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Original article

Coronary abnormal response has increased in Japanese patients: Analysis of 17 years' spasm provocation tests in 2093 cases

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KEYWORDS
Spasm provocation test;
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Summary
Background: Abnormal coronary response on acetylcholine test is observed in patients with early coronary atherosclerosis.
Objectives: We analyzed retrospectively the abnormal response rate during 17 years of spasm provocation tests in 2093 consecutive patients.
Methods: We performed 2093 spasm provocation tests, consisting of 1198 acetylcholine tests and 895 ergonovine tests, between January 1991 and December 2007. Spasm provocation test was mainly performed in patients with ischemic heart disease. Abnormal response was defined as transient >90% luminal narrowing during spasm provocation tests. We classified these 17 years into two periods: former period from January 1991 to December 2000, and the latter period from January 2001 to December 2007. In the former period, 1300 spasm provocation tests were performed and 793 spasm provocation tests were done in the latter period.
Results: The incidences of hypertension, dyslipidemia, and diabetes mellitus were significantly increased in the latter period. The values of total cholesterol, triglycerides, and fasting blood sugar were also significantly increased in the latter period. The frequency of abnormal response in the latter period was significantly higher than that in the former period (46.0% vs. 33.2%, $p < 0.05$). The frequency of abnormal coronary response to acetylcholine in the latter period was significantly higher than that in the former period (60.0% vs. 34.0%, $p < 0.01$),

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whereas there was no difference concerning abnormal response of ergonovine between the two periods (31.9% vs. 30.7%, ns).
Conclusions: In Japanese patients, abnormal coronary response to acetylcholine has increased and coronary endothelial dysfunction is suggested to have progressed.

Introduction

As spasm provocation agents, we have employed intracoronary administration of acetylcholine (ACh) and ergonovine (ER) since the latter half of the 1980s. In 1986 and 1988, Yasue et al. [1] and Okumura et al. [2,3] reported the usefulness of intracoronary administration of ACh as a spasm provocation test, while Hackett et al. [4] also reported the intracoronary administration of ER as a spasm provocation test in 1987. We have already reported the incidence of provoked spasms in patients undergoing coronary arteriography with spasm provocation tests using ACh and ER [5—7].

ACh dilates if the artery has no atherosclerosis, whereas ACh constricts coronary artery if the artery has mild atherosclerosis [8,9]. Thus, the coronary artery showing abnormal response to ACh has endothelial dysfunction at least. Recently, coronary artery endothelial dysfunction has increased due to the increase in hypertension, dyslipidemia, and diabetes mellitus associated with the metabolic syndrome even in Japan [10].

This study sought to compare the annual incidence of abnormal coronary response by intracoronary administration of ACh and ER retrospectively over 17 years. We also compared the relationship between abnormal coronary response and coronary risk factors.

Methods

Study patients

We performed selective spasm provocation tests to examine the incidence of provoked spasm in Japanese patients who had undergone first coronary angiography. Between January 1991 and December 2007, we performed 2093 selective ACh and ER spasm provocation tests. 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 spasms were observed, or if isosorbide dinitrate was initially used to relieve spasms in the coronary artery tested. We also did not perform spasm provocation tests if the patients were due to undergo coronary angioplasty or bypass surgery. Thus, final study subjects were 2093 patients (1386 men, mean age 64.9 ± 10.3 years) without the above exclusion criteria. Selective spasm provocation tests using ACh were performed in 1198 patients (832 men, mean age 64.3 ± 10.1 years) and using ER in 895 patients (554 men, mean age 65.6 ± 10.7 years) (Table 1).

As shown in Table 2, patients were classified into eight groups based on the clinical diagnosis, according to previous reports [5—7]. We classified these periods into two phases, consisting of former procedures done between 1991 and 2000, and of latter procedures performed between 2001 and 2007 with each agent.

The procedure was explained in detail to each patient, informed consent was obtained, and the protocol of this study was in agreement with the guidelines of the ethical committee at our institution.

The diagnosis of typical angina was made in patients meeting all of the following criteria: (1) retrosternal burning or squeezing chest pain; (2) quick relief of pain (<5 min) after administration of sublingual nitroglycerin; (3) chest pain thought to have myocardial ischemia as its source.

ACh and ER spasm provocation test

Coronary arteriography was obtained by injection of 8—10 mL of contrast medium with the Sones technique from 10:00 h to 16:00 h with no medication for at least 24 h. A bipolar electrode catheter was inserted into the right ventricular apex through the femoral vein or antecubital vein and was connected to a temporary pacemaker set at the rate of 45 beats/min.

