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ORIGINAL ARTICLE

Differential incidence and morphology of provoked spasm between intracoronary acetylcholine and ergonovine testing: recommendation of supplementary use

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Abstract
When cardiologists diagnose patients with coronary spastic angina, Japanese Circulation Society (JCS) guidelines recommend the intracoronary injection of acetylcholine (ACh) and ergonovine (ER) as class I. However, the pharmacological difference between ACh and ER is controversial in the clinic. We performed both ACh and ER tests in the same 528 patients during 26 years. We investigated the provoked spasm configuration, spasm site, and clinical characteristics of provoked spasm between ACh and ER, retrospectively. We defined positive spasm as ≥90% luminal narrowing. Provoked positive spasm was observed in 161 right coronary arteries (RCA) including 83 ACh just positive, 35 ER just positive, and 43 both positive. In contrast, positive spasm was documented in 172 left coronary arteries (LCA) including 94 ACh just positive, 28 ER just positive, and 50 both positive. ACh provoked spasm more distally and diffusely, while ER induced spasm more proximally and totally or focally in the RCA. In the LCA, ACh provoked spasm more proximally, whereas ER induced spasm more distally. ER testing after the negative ACh tests of RCA and LCA documented new positive spasms in 10.3% (35/340) and 7.4% (28/376), respectively. Coronary artery trees may each have a sensitive receptor on each segment. We recommend the supplementary use of ACh and ER to document coronary artery spasm in the cardiac catheterization laboratory.

Keywords Positive spasm · Acetylcholine · Ergonovine · Supplementary use

Introduction

Japanese Circulation Society (JCS) guidelines and Coronary Vasomotor Disorder (COVADIS) group recommend that the intracoronary acetylcholine (ACh) test or ergonovine (ER) test is defined class I, when cardiologists suspected coronary spastic angina (CSA) in patients who have not been diagnosed with coronary spasm by non-invasive evaluations [1, 2]. Other Caucasian guidelines such as American College of Cardiology (ACC)/American Heart Association (AHA) or European Society of Cardiology (ESC) recommend the pharmacological spasm provocation tests as class IIb or IIa [23, 4]. ACh acts by way of muscarinic cholinergic receptor, while ER acts by way of serotogenic receptor. Because of the different mediators, these two pharmacological agents may have different coronary responses in even the same patients. However, the majority of cardiologists employed a single pharmacological agent in the cardiac catheterization laboratory in each hospital. Then, the cardiologists did not know the difference in the coronary artery response between the two agents. We have already reported the difference in provoked spasm configuration and spasm site between the two agents [5]. ACh provoked diffuse spasm more distally, whereas ER induced focal spasm more proximally. Moreover, the incidence of provoked spasm in ACh testing was significantly higher than that in ER tests [6]. Furthermore, ACh is supersensitive to females [7]. However, the clinical detailed characteristics of provoked spasm site and configuration between the two agents were controversial.

In this article, we examined the difference in provoked spasm frequency, provoked spasm sites, detailed spasm

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configuration in patients who had undergone both ACh and ER tests, retrospectively.

Methods

Study patients

From January 1991 to December 2016, we performed a total of 8014 coronary angiography procedures, including 2185 percutaneous coronary intervention procedures and 5829 diagnostic and follow-up cardiac catheterization, as shown in Fig. 1. During the same time, we performed ACh spasm provocation tests in 1767 patients and ER spasm provocation tests in 1210 patients. Both ACh and ER tests were performed in 528 patients. During these periods, we tried to perform the selective spasm provocation tests to examine the incidence of provoked spasm in patients who had undergone coronary angiography whenever possible. As show in Table 1, ischemic heart disease (IHD) was observed in 345 patients including 198 patients with rest angina, 42 patients with effort angina, 47 patients with rest and effort angina, 31 patients with healed myocardial infarction, and 27 patients after percutaneous coronary intervention, whereas non-IHD was found in 183 patients including 100 patients with atypical chest pain, 3 patients with valvular heart disease, 14 patients with cardiomyopathy, and 66 patients with others. Organic stenosis (> 75%) was recognized in 58 patients (11.0%), while 303 patients (57.4%) had a history of smoking. Hypertension was observed in 232 patients (43.9%), whereas 222 patients (42.0%) had dyslipidemia. Diabetes mellitus was found in 106 patients (20.1%). Subjects were excluded and the provocation test was not performed if patients had left main narrowing (> 50%), triple-vessel disease, two-vessel disease with total occlusion, heart failure (New York Heart Association functional class III or IV), renal failure (creatinine > 2.0 mg/dl), if spontaneous spasm

