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【 ORIGINAL ARTICLE 】

Bronchial Asthma and Rest Angina: Is It Safe to Perform Acetylcholine Spasm Provocation Tests in These Patients?

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Abstract:

Objective Acetylcholine (ACh) use in patients with bronchial asthma (BA) is contraindicated. We examined the clinical usefulness and safety of ACh spasm provocation tests in rest angina patients with BA.

Patients The study subjects were 495 rest angina patients (mean age: 64.4±10.9 years old, male: 81.0%). Organic stenosis was found in 69 patients (13.9%).

Methods We investigated 495 rest angina patients who underwent ACh spasm provocation tests. ACh was injected in incremental doses of 20/50/100/200 μg into the left coronary artery and 20/50/80 μg into the right coronary artery. Provoked positive spasm was defined as transient ≥90% luminal narrowing and usual chest pain or ischemic electrocardiogram changes.

Results Among 495 rest angina patients, 13 (2.6%) were complicated with BA. Eleven patients with BA were controlled under medications, and two patients had a history of medication for BA. The clinical characteristics were not markedly different between rest angina patients with and without BA. The rate of multivessel spasm was markedly higher in patients with BA than that in those without BA. No complications during ACh spasm provocation tests were recognized in rest angina patients with BA, whereas major complications in those without BA were observed in eight patients including two ventricular fibrillations, three nonsustained ventricular tachycardias, and three shocks. We were able to perform all 495 ACh spasm provocation tests without any irreversible complications, while electrical defibrillation was necessary for 2 patients without BA.

Conclusion We were able to perform ACh spasm provocation tests in rest angina patients with BA irrespective of the off-label use of ACh.

Key words: coronary spastic angina, bronchial asthma, rest angina, acetylcholine spasm provocation test, complications

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Introduction

Possibly due to pharmacological action, acetylcholine (ACh) should not be employed in patients with bronchial asthma (BA) according to the medical package insert of ACh. The Japanese Circulation Society (JCS) guidelines for the diagnosis and treatment of patients with coronary spastic angina do not discuss ACh spasm provocation tests in patients with BA (1). However, in the real world, cardiologists may encounter some patients with rest angina and BA. Spasm provocation tests are necessary for the diagnosis of coronary artery spasm in the cardiac catheterization laboratory, but cardiologists may hesitate to perform intracoronary injection of ACh in patients with BA.

In this article, we examined the clinical usefulness of ACh spasm provocation tests in patients with rest angina and BA and investigated the clinical characteristics of patients with rest angina complicated with BA.

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Materials and Methods

Study patients

From January 1991 to December 2018, we performed total 8,339 coronary angiography procedures, including 2,356 percutaneous coronary intervention procedures and 5,983 diagnostic and follow-up coronary arteriography procedures. During the same time, we performed ACh spasm provocation tests in 1,830 patients. During the period, 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. Subjects were excluded and the spasm provocation test of ACh not performed if patients had left main narrowing (>50%), triple-vessel disease, double-vessel disease with total occlusion, heart failure (New York Heart Association functional class III or IV), renal failure (creatinine >2.0 mg/dL), or if isosorbide dinitrate was initially used to relieve spasm in the coronary artery tested. We investigated the clinical usefulness and major complications of ACh spasm provocation tests as well as the clinical characteristics between rest angina patients with and without BA.

Definition of positive spasm and major complications during ACh tests and BA

We defined positive provoked spasm as ≥90% transient narrowing and usual chest pain or ischemic electrocardiogram (ECG) changes by the ACh spasm provocation tests. The degree of ST-segment depression was measured 80 mseconds 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 a negative U wave as a positive ischemic ECG change. Major complications during ACh spasm provocation tests were defined as ventricular fibrillation, non-sustained ventricular tachycardia, or shock (<60 mmHg). We defined BA as currently medically treated or having a history of medical treatment.

Spasm provocation test

All drugs except for nitroglycerine were discontinued for ≥24 hours before the study and nitroglycerine was also discontinued ≥4 hours before the study. Cardiac catheterization was performed from 9:00 AM to 4:00 PM in the fasting state, as previously reported (2-4). 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 pace maker was inserted into the right ventricle of each patient and the pacing rate was set at 40 beats/min.

Provocation of coronary artery spasm was performed with an intracoronary injection of ACh, as previously reported (5-8). 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, 100 and 200 μg into the LCA over 20 seconds with at least a 3-minute interval between each injection.

