Original article

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

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A B S T R A C T

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.

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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 ≤ horizontal or downsloping type < 0.1 mV or 0.1 mV ≤ 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 compiled 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.

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

Table 1  Patients' characteristics.

<table>
<thead>
<tr>
<th>Number</th>
<th>Male</th>
<th>252 (84%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 ± 10</td>
<td></td>
</tr>
<tr>
<td>Organic stenosis (&gt;75%)</td>
<td>44 (14.7%)</td>
<td></td>
</tr>
<tr>
<td>Old myocardial infarction</td>
<td>6 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Accelerated treadmill exercise (stage-up 1 min)</td>
<td>181 (60.3%)</td>
<td></td>
</tr>
<tr>
<td>Standard treadmill exercise test (stage-up 3 min)</td>
<td>119 (39.7%)</td>
<td></td>
</tr>
<tr>
<td>Rest angina</td>
<td>152 (50.6%)</td>
<td></td>
</tr>
<tr>
<td>Effort angina</td>
<td>77 (25.7%)</td>
<td></td>
</tr>
<tr>
<td>Rest and effort angina</td>
<td>71 (23.7%)</td>
<td></td>
</tr>
<tr>
<td>Single spasm</td>
<td>96 (32.0%)</td>
<td></td>
</tr>
<tr>
<td>Multiple spasm</td>
<td>204 (68.0%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>107 (35.7%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>47 (15.7%)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>142 (47.3%)</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td>237 (79%)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>192 ± 35</td>
<td></td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>142 ± 91</td>
<td></td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>117 ± 28</td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>48 ± 12</td>
<td></td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dl)</td>
<td>106 ± 37</td>
<td></td>
</tr>
<tr>
<td>Glycohemoglobin (%)</td>
<td>5.5 ± 1.0</td>
<td></td>
</tr>
</tbody>
</table>

LDL, low-density lipoprotein; HDL, high-density lipoprotein.
was defined as >75% luminal narrowing according to the American Heart Association classification [22]. Coronary arteries were measured after intracoronary administration of nitrate (5.0 mg) to evaluate coronary atherosclerosis.

**Statistical analysis**

All values are expressed as mean ± SD. The chi square test was used for differences in the prevalence of complications. A value of \( p < 0.05 \) was considered statistically significant.

**Results**

**Pathologic response**

As shown in Table 2, a positive response was observed in 113 patients consisting of 98 ST-segment depressions and 15 ST-segment elevations. Negative response was recognized in 157 patients, while 30 patients showed borderline response. Organic stenosis was more frequent in patients with positive response than in those with negative response. Effort angina was significantly higher in patients with positive and borderline response than in those with negative response. However, there was no difference concerning the coronary risk factors among the three groups.

**Pathologic response in patients with and without organic stenosis**

Table 3 shows that positive response was significantly higher in patients with organic stenosis than in those without organic stenosis (63.6% vs. 33.2%, \( p < 0.001 \)), while negative response was also significantly higher in patients with non-organic stenosis than in those with organic stenosis. Moreover, ST-segment elevation was more frequently observed in patients with organic stenosis compared with those with non-organic stenosis (27.3% vs. 1.2%, \( p < 0.001 \)). Diabetes mellitus and dyslipidemia were higher in patients with organic stenosis than in patients without organic stenosis. Demonstrable cases are shown in Fig. 1 [Fig. 1a, case 1 (non-organic stenosis) and Fig. 1b, case 2 (organic stenosis)].

**Comparisons of pathologic response in patients without organic stenosis**

As shown in Table 4, there were no differences except effort angina and diabetes mellitus among the three groups. Effort angina was significantly lower in the negative group than other groups and diabetes mellitus was significantly higher in patients with positive than those with negative results. The maximal heart rate was not different among the three groups, whereas the exercise time was lower in patients with negative than the other two groups but not significant.

**Pathologic response among the patients with rest angina, effort angina, and rest and effort angina**

A positive response was higher in patients with effort angina than in those with rest angina and rest and effort angina, but not significant, as shown in Fig. 2. There was no difference concerning the remaining issues including the coronary risk factors among the three groups.

