**Therapeutic Benefits of Cilazapril in Patients with Syndrome X**

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**Key Words**
- Syndrome X
- Cilazapril
- ACE inhibitors

**Abstract**

**Objectives:** Although the pathophysiology of syndrome X (angina pectoris, positive ECG test findings and normal coronary arteriogram) is unclear, it is generally accepted that intracellular metabolic changes resulting from abnormal constriction of prearteriolar vessels due to endothelium-dependent vasodilation abnormalities may play a role in the pathogenesis. We established the effect of long-term treatment with cilazapril, an angiotensin-converting enzyme inhibitor, which prevents the effect of angiotensin II in the tonic control of vascular resistance. **Methods:** 18 patients (15 women and 3 men, mean age 43.2 ± 4.6 years) with syndrome X were included in this study. A randomized double-blind crossover placebo-controlled trial was done. After a 1-week washout period, patients received either cilazapril 2 × 2.5 mg or placebo for 3 weeks, followed by 3 weeks of the other therapy. At the end of two periods, an exercise ECG test (modified Bruce protocol) was employed. **Results:** The magnitude of ST segment depression was significantly decreased during treatment with cilazapril compared with placebo. On the other hand, total exercise time and time to 1 mm ST segment depression were significantly prolonged by cilazapril. However, rate pressure products were not significantly different at peak exercise at or at 1 mm of ST segment depression during both therapies. **Conclusion:** Cilazapril exerted a beneficial therapeutic effect in cases with syndrome X. The possible mechanism of this effect may be a modulation of coronary tone at the microcirculation level.
hyperinsulinemia, inappropriate adenosine release, imbalance in the autonomic nervous system and impaired endothelium function are the main factors that have been suggested [2–9]. It is thus not surprising that there is no consensus about treatment, and calcium channel blockers, β-blockers, aminophylline, angiotensin-converting enzyme (ACE) inhibitors and estrogen replacement have all been used [10–12]. In the study described here we evaluated the therapeutic effects of cilazapril, an ACE inhibitor, in patients with syndrome X.

Methods

Patients

Eighteen patients (15 women and 3 men; mean age, 43.2 ± 4.6 years) diagnosed with syndrome X, based on typical exertional angina, a positive exercise test and normal coronary angiogram, were enrolled. Exclusion criteria were valvular heart disease, mitral valve prolapse, cardiomyopathy, hypertension, congestive heart disease, a history of myocardial infarction, coronary artery spasm, conduction abnormalities or diabetes mellitus. Left ventricular mass index, determined by echocardiography, was within the normal range (<105 g/m² in the women, <120 g/m² in the men). Musculoskeletal, stomach and esophageal causes of chest pain were ruled out using radiological methods.

All patients underwent left ventriculography and selective coronary angiography using Judkin’s method. Coronary angiograms were evaluated separately by three investigators and found to be completely normal. Thirteen patients underwent thallium-201 stress scintigraphy, and 5 (38%) of these showed reversible focal myocardial perfusion defects.

Study Design

A randomised, double-blind, placebo-controlled, crossover trial was performed. After a 1-week washout period, patients first received either cilazapril 2.5 mg twice daily or placebo for 3 weeks. Then, after a further 1-week washout period, they received the other treatment. An exercise electrocardiogram (ECG) was performed at the end of each treatment period (fig. 1).

The study protocol was approved by the local ethics committee. The nature of the trial was explained to each patient, and written consent was obtained.

Exercise ECG Test

Patients underwent two off-therapy, symptom-limited exercise ECG tests using the modified Bruce protocol. A test was stopped if any of the following occurred: progressive angina, severe fatigue, ST segment depression >3 mm, systolic blood pressure >220 mm Hg or a drop in systolic blood pressure >20 mm. Blood pressure and twelve-lead ECG were recorded before exercise, then at 1-min intervals during exercise and for at least 6 min after exercise had ceased. The level of ST segment depression 80 ms after the J-point was calculated in all twelve leads. The following additional variables were measured: total exercise time; time to 1 mm of ST segment depression; heart rate, systolic blood pressure and rate pressure products at peak exercise and 1 mm of ST segment depression and level of ST segment depression at peak exercise.