Coronary arteriography was performed when ST-segment changes and/or, chest pain occurred or 1-2 minutes after the completion of each injection. When an induced coronary spasm did not resolve spontaneously within 3 minutes after the completion of ACh injections or when hemodynamic instability occurred as the result of coronary spasm, 2.5 to 5.0 mg of isosorbide dinitrate was injected into the involved vessel. A standard 12-lead ECG was recorded every 30 seconds. The ECG diagnosis was made at least 60 seconds after the study drug or medium was injected into the corresponding vessels. After the spasm provocation tests had been 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 two 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 discrete transient vessel narrowing ≥90% (>76% narrowing of the luminal diameter) localized in a major coronary artery, whereas diffuse spasm was diagnosed when transient vessel narrowing ≥90% (>76% narrowing of the luminal diameter), compared with the baseline coronary angiography findings, was observed in ≥2 adjacent coronary segments of epicardial coronary arteries. The spasm provoked site was classified according to the America College of Cardiology (ACC)/American Heart Association (AHA) classification. Significant organic stenosis was defined as >75% luminal narrowing according to the ACC/AHA classification (9).

The study protocol complied with the Declaration of Helsinki. Written informed consent to perform the ACh spasm provocation tests were obtained from all patients, and the protocol of this study was in agreement with the guidelines of the ethics committee at our institution.

Statistical analysis

Data analyses were carried out with the SPSS software program (version 22.0, IBM Japan, Tokyo, Japan). All data except for the dose of ACh used were presented as the mean±1 standard deviation (SD). The ACh dose used was presented as the median with interquartile range (minimum-maximum). The clinical characteristics between the two

Table 1. Comparisons of Clinical Data, Provoked Spasm and Complications during Acetylcholine Tests in Rest Angina Patients with and without Bronchial Asthma.

	With bronchial asthma	Without bronchial asthma	Total
Number	13	482	495
Male (%)	8 (61.5%)	393 (81.5%)	401 (81.0%)
Age (year)	68.5±9.6	64.3±11.0	64.4±10.9
Organic stenosis	2 (15.4%)	67 (13.9%)	69 (13.9%)
Hypertension	5 (38.5%)	175 (36.3%)	180 (36.4%)
Dyslipidemia	5 (38.5%)	233 (48.3%)	238 (48.1%)
Diabetes mellitus	3 (23.1%)	108 (22.4%)	111 (22.4%)
History of smoking	7 (53.8%)	373 (77.4%)	380 (76.8%)
Variant angina	1 (7.7%)	17 (3.5%)	18 (3.6%)
Total cholesterol (mg/dL)	182.3±22.0	193.6±35.7	193.3±35.4
Triglyceride (mg/dL)	103.4±45.2	137.4±92.7	136.5±91.8
LDL-cholesterol (mg/dL)	101.9±16.4	115.5±31.1	115.2±30.9
HDL-cholesterol (mg/dL)	55.5±10.0	51.1±13.3	51.3±13.3
Fast blood glucose (mg/dL)	112.8±23.1	110.1±40.4	110.0±39.3
Glycohemoglobin (% JDS)	6.0±1.0	5.5±0.9	5.5±0.9
Provoked spasm positive	11 (84.6%)	363 (75.3%)	374 (75.6%)
RCA	11 (84.6%)	265 (55.0%)	276 (55.8%)
LCX	6 (46.2%)	117 (24.3%)	123 (24.8%)
LAD	11 (84.6%)	249 (51.7%)*	260 (52.5%)
I vessel spasm	0	146 (30.3%)*	146 (29.5%)
2 vessel spasm	5 (38.5%)	127 (26.3%)	132 (26.7%)
3 vessel spasm	6 (46.2%)	77 (16.0%)	83 (16.8%)
Multi-vessel spasm	11 (84.6%)	204 (42.3%)**	215 (43.4%)
Complications during ACh tests	0	8 (1.7%)	8 (1.6%)
Ventricular fibrillation	0	2 (0.4%)	2 (0.4%)
Non-sustained ventricular tachycardia	0	3 (0.6%)	3 (0.6%)
Shock (<60 mmHg)	0	3 (0.6%)	3 (0.6%)
Electrical defibrillation	0	2 (0.4%)	2 (0.4%)

**p<0.01, *p<0.05 vs. with bronchial asthma. RCA: right coronary artery, LCX: left circumflex artery, LAD: left anterior descending artery, ACh: acetylcholine, LDL: low-density-lipoprotein, HDL: high-density-lipoprotein

groups were analyzed by the Fisher's exact test with correction or the Mann-Whitney U test. P<0.05 was considered significant.

Results

Comparisons of clinical characteristics in rest angina patients with and without BA

As shown in Table 1, BA was observed in 13 (2.6%) of 495 rest angina patients who had spasm provocation tests of ACh. There was no marked clinical difference between the two groups. The frequency of men among rest angina patients with BA was not markedly different from that among those without BA (61.5% vs. 81.5%, p=0.1455). The incidence of variant angina was not markedly different between the two groups.