**Comparisons between the standard exercise tests and the accelerated exercise tests**

A positive response was not different between the standard treadmill exercise test and the accelerated treadmill exercise test as shown in Fig. 2. Chest pain during exercise tests was significantly higher in patients with standard treadmill exercise test than those with accelerated treadmill exercise test (42% vs. 25.4%, \( p < 0.01 \)), whenever dyspnea during and after the treadmill exercise was more frequently observed in patients with accelerated exercise test than those with standard exercise test (20.4% vs. 9.2%, \( p < 0.01 \)). Ischemic ST-T change was not different between the two groups.
Fig. 1. Demonstrable cases. **Case 1 (non-organic stenosis):** He was a 61-year-old man admitted to our hospital due to rest and effort angina. Because resting electrocardiogram (ECG) was normal (E), we performed treadmill exercise test in the morning. After the sub-maximal exercise (maximum heart rate: 145 min⁻¹), he complained of usual chest discomfort accompanied with horizontal ST-segment depression in V4-6 leads (F). His coronary angiogram was normal (A and B) and we performed the acetylcholine (ACh) test. Intracoronary injection of 100 μg ACh into the left coronary artery provoked subtotal in the distal left anterior descending artery (LAD) and diffuse spasm in the distal left circumflex artery (D). Subtotal spasm at proximal right coronary artery (RCA) was recognized after the administration of 20 μg ACh into the RCA (C). **Case 2 (organic stenosis):** He was a 73-year-old man admitted to our hospital because of chest pain attacks early in the morning. Resting ECG was within normal limit (K) and we performed the treadmill exercise test at 11:30 am. After sub-maximal exercise (maximum heart rate: 135 min⁻¹), he complained of the usual chest pain similar to the morning attack accompanied with ST-segment elevation in inferior and anterior leads (L). After sublingual nitroglycerine, ST-segment elevation returned to normal ECG. Fixed stenosis was observed at mid LAD (H) and no stenosis was found in the RCA (G). We performed ACh test. Total occlusion was observed at the fixed stenosis site after intracoronary injection of 50 μg ACh (J), while diffuse distal spasm was found by the intracoronary injection of 80 μg ACh after ergonovine test (I). We implanted the drug-eluting stent in the fixed stenotic lesion.
Table 4
Comparisons of the variable issues in patients without organic stenosis.

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Borderline</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>85</td>
<td>29</td>
<td>142</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.5 ± 9.2</td>
<td>63.9 ± 7.6</td>
<td>63.9 ± 11.2</td>
</tr>
<tr>
<td>Male</td>
<td>75 (88.2%)</td>
<td>22 (75.9%)</td>
<td>118 (83.1%)</td>
</tr>
<tr>
<td>Old myocardial infarction</td>
<td>1 (1.2%)</td>
<td>1 (3.4%)</td>
<td>4 (2.8%)</td>
</tr>
<tr>
<td>Exercise time (s)</td>
<td>288.0 ± 143.6</td>
<td>303.4 ± 159.8</td>
<td>255.0 ± 127.3</td>
</tr>
<tr>
<td>Maximal heart rate (/min)</td>
<td>137.0 ± 16.7</td>
<td>132.9 ± 20.5</td>
<td>133.3 ± 19.6</td>
</tr>
<tr>
<td>Accelerated treadmill exercise</td>
<td>45 (52.9%)</td>
<td>16 (55.2%)</td>
<td>91 (64.1%)</td>
</tr>
<tr>
<td>Standard treadmill exercise</td>
<td>40 (47.1%)</td>
<td>13 (44.8%)</td>
<td>51 (35.9%)</td>
</tr>
<tr>
<td>Rest angina</td>
<td>39 (45.9%)</td>
<td>11 (37.9%)</td>
<td>81 (57.1%)</td>
</tr>
<tr>
<td>Effort angina</td>
<td>29 (34.1%)</td>
<td>12 (41.4%)</td>
<td>26 (18.3%)</td>
</tr>
<tr>
<td>Rest and effort angina</td>
<td>17 (20.0%)</td>
<td>6 (20.7%)</td>
<td>35 (24.6%)</td>
</tr>
<tr>
<td>Single spasm</td>
<td>25 (29.4%)</td>
<td>10 (34.5%)</td>
<td>49 (34.5%)</td>
</tr>
<tr>
<td>Multiple spasm</td>
<td>60 (70.6%)</td>
<td>19 (65.5%)</td>
<td>93 (65.5%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (40.0%)</td>
<td>9 (31.0%)</td>
<td>47 (33.1%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17 (20.0%)</td>
<td>4 (13.8%)</td>
<td>13 (9.2%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>41 (48.2%)</td>
<td>13 (44.8%)</td>
<td>61 (43.0%)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>60 (81.2%)</td>
<td>21 (72.4%)</td>
<td>111 (78.2%)</td>
</tr>
</tbody>
</table>

