Disparity between Serotonin- and Acetylcholine-Provoked Coronary Artery Spasm

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Summary

Background and hypothesis: Intrinsic vasoactive substances, such as serotonin and acetylcholine, are known to provoke coronary artery spasm in patients with vasospastic angina. It remains unclear, however, whether these different agents, which activate different receptors, produce spasms at the same sites in these patients. The present study was designed to clarify the disparity of receptor agonist-induced coronary artery spasms in the same patients.

Methods: We conducted sequential provocative tests of coronary artery spasm by acetylcholine, serotonin, and ergonovine in 20 patients with rest angina examined with quantitative coronary angiography.

Results: Coronary artery spasms were provoked in all patients at 27 spastic sites. In 13 patients, ergonovine provoked spasms and in 10 of 13 patients who were diagnosed with variant angina, both acetylcholine and serotonin provoked spasms at the same sites where ergonovine also did. In 4 of 13 patients, spasms were provoked by serotonin but not by acetylcholine. In the remaining seven patients, whose spasms were induced by ergonovine, spasms were produced by acetylcholine but not by serotonin. On coronary angiography, the spastic sites for both acetylcholine and serotonin, and those for serotonin alone, were located in the proximal segments of coronary ar-

teries, whereas the spastic sites for acetylcholine alone were located in the distal segments.

Conclusions: This study documented the disparity between serotonin- and acetylcholine-induced spasms. Provocative tests using agents that activate different receptors may produce coronary artery spasms at the same and/or different sites, and this disparity may reflect the clinical heterogeneity of vasospastic ischemic syndrome.

Key words: serotonin, acetylcholine, coronary vasospasm, ergonovine, vasospastic angina

Introduction

Coronary artery spasm is well known to play an important role in the pathogenesis of ischemic heart disease.^{1–3} Ergonovine maleate has been most commonly used as a provocative agent for coronary artery spasm⁴ in susceptible patients, because an ergonovine-induced spasm is considered to be identical to the spontaneous spasm in a patient with variant angina.⁵ Recently, serotonin (5-HT) and acetylcholine, which are intrinsic vasoactive substances, have been reported to induce coronary artery spasm in patients with variant angina, but the precise mechanism responsible for producing these spasms has remained unclear.^{6,7} These intrinsic substances contract vascular smooth muscle cells through the activation of different receptors located on the cell surfaces, and the endothelium modulates vascular tone through receptor-mediated release of endothelium-derived relaxing factor(s). However, whether these different agents provoke coronary artery spasm at the same or different sites in the patient with angina has not been studied.

The purpose of this study was to clarify the disparity of provocative agent-induced coronary artery spasms in the same patients. We therefore compared the distributions of coronary artery sites, where serotonin or acetylcholine induced spasms in patients with rest angina without significant coronary stenosis demonstrated on coronary angiography. We further compared spastic sites for serotonin or acetylcholine with those for ergonovine as a reference standard.

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Methods

Patients

We studied 20 patients (14 men and 6 women, age 57 ± 10 years). Complete informed, written consent was obtained from each patient before the study, and no complication occurred as a result of this investigation. The study protocol was approved by the Institutional Committee on Human Research at Kobe University Hospital. All patients had experienced anterior chest pain at rest and had objective evidence of ischemia: in 10 of 20 patients (Patients No. 1 to 10), transient ST-segment elevation > 2 mm was documented on standard 12-lead or Holter monitoring electrocardiography during spontaneous episodes at rest or elicited by bedside provocative tests (hand grip and hyperventilation tests) before catheterization; these patients were diagnosed as having variant angina. In the remaining 10 patients, the presence of myocardial ischemia was confirmed by the presence of ST-segment depression during chest pain at rest and/or after exercise, or reversible defects in exercise thallium-201 scintigraphy. No patient had coronary stenosis with $> 75\%$ luminal diameter narrowing as demonstrated on coronary angiograms after nitroglycerin administration. Eight of 20 patients had luminal diameter narrowing $\geq 25\%$ on the coronary angiogram. No patient had a history of myocardial infarction, and none underwent percutaneous transluminal coronary an-

gioplasty. The clinical and angiographic characteristics of these patients are shown in Table I.