Table 1. Patients' clinical characteristics

	Total
Number	528
Men	333 (63.1%)
Age (year)	64.5±11.4
Organic stenosis	58 (11.0%)
Risk factors	
Smoking history	303 (57.4%)
Hypertension	232 (43.9%)
Dislypidemia	222 (42.0%)
Diabetes mellitus	106 (20.1%)
IHD	345 (65.3%)
Rest angina	198 (37.5%)
Effort angina	42 (8.0%)
Rest and effort angina	47 (8.9%)
Healed myocardial infarction	31 (5.9%)
After PCI	27 (5.1%)
Non-IHD	183 (34.7%)
Atypical chest pain	100 (18.9%)
Valvular heart disease	3 (0.6%)
Cardiomyopathy	14 (2.7%)
Others	66 (12.5%)
Total cholesterol (mg/dl)	193.2±36.7
Triglyceride (mg/dl)	128.5±77.3
HDL-cholesterol (mg/dl)	50.0±13.3
LDL-cholesterol (mg/dl)	114.4±32.3
Fast blood sugar (mg/dl)	110.0±36.1
Glycohemoglobin (%)	5.6±0.9

ACh acetylcholine, *ER* ergonovine, *IHD* ischemic heart disease, *HDL* high-density-lipoprotein, *LDL* low-density-lipoprotein

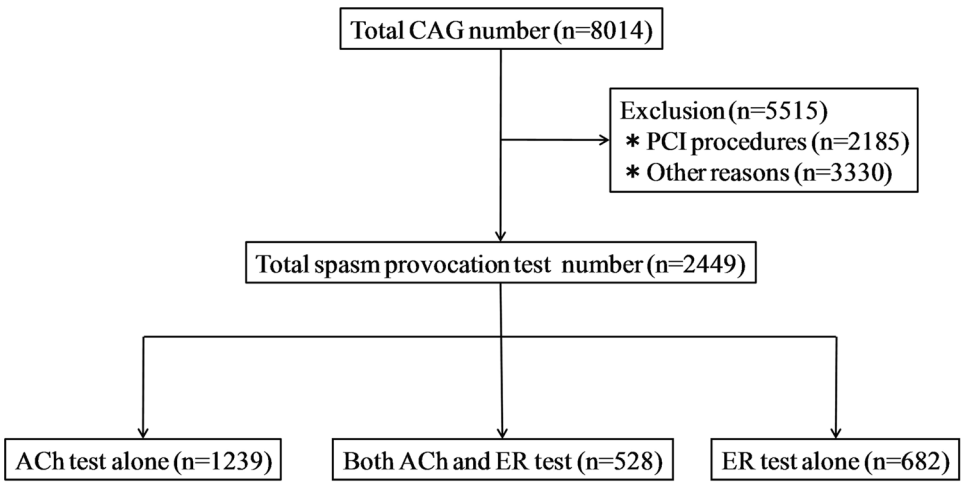


Figure 1. Flow chart of this study

(CAG: coronary angiography, PCI: percutaneous coronary intervention, ACh: acetylcholine, ER: ergonovine)

was observed, or if isosorbide dinitrate was initially used to relieve spasm in the coronary artery tested.

The definition of positive spasm Generally, we defined positive spasm as ≥ 90% transient stenosis and usual chest symptom or ischemic ECG changes. The degree of ST-segment depression was measured 80 msec after the J point. We considered a result to be positive when at least 1 of the following ischemic ECG changes was demonstrated during and/or after the ACh test: (1) ST-segment elevation of ≥ 0.1 mV in at least 2 contiguous leads; (2) ST-segment depression of 0.1 mV in at least two contiguous leads. We also considered negative U wave as positive ischemic ECG change.

Spasm provocation test

All drugs except for nitroglycerin were discontinued for ≥ 24 h before the study and nitroglycerin was also discontinued ≥ 4 h before the study. Cardiac catheterization was performed from 9:00 am to 4:00 pm in the fasting state. Furthermore, we attempted to perform ACh and ER spasm provocation tests whenever possible. After control coronary arteriograms 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 injection of 8–10 ml of contrast medium, a temporary pacemaker was inserted into the right ventricle of each patient and the pacing rate was set at 40–45 beats/min.

Provocation of coronary artery spasm was performed with an intracoronary injection of ACh and ER, as previously reported [8–13]. We performed the intracoronary ER test following the intracoronary ACh tests. ACh chloride (Neucholin-A, 30 mg/2mL; Zeria Seiyaku, Tokyo, Japan) was injected in incremental doses of 20, 50 and 80 μg into the RCA and of 20, 50 and 100 (200) μg into the LCA over 20 s with at least a 3-min interval between each injection. ER (ergometrine by injection F, 0.2 mg/mL; Fuji Seiyaku, Tokyo, Japan) in a 0.9% warm saline solution was injected at 10 μg/min for 4 min for a maximal dose of 40 μg into the RCA and 16 μg/min over 4 min for a total dose of 64 μg into the LCA, with at least a 5-min interval between each injection. Coronary arteriography was performed when ST-segment changes and/or, chest pain occurred or 1–2 min after the completion of each injection. When an induced coronary spasm did not resolve spontaneously within 3 min after the completion of ACh and ER injections or when hemodynamic instability occurred as a result of coronary spasm, 2.5–5.0 mg of nitrate was injected into the involved vessel. A standard 12-lead electrocardiogram was recorded every 30 s. We used the ECG findings when ACh/ER, saline and contrast medium were not injected into the responsible vessels for at least 60 s. After the spasm provocation tests were completed, an intracoronary injection of 5.0 mg isosorbide dinitrate was administered, and coronary arteriography was then performed in multiple projections.

