Different Long-Term Course Between Chest Pain and Exercise-Induced ST Depression in Syndrome X

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SUMMARY

The aim of the present study was to assess the long-term clinical course of patients with syndrome X, focusing on different courses between exercise-induced ST depression and chest pain. Forty-three patients with syndrome X were followed up for 6.4 ± 3.8 years. They were divided into the 3 groups according to chest pain: disappeared (n = 24), improved (n = 14), or unchanged (n = 5). No patients had cardiac events and all had a favorable long-term prognosis. In patients showing disappearance of chest pain, exercise-induced ST depression and rate-pressure product (RPP) at peak exercise did not change during follow-up. However, ST depression and RPP decreased significantly in those with improved chest pain. These observations suggest that abnormal pain perception plays an important role in the development of chest pain. (Jpn Heart J 2003; 44: 471-479)

Key words: Chest pain, Exercise-induced ST depression, Prognosis, Syndrome X

THE term “syndrome X,” first proposed by Kemp1) in 1973, is now frequently used as a diagnostic label for patients who have chest pain and a positive response to exercise testing despite having angiographically normal coronary arteries. Although previous studies2-6) reported that this condition found a favorable long-term prognosis, most patients remain symptomatic for a long time and some are subjected to hospital readmission with symptoms and electrocardiographic changes suggestive of unstable angina. On the other hand, Romeo, et al5) reported that 27% of patients with syndrome X presented deterioration of left ventricular function and implied that the condition is an initial manifestation of cardiomyopathy. However, the long-term clinical courses of symptomatic status and exercise stress test are not yet fully understood. The aim of the present study was to assess the long-term clinical course of patients with syndrome X, focusing on different courses between exercise-induced ST depression and chest pain.

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METHODS

Study patients: The study included 49 patients with syndrome X who met the following inclusion criteria; 1) angina-like chest pain, 2) ischemic ST-T change (≥1 mm ST-segment depression) on treadmill exercise tests, and 3) normal coronary arteriograms. We excluded patients with left ventricular hypertrophy, complete left bundle branch block, nonspecific ST-T change at rest, valvular heart diseases, or those with medications which may induce electrocardiographic changes. Provocative tests for coronary artery spasm with acetylcholine were negative in 37 patients. Informed consent was obtained from each patient.

Exercise testing: All patients underwent exercise testing using a Sheffield or Bruce protocol. Exercise testing was performed while the patients were taking no antianginal medications. End points of the exercise test were progressive angina, ST segment depression ≥ 2 mm, a fall of systolic blood pressure from the preceding stage ≥ 20 mmHg, life-threatening arrhythmia, predicted target heart rate, or fatigue. Twelve-lead electrocardiograms and blood pressure were obtained at rest, and every minute during and after exercise. The level of ST segment depression was determined at 60 ms after the J point by a computer-assisted system (ML-5000, Fukuda Denshi) in all 12 leads. An ischemic ST-T change was defined as horizontal or down sloping ST segment depression ≥ 1 mm. Metabolic equivalents (METs) were calculated with 1 MET being defined as 3.5 mL/kg/min.

Follow-up: Patients were followed up for one year or more (mean, 6.4 ± 3.8 years). Health status and symptoms were assessed by telephone interview using a standardized questionnaire inquiring about temporal onset, location and radiation of chest pain, number of anginal episodes/week, average duration of episodes, association between chest pain with exertion, and presence of chest pain at rest. Follow-up information was obtained for 44 of 49 patients (91%). The end point of follow-up was cardiac or noncardiac death, acute myocardial infarction, unstable angina, serious conduction disturbance, or heart failure. Follow-up exercise stress tests were performed in 19 patients.

The study patients were divided into the 3 groups as follows according to the change in the frequency of chest pain during the last month of the follow-up period as compared with the symptomatic conditions at entry: those whose chest pain disappeared completely (D group), those whose chest pain improved by a decrease in the frequency of less than 50% (I group), and those whose chest pain remained unchanged (U group).

Statistical analysis: Values are presented as the mean ± SD. Comparisons between the 3 groups were made by one-way ANOVA and χ² test. The Scheffe F-test was used for additional analysis. Serial changes were compared by the paired t-test. The event free curve was calculated by the Kaplan-Meier method. Statistical significance was defined as P < 0.05.
RESULTS

Clinical course: Forty-four patients responded to the follow-up interview. They consisted of 41 women and 3 men (mean age, 55 years; range, 32 to 69 years).

