患を示唆する典型的胸痛を有する19例，非定型的胸痛を有する6例，経皮的冠動脈形成術後6例，無痛性虚血4例，Adams-Stokes発作3例，来院時心肺停止1例の39例である．典型的胸痛を有する19例の症状の内訳は，早期安静時11例，安静時4例，労作時4例であった．誘発前に明らかな虚血性の心電図変化を示すイベントが確認された例はなかった．

冠攣縮はアセチルコリン追加後の23例(59.0%) に誘発され，そのうち30.4%は完全閉塞，60.9%は90−99%のび慢性攣縮，8.7%は局所的攣縮であった．典型的胸痛を示した例で誘発率が78.9%と最高であったが，非定型的胸痛を有する例やその他の例でもそれぞれ33.3%，42.9%の陽性率を示した．1例で心室頻拍，2例で心房細動が出現したが，一過性で処置を要しなかった．

本冠攣縮誘発法は，エルゴノビン静注で冠攣縮が誘発されなかった種々の患者群において，冠攣縮を同定するのに有用である．

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