During the study, arterial blood pressure and ECG were continuously monitored on an oscilloscope by Nihon Kohden polygraphy (Tokyo, Japan). In the present study, coronary arteriograms were analyzed separately by 2 independent observers. The percent luminal diameter narrowing of coronary arteries was measured using an automatic edge-counter detection computer analysis system. The size of the coronary catheter was used to calibrate the images in millimeters and the measurement was performed in the same projection of coronary angiography at each stage. Focal spasm was defined as a discrete transient vessel narrowing ≥ 90% localized in a major coronary artery, whereas diffuse spasm was diagnosed when transient vessel narrowing ≥ 90%, compared with baseline coronary angiography, was observed from the proximal to distal segment in all 3 major coronary arteries. According to the ACC/AHA classification of segments, we employed the detailed provoked spasm site. Patients with catheter-induced spasms were excluded from this study. Significant organic stenosis was defined as > 75% luminal narrowing according to the ACC/AHA classification [14].

The study protocol complied with the Declaration of Helsinki. Written informed consent was obtained from all patients before the study and the protocol of this study was in agreement with the guidelines of the ethical committee at our institution.

Statistical analysis

Data analysis was carried out with SPSS (version 22.0, IBM Japan, Ltd., Tokyo, Japan). All data were presented as the mean ± 1 SD. Clinical characteristics including coronary risk factors, provoked spasm rate, provoked spasm site or configuration were analyzed by the Fisher's exact test with correction or the Mann–Whitney test. $P < 0.05$ was considered significant.

Results

Clinical and angiographic characteristics of the RCA

We could perform both tests in 476 patients in the RCA. As shown in Fig. 2, 161 vessels had positive spasm among 476 arteries, while the remaining 315 vessels had no provoked spasm. In the 161 patients with RCA-positive spasm, 91 patients (56.5%) had positive spasm in the LCA. Positive spasm was documented in 126 vessels by ACh, whereas ER provoked spasm in 78 vessels. Both ACh and ER induced spasm in 43 vessels. ER test documented new positive spasm in 10.3% (35/340) of patients who

had no provoked spasm by the ACh testing. Compared with negative patients, patients with positive spasm by ACh or ER had significantly higher incidence of men, history of smoking, and IHD including rest angina, as shown in Table 2. In contrast, non-IND and atypical chest pain were significantly often observed in spasm-negative group. Men and history of smoking in ER just positive and both positive patients were significantly higher than that in ACh just positive patients. Other risk factors and clinical characteristics among the three groups were not different. Figure 3 shows that ACh-provoked spasm was remarkable at segment 4 [55.6% (70/126)], while ER-induced spasm was prominent at segment 2 [43.6% (34/78)]. The majority of provoked spasm was diffuse [69% (87/126)] in ACh testing, whereas total or focal spasm [67.9% (53/78)] was more prominent in ER tests in the RCA, as shown in Fig. 4.

Clinical and angiographic characteristics in the LCA

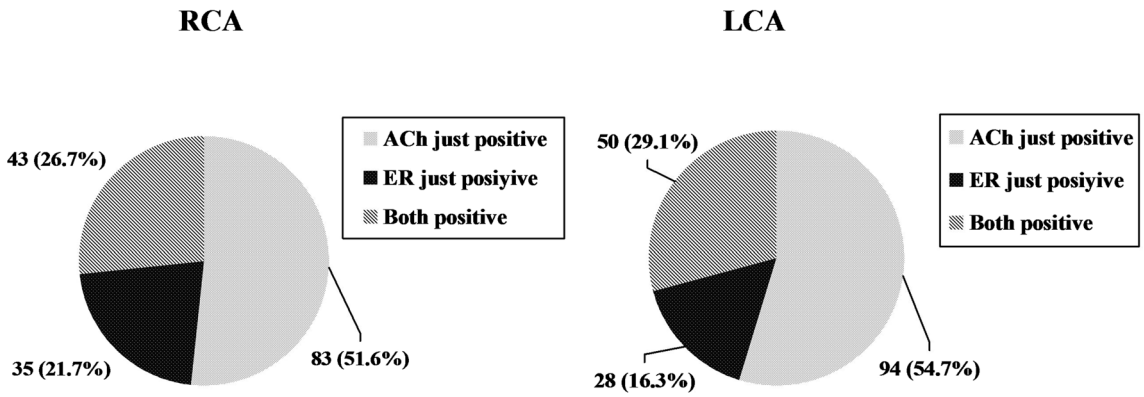
We could perform both tests in 520 patients in the LCA. Figure 2 shows that positive spasm was observed in 172 patients including 94 patients with ACh just positive, 28 patients with ER just positive and 50 patients with both positive. In the 172 patients with LCA-positive spasm, 81 patients (47.1%) had positive spasm in the RCA. ER test had new positive spasm in 7.4% (28/376) of patients who had no provoked spasm by the ACh testing. Men, history of smoking, and IHD including rest angina and effort angina were significantly higher in patients with positive spasm by ACh or ER than those in patients with negative spasm. In contrast, non-IHD including atypical chest pain and others was higher in patients with negative spasm than that in positive spasm. There were significantly higher number of men and smoking history in patients with ER just positive and both positive than in ACh just positive,