*p < 0.05.  **p < 0.01 vs. negative.

Comparisons between the single spasm and multiple spasms

As shown in Fig. 2, positive response was slightly higher in patients with multiple spasms than in those with single spasm, but not significantly. All other issues including coronary risk factors were not different between the two groups.

Comparisons between males and females

A positive response was slightly higher in male patients than in female patients, but not significantly (39% vs. 29%, ns), as shown in Fig. 2. All other issues except for smoking history (90.5% vs. 18.8%, p < 0.001) were not different between the two groups.

The 24-h Holter monitoring

Before the cardiac catheterization, ST segment elevation was observed in four patients (1.3%). Non-sustained ventricular tachycardia was found in 5 patients, while paroxysmal supraventricular tachycardia was recognized in one patient. Transient atrio-ventricular block was found in four patients (one complete atrio-ventricular block, two advanced atrio-ventricular block, and one Wenkebach-type block) and more than two seconds’ pause was recognized in four patients (2.3 s, 3.5 s, 3.7 s, and 4.8 s). Abnormal findings on the 24-h Holter monitoring were recognized in 18 patients (6%).

Discussion

In this report, we showed that a third of patients with CSA had positive response in the single treadmill exercise tests. Moreover, we obtained the pathologic treadmill exercise response (positive and borderline) in approximately half of patients with CSA. However, ST segment elevation on 24-h Holter monitoring was recognized in just four patients (1.3%). Moreover, abnormal findings on the 24-h Holter monitoring were 6% (18 patients). Clinical pathologic response was significantly higher on the single treadmill exercise testing than the 24-h Holter monitoring (37.7% vs. 6%, p < 0.001). Organic stenosis was often observed when ST-segment elevations on treadmill exercise tests were recognized in patients with CSA. However, there was no difference concerning the classification of angina type, treadmill exercise procedures, provoked single spasm or multiple spasms, and male or female patients. We recommend the clinical routine use of the single treadmill exercise tests (Class IIb) in patients with stable CSA as well as 24–48 h Holter recording (Class I).

Possible mechanism of positive response

We speculate the two mechanisms of ischemia after and during the treadmill exercise test in patients with CSA. One is spontaneous vasoconstriction-induced ischemia and another is exercise-induced coronary spasm [6,23]. The ST-segment depression during and after treadmill exercise tests in patients with non-organic stenosis and coronary spasm may occur under the spontaneous vasoconstriction-induced ischemia. In contrast, ST-segment elevation during and after treadmill exercise tests in patients with organic stenosis and coronary spasm may also be vasoconstriction-induced ischemia which leads to total or subtotal obstruction. Ischemia possibly due to spontaneous vasoconstriction may lead to more ischemia by the treadmill exercise and cause more ischemia and finally lead to total obstruction. Exercise-induced spasm is another mechanism of ST-segment elevation. In this study, the majority of patients with non-organic stenosis and coronary spasm showed ST-segment depression. We speculate that spontaneous vasoconstriction-induced ischemia is the most important issue for the mechanism of ST-segment depression. Coronary microvascular dysfunction may be another mechanism of ST-segment depression.
during/after treadmill exercise test [24]. However, all 300 patients had typical provoked spasms accompanying with the significant ischemic ECG changes during the pharmacological testing.

