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Original article

Approximately half of patients with coronary spastic angina had pathologic exercise tests

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ABSTRACT

Objectives: We examined the clinical usefulness of treadmill exercise tests (TETs) in diagnosing coronary spastic angina (CSA).
Methods: We performed the TETs and 24-h Holter monitoring in 300 CSA patients consisting of 152 patients with rest angina, 77 patients with effort angina, and 71 patients with rest and effort angina. Organic stenosis (>75%) was observed in 44 patients. Multiple spasms were recognized in 204 patients (68%).
Results: Positive TETs were recognized in 113 patients (38%) and borderline was observed in 30 patients (10%). Positive response was significantly higher in patients with organic stenosis than those without fixed stenosis (63.6% vs. 33.2%, $p < 0.001$). Moreover, ST elevation was more frequent in patients with organic stenosis than those without fixed stenosis (27.3% vs. 1.2%, $p < 0.001$). Positive response in patients with effort angina (46.8%) was higher than those in patients with rest angina (33.6%) and rest and effort angina (36.6%), but not significant. Positive response was not different between single spasm and multiple spasms. In all 300 patients, ST segment elevation was observed in only four patients (1.3%) on the 24-h Holter monitoring.
Conclusions: TET was useful in documenting ischemia in patients with CSA. More than a third of patients with CSA had positive TETs. Moreover, we obtained the pathologic TET response in approximately half of patients with CSA.

Introduction

Coronary endothelial dysfunction is one of the mechanisms of coronary artery spasm and the majority of cases of coronary spastic angina (CSA) have a benign clinical course with optimal medications including long-acting calcium channel antagonists [1,2]. Non-invasive tests as well as invasive testing are employed as diagnostic methods. Treadmill exercise tests, hyperventilation tests, and cold stress tests are used for the induction of ischemia due to coronary artery spasm as a non-invasive examination [3–15]. In patients with ischemic heart disease and obstructed coronary artery disease, treadmill exercise tests are useful to obtain the pathologic findings; however, they may not be so useful to detect the ischemic findings in patients with CSA and non-obstructed coronary artery disease. According to the Japanese Circulation Society (JCS) guidelines [16], 24–48 h Holter recording is defined as Class I, while the exercise test in the early morning and daytime in patients with diurnal variation in exercise tolerance is classified as Class IIa. Moreover, single exercise test in patients who are in a stable condition and suspected of having CSA is defined as Class IIb. Cardiologists perform the 24–48 h Holter monitoring when they suspect CSA. However, they do not routinely perform treadmill exercise tests in patients who are suspected of having CSA. In this study, we investigated the pathologic treadmill exercise tests and also reexamined the usefulness of single exercise tests in patients with CSA retrospectively. We also compared single treadmill exercise testing with the usefulness of 24-h Holter monitoring.

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Methods

Study patients

During 24 years (1991–2014), we performed both the treadmill exercise tests and 24-h Holter monitoring in 300 patients with CSA who had chest symptoms (rest angina, effort angina, or rest and effort angina) and provoked spasms by the pharmacological spasm provocation testing. Treadmill exercise tests and 24-h Holter monitoring were performed prior to 24 h cessation of medications within a week before the cardiac catheterization. As shown in Table 1, organic stenosis was recognized in 44 (14.7%) patients and old myocardial infarction was observed in 6 patients (2.0%). Rest angina, effort angina, and rest and effort angina were present in 152 patients, 77 patients, and 71 patients, respectively. There were 16 patients (5.3%) with variant angina before the cardiac catheterization. Multiple spasms were observed in 204 (68%) patients including 132 patients with two-vessel spasm and 72 patients with triple-vessel spasm by pharmacological spasm provocation tests. Standard treadmill exercise tests were performed in 119 patients, while accelerated exercise tests which were one minute's stage-up based on the Bruce's protocol were done in 181 patients. We asked about chest pain and chest oppression during and after the treadmill exercise tests in all patients. We also asked about dyspnea in all patients. None of the 300 patients had abnormal electrocardiographic (ECG) findings at rest or right/left bundle branch block or hypertrophy due to hypertension or hypertrophic cardiomyopathy. Four patients had atrial fibrillations and two patients had paroxysmal atrial fibrillations.

The degree of ST-segment depression was measured 80 ms after the J point. Pathologic response was defined as positive when one of the following ischemic ECG changes was demonstrated: (1) ST-segment elevation of more than 0.2 mV in at least 2 related leads during and/or after the procedures; (2) ST-segment depression of more than 0.1 mV as a horizontal or downsloping type, or more than 0.2 mV as a junctional type during and/or after the procedures. Borderline was defined as the appearance of usual chest pain, or dyspnea accompanied with borderline ECG changes during/after treadmill exercise tests. Borderline ECG changes were defined as transient ST-segment depression 0.05 mV $\leq$ horizontal or downsloping type $<$ 0.1 mV or 0.1 mV $\leq$ junctional type $<$ 0.2 mV. We also defined as negative when we obtained the appearance of dyspnea alone without borderline ECG changes. The study protocol was complied with the Declaration of Helsinki. The procedure was explained in detail to each patient and informed consent was obtained; the protocol of this study was in agreement with the guidelines of the ethical committee of each of our institutions.

Table 1
Patients' characteristics.

Number	300
Male	252 (84%)
Age (years)	63.5 ± 10
Organic stenosis (>75%)	44 (14.7%)
Old myocardial infarction	6 (2.0%)
Accelerated treadmill exercise (stage-up 1 min)	181 (60.3%)
Standard treadmill exercise test (stage-up 3 min)	119 (39.7%)
Rest angina	152 (50.6%)
Effort angina	77 (25.7%)
Rest and effort angina	71 (23.7%)
Single spasm	96 (32.0%)
Multiple spasm	204 (68.0%)
Hypertension	107 (35.7%)
Diabetes mellitus	47 (15.7%)
Dyslipidemia	142 (47.3%)
Smoking history	237 (79%)
Total cholesterol (mg/dl)	192 ± 35
Triglyceride (mg/dl)	142 ± 91
LDL-cholesterol (mg/dl)	117 ± 28
HDL-cholesterol (mg/dl)	48 ± 12
Fasting blood sugar (mg/dl)	106 ± 37
Glycohemoglobin (%)	5.5 ± 1.0

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Spasm provocation tests

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 without 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 acetylcholine (ACh) and ergonovine (ER), as previously reported [17–20]. 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. Since August 2012, we employed the maximal ACh dose of 200 μg into the left coronary artery if the intracoronary injection of 100 μg ACh failed to provoke spasm [21]. 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 prior to 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. In addition, we performed the additional intracoronary injection of ACh after ER tests if spasm was not provoked by either ACh or ER test. The dose of ACh was 50/80 μg into the RCA and 100/200 μg into the LCA over 20 s with at least a 3-min interval between each injection. When a coronary spasm was induced and did not resolve spontaneously within 3 min after the completion of ACh/ER and adding intracoronary injection of ACh after ER tests, or when hemodynamic instability due to coronary spasms occurred, 2.5–5.0 mg of nitrate was injected into the responsible vessel. During the study, arterial blood pressure and a standard 12-lead electrocardiogram were continuously monitored on an oscilloscope using a Nihon-Kohden polygraph. A standard 12-lead electrocardiogram was recorded every 30 s.

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. 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. Coronary artery spasm was assessed as >99% luminal narrowing. Patients with catheter-induced spasms were excluded from this study. Significant organic stenosis