Provocation of coronary artery spasm was performed with an intracoronary injection of ACh and ER, as previously reported [5—7,11,12]. ACh chloride (Neucholin-A, 30 mg/2 mL; Zeria Seiyaku, Tokyo, Japan) was injected in incremental doses of 20, 50, and 80 μg into the right coronary artery and of 20, 50, and 100 μg into the left coronary artery over 20 s with at least a 3-min interval between each injection. Coronary arteriography was performed when either ST-segment changes or chest pain (or both) occurred, or after 1 min following the completion of each injection. Intracoronary injection of ACh into the responsible vessel was not performed if coronary artery spasm occurred spontaneously during coronary angiography. ER (ergometrine injection F, 0.2 mg/mL; Fuji Seiyaku, Tokyo, Japan) in 0.9% warm saline solution was injected in 10 μg/min for 4 min for a maximal dose of 40 μg into the right coronary artery and 16 μg/min over 4 min for a total dose of 64 μg into the left coronary artery, with at least a 5-min interval between each injection. If systolic blood pressure was >190 mmHg before performing ER tests, we did not perform ER tests in these patients. Coronary arteriography was performed when ST-segment changes, chest pain (or both), occurred, or following 2 min after the completion of each injection. When a coronary spasm was induced and did not resolve spontaneously within 3 min after the completion of ACh and ER injection, or when hemodynamic instability due to the coronary spasm occurred, 2.5—5.0 mg of isosorbide dinitrate was injected into the responsible vessel. During the study, arterial blood pressure and an electrocardiogram lead (II) were continuously monitored on an oscilloscope using a Nihon-Kohden polygraph. A standard 12-lead electrocardiogram was recorded every 30 s.

Table 1 Patients' characteristics.

	Acetylcholine	Ergonovine	Total
Number of patients	1198	895	2093
Male	832 (69.4)*	554 (61.9)	1386 (66.2)
Age (year)	64.3 ± 10.1	65.6 ± 10.7	64.9 ± 10.3
Organic stenosis (>75%)	314 (26.2)	232 (25.9)	546 (26.1)
Hypertension	516 (43.1)	388 (43.4)	904 (43.2)
Smoking history	795 (66.4)*	492 (55.0)	1287 (61.5)
Dyslipidemia	462 (38.6)	327 (36.5)	789 (37.7)
Diabetes mellitus	229 (19.1)	165 (18.4)	394 (18.8)
Total cholesterol (mg/dl)	190.9 ± 35.0	193.3 ± 35.7	192.0 ± 35.3
Triglyceride (mg/dl)	132.5 ± 77.9	131.8 ± 88.3	132.2 ± 82.8
HDL-cholesterol (mg/dl)	46.9 ± 13.2	48.1 ± 13.0	47.4 ± 13.1
LDL-cholesterol (mg/dl)	115.4 ± 30.1	116.8 ± 30.2	116.1 ± 30.1
Fasting blood sugar (mg/dl)	109.8 ± 39.6	111.8 ± 40.5	110.7 ± 40.0
Glycohemoglobin (%)	5.44 ± 1.00	5.52 ± 1.20	5.47 ± 1.09

HDL, high-density lipoprotein; LDL, low-density lipoprotein; values within parentheses are in %.
* $p < 0.01$ vs. other.

In this study, we performed frequent test shots at about 30-s intervals with a contrast medium during ACh and ER testing, if possible. We tried to perform coronary angiography before complete spasms were induced by pharmacologic agents.

We also examined the relationship between abnormal coronary response and age, gender, smoking, and coronary risk factors. Dyslipidemia was defined as either a cholesterol level >220 mg/dl or a triglyceride level >150 mg/dl. Diabetes mellitus was defined according to the World Health Organization criteria [13]. Systemic hypertension was defined as either a systolic blood pressure of >140 mmHg or a diastolic blood pressure of >90 mmHg or as patients already treated with antihypertensive drugs [14]. A smoking history was obtained from all the patients on admission. In this study, >5 years' habitual smoking in the past was considered positive.

Angiographic analysis

The coronary arteriograms were analyzed separately by two independent observers. The percent luminal diameter narrowing of coronary arteries was measured by an automatic edge-contour detection computer analysis system (CARDIO 500, Kontron Instruments, Tokyo, Japan). The size of the coronary catheter was used to calibrate the image in millimeters, and the measurement was performed in the same coronary angiography projection at each stage. Abnormal

Table 2 Comparison of proportion of patients undergoing acetylcholine and ergonovine tests.