Table 2. Comparisons of various cardiac disorders and coronary risk factors in the right coronary artery

	ACh just positive	ER just positive	Both positive	ACh or ER positive	Negative	Total
Number	83	35	43	161	315	476
Men	47 (56.6%)	34 (97.1%)$^{\$}$	35 (81.4%)$^{\$}$	116 (72.0%)*	186 (59.0%)	302 (63.4%)
Age (year)	67.3±10.2	63.2±10.3	66.3±10.0	66.1±10.2	64.0±11.4	64.7±11.1
Organic stenosis	1 (1.2%)	3 (8.6%)	3 (7.0%)	7 (4.3%)	6 (1.9%)	13 (2.7%)
Risk factors						
Smoking history	44 (53.0%)	32 (91.4%)$^{\$}$	34 (79.1%)$^{\$}$	110 (68.3%)*	166 (52.7%)	276 (58.0%)
Hypertension	40 (48.2%)	15 (42.9%)	21 (48.8%)	76 (47.2%)	126 (40.0%)	202 (42.4%)
Dislypidemia	36 (43.4%)	11 (31.4%)	22 (51.2%)	69 (42.9%)	120 (38.1%)	189 (39.7%)
Diabetes mellitus	16 (19.3%)	6 (17.1%)	7 (16.3%)	29 (18.0%)	56 (17.8%)	85 (17.9%)
IHD	63 (75.9%)	32 (91.4%)	35 (81.4%)	130 (80.7%)#	174 (55.2%)	304 (63.9%)
Rest angina	39 (47.0%)	20 (57.1%)	23 (53.5%)	82 (50.9%)#	99 (31.4%)	181 (38.0%)
Effort angina	9 (10.8%)	3 (8.6%)	5 (11.6%)	17 (10.6%)	22 (7.0%)	39 (8.2%)
Rest & effort angina	11 (13.3%)	4 (11.4%)	0	15 (9.3%)	23 (7.3%)	38 (8.0%)
Healed MI	3 (3.6%)	1 (2.9%)	4 (9.3%)	8 (5.0%)	16 (5.1%)	24 (5.0%)
After PCI	1 (1.2%)	4 (11.4%)$^{\&}$	3 (7.0%)	8 (5.0%)	14 (4.4%)	22 (4.6%)
Non-IHD	20 (24.1%)	3 (8.6%)	8 (18.6%)*	31 (19.3%)	141 (44.8%)	172 (36.1%)
Atypical chest pain	9 (10.8%)	0	4 (9.3%)	13 (8.1%)	85 (27.0%)	98 (20.6%)
Valvular heart disease	0	0	0	0	2 (0.6%)	2 (0.4%)
Cardiomyopathy	2 (2.4%)	1 (2.9%)	0	3 (1.9%)	9 (2.9%)	12 (2.5%)
Others	9 (10.8%)	2 (5.7%)	4 (9.3%)	15 (9.3%)	45 (14.3%)	60 (12.6%)
Total cholesterol (mg/dl)	192.1±36.1	181.2±34.4	184.7±38.5	187.9±36.4	190.5±35.1	189.5±35.6
Triglyceride (mg/dl)	119.2±32.8	118.1±43.6	150.1±93.3	123.5±63.5	126.2±83.6	125.2±76.5
HDL-cholesterol (mg/dl)	53.2±13.4	45.7±11.0	45.7±11.4	49.7±12.9	51.1±13.8	50.6±13.5
LDL-cholesterol (mg/dl)	115.1±31.9	111.3±28.2	107.2±30.3	112.2±30.7	113.9±20.6	113.6±30.0
Fast blood sugar (mg/dl)	110±38.6	98.7±15.1	105.2±24.2	106.4±31.6	109.8±34.6	108.5±33.5
Glycohemoglobin (%)	5.6±1.0	5.5±0.9	5.4±0.7	5.6±0.9	5.6±0.8	5.6±0.9