Drugs

Serotonin creatinine sulfate (10 mmol/l), prepared for human use by Kobe University Hospital Pharmacy, was stored at 4°C . This stock solution was diluted with physiologic saline (0.9% NaCl) to final concentrations for administration of 100 nmol/l, 1 $\mu\text{mol/l}$, and 10 $\mu\text{mol/l}$. Acetylcholine chloride (Daiichi Pharmaceuticals, Tokyo) ergonovine maleate (Takeda Pharmaceuticals, Osaka), and nitroglycerin (Nihon Chemical Pharmaceuticals, Tokyo) were diluted with physiologic saline to concentration of 10 $\mu\text{g/ml}$, 10 $\mu\text{g/ml}$, and 50 $\mu\text{g/ml}$, respectively.

Procedure

All medications except for aspirin (86 mg/day) were discontinued for at least 24 h before catheterization, but patients were allowed to continue using sublingual nitroglycerin, although no patient took nitroglycerin within 2 h before catheterization. Symptoms, arterial pressure, heart rate, and 12-lead electrocardiogram (ECG) were continuously monitored throughout the study. Cardiac catheterization was performed by the femoral puncture method. After an intravenous bolus administration of heparin (2,000 IU), diagnostic angiography

TABLE I Clinical characteristics of the patients

Patient No.	Age/sex	Angina type	ST change of the leads during spontaneous attack	Risk factors			
				Sm	DM	HT	HC
1	43/M	R	V ₁₋₆ $\uparrow$	+	+	—	+
2	34/F	R	V ₂₋₅ $\uparrow$	+	—	—	—
3	57/M	R+E	V ₂₋₄ $\uparrow$	+	—	+	—
4	68/M	R	V ₂₋₆ $\uparrow$	+	—	—	—
5	60/M	R	II, III, aVF $\uparrow$	+	—	—	—
6	55/M	R	II, III, aVF $\uparrow$	+	—	+	—
7	62/M	R	V ₁₋₅ $\uparrow$	+	—	+	—
8	60/M	R	V ₁₋₅ $\uparrow$	+	—	—	—
9	67/M	R	II, III, aVF $\uparrow$	+	—	+	—
10	67/F	R	II, III, aVF $\uparrow$	—	—	—	—
11	50/M	R	NR	+	—	—	—
12	67/M	R	NR	+	—	—	—
13	71/M	R+E	NR	+	—	+	—
14	60/M	R+E	V ₅₋₆ $\downarrow$	+	—	+	—
15	45/F	R+E	NR	—	—	—	—
16	55/M	R+E	NR	+	—	—	+
17	57/M	R+E	NR	+	+	+	—
18	74/F	R	NR	—	—	+	—
19	45/M	R	NR	+	—	—	—
20	50/F	R+E	NR	—	—	—	—

Abbreviations: Sm = smoking, DM = diabetes mellitus, HT = hypertension, HC = hypercholesterolemia (total cholesterol > 220 mg/dl), R = rest, E = effort, $\uparrow$ = elevation, $\downarrow$ = depression, NR = no electrocardiogram during spontaneous attack was recorded.

was started. All coronary angiograms were obtained in the right and left anterior oblique projections simultaneously using a cineangiogram system (Toshiba, Tokyo). A temporary pacemaker lead was inserted into the right ventricle and the pacing rate was set at 50 beats/min.