Group	Clinical diagnosis	Proportion of patients [*n* (%)]			
		Acetylcholine		Ergonovine	
		1991–2000	2001–2007	1991–2000	2001–2007
Ischemic heart disease		494 (63.1)	285 (68.7)	337 (65.2)	234 (61.9)
A	Angina at rest	163 (20.8)	140 (33.7)*	106 (20.5)	92 (24.3)
B_1	Angina on effort	77 (9.8)	33 (8.0)	59 (11.4)	38 (10.1)
B_2	Angina on both	60 (7.7)	20 (4.8)	35 (6.8)	29 (7.7)
C_1	Acute myocardial infarction	82 (10.5)*	22 (5.3)	46 (8.9)*	16 (4.2)
C_2	Old myocardial infarction	41 (5.2)	39 (9.4)*	36 (7.0)	32 (8.5)
D	Post PCI	71 (9.1)	31 (7.5)	55 (10.6)	27 (7.1)
Non-ischemic heart disease		289 (36.9)	130 (31.3)	180 (34.8)	144 (38.1)
E	Atypical chest pain	94 (12.0)**	34 (8.2)	91 (17.6)	53 (14.0)
F	Valvular heart disease	34 (4.3)**	8 (1.9)	6 (1.2)	6 (1.6)
G_1	Cardiomyopathy (dilated)	37 (4.7)	11 (2.7)	9 (1.7)	7 (1.9)
G_2	Hypertrophic cardiomyopathy	22 (2.8)	10 (2.4)	10 (1.9)	8 (2.1)
H	Other	102 (13.1)	67 (16.1)	64 (12.4)	70 (18.5)**
Total		783	415	517	378

PCI, percutaneous coronary intervention.
* $p < 0.01$ vs. other.
** $p < 0.01$ vs. other.

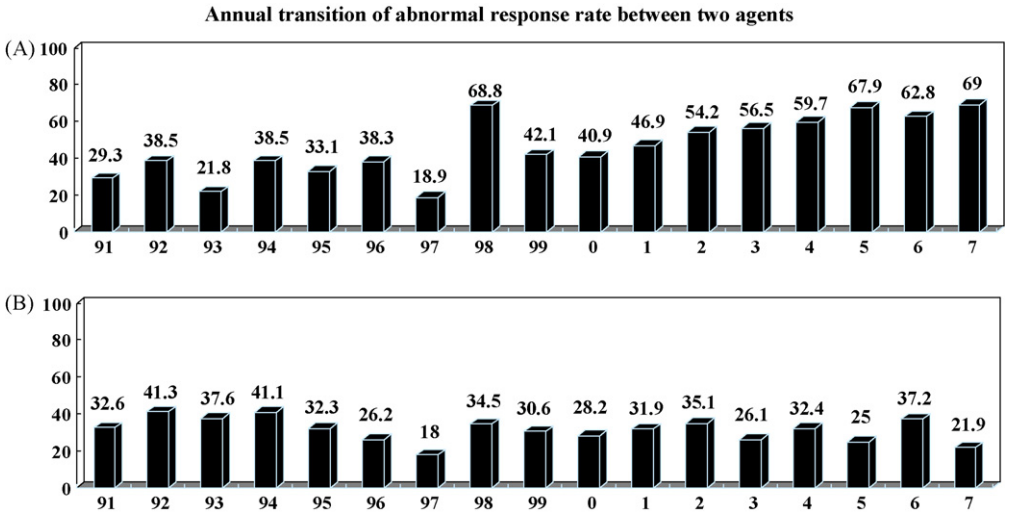

Figure 1 Annual transition of abnormal response rate between the two agents. (A) Acetylcholine. (B) Ergonovine.

coronary response was assessed as >90% luminal narrowing. Patients with catheter-induced spasms were excluded from this study. Significant organic stenosis was defined as >75% luminal narrowing according to the American Heart Association (AHA) classification [15]. Coronary arteries were measured after intracoronary administration of isosorbide dinitrate (5.0 mg) to evaluate coronary atherosclerosis.

Statistical analysis

All values are expressed as mean ± SD. Clinical characteristics between patients with and without abnormal response and differences among proportions were analyzed by the χ^2 test with correction or the ANOVA test. The spasm frequency was compared by use of Yates' corrected χ^2 test or Fisher's exact test as appropriate. A value of $p < 0.05$ was considered statistically significant.

