Microvascular Angina Accompanied by Epicardial Coronary Artery Spasm

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Abstract

A case of microvascular angina accompanied by coronary artery spasm is described. A 54-year-old woman had anginal pain at rest and during exercise. Both exercise testing and rapid atrial pacing caused significant ST depression in the inferior and all precordial leads. Exercise thallium myocardial scintigraphy was negative despite similar ST depressions. Coronary angiography revealed insignificant stenoses of the left anterior descending coronary artery after the injection of nitrate. Intracoronary acetylcholine provoked diffuse spasm of the artery with concurrent myocardial lactate production. Coronary flow reserve assessed with papaverine was 2.75. The combined use of amlodipine and high-dose nicorandil was effective for the treatment of angina.

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Key words: acetylcholine, coronary flow reserve, amlodipine, nicorandil

Introduction

Microvascular angina is mainly caused by reduced vasodilator capacity of the coronary small vessels. This angina is characterized as typical chest pain mostly at exercise, a positive exercise test with electrocardiographic ST-segment depression, normal coronary arteriograms and reduced coronary flow reserve (1–5). Although this type of angina is unassociated with epicardial coronary artery spasm, we describe a rare case of microvascular angina accompanied by coronary artery spasm in this report. The drug efficacy for the angina is also discussed.

Case Report

A 54-year-old woman was admitted to our hospital in November 1998 because of anginal pain at rest and during exercise. She had experienced chest pain at night or in the early

morning since July 1995 and had developed exertional angina in August 1998. She had no past medical history, no family history of coronary artery disease, and no coronary risk factors. Physical examination on admission showed no abnormalities. Her blood pressure was 122/74 mmHg and pulse was regular at 64 bpm. Laboratory data revealed no abnormalities and chest X-ray was also normal. However, an electrocardiogram at rest showed small or inverted T-waves in the inferior and all precordial leads (Fig. 1). Echocardiography showed no hypertrophy or asynergy of the left ventricle, and no valvular abnormalities. A treadmill exercise test caused chest pain with significant ST-segment depression in the inferior and all precordial leads (Fig. 1). Exercise thallium myocardial scintigraphy revealed no perfusion defects, despite the appearance of chest pain with similar ST-segment depressions.

Baseline coronary angiography revealed a 50% narrowing at the ostium of the left anterior descending coronary artery (LAD) (Fig. 2A). Injection of 2.5 mg of isosorbide dinitrate into the left coronary artery resolved the narrowing (Fig. 2B), suggesting the presence of coronary artery spasm. The artery showed 25% and 50% organic stenoses at its proximal and mid portions, respectively. The right coronary artery showed 25% stenoses at its mid and distal portions after the nitrate injection into the artery. Because of the exertional angina without significant coronary stenoses and the spontaneous coronary artery constriction, we suspected microvascular angina accompanied by coronary artery spasm. To first verify microvascular angina, rapid atrial pacing with concurrent coronary angiography was performed. Right atrial pacing at a rate of 140 bpm provoked chest pain with 0.2 mV of ST-segment depression and T-wave inversion in the inferior and all precordial leads (Fig. 3) in the absence of epicardial coronary spasm (Fig. 4), which suggested microvascular angina.

To verify the presence of coronary artery spasm, graded doses of ACh (20, 50, and 100 µg) in 5 ml of saline were infused in 20 seconds into the left main coronary artery on a separate day after informed consent was obtained from the patient. Blood was sampled from the left main coronary artery and the great cardiac vein to determine the arteriovenous difference in lactate concentration during ST-segment changes with

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intracoronary ACh. A Doppler guide wire of 0.014 inch in diameter was advanced into the mid portion of the LAD to measure blood flow velocity. Coronary flow reserve was determined as the ratio of maximum average peak velocity after the intracoronary injection of 10 mg of papaverine to the average peak velocity at baseline.

The baseline electrocardiogram showed small or flattened T-waves in the inferior and precordial leads (Fig. 5) and coronary angiograms revealed a moderate stenosis at the mid portion of the LAD (Fig. 6A). The injection of 20 μ g and 50 μ g of ACh did not cause chest pain, ST-segment changes or coronary spasm. However, 100 μ g of ACh caused chest pain with slight ST-segment elevation in leads V_2 – V_3 (Fig. 5) and intense constriction of the LAD at its just proximal and distal portions (Fig. 6B). Myocardial lactate production did not occur with 20 or 50 μ g of ACh, but was detected with 100 μ g of ACh. Lactate concentrations in the left coronary artery and the great cardiac vein at baseline were 5.7 and 3.9 mg/dl, respectively, whereas

Figure 1. A resting electrocardiogram showed low voltage or inverted T-waves in the inferior and precordial leads. During treadmill exercise test, ST-segment depression occurred in the inferior and precordial leads.

Figure 2. Baseline coronary angiogram (straight cranial view) revealed 50% narrowing at the ostium of the left anterior descending coronary artery (arrow in A). The narrowing resolved with intracoronary nitrate (B).

Figure 3. Rapid right atrial (RA) pacing caused electrocardiographic ST-segment depression and T-wave inversion in the inferior and precordial leads.

Figure 4. A left coronary angiogram at rapid right atrial (RA) pacing showed no significant coronary stenosis or spasm.