ACh acetylcholine, *ER* ergonovine, *IHD* ischemic heart disease, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *HDL* high-density-lipoprotein, *LDL* low-density-lipoprotein

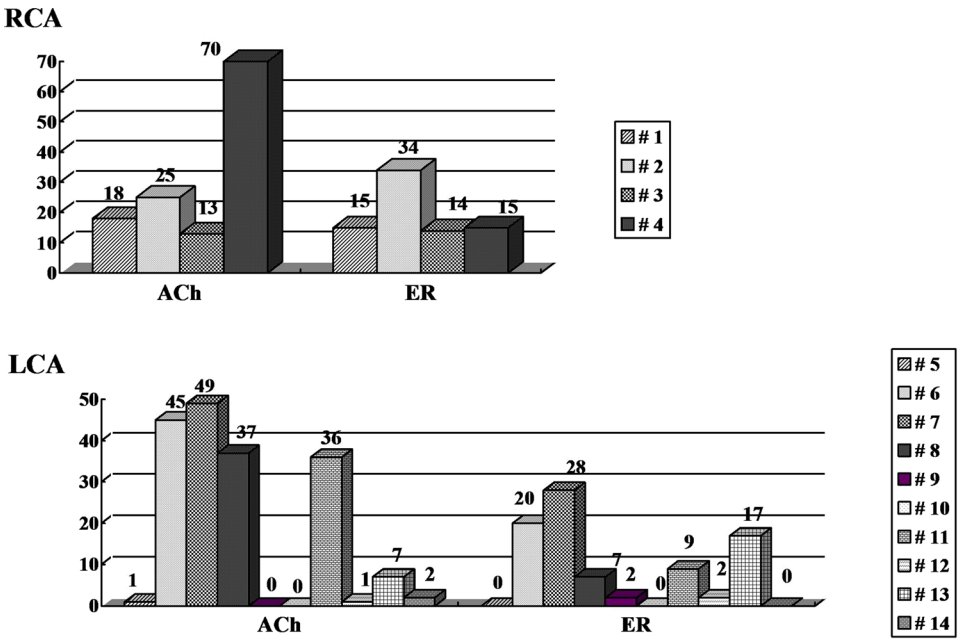
$^{\$}p < 0.001$ and $^{\&}p < 0.05$ vs. ACh just positive, $^{*}p < 0.01$ and $^{\#}p < 0.001$ vs. negative



(RCA: right coronary artery, LCA: left coronary artery, ACh: acetylcholine, ER: ergonovine)

Figure 2. Comparisons of provoked spasm between acetylcholine and ergonovine on both coronary arteries

Figure 3. Comparisons of provoked spasm site between acetylcholine and ergonovine on both coronary arteries

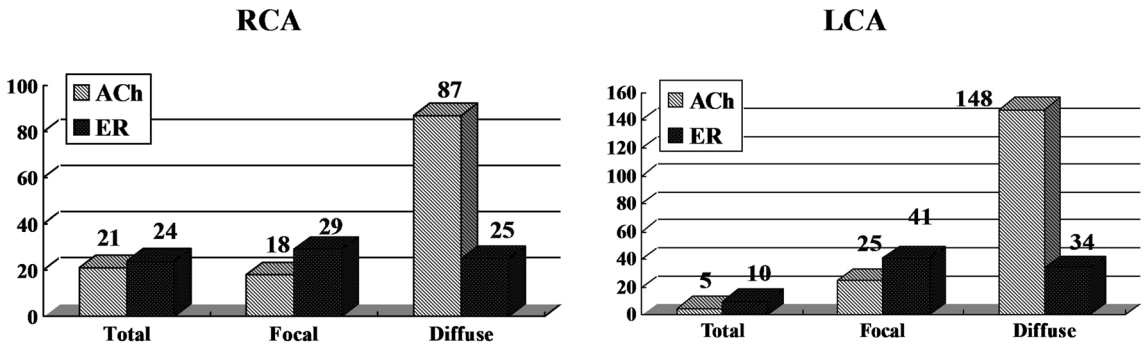


(RCA: right coronary artery, LCA: left coronary artery, ACh: acetylcholine, ER: ergonovine)

while other factors were not different among the three groups. As shown in Fig. 3, the distribution of provoke spasm site was not different in the left anterior descending artery. However, in the left circumflex artery, ACh-positive spasm was more frequently observed at segment 11 [78.3% (36/46)], whereas ER-positive spasm was remarkably found at segment 13 [60.1% (17/28)]. Figure 4 shows that diffuse spasm [83.1% (148/178)] was more frequent in ACh-positive patients, while total or focal spasm [60% (51/85)] was more remarkable in ER-positive patients.