Comparisons of provoked spasm incidence and complications during ACh tests between the two groups

As shown in Table 1, incidence of provoked spasm was not different between the two groups (84.6% vs. 75.3%, p=0.6576). The frequency of provoked spasm in the right coronary artery and left circumflex artery was not markedly different, while the incidence of provoked spasm in the left anterior descending artery in rest angina patients with BA was markedly higher than that in those without BA (84.6% vs. 51.7%, p=0.0388). No complications during ACh tests were recognized in rest angina patients with BA, whereas 8 complicated cases, including 2 with ventricular fibrillations, 3 with non-sustained ventricular tachycardias, and 3 with shock (<60 mmHg), were observed among rest angina patient without BA. However, there was no marked difference in the incidence of major complications between the two groups. Electrical defibrillation was necessary for two patients without BA. However, we had no irreversible complications occurred during 495 ACh tests.

Clinical characteristics and medications for BA in 13 rest angina patients with BA

As shown in Table 2, two patients had taken oral steroid hormone, whereas nine were receiving steroid hormone inhalation therapy. Beta stimulants were taken in five patients, and xanthine derivatives were taken by three patients. Four patients were treated with anti-allergic drugs. Eight patients

Table 2. Clinical Characteristics and Medications for Bronchial Asthma in Patients with Bronchial Asthma and Rest Angina.

No	Age	Sex	Risk factor	Oral prednisolone	Inhalated steroid hormone	Beta stimulator	Xanthine derivative	Anti-allergic drug	Asthma attack during the last 3 months	Spontaneous ST change
1	66	F	HT/DL	10 mg	(+)	(+)	no	no	no	no
2	45	F		no	(+)	no	200 mg	no	no	ST ele I aVL
3	72	M	HT/DM/ /Smoking	no	(+)	(+)	no	no	no	no
4	75	M	DM/Smoking	no	(+)	no	no	no	no	no
5	85	M	HT	no	no	no	no	(+)	no	no
6	74	M	DL/Smoking	no	(+)	no	no	(+)	no	no
7	70	M	HT/Smoking	no	(+)	no	no	(+)	no	no
8	55	F		no	no	no	no	no	no	no
9	69	M	DL/Smoking	no	no	no	no	(+)	no	no
10	70	F	DM/DL	no	no	no	no	no	no	no
11	68	M	Smoking	5 mg	(+)	(+)	200 mg	no	no	no
12	67	M	HT /Smoking	no	(+)	(+)	200 mg	no	no	no
13	74	F	DL	no	(+)	(+)	no	no	no	no

F: female, M: male, DM: diabetes mellitus, HT: hypertension, DL: dyslipidemia, ele: elevation

Table 3. Acetylcholine Spasm Provocation Tests in Patients with Bronchial Asthma and Rest Angina.

No	RCA [dose (μg)]	Chest pain	ST change	Spasm	LCA [dose (μg)]	Chest pain	ST change	Spasm	Total ACh dose (μg)
1	20/50	UCP	Negative T in INF	4 (d)	20/50/100	UCP	ST(DS) dep in V3-6 (3.0)	7 (d) 13 (d)	240
2	50/100	UCP	(-)	4 (d)	20/50/100/200	UCP	ST dep (H) in V4-6 (1.0)	6-8 (d)	520
3	20/50/80	UCP	(-)	4 (d)	20/50/100	UCP	ST ele in V34 (2.0)	8 (t)	320
4	50/80	UCP	ST (J) in INF (2.0)	4 (t)	20	UCP	ST ele in INF (2.0)	9 (t) 11 (t)	150
5	25/50/75	(-)	(-)	No spasm	25/50/100/200	UCP	ST(H) dep in V4-6 (2.0)	No spasm	525
6	50	(-)	(-)	No spasm	50/100/200	(-)	(-)	No spasm	400
7	25/50	UCP	ST(H) dep in INF (1.0)	4 (d)	12.5/25/50/100	UCP	ST (H) dep in V56 (1.0)	8 (d) 13 (d)	262.5
8	20	UCP	Negative T in INF	3-4 (d)	20/50/100	UCP	ST ele in V2-4 (5.0)	7 (d)	190
9	20/50/80	UCP	ST ele in INF (1.0)	4 (d)	20/50/100/200	UCP	(-)	8 (d)	520
10	20/50	UCP	ST (H) dep in INF (1.0)	4 (d)	20/50/100	UCP	ST (H) dep in V4-6 (1.0)	6 (d) 11 (d)	240
11	20/50/80	UCP	ST (J) dep in INF (1.5)	2-4 (d)	50/100	UCP	ST (J) dep in V4-6 (1.5)	7 (d) 11 (d)	300
12	50/80	UCP	(-)	4 (d)	50/100	UCP	(-)	7 (d)	280
13	20	UCP	ST ele in INF (2.0)	1 (d)	20/50	UCP	ST (H) dep in V34 (2.0)	8 (d) 13 (d)	90
									311 (90-520)

RCA: right coronary artery, LCA: left coronary artery, UCP: usual chest pain, INF: inferior, d: diffuse spasm, t: total spasm, J: junctional, H: horizontal, DS: down sloping, ele: elevation, dep: depression

had received more than two medical treatments for BA, while two were medical therapy-free for BA during the ACh tests. No asthma attacks had been observed during the last 3 months before ACh spasm provocation tests in any of the 13 patients.

