Acetylcholine- and Ergonovine-Induced Coronary Microvascular Spasm Reflected by Increased Coronary Vascular Resistance and Myocardial Lactate Production

MASASHI HORIMOTO, M.D., KEIICHI IGARASHI, M.D., TAKASHI TAKENAKA, M.D., HITOKI INOUE, M.D., KOHKO YAMAZAKI, M.D., HITOSHI SAKURAGI, M.D.

Division of Cardiology, Sapporo National Hospital, Sapporo, Japan

Summary: Diagnosis of coronary microvascular spasm remains largely speculative because it has been mostly based on chest pain and electrocardiographic ST-segment shift with slow filling of contrast medium into the coronary artery. A patient with resting chest pain and normal coronary angiograms underwent provocative tests with intracoronary acetylcholine (ACh) and ergonovine. During the tests, coronary diameter and flow velocity in the left anterior descending (LAD) coronary artery were measured with quantitative coronary angiography and intracoronary Doppler guide wire, respectively. Vascular resistance of the LAD and lactate production were determined separately. With injections of 100 µg of ACh and 20 µg of ergonovine, chest pain occurred with ST-segment elevation in the precordial leads in the absence of epicardial coronary spasm. Coronary vascular resistance increased by 2.2- and 1.6-fold of the baseline value with ACh and ergonovine, respectively. Myocardial lactate production was noted during the ST-segment elevation. Coronary microvascular spasm was verified by the increment in coronary vascular resistance and myocardial lactate production with concomitant ST-segment elevation in the presence of normal coronary angiograms.

Key words: coronary microvascular spasm, acetylcholine, ergonovine, coronary vascular resistance, ST-segment elevation

Introduction

Microvascular spasm due to intense and dynamic constriction of coronary microvessels has not been fully investigated. As the spasm cannot be visualized by conventional methods, its diagnosis has mostly been based on electrocardiographic (ECG) ST-segment shift associated with chest pain and a delayed filling of contrast medium into the coronary artery in the presence of normal coronary arteriograms.^{1–7}

We present a case of microvascular spasm provoked with intracoronary acetylcholine (ACh) and ergonovine. The spasm was accompanied by chest pain and ECG ST-segment elevation in the absence of epicardial coronary spasm. To verify dynamic constriction of coronary microvessels and myocardial ischemia during the spasm, we evaluated coronary vascular resistance and myocardial lactate production.

Case Report

A 71-year-old woman was admitted to the hospital in December 1992 because of recurrent chest pain at night and in the early morning. The chest pain started 2 years earlier and was relieved with sublingual administration of isosorbide dinitrate. She had neither coronary risk factors nor a family history of coronary artery disease. Physical examination on admission showed a blood pressure of 140/76 mmHg and a regular pulse of 72 beats/min. Heart auscultation revealed a diastolic blowing murmur of grade II/VI at the left lower sternal border. Chest x-ray and ECG were normal. Treadmill exercise test and exercise thallium myocardial scintigraphy were negative for myocardial ischemia. Two-dimensional color-Doppler echocardiography showed no left ventricular asynergy but the echo-enhanced right coronary cusp of the aortic valve with mild aortic regurgitation. A 24-h Holter monitoring disclosed ventricular premature contractions of Lown grade I and no ST-segment shift. As coronary arteriograms were normal, vasospastic angina was suspected.

Address for reprints:

Masashi Horimoto, M.D.
Division of Cardiology
Sapporo National Hospital
Kikusui 4-2, Shiroishi Ward
Sapporo 003-0804, Japan

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FIG. 1 Coronary angiograms from right anterior oblique 30° view showed normal left coronary arteries at baseline (A) and after the administration of isosorbide dinitrate (D). No significant constriction of epicardial coronary arteries is shown with intracoronary injection of 10 µg (B) and 100 µg (C) of acetylcholine.

A provocative test for coronary spasm with intracoronary ACh was performed together with flow velocity measurement in the left anterior descending (LAD) coronary artery. Stepwise doses of ACh such as 10, 20, 50, and 100 µg diluted with 5 ml of saline were injected into the left coronary artery and subsequently 20 and 50 µg into the right coronary artery. A Doppler guide wire of 0.014" in diameter (Cardiometrics Inc, Mountain View, Calif.) was placed in the proximal LAD to measure blood flow velocity at 5 mm distal to the wire tip. Coronary angiography with 30 frames/s was performed at baseline and at every min up to 3 min after each injection of ACh or at chest pain with ECG ST-segment shift. Coronary artery diameter at the site of the velocity measurement was quantitatively measured by use of a densitometric analyzer CAD-98 (Nishimoto Sangyo Co. Ltd., Japan). Coronary blood flow (ml/min) was calculated from $\pi D^2/8 \times APV \times 60$, where D and APV denote diastolic diameter of the coronary artery in centimeters and average peak velocity in centimeters/s, respectively. As blood flow was affected by an injection of contrast medium, the APV value immediately before each angiography was adopted. Electrocardiograms and coronary blood pressure were continuously monitored during the test. Vascular resistance of the LAD was calculated from mean coronary artery pressure divided by coronary blood flow.