Angiographical characteristics of just ACh positive and just ER positive

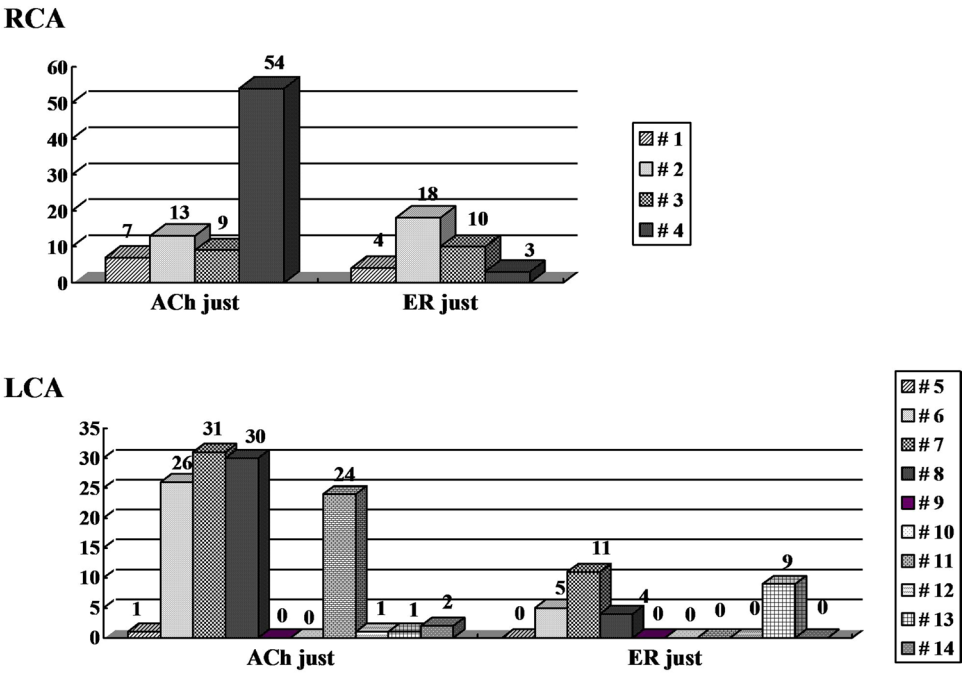
As shown in Figures 5 and 6, there was no difference in the provoked spasm configuration and provoked spasm site between all ACh/ER-positive patients and just ACh/ER-positive patients. In the RCA, just ACh-provoked spasm was prominent at segment 4 [65.1% (54/83)], while just ER-induced spasm was remarkable at segment 2 [51.4% (18/35)], whereas the majority of provoked spasm was diffuse [73.5% (61/83)] in ACh testing and total or focal spasm



(RCA: right coronary artery, LCA: left coronary artery, ACh: acetylcholine, ER: ergonovine)

Figure 4. Comparisons of provoked spasm configuration between acetylcholine and ergonovine on both coronary arteries

Figure 5. Comparisons of provoked spasm site between just acetylcholine positive and just ergonovine positive on both coronary arteries



(RCA: right coronary artery, LCA: left coronary artery, ACh: acetylcholine, ER: ergonovine)

[85.7% (30/35)] was more prominent in ER tests. In the left circumflex artery, just ACh-positive spasm was more frequently observed at segment 11 [85.7% (24/28)], whereas just ER-positive spasm was all found at segment 13 [100% (9/9)]. In the LCA, diffuse spasm [86.2% (100/116)] was more frequent in just ACh-positive patients, while total or focal spasm [65.5% (19/29)] was more remarkable in just ER-positive patients (Table 3).

Complications during pharmacological testing

As shown in Table 4, ventricular fibrillation was observed in one patient and non-sustained ventricular tachycardia was found in four patients. Paroxysmal atrial fibrillation was recognized in 117 patients, while reciprocal ST elevation was observed in 9 patients. Direct current and thump version was necessary to recover sinus rhythm in one patient each. Administration of anti-arrhythmic agents for paroxysmal atrial fibrillation to recover sinus rhythm was necessary in 34 patients, whereas the injection of nitrate to relieve the provoked spasm before another vessel during ER testing was necessary in 21 patients. However, we had no irreversible complications during both testing in this study.