ACh spasm provocation tests in 13 rest angina patients with BA

Table 3 shows the results of ACh spasm provocation tests in 13 rest angina patients with BA. In the LCA, positive provoked spasm associated with ischemic ECG changes were recognized in nine patients, while two patients showed angiographical positive spasm without ischemic ECG changes. No provoked spasm was observed in one patient, whereas microvascular disorder was found in one patient. Usual chest pain was observed in 12 of the 13 patients. In the RCA, positive provoked spasm associated with ischemic ECG changes was found in eight patients, while three had angiographical positive spasm without ischemic ECG changes. No provoked spasm was found in two patients. Eleven patients complained of usual chest pain. We were able to perform all ACh tests without any complications in 13 patients. The median total ACh dose was 311 μg (90-520) in 13 rest angina patients with BA.

Discussion

In this article, we were able to perform ACh spasm provocation tests in all 13 rest angina patients who had BA without any irreversible complications, regardless of the off-label use of ACh. The clinical characteristics in rest angina patients with and without BA were not markedly different, but the rate of multi-vessel spasm was markedly higher in patients with BA than in those without BA. We can perform

ACh spasm provocation tests safely in BA patients who had been medically controlled in the clinic, although the medical package inserts of ACh mention contraindications for patients with BA.

BA and coronary spastic angina

In the previous reports, the clinical outcomes in some patients with BA and coronary spasm were not very good (10). Sudden death or cardiac arrest was sometimes observed in these patients (11-14). Coronary spasm was diagnosed by the intracoronary administration of ergonovine or based on spontaneous coronary spasm documented in the previous reports (15). To our knowledge, this is the first report concerning the clinical usefulness and safety of ACh spasm provocation tests for the diagnosis of coronary spasm in patients with BA, despite its small sample size.

Intracoronary injection of ACh acts by way of the muscarinic cholinergic receptor and may cause coronary vasoconstriction as well as bronchial constriction. However, we have no data on the ACh effect on bronchial smooth muscle following the intracoronary administration of 20-200 μg ACh to the responsible vessels. Because the effect of ACh on the coronary artery disappears quickly, increasing the dose incrementally with 3- to 5-minute intervals has been considered. Although we performed 1,821 examinations of ACh spasm provocation tests, we experienced no cases complicated with BA. Furthermore, in previous reports, we also detected no cases complicated with BA during ACh spasm provocation tests (16-22). If patients with BA are well controlled with medications, cardiologists can perform ACh spasm provocation tests without worrying about inducing bronchial spasm in the clinic.

Total dose of ACh used during ACh spasm provocation tests

If we had administered intracoronary ACh a 20/50/80 μg into the RCA and of 20/50/100/200 μg into the LCA, the total ACh dose used for both coronary arteries would have reached a maximum of 520 μg. Actually, the mean ACh dose used in this study was 311 μg (90-520) in 13 rest angina patients with BA. Because Neucholine-A has 30 mg of ACh per an ample, 30,000 μg of ACh contains in an ample. Thus, cardiologists may use <1.8% (520/30,000) of a Neucholine-A ample for 20-30 minutes when performing spasm provocation tests of ACh on both coronary arteries. If cardiologists used ACh chloride (Ovisot, 0.1 g/2mL; Daiichi Sankyo, Tokyo, Japan), they may use <0.6% (520/100,000) of Ovisot ample. A very low dose of ACh may not induce bronchial constriction in the real world. Cardiologists can thus perform ACh spasm provocation tests in rest angina patients complicated with BA without inducing any irreversible complications, according to the JCS guidelines (1).

Study limitations

Several limitations associated with the present study warrant mention. First, this is a retrospective, single-center study with a small sample size. Second, the study populations had well-controlled BA. We did not perform the ACh tests in patients with medically resistant BA. Further studies may be needed to confirm the usefulness and safety of ACh spasm provocation tests for BA patients.

Conclusion

Irrespective of the off-label use of ACh, we were able to perform ACh spasm provocation tests in rest angina patients who had well-controlled BA under medications without any irreversible complications. Multi-vessel spasm was more frequently observed in rest angina patients with BA than in those without BA.

The author states that he has no Conflict of Interest (COI).

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