Provocation Protocol

Each bolus infusion was given through a 6F Judkins catheter. The schematic representation of the provocation protocol is shown in Figure 1. Acetylcholine was administered at the dose of 50 and 100 μg , respectively, into the right coronary artery and the left coronary artery, each over 30 s. Coronary angiograms were obtained 90 s after the start of acetylcholine injection. Five ml of serotonin at the concentration of 100 nmol/l, 1, and 10 $\mu\text{mol/l}$, respectively, was injected into the left and right coronary arteries, each over 30 s. Coronary angiograms were obtained 2 min after the start of injection of serotonin at each dose. The time interval between injections for acetylcholine and serotonin was >3 min. To minimize the effect of the order of provocative drugs, the order of administration of acetylcholine and serotonin was randomized; in 11 of 20 patients acetylcholine was infused prior to serotonin, whereas 9 patients received serotonin first. When anginal pain or ischemic ST change was noted on ECG, coronary angiography was performed immediately and the scheduled administration of acetylcholine or serotonin was not performed. When coronary artery spasm induced by acetylcholine or serotonin did not disappear spontaneously within 3 min, 0.3 mg of nitroglycerin was administered sublingually. The subsequent provocative test was started >5 min after the disappearance of spasm on coronary angiogram.

Ergonovine was injected at the dose of 40 μg into right and left coronary arteries over 30 s. The coronary angiogram was obtained 4 min after the start of ergonovine injection. When anginal pain or ischemic ST-segment changes were noted on ECG, coronary angiography was performed immediately. After administration of ergonovine, 250 μg of intracoronary nitroglycerin was injected and an angiogram was obtained.

FIG. 1 A schematic representation of the provocative protocol. RCA = right coronary artery, LCA = left coronary artery, ACh = acetylcholine, 5-HT = serotonin, EM = ergonovine, NTG = nitroglycerin.

All angiograms were obtained after manual injection with nonionic contrast medium (Omnipaque 350, Daiichi Pharmaceuticals, Tokyo).

Quantitative Coronary Angiography

The diameter and percent luminal diameter narrowing of coronary arteries were measured by an automatic edge-contour detection computer analysis system (CARDIO 500, Kontron Instrument, Tokyo). The size of the coronary catheter was used to calibrate the image in millimeters and the measurement was performed in the same projection of coronary angiography at each stage. There were no significant differences in the variances of repeated analysis in this system [intraobserver variance; $r = 0.97$, standard error of estimation (SEE) = 0.09 mm; interobserver variance; $r = 0.95$, SEE = 0.12 mm]. Coronary artery spasm was defined as production by provocative agents of stenosis with $\geq 90\%$ luminal diameter narrowing accompanied by anginal pain or ischemic ECG changes. The arterial segments of coronary arteries and the percent luminal diameter narrowing were determined according to the classification of the American Heart Association Committee Report.

Statistical Analysis

Hemodynamic data are expressed as the mean $\pm$ standard deviation. A one-way analysis of variance test was used for the comparison of the sequential changes in these data. The intraobserver and interobserver agreement in the assessment of quantitative coronary angiography were determined by the linear regression equation. Values were considered to be statistically different when $p < 0.05$.

Results

Relation between the Responses to Acetylcholine and Serotonin and Clinical Characteristics of the Patients

There were no significant changes in systolic arterial pressure and heart rate associated with or following the intracoronary injection of acetylcholine, serotonin, or ergonovine [blood pressure: 143 ± 24 (baseline), 140 ± 20 , 144 ± 24 , and 146 ± 28 mmHg, respectively; heart rate: 71 ± 12 (baseline), 72 ± 14 , 76 ± 18 , and 71 ± 14 beats/min, respectively]. The results of provocative tests and angiographic findings were summarized in Table II. Serotonin and/or acetylcholine produced spasm at 27 sites in all 20 patients: serotonin produced spasm in 13 patients (Patients No. 1–13) and acetylcholine in 16 (Patients No. 1–9 and 14–20). Sublingual administration of nitroglycerin was used in four acetylcholine-induced spasms (Patients No. 4, 7, 8, and 19) and in nine serotonin-induced spasms (Patients No. 2, 4, 5, 7, 8, 10–13). To clarify the relation between the responses to each provocative agent and the clinical characteristics of the patients, we classified the patients into two groups according to the results of ergonovine