Figure 5. A baseline electrocardiogram was almost normal but slight ST-segment elevation in V₂-V₃ was noted with intracoronary injection of 100 µg of acetylcholine.

the concentrations during the injection of 100 µg of ACh were 6.3 and 8.6 mg/dl, respectively. This indicated the presence of myocardial ischemia due to the spasm of the LAD despite the minimal ST-segment elevation in leads V₂-V₃. The obtained coronary flow reserve was 2.75. Thus, the diagnosis of microvascular angina accompanied by epicardial coronary artery spasm was most likely.

Drug efficacy for the angina was assessed by serial treadmill exercise testing using the Bruce protocol. To prevent the occurrence of coronary artery spasm during the test, 5 mg/day of amlodipine was included in the therapy. The time from the beginning to the development of 0.1 mV of ST-segment depression during the test was defined as exercise duration. Exercise testing was performed at least 5 days after the administration of each drug. The results are summarized in Table 1. Aminophylline, doxazosin, long-acting isosorbide mononitrate, and verapamil were ineffective in increasing exercise duration, while bisoprolol, long-acting nifedipine, and low-dose nicorandil were effective. However, high-dose nicorandil (30 mg/day) was the most effective. The patient has been almost free of rest and exertional angina with the combined use of amlodipine and high-dose nicorandil.

Figure 6. A moderate stenosis at the mid portion of the left anterior descending coronary artery is shown at baseline (A, caudally-tilted right anterior oblique 30° view). Intense constriction of the just proximal and distal portions of the artery occurred after the injection of 100 µg of acetylcholine (B).

Table 1. Drug Efficacy for Exercise Duration

Drugs	Exercise duration	RPP (×100)
None	2 min 45 sec	201
Amlodipine (5 mg/day)	3 min 30 sec	302
<i>In addition to amlodipine (5 mg/day)</i>		
Aminophylline (250 mg, DIV)	3 min 0 sec	173
Doxazosin (2 mg/day)	3 min 24 sec	192
Long-acting ISMN (40 mg/day)	3 min 40 sec	246
Verapamil (120 mg/day)	3 min 41 sec	198
Bisoprolol (5 mg/day)	4 min 21 sec	190
Long-acting nifedipine (20 mg/day)	4 min 39 sec	211
Nicorandil (15 mg/day)	4 min 41 sec	202
Nicorandil (30 mg/day)	6 min 12 sec	246

RPP: rate-pressure product at ST segment depression of 0.1 mV, ISMN: isosorbide mononitrate, DIV: intravenous drip infusion.

Discussion

Microvascular angina has been defined as chest pain, mostly occurring at exercise with concomitant ST-segment depression, normal coronary angiograms and reduced coronary flow reserve (1–5). Patients with systemic hypertension, cardiomyopathy or valvular heart disease are excluded from the diagnosis of this type of angina. The angina is reproducible by exer-

cise testing and rapid atrial pacing, and is generally unassociated with coronary artery spasm. The mechanism responsible for microvascular angina is believed to be impaired coronary vasodilator capacity caused by inappropriate constriction of the coronary microvessels and an attenuated response to vasodilator stimuli such as atrial pacing, exercise, dipyridamole, and papaverine (2–4). The present patient met the criteria for microvascular angina with respect to typical chest pain with ST-segment depression during exercise and atrial pacing, but did

not meet it in terms of the presence of a moderate coronary stenosis. However, the moderate stenosis of the LAD in our patient was unlikely a cause of exertional angina. This was because no perfusion defects were shown in exercise thallium myocardial scintigrams and the ST-segment depression during exercise and atrial pacing was too diffuse to account for the myocardial ischemia in the LAD territory.

The intense and diffuse constriction of the LAD in response to 100 µg of ACh, which led to myocardial lactate production, was considered as coronary artery spasm rather than coronary constrictor response to a high dose of ACh. This was because the patient had anginal pain at rest and showed focal and spontaneous constriction of the LAD. A previous study demonstrated that the response of angiographically normal coronary segments to ergonovine was similar between patients with microvascular angina, noncardiac chest pain, or coronary artery disease (5). This indicates that there is no predisposition of the epicardial coronary artery to spasm in patients with microvascular angina. Therefore, microvascular angina accompanied by epicardial coronary artery spasm seems extremely rare.

The coronary flow reserve in our patient appeared to be reduced and coincided with the value previously reported in microvascular angina (6). As myocardial lactate production during pacing stress test has been noted in only 0 to 37% of patients with microvascular angina (1, 7), the lactate production is not adopted as a diagnostic criterion of the angina. The diagnosis of microvascular angina in the present case is most likely but may be still indefinite, because myocardial lactate production, i.e., myocardial ischemia during the rapid atrial pacing and ST-segment depression was not evaluated.

Appropriate medication for microvascular angina remains elusive. Ca-blockers (8, 9), β -blockers (10), and nicorandil (11), and aminophylline (12) have been shown to be effective in increasing ischemic threshold defined as exercise duration, while nitrates (13) and β -blockers (14) were ineffective. Our case demonstrated that nifedipine, bisoprolol, and nicorandil were effective for prolongation of exercise duration, while aminophylline and verapamil were not (Table 1). Since a relatively large dose of nicorandil was the most effective, this drug should be used in a large dose for the treatment of microvascular angina that is refractory to various drugs.

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