Results

Proportion of patients receiving two agents

As shown in Table 1, the frequency of male gender and history of smoking was significantly higher in patients receiving ACh than in those receiving ER. However, other items including the values of total cholesterol, triglyceride, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, fasting blood sugar, and glycohemoglobin was not different between the two groups.

As shown in Table 2, the proportion of ischemic heart disease and non-ischemic heart disease was not different between the two periods on both agents. However, in ACh testing, the incidence of patients with angina at rest and old myocardial infarction was frequently observed in the latter period (2001—2007), whereas the frequency of patients with acute myocardial infarction, atypical chest pain, and valvular heart disease was significantly higher in the former period (1991—2000). In ER testing, the incidence of patients with acute myocardial infarction was more frequently observed in the former period than in the latter period, while the frequency of patients with other diagnoses was significantly higher in the latter period than in the former period. Although a retrospective study, the distribution of ischemic and non-ischemic heart disease in both periods was similar to that on both tests.

Annual transition of abnormal response rate on both agents

As shown in Fig. 1, the incidence of abnormal response in ACh testing significantly and gradually increased, while the frequency of abnormal response in ER tests was not different during 17 years.

Abnormal coronary response and coronary risk factors

A summary of coronary risk factors is shown in Table 3. On both tests, the incidence of hypertension, dyslipidemia, and diabetes mellitus was significantly increased in 2001—2007 compared with that in 1991—2000. The values of total cholesterol, triglyceride, fasting blood sugar, and high-density lipoprotein-cholesterol were significantly increased in 2001—2007. In ACh testing as shown in Table 4, the incidence of male gender, history of smoking, and dyslipidemia was significantly higher in patients with abnormal response than those without, while the incidence of male gender and history of smoking was frequently observed in patients with abnormal response compared with those without.

Frequency of abnormal response in patients with and without IHD

A summary of the results of all 2093 patients is shown in Fig. 2 and Table 5. Table 5 shows that in patients with ischemic heart disease, the frequency of abnormal response by intracoronary injection of ACh in 2001—2007 was significantly higher than that in 1991—2000, whereas the incidence of abnormal response by ER test was not different between

Table 3 Comparison of coronary risk factors between the two periods.

	Acetylcholine		Ergonovine	
	1991–2000	2001–2007	1991–2000	2001–2007
Number of patients	783	415	517	378
Male	533 (68.1)	299 (72.0)	322 (62.3)	232 (61.4)
Age (year)	63.3 ± 9.6	66.1 ± 10.7	64.0 ± 10.3	67.9 ± 10.5
Organic stenosis	214 (27.3)	100 (24.1)	142 (27.5)	90 (23.8)
Hypertension	315 (40.2)	201 (48.4)*	200 (38.7)	188 (49.7)*
Smoking history	512 (65.4)	283 (68.2)	278 (53.8)	213 (56.3)
Dyslipidemia	257 (32.8)	205 (49.4)*	140 (27.1)	187 (49.5)*
Diabetes mellitus	129 (16.5)	100 (24.1)*	84 (16.2)	81 (21.4)**
Total cholesterol (mg/dl)	184.5 ± 32.5	196.7 ± 36.3*	186.2 ± 32.8	199.8 ± 36.6*
Triglyceride (mg/dl)	129.0 ± 64.1	135.5 ± 87.7*	124.4 ± 59.3	138.2 ± 106.7
HDL-cholesterol (mg/dl)	43.6 ± 12.4	49.6 ± 13.3*	46.5 ± 12.0	49.3 ± 13.7*
LDL-cholesterol (mg/dl)	116.0 ± 28.2	114.8 ± 31.7	115.2 ± 29.6	118.3 ± 30.7
Fasting blood sugar (mg/dl)	101.2 ± 29.6	117.2 ± 45.2*	105.6 ± 34.7	117.7 ± 45.5*
Glycohemoglobin (%)	5.31 ± 0.84	5.52 ± 1.08	5.53 ± 1.14	5.52 ± 1.23

HDL, high-density lipoprotein; LDL, low-density lipoprotein; values within parentheses are in %.
* $p < 0.01$ vs. 1991–2000.
** $p < 0.05$ vs. 1991–2000.

Table 4 Comparisons of sex and coronary risk factors in patients with and without abnormal response.

	Acetylcholine		Ergonovine	
	Negative	Positive	Negative	Positive
Number of patients	683	515	614	281
Male	418 (61.2)	414 (80.4)*	310 (50.5)	244 (86.8)*
Hypertension	289 (42.3)	227 (44.1)	274 (44.6)	114 (40.6)
Smoking history	389 (57.0)	406 (78.8)*	270 (44.0)	221 (78.6)*
Dyslipidemia	223 (32.7)	239 (46.4)*	217 (35.3)	110 (39.1)
Diabetes mellitus	122 (17.9)	107 (20.8)	107 (17.4)	58 (20.6)

Values within parentheses are in %.
* $p < 0.01$ vs. each negative group.