TABLE II Angiographic response to intracoronary infusion of acetylcholine, serotonin, ergonovine, and nitroglycerin

Group	Patient No.	CAG (pNTG) (%)	Spasm No.	Spastic segment No.	CAG		
					ACh	5-HT	EM
Group A	1	#7:50	1	7	99	99	99
			2	13	90	N	N
	2	#6:75	3	6	99	99	99
			4	3	90	N	N
	3	#6:50	5	6	90	90	99
			6	13	100	N	N
	4	#7:75	7	7	99	100	100
	5	Normal	8	1	100	100	100
			9	8	99	N	N
	6	Normal	10	1	100	100	100
	7	#7:75	11	7	100	100	100
	8	#7:25	12	7	100	99	99
	9	Normal	13	1	N	90	90
			14	12	99	N	N
Group B	10	Normal	15	2	N	100	99
	11	#7,9:50	16	1	N	100	100
	12	Normal	17	2	N	99	90
	13	Normal	18	2	N	100	90
	14	Normal	19	8	90	N	N
	15	Normal	20	8	90	N	N
			21	12	90	N	N
			22	3	90	N	N
	16	Normal	23	13	90	N	N
			24	9	99	N	N
	17	Normal	25	4	90	N	N
	18	#4:75	26	13	100	N	N
	19	Normal	27	8	99	N	N
	20	Normal					

Abbreviations: CAG = coronary angiogram, pNTG = after intracoronary administration of nitroglycerin, ACh = acetylcholine, 5-HT = serotonin, EM = ergonovine, N = no spasm was provoked. All segments and the percentage of luminal narrowing of the coronary arteries are expressed according to the classification of the American Heart Association Committee Report.

test. Group A consisted of 13 patients in whom spasms were provoked by ergonovine, and Group B of 7 patients in whom spasms were provoked by ergonovine. The previous diagnosis was variant angina in 10 of 13 patients in Group A and none in those in Group B.

Localization of Spastic Sites for Acetylcholine and Serotonin

Sites of spasm induced by acetylcholine and/or serotonin were compared with those induced by ergonovine. In Group A, acetylcholine and/or serotonin produced coronary artery spasms at 18 spastic sites, at 8 of which both serotonin and acetylcholine produced spasms (Spasm Nos. 1, 3, 5, 7, 8, 10–12; Fig. 2). These spastic sites were located in the proximal segments of the coronary arteries: two spastic sites in segment 1, two in segment 6, and four in segment 7. These sites were identical to the spastic sites for ergonovine (Fig. 3 A-i). Six of the eight sites in Group A exhibited stenotic lesions with $\geq 25\%$ stenosis after nitroglycerin administration on coronary angiograms. At five sites in Group A (Spasm Nos. 13, 15–18), serotonin provoked coronary artery spasm but

acetylcholine did not (Fig. 4). These sites were also located in the proximal segment of the coronary artery (segment 1), and ergonovine also produced coronary artery spasm at the same site (Fig. 3 A-ii). At the remaining five sites (Spasm Nos. 2, 4, 6, 9, and 14), spasm was provoked by acetylcholine but not by serotonin. These five spastic sites were located in the distal segments of coronary arteries, where ergonovine failed to induce coronary artery spasm: one was located in segment 3, one in segment 8, one in segment 12, and two in segment 13 (Fig. 3 A-iii).

In Group B, only acetylcholine produced coronary artery spasms at nine sites in seven patients (Fig. 5). All sites were located in the distal segments of the coronary arteries: one each in segment 3, 4, 9, and 12; three in segment 8; and two in segment 13. At all sites in Group B, ergonovine failed to provoke coronary artery spasms (Fig. 3-B).