**Comparisons with past data**

According to the past reports, de Servi et al. reported treadmill exercise results in 114 patients with variant angina [25]. A positive response was observed in 77 patients (67.5%) consisting of 40 ST-segment elevations and 37 ST-segment depressions, whereas the remaining 37 patients (32.5%) showed normal exercise tests. A positive response was significantly higher in patients with organic stenosis than in those with non-organic stenosis (77.6% vs. 37.9%, $p < 0.001$). We obtained the same pathologic response although all our study patients did not have active variant angina. Castello et al. reported the value of exercise testing by electrically braked bicycle ergometer in 91 patients with coronary artery spasm [26]. A positive response was recognized in 45 patients (49.5%) with CSA including 8 ST-segment elevations and 37 ST-segment depressions, while the remaining 46 patients (50.5%) with CSA had no ST-T changes, as shown in Fig. 3a and b. A positive response was significantly higher in the study reported by Castello et al. than in ours (49.5% vs. 37.7%, $p < 0.05$), because organic stenosis was frequently observed in their data than ours (67% vs. 14.7%, $p < 0.01$). According to the data of Castello et al., ST-segment elevation was not different between the active CSA patients with and without organic stenosis (8.2% vs. 10%, ns), whereas ST-segment depression in patients with CSA who had organic stenosis was remarkably higher than that in patients with CSA who had non-organic stenosis (54.1% vs. 13.3%, $p < 0.001$). They concluded that the occurrence of exercise-induced ST-segment depression in patients with active CSA strongly suggested the presence of underlying fixed coronary artery disease. However, our data were different from those of Castello et al. In patients with organic stenosis, ST-segment elevation was remarkably higher in our study than in that by Castello et al. In contrast, ST-segment depression in patients with non-organic stenosis was significantly higher in our data than in Castello et al. Our study indicates that the occurrence of exercise-induced ST-segment elevation in patients with CSA suggests the presence of underlying fixed stenosis and coronary spasm. We recommend performing coronary angiography in these patients as soon as possible.

**Clinical implications**

Even if we suspected a coronary spasm, we should perform treadmill exercise tests routinely as well as the 24-h Holter monitoring. In patients with ST-segment elevation during and after treadmill exercise tests, the disease activity of coronary artery spasm may be high, or organic stenosis may combine in these patients. When ST-segment depression is observed it may be due to fixed stenosis or coronary spasm. Although a single treadmill exercise test is defined as Class Iib in the JCS guidelines, we recommend performing the treadmill exercise test when suspecting CSA in the clinic. If we performed the routine treadmill exercise tests when suspecting coronary spasm, we may get some ischemic findings in a half of patients with CSA before the cardiac catheterization. Although the JCS guidelines said that the 24-h Holter monitoring was defined as Class I, we could not get the high abnormal findings in the clinic. According to the definition of JCS guidelines, single treadmill exercise tests may not be so useful for diagnosing patients with CSA because of its Class Iib rating.

![Fig. 3](image-url) (a) Comparisons of the treadmill exercise tests in patients with coronary spastic angina (CSA) and non-organic stenosis. (b) Comparisons of the treadmill exercise tests in patients with CSA and organic stenosis.
However, in the clinical situation, we could obtain significantly higher pathologic responses on the single treadmill exercise tests. Specificity is high with the 24-h Holter monitoring but sensitivity is high on treadmill exercise testing when we performed non-invasive tests to get any ischemic abnormal findings.

**Study limitations**

Our study has several limitations. The first limitation is the retrospective design and small study. We did not perform the treadmill exercise tests in all angiographically confirmed 820 CSA patients during 24 years. We performed treadmill exercise tests in only 36.6% of CSA patients. The second limitation is the two different treadmill protocols which are a standard method and an accelerated modified procedure. These different protocols for exercise stress testing may limit the conclusiveness of the results substantially. However, there was no critical difference between the two procedures. The third limitation is that not only coronary epicardial spasm but also microvascular dysfunction may be concerned with the appearance of ischemic findings on the treadmill exercise testing in patients with CSA. However, all 380 patients had the angiographically confirmed epicardial spasms in our study. Further non-invasive studies are needed to diagnose patients with CSA in the future.

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**Conflict of interest**

The authors declare that they have no conflict of interest.

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