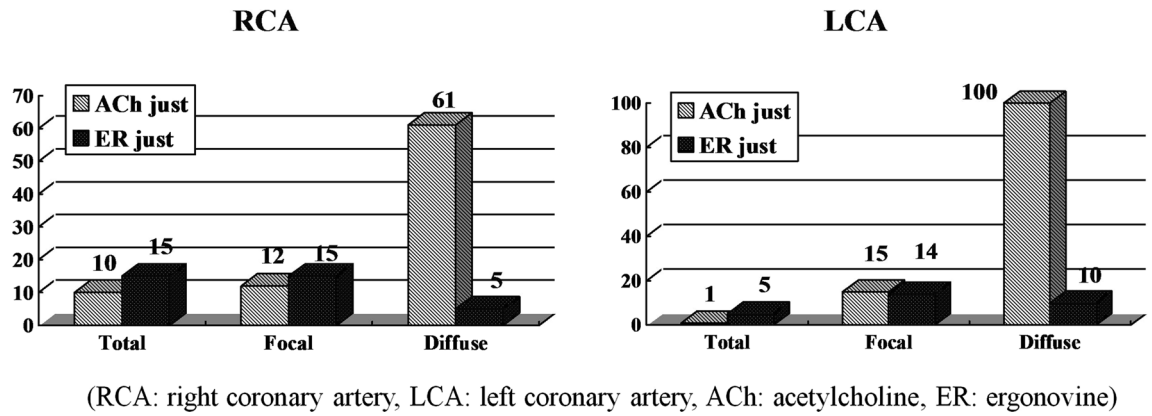


Figure 6. Comparisons of provoked spasm configuration between just acetylcholine positive and just ergonovine positive on both coronary arteries

Table 3. Comparisons of various cardiac disorders and coronary risk factors in the left coronary artery

	ACh just positive	ER just positive	Both positive	ACh or ER positive	Negative	Total
Number	94	28	50	172	348	520
Men	60 (63.8%)	25 (89.3%)[&]	42 (84.0%)[&]	127 (73.8%)#	199 (57.2%)	326 (62.7%)
Age (year)	64.8±10.8	64.4±9.4	65.3±10.8	64.9±10.6	64.4±11.3	64.6±11.0
Organic stenosis	9 (9.6%)	6 (21.4%)	9 (18.0%)	24 (14.0%)	33 (9.5%)	57 (11.0%)
Risk factors						
Smoking history	58 (61.7%)	20 (71.4%)	33 (66.0%)	111 (64.5%)*	186 (53.4%)	297 (57.1%)
Hypertension	41 (43.6%)	15 (53.6%)	22 (44.0%)	78 (45.3%)	149 (42.8%)	227 (43.7%)
Dislypidemia	41 (43.6%)	16 (57.1%)	22 (44.0%)	79 (45.9%)	139 (39.9%)	218 (41.9%)
Diabetes mellitus	13 (13.8%)	9 (32.1%)	7 (14.0%)	29 (16.9%)	75 (21.6%)	104 (20.0%)
IHD	74 (78.7%)	24 (85.7%)	43 (86.0%)	141 82.0%)#	198 (56.9%)	339 (65.2%)
Rest angina	48 (51.1%)	15 (53.6%)	27 (54.0%)	90 (52.3%)#	105 (30.2%)	195 (37.5%)
Effort angina	10 (10.6%)	4 (14.3%)	6 (12.0%)	20 (11.6%)*	20 (5.7%)	40 (7.7%)
Rest & effort angina	8 (8.5%)	2 (7.1%)	5	15 (8.7%)	31 (8.9%)	46 (8.8%)
Healed MI	3 (3.2%)	2 (7.1%)	2 (4.0%)	7 (4.1%)	24 (6.9%)	31 (6.0%)
After PCI	5 (5.3%)	1 (3.6%)	3 (6.0%)	9 (5.2%)	18 (5.2%)	27 (5.2%)
Non-IHD	20 (21.3%)	4 (14.3%)	7 (14.0%)*	31 (18.0%)#	150 (43.1%)	181 (34.8%)
Atypical chest pain	9 (9.6%)	0	4 (8.0%)	13 (7.6%)#	87 (25.0%)	100 (19.2%)
Valvular heart disease	2 (2.1%)	0	0	2 (1.2%)	1 (0.3%)	3 (0.6%)
Cardiomyopathy	0	2 (7.1%)	0	2 (1.2%)	12 (3.4%)	14 (2.7%)
Others	9 (9.6%)	2 (7.1%)	3 (6.0%)	14 (8.1%)*	50 (14.4%)	64 (12.3%)
Total cholesterol (mg/dl)	193.6±40.1	191.1±30.3	185.0±41.1	190.8±39.0	191.0±35.6	190.9±36.8
Triglyceride (mg/dl)	121.2±60.5	149.3±76.0	125.2±57.5	126.7±63.0	130.8±92.9	127.8±77.7
HDL-cholesterol (mg/dl)	52.7±13.4	48.4±13.8	49.8±12.4	51.2±13.2	50.8±14.0	50.9±13.7
LDL-cholesterol (mg/dl)	116.0±32.6	113.8±27.1	110.2±35.2	114.0±32.4	114.0±30.6	114.1±31.2
Fast blood sugar (mg/dl)	110.1±26.1	110.5±30.2	107.7±46.6	109.5±33.2	110.6±39.2	110.2±37.1
Glycohemoglobin (%)	5.5±0.7	5.9±1.1	5.6±.5	5.6±1.0	5.7±1.0	5.6±1.0

ACh acetylcholine, *ER* ergonovine, *IHD* ischemic heart disease, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *HDL* high-density-lipoprotein, *LDL* low-density-lipoprotein