With each injection of ACh, chest pain developed in the absence of epicardial coronary spasm and apparent slow filling of contrast medium (Fig. 1). Electrocardiographic ST-segment elevation in leads V₃–V₅ and V₁–V₄ were noted with 10 and 100 µg of ACh, respectively, whereas no ST-segment shift was shown with 20 and 50 µg of ACh (Fig. 2). The blood

FIG. 2 ST-segment elevations in leads V₃–V₅ and V₁–V₄ were noted with intracoronary injection of 10 µg and 100 µg of acetylcholine (ACh), respectively.

flow was increased after the injection of 10, 20, and 50 µg of ACh, while it significantly decreased with 100 µg of ACh (Table I). Vascular resistance of the LAD was decreased with 10 to 50 µg of ACh but was increased by 2.24-fold of a baseline value with 100 µg of ACh. Injection of ACh into the right coronary artery provoked neither epicardial coronary spasm nor ECG changes.

To identify myocardial ischemia during the ST-segment elevation with ACh, myocardial lactate extraction ratio was determined a week later. A Goodale-Lubin catheter was advanced into the great cardiac vein for blood sampling. Stepwise dose of ACh was injected into the left coronary artery in the same manner as mentioned above. Both at baseline and during chest pain and/or ST-segment elevation with ACh, blood was sampled for lactate measurement from the left coronary artery and from the great cardiac vein. Lactate concentration was determined by an enzymatic method. Myocardial extraction ratio of lactate was expressed as $[Lac(A) - Lac(V)] / Lac(A) \times 100$, where Lac(A) and Lac(V) denote lactate con-

TABLE I Coronary hemodynamic changes with acetylcholine

	Baseline	Acetylcholine			
		10 µg	20 µg	50 µg	100 µg
LAD diam. (mm)	3.41	3.32	3.07	3.24	3.07
APV (cm/s)	20	32	28	28	11
Flow rate (ml/min)	54.8	83.4	63.0	69.2	24.4
Mean AoP (mmHg)	94	97	95	93	94
CVR (mmHg/ml/min)	1.72	1.17	1.51	1.35	3.85

Abbreviations: AoP = aortic pressure, APV = average peak velocity, CVR = coronary vascular resistance, LAD diam. = diameter of the left anterior descending coronary artery.

FIG. 3 ST-segment elevation in leads V₃–V₅ was shown with intra-coronary injection of 20 µg of ergonovine (Ergo.).

centration of the blood from the left coronary artery and that from the great cardiac vein, respectively.

At each injection of ACh, the heart rate–blood pressure product as an index of myocardial oxygen consumption was not significantly changed from baseline. With each dose of ACh, the patient developed chest pain in the presence of normal coronary angiograms. At the injection of 50 µg of ACh, ST-segment elevation in leads V₂–V₆ was noted. Lactate extraction ratio decreased with any dose of ACh (42.3 % at baseline, 17.0 % with 10 µg, 12.1 % with 20 µg, –86.1 % with 50 µg, –3.8 % with 100 µg). Thus, lactate production was verified at the injections of 50 and 100 µg of ACh. Coronary microvascular spasm was diagnosed and medication was started with long-acting nifedipine and isosorbide dinitrate twice a day, that is, after breakfast and dinner. The incidence of angina was reduced to approximately once a month or 2 months after the medication, and the nocturnal angina was almost completely abolished with administration of both drugs before sleep. Infrequent angina appearing in the morning was resolved with sublingual nitrate.

The patient was readmitted in June 1997 for assessment of coronary microvascular response to ergonovine and to undergo endomyocardial biopsy of the right ventricular septum. An ECG showed complete right bundle-branch block with left anterior hemiblock. All drugs were discontinued at least 48 h prior to the study. Stepwise doses of ergonovine such as 10, 20, and 30 µg diluted with 5 ml of saline were injected into the left coronary artery and subsequently into the right coronary artery. Coronary angiography and flow velocity measurement in the proximal segment of the LAD were performed in the same way as mentioned above.

FIG. 4 Coronary angiograms from cranially 45° tilted left anterior oblique 45° view disclosed normal left coronary arteries at baseline (A) and no significant constriction of epicardial coronary arteries at the injection of 20 µg ergonovine (B). A pacing lead for back-up pacing was placed in the right ventricular apex.