There was one death due to cancer. One patient developed complete left bundle branch block after 5 years and one had complete atrioventricular block after 14 years. No other cardiac events, including myocardial infarction, were observed. Figure 1 shows the cardiac event free curve. The 5 and 10 year event free rates were 100% and 98%, respectively.

At the follow-up interview, 24 patients (53%) in the D group reported being chest pain-free, and 14 (33%) in the I group of 19 patients who reported persistent chest pain had less frequent chest pain. The frequency of chest pain was thus improved in 86% of the study patients. In the 5 other patients (14%) in the U group, chest pain remained unchanged.

Table I compares the baseline characteristics of the 3 groups. In the entry examinations, 10 patients had hypertension, 7 had hyperlipidemia, and 3 had dia-

![Cardiac events](image)

**Figure 1.** Kaplan-Meier event free curve. One patient developed complete left bundle branch block at year 5 and one had complete atrioventricular block at year 14.
During the follow-up period, 3 patients developed hypertension and one diabetes mellitus. Thus, 46.5% of the study patients had major cardiovascular risk factors.

Five patients in the D group and 3 in the I group were taking antianginal medications, including nicorandil. Seven patients in the D group and 1 in the U group were taking Ca antagonists. In both the D and I groups, 3 patients were taking a β-blocker and 1 patient was taking an angiotensin converting enzyme inhibitor. One patient in the U group was prescribed theophylline for chest pain. Hypertension, hyperlipidemia, and diabetes mellitus were treated by family physicians.

**Exercise test:** Table II compares the parameters of the baseline exercise stress test in the 3 groups. Heart rate and systolic blood pressure at rest and at peak exercise were not significantly different among the three groups. The I group had a significantly higher exercise tolerance (METs) than the D and U groups. However, the extent of exercise-induced ST depression and rate-pressure product (RPP) at peak exercise did not differ significantly among the three groups.

Figure 2 shows the serial changes in exercise-induced ST depression and RPP at peak exercise between the baseline and follow-up exercise tests. Despite the disappearance of chest pain in 8 patients in the D group, exercise-induced ST depression and RPP at peak exercise did not show significant changes in the follow-up test. In contrast, 9 patients in the I group with improved chest pain showed significant decreases in both exercise-induced ST depression and RPP at peak exercise.
Table II. Baseline Exercise Parameters of Patients Whose Chest Pain Disappeared (D group), Improved (I group), or was Unchanged (U group).

<table>
<thead>
<tr>
<th></th>
<th>D group (n = 24)</th>
<th>I group (n = 14)</th>
<th>U group (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at rest</td>
<td>75 ± 14</td>
<td>73 ± 11</td>
<td>76 ± 12</td>
</tr>
<tr>
<td>at peak</td>
<td>150 ± 16</td>
<td>153 ± 13</td>
<td>139 ± 18</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at rest</td>
<td>129 ± 19</td>
<td>127 ± 19</td>
<td>142 ± 19</td>
</tr>
<tr>
<td>at peak</td>
<td>179 ± 32</td>
<td>183 ± 27</td>
<td>182 ± 17</td>
</tr>
<tr>
<td>RPP (x 10^2)</td>
<td>270 ± 61</td>
<td>281 ± 60</td>
<td>254 ± 38</td>
</tr>
<tr>
<td>METs</td>
<td>7.1 ± 2.1*</td>
<td>8.8 ± 2.0</td>
<td>6.1 ± 1.8*</td>
</tr>
<tr>
<td>ST dep (mm)</td>
<td>1.8 ± 0.6</td>
<td>1.4 ± 0.5</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>End point (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST dep</td>
<td>8 (33)</td>
<td>4 (29)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>chest pain</td>
<td>4 (17)</td>
<td>1 (7)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>both</td>
<td>3 (12.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>leg fatigue</td>
<td>5 (21)</td>
<td>5 (36)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>target HR</td>
<td>3 (12.5)</td>
<td>2 (14)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>SOB</td>
<td>1 (4)</td>
<td>2 (14)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are mean ± SD or number of patients
SBP = systolic blood pressure; RPP = rate-pressure product; ST dep = ST depression; both = ST depression and chest pain; SOB = shortness of breath
*P < 0.05 in I group vs D or U group.

Figure 2. Relationship between ST-depression and peak RPP at baseline (●) and follow-up (○) exercise tests. In the D group (disappearance of chest pain), exercise induced ST-depression persisted at the follow-up exercise test. In contrast, exercise-induced ST-depression decreased with a reduction in RPP in the I group (improved chest pain).

exercise. Although the U group was excluded from this analysis due to the small number of study patients (n = 2), one patient did not show appreciable changes in
either exercise-induced ST depression or RPP at peak exercise. In the other patient, both exercise-induced ST depression and RPP at peak exercise decreased in the follow-up test.