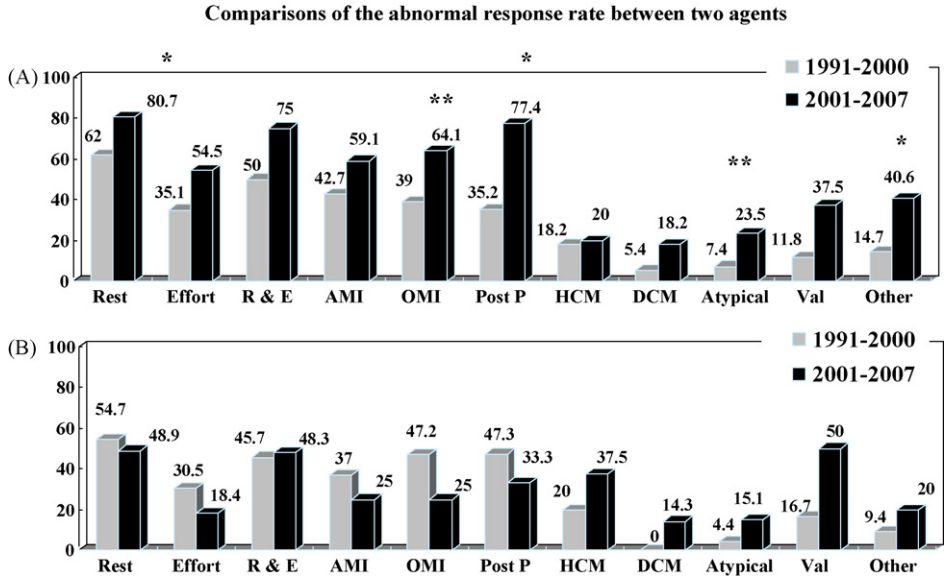

Figure 2 Comparison of the frequency of abnormal response in various cardiac disorders between the two agents. (A) Acetylcholine. (B) Ergonovine. R&E, rest and effort; AMI, acute myocardial infarction; OMI, old myocardial infarction; Post P, post-percutaneous coronary intervention; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; Val, valvular heart disease.

Table 5 Comparisons of the frequency of abnormal response in patients with and without ischemic heart disease.

	IHD	Non-IHD	All
ACh			
1991—2000	234/494 (47.4)	32/289 (11.1)	266/783 (34.0)
2001—2007	208/285 (73.0)*	41/130 (31.5)*	249/415 (60.0)*
ER			
1991—2000	152/337 (45.1)	13/180 (7.2)	165/517 (31.9)
2001—2007	87/234 (37.2)	29/144 (20.1)*	116/378 (30.7)

IHD, ischemic heart disease; Ach, acetylcholine; ER, ergonovine.
* $p < 0.01$ vs. 1991—2000 each.

the two periods. In contrast, in patients with non-ischemic heart disease, the frequency of abnormal responses in 2001—2007 was significantly higher than that in 1991—2000 on both tests.

Frequency of abnormal response in ACh test

As shown in Fig. 2, the frequency of abnormal response in various cardiac disorders, such as angina on effort [35.1% (27) vs. 54.5% (18), ns], on both rest and effort [50.0% (30) vs. 75.0% (15), ns], acute myocardial infarction [42.7% (35) vs. 59.1% (13), ns], valvular heart disease [11.8% (4) vs. 37.5% (3), ns], dilated cardiomyopathy [5.4% (2) vs. 18.2% (2), ns], and hypertrophic cardiomyopathy [18.2% (4) vs. 20.0% (2), ns] was not different between the two periods. The frequency of abnormal response in patients with rest angina [62.0% (101) vs. 80.7% (113), $p < 0.01$], old myocardial infarction [39.0% (16) vs. 64.1% (25), $p < 0.05$], post-percutaneous coronary intervention (PCI) [35.2% (25) vs. 77.4% (24), $p < 0.01$], atypical chest pain [7.4% (7) vs. 23.5% (8), $p < 0.05$], and other groups [14.7% (15) vs. 40.6% (26), $p < 0.01$] was significantly higher in 2001—2007 than in 1991—2007.