Discussion

We demonstrated that there was a disparity between acetylcholine- and serotonin-induced coronary artery spasm. Pa-

FIG. 2 Coronary angiograms showing the left coronary artery in a patient whose spasms were induced by both acetylcholine and serotonin (Patient No. 1). Injection of acetylcholine (100 μ g) produced coronary artery spasm (99% narrowing of luminal diameter) at segments 7 and 13 (A). Injection of serotonin (10 μ mol/l) induced coronary artery spasm (99% of luminal diameter narrowing) at segment 7 at the same site where acetylcholine provoked spasm (B).

tients whose spasms were provoked by both acetylcholine and serotonin had variant angina, and all patients whose spasms were provoked only by serotonin had positive results for the ergonovine test, which is a standard test for the diagnosis of vasospastic angina. In contrast, none of the patients whose spasms were provoked only by acetylcholine had positive ergonovine test results. On coronary angiograms, the sites of spasm induced by both acetylcholine and serotonin were located in the proximal segments, and half of these sites showed organic stenosis $\geq 50\%$. The sites of spasm elicited only by serotonin were also located in the proximal segments, but those of spasm elicited only by acetylcholine were located in the distal segments. Ergonovine provoked spasms at the same spastic sites as those for both acetylcholine and serotonin and those for serotonin alone in all the patients tested, but none at those for acetylcholine alone.

Previous studies have revealed that the spastic sites in patients with variant angina have local supersensitivity to various vasoconstrictive stimuli rather than selective supersensitivity to specific agonist.⁸ At 8 of 14 spastic sites in our patients with variant angina (Patients No. 1–9), both acetylcholine and serotonin produced spasms at the same sites and ergonovine also provoked spasms. In these patients, a local non-specific supersensitivity to multiple agonists may play an important role in the induction of coronary artery spasms. On the other hand, in all patients in Group B, which included only one patient with documented variant angina, ergonovine provoked spasm and the sites were consistent with those for serotonin. Ergonovine is an agonist for serotonergic receptors and α -adrenoceptors of vascular smooth muscles.⁹ Neither ketanserin, a 5-HT₂ receptor antagonist, nor phentolamine, an α -receptor antagonist, prevents ergonovine-induced coronary artery spasm in patients with variant angina,^{10, 11} nor is serotonin-induced spasm in patients with variant angina prevented by ketanserin.¹² Therefore, both ergonovine- and serotonin-induced coronary artery spasms in variant angina were suggested to be mediated by the activation of ketanserin-resis-

tant serotonergic receptors; however, it still remains unclear which subtype of serotonergic receptor is mainly involved in this enhanced contraction. Recently, an angiographic study, in which acetylcholine was compared with ergonovine as a provocative test, demonstrated that acetylcholine failed to provoke some coronary artery spasms that were provoked by ergonovine in patients with variant angina.¹³ In the present study, acetylcholine also failed to provoke spasm at the sites of spasm induced by serotonin alone (Nos. 13, 15–18), whereas ergonovine did provoke them. These data suggest that these spastic sites had supersensitivity specific for serotonin but not

FIG. 3 Schematic localization of spastic sites on the coronary arteries. ○ = spastic site for serotonin, Δ = spastic site for acetylcholine, ● = spastic site for ergonovine. (A-i) Spastic sites where spasms were provoked by both acetylcholine and serotonin in Group A. (A-ii) Spastic sites where spasms were provoked by serotonin but not by acetylcholine in Group A. (A-iii) Spastic sites where spasms were provoked by acetylcholine but not by serotonin in Group A. (B) Spastic sites where spasms were provoked by acetylcholine but not by serotonin in Group B.

FIG. 4 Coronary angiograms showing the right coronary artery in a patient whose spasms were induced by serotonin but not by acetylcholine (Patient No. 11). Injection of acetylcholine (50 μ g) produced no coronary artery spasm (A). However, injection of serotonin (10 μ mol/l) produced coronary artery spasm (99% narrowing of luminal diameter) at segment 2 (B).