[&] $p < 0.05$ vs. ACh just positive, * $p < 0.05$ and [#] $p < 0.001$ vs. negative

Table 4. Major and minor complications and procedures among both tests

Major complications	5 (0.95%)
Ventricular fibrillation	1 (0.19%)
Sustained ventricular tachycardia	0
Non sustained ventricular tachycardia	4 (0.76%)
Shock (like left main trunk spasm)	0
Hypotension (severe <60 mmHg)	0
Cardiac arrest	0
Cardiac tamponade	0
Myocardial infarction	0
Cardiac death	0
Minor complications	117 (22.16%)
Paroxysmal atrial fibrillation (Paf)	117 (22.16%)
Other complications	9 (1.7%)
Reciprocal ST elevation	9 (1.7%)
Procedures	2 (0.38%)
Direct current	1 (0.19%)
Thump version	1 (0.19%)
Administration	55 (10.42%)
Anti arrhythmic agents (Paf)	34 (6.44%)
Nitrate (intra coronary) before another vessel	21 (3.98%)

Discussion

In this article, we reported the difference between ACh- and ER-positive spasm in the clinic. In the RCA, ACh provoked diffuse spasm distally at segment 4, while ER induced total or focal spasm proximally at segment 2. In the left anterior descending artery, spasm configuration and site were not different between ACh and ER, whereas ACh provoked spasm proximally at segment 11 and ER induced spasm distally at segment 13 in the left circumflex artery. In the RCA, ER provoked spasm in 10.3% (35/340) of patients who had no spasm by the intracoronary administration of ACh. In the LCA, ER induced spasm in 7.4% (28/376) of patients who had no provoked spasm after the ACh testing. In the clinic, we found the ER-positive and ACh-negative spasm in approximately one of ten patients who had no provoked spasm by ACh testing. Considering our results, coronary artery tree may have some dominancy of each special receptor on both coronary arteries. We recommend the supplementary use of ACh and ER as a pharmacological agent in the cardiac catheterization laboratory whenever possible.

We have already reported the sex difference, spasm configuration and spasm site between the ACh and ER. ACh provoked spasm more diffusely and more distally, while ER induced spasm more focally and proximally. Furthermore, ACh is supersensitive in female patients compared with male patients. In this article, we recognized similar results. If we performed the ACh test alone in the cardiac catheterization laboratory, we may miss a positive spasm in approximately 7.4–10.3% of patients who had no provoked spasm by ACh tests. We should employ the supplementary use of ACh and ER not to misdiagnose patients with CSA. Furthermore, Ciliberti et al reported that major complications of ACh testing were 1.09%, while we experienced the major complications in 0.95% of both tests [15]. Major complications during both tests were similar to just ACh testing.

Clinical implications

The majority of cardiologists employed the single pharmacological agent such as just ACh or just ER to diagnose the presence of spasm [16–21]. However, spasm provocation tests have self-limitations in documenting the daily life spontaneous spasm. Cardiologists should understand this limitation in the cardiac catheterization laboratory. If patients had strongly suspected positive spasm after negative ACh testing, cardiologists should administer the intracoronary ER to diagnose coronary artery spasm. If cardiologists performed the ER tests after the negative ACh tests, approximately 10% of patients with ACh-negative spasm may have correct diagnosis of CSA. We recommend the supplementary use of ACh and ER tests to diagnose coronary artery spasm in the cardiac catheterization laboratory [22, 23]. Because the pharmacological effect of ACh is shorter than ER, we recommend ER testing after the ACh tests in the clinic.

Study limitations

This study had several limitations: one is cessation of medication before ACh and ER tests. At least after 24 h of cessation of vasodilatory drugs, we performed both tests. However, residual pharmacological effect might be observed during ACh and ER tests. The second limitation is angiographic timing. We performed coronary arteriograms one–two minutes after each intracoronary injection of ACh and ER, or when usual chest pain/discomfort or significant ischemic ST changes were present on the electrocardiogram. We may miss the typical spasm provoked on angiography because of restrictive angiography. The third limitation is the time when we performed cardiac catheterization. We performed both spasm provocation tests in the morning whenever possible. However, we could not perform all of the two spasm provocation tests in the early morning. The fourth limitation is that we could not employ the alternative use of ACh and ER. We performed ACh tests first, and after the ACh tests we performed the ER tests. The residual effect of ACh might be recognized during ER testing, although we performed the ER tests after 5–10 min cessation of procedures. The last limitation is that the subjects of this study included not only IHD patients, but also non-IHD patients. Non-IHD patients were recognized in 34.7% of our study subjects. However, we recently reported that one

of six patients with non-IHD and non-obstructive coronary artery disease had provoked coronary spasm by intracoronary injection of acetylcholine [4]. We should investigate the presence of coronary spasm in not only patients with IHD, but also non-IHD in the future. Further study is necessary to investigate the pathophysiology of coronary spasm induced by ACh or ER.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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