Frequency of abnormal response in ER test

As shown in Fig. 2, the frequency of abnormal response in various cardiac disorders, such as angina at rest [54.7% (58) vs. 48.9% (45), ns], on effort [30.5% (18) vs. 18.4% (7), ns], on both [45.7% (16) vs. 48.3% (14), ns], acute myocardial infarction [37.0% (17) vs. 25.0% (4), ns], old myocardial infarction [47.2% (17) vs. 25.0% (8), ns], after PCI [47.3% (26) vs. 33.3% (9), ns], atypical chest pain [4.4% (4) vs. 15.1% (8), ns], valvular heart disease [16.7% (1) vs. 50.0% (3), ns], dilated cardiomyopathy [0% (0) vs. 14.3% (1), ns], hypertrophic cardiomyopathy [20.0% (2) vs. 37.5% (3), ns], and other groups [9.4% (6) vs. 20.0% (14), ns] was not different between the two periods.

Frequency of abnormal response in overall results

A summary of the results of all 2093 patients is shown in Table 5. The frequency of abnormal response in patients with and without ischemic heart disease with ACh tests during 2001—2007 was significantly higher than that during 1991—2000, while the frequency of abnormal response with ER tests during 1991—2000 was not different from that during 2001—2007. However, the frequency of abnormal response with ER tests during 2001—2007 in patients without ischemic heart disease was significantly higher than that during 1991—2000 and no difference was found between the two periods in patients with ischemic heart disease. In overall results, the incidence of abnormal response during 2001—2007 was significantly higher than that during 1991—2000.

Abnormal response site and vessel number

As shown in Table 6, the distribution of abnormal response artery was not different between the two periods with

Table 6 Comparison of abnormal response vessel between the two periods in acetylcholine and ergonovine tests.

	Acetylcholine		Ergonovine	
	1991—2000	2001—2007	1991—2000	2001—2007
Site of abnormal response vessel				
Right coronary artery	164 (41.8)	213 (43.5)	95 (45.5)	77 (48.5)
Left circumflex artery	60 (15.3)	81 (16.6)	32 (15.3)	26 (16.3)
Left anterior descending artery	168 (42.9)	195 (39.9)	82 (39.2)	56 (35.2)
Total	392	489	209	159
1 abnormal response vessel (right)	164 (61.7)*	73 (29.3)	128 (77.6)	79 (68.1)
2 abnormal response vessel (right)	78 (29.3)	112 (45.0)*	30 (18.2)	31 (26.7)
3 abnormal response vessel (right)	24 (9.0)	64 (25.7)*	7 (4.2)	6 (5.2)
2 and 3 abnormal response vessel	102 (38.3)	176 (70.7)*	37 (22.4)	37 (31.9)

Values within parentheses are in %.
* $p < 0.01$ vs. other.

both agents. Multiple abnormal responses induced by ACh test was significantly higher in 2001—2007 than that in 1991—2000, while there was no difference in both periods between one-vessel abnormal response and multiple-vessel abnormal response with ER.

Discussion

The present study was the first to compare the annual frequency of abnormal coronary responses between ACh and ER in a large group of patients who underwent coronary arteriography over 17 years. The frequency of abnormal coronary responses with ACh tests increased significantly over time. The frequency of abnormal multiple responses by ACh tests also increased significantly with increasing time. ACh dilates the coronary artery if the artery has no atherosclerosis and normal endothelial function, whereas ACh constricts the coronary artery if the artery has a certain degree of atherosclerosis and endothelial dysfunction. Thus, coronary arteries showing abnormal responses by ACh tests have at least some initial atherosclerosis. In Japanese patients who underwent coronary arteriography, coronary endothelial dysfunction had certainly progressed during the 17 years. This may be due to a gradual increase in coronary risk factors, such as hypertension, dyslipidemia, and diabetes mellitus. This phenomenon observed in the present study in Japan may apply to other Oriental countries, such as Korea, Chinese Taipei, and China.

Necessity of investigation of abnormal coronary response

We previously reported the reduced frequency of variant angina due to the widespread use of calcium antagonists in Japan [16]. In the present study, the frequency of coronary spastic angina in patients who had undergone coronary arteriography did not decrease with increasing time.

In the USA and Europe, routine investigation of coronary artery spasm in patients with ischemic heart disease is not recommended [17]. The prevalence of coronary artery spasm in Japan is three times higher than that in the USA or Europe [5,6,18—21]. About 20 years ago, the spasm provocation test was carried out in most cardiology institutions in Japan. Recently, some Japanese cardiologists have been interested in performing PCI and paid no attention to perform spasm provocation tests due to their daily overwork and its intricacy [22].