**DISCUSSION**

The present results confirmed previous observations of a female predominance among patients with syndrome X. During a mean follow-up of 6.4 ± 3.8 years, we observed conduction disturbances in two patients but no cardiac death or myocardial infarction. The present study demonstrates again a favorable prognosis in patients with this condition, in agreement with most previous studies.

The follow-up examination demonstrated that exercise-induced ST segment depression persisted for at least several years. The observation was consistent with previous studies by Pupita, *et al* [8] Kaski, *et al* [6] and Romeo, *et al* [5] and suggested that abnormal pathophysiology producing the ECG change lasts over the long term. In contrast, chest pain disappeared or improved in 86% of the present study patients, and a restriction of daily activities or absence from work was rare. Most previous studies, [4,6,8] on the other hand, have reported that chest pain persisted and impaired the quality of life in a majority of patients. Although we can not provide a reasonable explanation, this discrepancy might be due to patient selection. It is widely recognized that patients with syndrome X constitute a heterogeneous population with regard to the possible underlying pathophysiological mechanisms for their chest pain. Chauhan, *et al* [4] studied the clinical presentation and functional prognosis of syndrome X by dividing their patients into two groups; those with stable angina and those with unstable angina. In their study, 68.3% of patients with unstable angina became pain-free at the follow-up, showing a significantly better functional prognosis than those presenting with stable angina. In an attempt to reduce clinical heterogeneity, the present study patients were selected to fulfill stringent criteria for syndrome X. All patients showed a positive exercise test in addition to chest pain and angiographically normal coronary arteries. Patients with resting ECG abnormalities like left bundle branch block or ST-T changes were excluded. It is possible that our study patients included more patients with unstable angina of shorter duration and therefore manifested a favorable prognosis. In contrast, it is likely that most previous studies from large referral centers selectively included more patients with stable and intractable chest pain with longer duration.

In the present study, the patients were assigned to one of the three groups based on their symptomatic status at the follow-up interview. The baseline clinical profiles and chest pain medications did not differ among the 3 groups. In the baseline exercise test, patients in the U group showed the lowest exercise toler-
ance, although the difference between the U and D groups was not significant. It is therefore likely that the U group patients were most severely affected and suffered from persistent chest pain. However, further analysis could not be performed because of the small study population. In the follow-up exercise test, rate-pressure product and degree of ST depression at peak exercise decreased significantly in the I group patients and in one U group patient. In contrast, rate-pressure product and ST depression at peak exercise did not change in the D group patients. This finding suggests that the I and U group patients unconsciously restricted their daily activities because of persistent chest pain, although no patients actually reported they restricted their daily activities or were absent from work in the questionnaire. On the other hand, the D group patients presented persistent exercise-induced ST depression despite the disappearance of chest pain.

The present study thus demonstrates that symptomatic status and exercise stress test manifested different courses, implying that the mechanisms responsible for chest pain and exercise-induced ST depression in syndrome X may differ. Various explanations have been proposed as mechanisms for syndrome X, such as small vessel abnormalities, cardiomyopathy, metabolic abnormalities, misinterpretation of coronary angiograms, impaired coronary flow reserve, oxyhemoglobin dissociation defects, psychosomatic factors, altered pain perception, increased sympathetic drive, and endothelial dysfunction. Among these, a decreased threshold for chest pain has been reported in patients with syndrome X using intravenous adenosine by Lagerqvist, et al or catheter stimulation of the right ventricle by Chauhan, et al. Turiel, et al reported that the pain threshold and tolerance for forearm ischemia and electrical skin stimulation were lower in female patients with syndrome X compared with those with chronic stable angina and severe coronary artery disease. Disappearance of chest pain despite persistent ST depression on the stress test in our follow-up study suggested that abnormal pain perception might play an important role in the development of chest pain in syndrome X, although the exact mechanisms of ST depression need to be further elucidated.

There is increasing evidence that cardiological syndrome X is accompanied by disturbances in metabolic factors, notably insulin resistance (metabolic syndrome X). In the present study, 36.4% of patients showed insulin resistance symptoms such as hypertension, hyperlipidemia, or diabetes mellitus at entry and 4 patients developed these symptoms during follow-up. Our observations support the recent hypothesis that cardiological and metabolic syndrome X may have a common underlying pathophysiological mechanism.
REFERENCES