Table 1. Influence of cilazapril and placebo on heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), rate pressure product (RPP) at rest, 1 mm of ST segment depression and peak exercise

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Cilazapril</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resting values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>72.6 ± 6.1</td>
<td>79.3 ± 7.5</td>
<td>0.0066</td>
</tr>
<tr>
<td>SBP</td>
<td>131.7 ± 3.6</td>
<td>122.3 ± 5.9</td>
<td>0.001</td>
</tr>
<tr>
<td>DBP</td>
<td>81.3 ± 2.5</td>
<td>80.7 ± 3.3</td>
<td>0.62</td>
</tr>
<tr>
<td>RPP</td>
<td>9,574 ± 840</td>
<td>9,693 ± 930</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>At 1 mm of ST segment depression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, s</td>
<td>433.8 ± 93.8</td>
<td>524.0 ± 108</td>
<td>0.011</td>
</tr>
<tr>
<td>Heart rate</td>
<td>124.8 ± 8.2</td>
<td>127.1 ± 8.2</td>
<td>0.41</td>
</tr>
<tr>
<td>SBP</td>
<td>152.4 ± 7.7</td>
<td>150.4 ± 6.7</td>
<td>0.41</td>
</tr>
<tr>
<td>RPP</td>
<td>19,042 ± 1,653</td>
<td>19,147 ± 1,703</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>At peak exercise</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, s</td>
<td>535 ± 97.2</td>
<td>641 ± 115</td>
<td>0.0053</td>
</tr>
<tr>
<td>Heart rate</td>
<td>142.1 ± 11.6</td>
<td>144.4 ± 12.2</td>
<td>0.57</td>
</tr>
<tr>
<td>SBP</td>
<td>172.2 ± 10.4</td>
<td>172.0 ± 9.9</td>
<td>0.95</td>
</tr>
<tr>
<td>RPP</td>
<td>24,508 ± 2,836</td>
<td>24,891 ± 3,060</td>
<td>0.70</td>
</tr>
<tr>
<td>ST segment depression (mm)</td>
<td>1.77 ± 0.64</td>
<td>1.33 ± 0.48</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Statistical Analysis

Data are presented as means ± SD. Comparison of cilazapril and placebo was carried out using Student’s t test.

Results

All patients completed the study, with no side effects observed during treatment. Routine hematologic and biochemical parameters were unchanged in all patients throughout the study.

The results are summarized in table 1. After treatment with cilazapril, resting systolic blood pressure decreased and heart rate increased significantly (p = 0.0066 and p = 0.001, respectively). However, there were no changes in the rate pressure products after placebo or cilazapril treatment (fig. 2).

There was no significant difference between cilazapril and placebo in systolic blood pressure, heart rate or rate pressure products at peak exercise or 1 mm of ST segment depression. Total exercise time and time to 1 mm of ST segment depression were significantly prolonged by cilazapril (p = 0.011 and p = 0.0053, respectively). The magnitude of ST segment depression was significantly decreased during treatment with cilazapril (p = 0.026) (fig. 3, 4).

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Discussion

The pathogenesis of syndrome X is unclear, and several etiologic mechanisms have been proposed. Recent publications have suggested that vasoconstriction could reduce coronary blood flow in these patients. Maseri et al. [13] have hypothesized that patients with syndrome X have patchily distributed abnormal constriction of prearteriolar vessels due to endothelium-dependent vasodilata-
tion abnormalities. It is generally accepted that the major mechanisms involved are those that potentially enhance coronary vasoconstriction or attenuate circulatory vasodilator capacity.

Our results indicate that, compared with placebo, the ACE inhibitor cilazapril prolonged exercise duration and time to 1 mm ST segment depression. The magnitude of ST segment depression at peak exercise was also reduced by treatment with cilazapril. There was no correlation...
between these findings and the rate pressure product. There was no difference between cilazapril and placebo with respect to the rate pressure product at rest, time to 1 mm of ST segment depression or peak exercise.

This suggests that the beneficial effects of cilazapril may result from direct modulation of coronary microvascular artery tone by the drug. It is well known that angiotensin plays an important role in the tonic control of vascular resistance [14]. It has also been shown that angiotensin II exerts a strong coronary arteriolar constricting effect [15] that can be prevented by ACE inhibitors [16]. To date however, there are not many published reports on the treatment of syndrome X with ACE inhibitors. Kaski and Rosano [10] showed that enalapril reduced exercise-induced angina and ST segment depression in patients with syndrome X, which is in agreement with our results.

**Conclusion**

Our results show that cilazapril is beneficial in the treatment of syndrome X. The mechanism of action may depend on the modulation of coronary tone at the microcirculatory level, as already suggested by Kaski and Rosano [10].

**References**