In general, cardiologists tend to carry out PCI without investigation of coronary artery spasm. Coronary artery spasm may cause transient ischemic events, such as acute coronary syndrome, sudden cardiac death, serious arrhythmia and syncope, and organic stenosis. Cardiologists may miss the real cause of ischemic events in patients suspected of ischemic heart disease. If we carried out PCI in all patients with organic stenosis, ischemic episodes would still occur. The usefulness of spasm provocation tests and the necessity of the investigation of coronary artery spasm in diagnosing patients with ischemic heart disease should be taught to cardiologists in training in Oriental countries.

Necessity of statin and diet therapy

The frequency of coronary artery spasm may decrease due to the administration of statins according to the report of Yasue et al. [23]. Coronary artery spasm may decrease due to the effect of statins because of Rho-kinase inhibition. Statin administration may reduce the level of total cholesterol and low-density lipoprotein-cholesterol, and may improve endothelial dysfunction and reduce the incidence of abnormal responses by pharmacologic agents. The decreasing level of total cholesterol and blood sugar may improve coronary endothelial function. These effects may lead to the improvement of coronary endothelial dysfunction.

Clinical implications

We should investigate coronary artery spasm in patients with and without ischemic heart disease when carrying out cardiac catheterization. We should lower the level of total cholesterol, triglycerides, and blood sugar. If the prevalence of dyslipidemia and diabetes mellitus decreases in the near future in Japan, the prevalence of abnormal responses may fall and coronary endothelial dysfunction may improve.

The prevalence of abnormal coronary responses by ER was not different in proportion as time passed. Damage to coronary vascular smooth muscle may not always be observed. Coronary endothelial dysfunction may be frequently recognized in Japanese patients. If ACh and ER had an identical pharmacological reaction, the incidence of abnormal coronary responses was not different between the two agents [24]. Initial coronary atherosclerosis such as intimal hyperplasia and localized plaques may lead to coronary artery endothelial dysfunction. Nevertheless, abnormal coronary response due to pharmacologic agents (ACh and ER) does not always lead to coronary artery spasm.

Study limitations

Our study had several limitations. The first was that this was a retrospective and non-randomized study design and neither test was performed in consecutive patients. The second limitation was that medication was not discontinued for several days before the ACh and ER tests. The third limitation was the dose of ACh and ER in the spasm provocation tests. If higher doses than used in this study were employed, the frequency of abnormal coronary response might be different from these results. The fourth limitation was that the proportion of various cardiac disorders was not always equal between the two periods on both agents. However, the proportion between ischemic and non-ischemic heart disease was not different in each period with both agents. Further study is necessary to investigate the pathophysiology of abnormal coronary response induced by pharmacologic agents. Moreover, further study is also necessary to investigate the incidence of abnormal coronary response in larger groups of patients over 20 years, including Caucasian and Oriental patients.

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References

[1] Yasue H, Horio Y, Nakamura N, Fujii H, Imoto N, Sonoda R, Kugiyama K, Obata K, Morikami Y, Kimura T. Induction of coronary artery spasm by acetylcholine in patients with variant angina: possible role of the parasympathetic nervous system in the pathogenesis of coronary artery spasm. Circulation 1986;74:955—63.

[2] Okumura K, Yasue H, Matsuyama K, Goto K, Miyagi H, Ogawa H, Matsuyama K. Sensitivity and specificity of intracoronary injection of acetylcholine for the induction of coronary artery spasm. J Am Coll Cardiol 1988;12:883—8.

[3] Okumura K, Yasue H, Horio Y, Takaoka K, Matsuyama K, Kugiyama K, Fujii H, Morikami Y. Multivessel coronary spasm in patients with variant angina: a study with intracoronary injection of acetylcholine. Circulation 1988;77:535—42.

[4] Hackett D, Larkins S, Chierchia S, Davies G, Kaski JC, Maseri A. Induction of coronary artery spasm by direct local action of ergonovine. Circulation 1987;75:577—82.

[5] Sueda S, Ochi N, Kawada H, Matsuda S, Hayashi Y, Tsuruoka T, Uraoka T. Frequency of provoked coronary vasospasm in patients undergoing coronary arteriography with spasm provocation test of acetylcholine. Am J Cardiol 1999;83:1186—90.

[6] Sueda S, Kohno H, Fukuda H, Ochi N, Kawada H, Hayashi Y, Uraoka T. Frequency of provoked coronary artery spasms in patients undergoing coronary arteriography using a spasm provocation test via intracoronary administration of ergonovine. Angiology 2003;55:403—11.