FIG. 5 Coronary angiograms showing the left coronary artery in a patient whose spasms were induced by acetylcholine but not by serotonin (Patient No. 14). Coronary angiograms of a spastic site in the left coronary artery of a Group B patient. Injection of acetylcholine (100 μ g) provoked coronary artery spasm (90% narrowing of luminal diameter) at segment 8 (A). On the other hand, injection of serotonin (10 μ mol/l) produced no coronary artery spasm at the site at which acetylcholine induced spasm (B).

for acetylcholine, and that a serotonergic mechanism is important in the induction of some coronary artery spasms.

According to a pathologic report, atherosclerotic lesions are most frequently distributed in the proximal coronary arteries,¹⁴ and in this study the spastic sites for both serotonin and acetylcholine and those for serotonin alone were located in the proximal segments. Pathologic studies have clarified that the spastic sites in patients with variant angina show atherosclerotic changes to some extent,^{15, 16} and recent advances in intravascular ultrasound imaging techniques have afforded the precise morphologic characterization of coronary atherosclerosis at spastic sites.¹⁷ Tousoulis *et al.* also showed that the coronary arteries exhibited an increased sensitivity to serotonin at the level of organic stenoses.¹⁸ Further study using intravascular ultrasound imaging methods may prove the hypothesis that certain atherosclerotic changes may play a crucial role in the pathogenesis of local supersensitivity.

The patients in Group B, whose spasms of the distal segment of coronary arteries were provoked only by acetylcho-

line, included no patients with variant angina or patients with positive ergonovine test results. Newman *et al.* reported that acetylcholine induced myocardial ischemia in patients with atypical chest pain, normal coronary angiograms, and negative results of both ergonovine provocation tests at bedside and maximum exercise tests.¹⁹ They speculated that myocardial ischemia resulted from diffuse constriction of the distal and angiographically invisible small coronary vessels by acetylcholine. Acetylcholine exhibits vascular actions as the net effect of relaxation mediated by the released endothelium-dependent relaxing factor and its direct contraction of vascular smooth muscle cells. Clinically, it is very difficult to differentiate whether acetylcholine-induced coronary artery spasm is due to a reduced endothelial production of endothelium-derived relaxing factor or the result of an increased reactivity of the vascular smooth muscle. Therefore, further investigations including measurement of coronary blood flow may serve to clarify the mechanism of distal coronary artery spasm induced by acetylcholine alone.

Study Limitation

One limitation of this study was that in some cases sublingual nitroglycerin was allowed 5 min before administration of serotonin and ergonovine. McFadden *et al.* reported that serotonin induced spasm in patients with variant angina even after inhalation of amyl nitrate.⁷ In our study, ergonovine also produced coronary artery spasms at the same sites where serotonin induced spasms after sublingual nitroglycerin. Our preliminary study revealed that in two patients with multivessel coronary artery spasms acetylcholine produced coronary artery spasms even after use of sublingual nitroglycerin to relieve coronary artery spasm in a contralateral coronary artery. However, further studies are needed to clarify the reproducibility of serotonin- or acetylcholine-induced coronary artery spasm even after the administration of sublingual nitroglycerin.

Finally, the present provocative protocol has the methodologic limitation in that intracoronary administration of ergonovine was performed after that of acetylcholine and serotonin in all patients examined. Ergonovine-induced spasm prolongs and needs the intravenous or intracoronary administration of nitroglycerin to release it.⁴ It was, therefore, necessary that ergonovine was infused after the other provocative agents to avoid an excessive prolongation of this protocol.

Conclusion

This study showed that there is a disparity in acetylcholine- and serotonin-induced coronary artery spasms. The coronary artery spasms in patients with variant angina are localized at the proximal portion of the coronary artery and are all induced by serotonin. There is a subgroup of patients with coronary artery spasms induced only by acetylcholine which requires further characterization of its clinical entity. This disparity in provocative agent-induced coronary artery spasms may reflect not only the difference in the pathogenic mechanisms of coronary artery spasms, but also the diversity of clinical features of patients with vasospastic angina.

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