At injection of 20 µg of ergonovine, chest pain occurred with ST-segment elevation in V₃–V₅ (Fig. 3). Neither epicardial coronary spasm nor slow filling of contrast medium were shown with any dose of ergonovine (Fig. 4). Coronary blood flow was significantly reduced with 20 µg of ergonovine, and coronary vascular resistance of the LAD was increased 1.61-fold of the baseline value (Table II). The injection of ergonovine into the right coronary artery provoked no chest pain, ST-segment shift, and epicardial coronary spasm. The endomyocardial biopsy revealed neither wall thickening of the intramural arterioles ranging from 30 to 60 µm in diameter nor periarteriolar fibrosis.

TABLE II Coronary hemodynamic changes with ergonovine

	Baseline	Ergonovine		
		10 µg	20 µg	30 µg
LAD diam (mm)	3.46	3.35	3.41	3.29
APV (cm/s)	22	22	14	23
Flow rate (ml/min)	62.2	58.2	38.2	58.8
Mean AoP (mmHg)	96	87	95	102
CVR (mmHg/ml/min)	1.55	1.50	2.49	1.74

Abbreviations as in Table I.

After discharge, the incidence of angina in this patient was approximately once in 2 or 3 months with the same medication as before.

Discussion

Coronary microvascular spasm has been suspected when chest pain with ECG ST-segment shift occurs with concurrent slow filling of contrast medium into the coronary artery in the presence of normal coronary angiograms. Such findings have been reported in humans spontaneously,⁷ after coronary balloon angioplasty,³ and with the administration of ACh,^{6, 8} ergonovine,^{1, 4, 5} or neuropeptide Y.²

Despite these reports on microvascular spasm, its diagnosis has been speculative because evidence for coronary microvascular constriction has not been obtained. The present case verified an increment in coronary vascular resistance during the ECG ST-segment elevation with ACh and with ergonovine in the absence of epicardial coronary spasm. Furthermore, the ST-segment elevation with administration of ACh was accompanied by myocardial lactate production, indicating myocardial ischemia. The findings demonstrated that transmural ischemia was caused by the elevation of microvascular resistance secondary to microvascular spasm. The increased resistance of the LAD suggested that spasm occurred in almost all contiguous small vessels in the LAD territory, whereas the slightly reduced coronary vascular resistance despite ST-segment elevation at the injection of 10 µg of ACh may be explained as follows: Acetylcholine has two opposing vascular effects; one is vasodilation mediated by the release of endothelium-derived relaxing factor, especially with a low dose of ACh,⁹ and the other is vasoconstriction by a direct effect on the coronary smooth muscle with a high dose of ACh¹⁰ or on the vessels with endothelial dysfunction.¹¹ Thus, heterogeneous distribution of both microvascular constriction and dilation seemed to occur at the administration of 10 µg of ACh. This probably led to intramural coronary steal from the ischemic area to the nonischemic adjacent area in the LAD territory. Consequently, overall vascular resistance of the LAD was reduced.

Cannon *et al.*^{12–15} have proposed the term “microvascular angina” for the patients who had anginal pain but normal coronary arteries without epicardial coronary spasm. In these patients, rapid atrial pacing alone or pacing after ergonovine administration led to chest pain and myocardial ischemia in the absence of significant luminal narrowing of the epicardial coronary arteries. Microvascular angina has been shown to be associated with inappropriate constriction of coronary microvessels and augmented response to vasoconstrictor stimuli, as well as attenuated response to vasodilator stimuli such as atrial pacing, exercise, or dipyridamole.^{12–16} Although atrial pacing or the pacing after the administration of ergonovine was not conducted in the present case, the case differs from the proposed microvascular angina as follows: First, chest pain occurred only at rest and was not precipitated by exertion; second, chest pain associated with both ST-segment elevation and

increased coronary microvascular resistance was reproducible with administration of ACh and ergonovine and without atrial pacing; third, the efficacy of isosorbide dinitrate and calcium-channel blocker was apparent.

Microvascular spasm provoked with ACh and ergonovine may indicate a reduced production of endothelium-derived relaxing factor in coronary microvessels and an enhanced reactivity of microvascular smooth muscle to vasoconstrictor stimuli, respectively. Chronic inhibition of nitric-oxide synthesis has been experimentally shown to cause medial thickening of coronary small vessels and their augmented constrictor response to serotonin in pigs.¹⁷ In the present case, however, wall thickening of the coronary microvessels was not shown, although arterioles > 100 µm in diameter were not detected. Therefore, the experimental model may not necessarily represent pathologic abnormalities of coronary small vessels in patients with microvascular spasm.