[7] Sueda S, Kohno H, Fukuda H, Ochi N, Kawada H, Hayashi Y, Uraoka T. Clinical impact of selective spasm provocation tests: comparisons between acetylcholine and ergonovine in 1508 examinations. Coron Artery Dis 2004;15:491—7.

[8] Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288:373—6.

[9] Ludmer PL, Selwyn AP, Shook TL, Wayne RR, Mudge GH, Alexander RW, Ganz P. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl J Med 1986;315:1046—51.

[10] Arai H, Yamomoto A, Matsuzawa Y, Saito Y, Yamada N, Oikawa S, Mabuchi H, Teramoto T, Sasaki J, Nakaya N, Itakura H, Ishikawa Y, Ouchi Y, Horibe H, Kita T. Serum lipid survey and its recent trend in the general Japanese population in 2000. J Atheroscler Thromb 2005;12:98—106.

[11] Sueda S, Saeki H, Otani T, Mineoi K, Kondou T, Yano K, Ochi T, Ochi N, Hayashi Y, Tsuruoka T, Kawada H, Matsuda S, Uraoka T. Major complications during spasm provocation tests with an intracoronary injection of acetylcholine. Am J Cardiol 2000;85:391—4.

[12] Sueda S, Fukuda H, Watanabe K, Ochi N, Kawada H, Hayashi Y, Uraoka T. Clinical characteristics and possible mechanism of paroxysmal atrial fibrillation induced by intracoronary injection of acetylcholine. Am J Cardiol 2001;88:570—3.

[13] WHO Expert Committee on Diabetes Mellitus. Second Report: World Health Organization Tech Report Series 646. Geneva: WHO; 1980.

[14] World Health Organization Expert Committee. Arterial hypertension. WHO Technical Report Series, No. 628; 1978. p. 7—11.

[15] Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the ad hoc committee for grading of coronary artery disease, council on cardiovascular surgery, American Heart Association. Circulation 1975;51:5—40.

[16] Sueda S, Kohno H, Fukuda H, Uraoka T. Did the widespread use of long-acting calcium antagonists decrease the occurrence of variant angina? Chest 2003;124:2074—8.

[17] Aldam D, Azeem T, Ali T, Gershlick A. Is there a role for provocation testing to diagnose coronary artery spasm? Int J Cardiol 2005;102:1—7.

[18] Pristipino C, Finocchiaro ML, Beltrame JF, Tommaso S, Cianflone N, Parisi N, Tamaki S, Yoshida A, Hattori R, Fujita M, Masseri A. Differences in coronary vasospastic response after recent myocardial infarction in Japanese and Caucasian patients. Circulation 1997;96(Suppl. I):I—534.

[19] Bertrand ME, LaBlanche JM, Tilmant PY, Thieuleux FA, Delforge MR, Carre AG, Asseman P, Berzin B, Libersa C, Laurent JM. Frequency of provoked coronary arterial spasm in 1089 consecutive patients undergoing coronary arteriography. Circulation 1982;65:1299—306.

[20] Nosaka H, Nobuyoshi M. Coronary arterial spasm and symptomatology in ischemic and nonischemic heart disease: study of the ergonovine maleate provocation test in 3,000 consecutive patients. J Cardiol Suppl 1987;12:35—47.

[21] Beltrame JF, Sasayama S, Maseri A. A racial heterogeneity in coronary artery vasomotor reactivity: differences between Japanese and Caucasian patients. J Am Coll Cardiol 1999;33:1442—52.

[22] Sueda S, Izoe Y, Kohno H, Fukuda H, Uraoka T. Need for documentation of guidelines for coronary artery spasm: an investigation by questionnaire in Japan. Circ J 2005;69:1333—7.

[23] Yasue H, Mizuno Y, Harada E, Itoh T, Nakagawa H, Nakayama M, Ogawa H, Tayama S, Honda T, Hokimoto S, Ohshima S, Hokamura Y, Kugiyama K, Horie M, Yoshimura M, et al. Effect of a 3-hydrooxy-3-methylglutaryl coenzyme A reductase inhibitor, fluvastatin, on coronary spasm after withdrawal of calcium-channel blockers. J Am Coll Cardiol 2008;51:1742—8.

[24] Sueda S, Kohno H, Fukuda H, Ochi N, Kawada H, Hayashi Y, Uraoka T. Induction of coronary artery spasm by two pharmacologic agents; comparison between intracoronary injection of acetylcholine and ergonovine. Coron Artery Dis 2003;14:451—7.