As a single-drug therapy with long-acting nifedipine or isosorbide dinitrate was not performed, it is uncertain which drug was more effective in preventing microvascular spasm. We can consider that administration of long-acting isosorbide dinitrate before sleep was effective in preventing nocturnal angina but not enough to abolish it. The combination with long-acting nifedipine before sleep could almost completely abolish the nocturnal angina. The beneficial effect of both drugs has been sustained.

Conclusion

This case demonstrated the increase in coronary vascular resistance and myocardial lactate production during microvascular spasm with ECG ST-segment elevation and without epicardial coronary spasm. The spasm was reproducible with both intracoronary ACh and ergonovine.

References

1. Hattori R, Takatsu Y, Yui Y, Nonogi H, Kawai C: Unusual vasomotor coronary arterial responses after reversal of ergonovine induced spasm with glyceryltrinitrate. *Br Heart J* 1984;51:312–315
2. Clarke JG, Davies GJ, Kerwin R, Hackett D, Larkin S, Dawbarn D, Lee Y, Bloom SR, Yacoub M, Maseri A: Coronary artery infusion of neuropeptide Y in patients with angina pectoris. *Lancet* 1987; 1:1057–1059
3. Wilson RF, Laxson DD, Lesser JR, White CW: Intense microvascular constriction after angioplasty of acute thrombotic coronary arterial lesions. *Lancet* 1989;1:807–811
4. Serota H, Kern MJ, Deligonul U, Aguirre F, Caralis DG: Ergonovine-induced myocardial ischemia without epicardial coronary vasospasm: Evidence for ischemia produced by small-vessel vasoconstriction. *Am Heart J* 1991;121:1807–1809
5. Kawakami K, Shimada T, Nakayama K, Nagasaka Y, Tsukihashi H, Murakami R, Morioka S, Moriyama K: Angina pectoris due to possible vasospasm of small coronary arteries. *Clin Cardiol* 1991; 14:775–777
6. Sekiya M, Okayama H, Suzuki M, Kobayashi T, Matsuoka H, Sumitomo T, Hamada M, Hiwada K: Acetylcholine-induced myocardial ischemia without epicardial coronary artery spasm: A possible vasospasm of small coronary arteries—a case report. *Angiology* 1993;44:811–815

7. Yamagishi H, Itagane H, Hato K, Suto Y, Minami S, Otsuka M, Tojo O, Okumachi F, Haze K: A case of rest angina due to microvascular spasm. *Jpn Circ J* 1997;61:87–89
8. Mohri M, Koyanagi M, Egashira K, Tagawa H, Ichiki T, Shimokawa H, Takeshita A: Angina pectoris caused by coronary microvascular spasm. *Lancet* 1998;351:1165–1169
9. Furchgott RF, Zawadzki JV: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980;288:373–376
10. Newman CM, Maseri A, Hackett DR, El-Tamimi HM, Davies GJ: Response of angiographically normal and atherosclerotic left anterior descending coronary arteries to acetylcholine. *Am J Cardiol* 1990;66:1070–1076
11. Ludmer PL, Selwyn AP, Shook TL, Wayne RR, Mudge GH, Alexander W, Ganz P: Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. *N Engl J Med* 1986;315:1046–1051
12. Cannon RO, Watson RM, Rosing DR, Epstein SE: Angina caused by reduced vasodilator reserve of the small coronary arteries. *J Am Coll Cardiol* 1983;1:1359–1373
13. Cannon RO, Leon MB, Watson RM, Rosing DR, Epstein SE: Chest pain and normal coronary arteries: Role of small coronary arteries. *Am J Cardiol* 1985;55:50B–60B
14. Cannon RO, Schenke WH, Leon MB, Rosing DR, Urquhart J, Epstein SE: Limited coronary flow reserve after dipyridamole in patients with ergonovine-induced coronary vasoconstriction. *Circulation* 1987;75:163–174
15. Cannon RO, Epstein SE: Microvascular angina as a cause of chest pain with angiographically normal coronary arteries. *Am J Cardiol* 1998;61:1338–1343
16. Cannon RO, Schenke WH, Quyyumi A, Bonow RO, Epstein SE: Comparison of exercise testing with studies of coronary flow reserve in patients with microvascular angina. *Circulation* 1991;83 (suppl III):III-77–III-81
17. Ito A, Egashira K, Kadokami T, Fukumoto Y, Takayanagi T, Nakaike R, Kuga T, Sueishi K, Shimokawa H, Takeshita A: Chronic inhibition of endothelium-derived nitric oxide synthesis causes coronary microvascular structural changes and hyperreactivity to serotonin in pigs. *Circulation* 1995;92:2636–2644