Reduction of Exercise-Induced Myocardial Ischemia During Add-On Treatment With the Angiotensin-Converting Enzyme Inhibitor Enalapril in Patients With Normal Left Ventricular Function and Optimal Beta Blockade

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OBJECTIVES
We sought to study the effect of angiotensin-converting enzyme inhibition on exercise-induced myocardial ischemia.

BACKGROUND
Although angiotensin-converting enzyme inhibitors have been shown to reduce ischemic events after myocardial infarction, few data are available regarding their direct anti-ischemic effects in patients with coronary artery disease.

METHODS
We studied 43 patients (average age 63 ± 8 years) with exercise-induced myocardial ischemia (≥0.1 mV ST depression, despite optimal beta blockade) and normal left ventricular function (ejection fraction ≥0.50). In a double-blind, placebo-controlled parallel design, patients were treated with angiotensin-converting enzyme inhibitor (enalapril 10 mg twice daily) or placebo. Assessments were made after three weeks (short-term) and 12 weeks (long-term).

RESULTS
At baseline, the groups were well matched for all clinical characteristics. After three weeks, there was a slight but not significant increase in time to 0.1 mV ST depression in both groups (p = NS); rate pressure product (RPP = heart rate * systolic blood pressure) was also unaffected. After 12 weeks, however, time to 0.1 mV ST depression further increased in the enalapril group (5.6 ± 1.9 min) but was unchanged in the placebo group (4.4 ± 1.3 min; p < 0.05 between groups). In contrast, RPP was not affected. Concentrations of both atrial and brain natriuretic peptides at peak exercise tended to be lower by enalapril, if compared to placebo (p = NS).

CONCLUSIONS
Angiotensin-converting enzyme inhibition may reduce exercise-induced myocardial ischemia in patients with normal left ventricular function. Further studies are needed to elucidate the mechanisms involved. (J Am Coll Cardiol 2001;37:470–4) © 2001 by the American College of Cardiology

Angiotensin-converting enzyme inhibitors are used on a large scale in the treatment of hypertension and heart failure. Many patients with these conditions also have coronary artery disease (CAD); current treatment consists of beta blockade, long-acting nitrates and/or calcium antagonists (1). The objective of this treatment is to reduce symptoms of angina pectoris and to prevent ischemic events. Angiotensin-converting enzyme inhibitors have also been shown to be of potential value in patients with CAD, with reduced impaired left ventricular (LV) ejection fraction (2) and after myocardial infarction (3), as their use reduces the incidence of recurrent ischemic events in these patient groups. How angiotensin-converting enzyme inhibitors exert this beneficial effect is largely unknown, although several mechanisms, including a reduction in afterload and wall stress, inhibition in neurohormonal activation, intracoronary plaque stabilization, improvement of endothelial function and myocardial perfusion have all been suggested (4–8). Nevertheless, data to support a direct anti-ischemic effect of angiotensin-converting enzyme inhibitors in CAD patients with normal blood pressure and normal LV function are scarce (9).

In the present study, we investigated the effect of angiotensin-converting enzyme inhibition (with enalapril) on exercise-induced myocardial ischemia in patients with stable CAD, normal blood pressure and normal LV function who were symptomatic despite optimal treatment with beta blockers. We examined this effect after short-term treatment (three weeks) and after prolonged, long-term treatment (12 weeks), because the majority of earlier studies investigated only the short-term effects.

METHODS
The present study was a 12-week, randomized, parallel double-blind comparison of enalapril (10 mg twice daily) and placebo in 44 patients with ischemic heart disease. Patients (male, aged 18–75 years) were normotensive and
had a history of angina and signs of myocardial ischemia during exercise (≤0.1 mV ST-segment depression) despite optimal beta blockade (resting heart rate <65 beats/min at rest). In patients with a history of myocardial infarction (non-Q), left ventricular ejection fraction had to be determined and had to be >50%. Exclusion criteria included unstable angina, symptoms and/or signs of congestive heart failure, resting supine systolic blood pressure >200 or <100 mm Hg, resting supine diastolic blood pressure >100 mm Hg, a resting electrocardiographic pattern that does not allow correct interpretation of ST-segment deviation during the exercise stress test, history of hypersensitivity to angiotensin-converting enzyme inhibitors, renal insufficiency (serum creatinine >130 μmol/L), electrolyte abnormalities (K >5.2 mmol/L, Na <130 mmol/L) and myocardial infarction within the previous three months. The only drugs allowed were beta-1-selective beta-blockers (which were mandatory), long-acting nitrates and diuretics (for hypertension) with dosages unchanged during the study period; all other cardiovascular medication was excluded. The protocol was approved by the Ethics Committee of each participating center and all patients had to give their written informed consent before entry into the study.

Analysis at screening included physical examination, bicycle exercise test and laboratory investigation including hematology and blood chemistry. The electrocardiogram was monitored continuously to measure heart rate. ST-segments were determined by hand, at a paper speed of 100 mm/s in five successive beats, 80 ms after the J point of the QRS complex using a calibrated magnifying lens. This monitoring was performed blinded to the study group. After eligibility was determined, patients performed a second symptom-limited exercise test one week later, with measurements of neurohormones (atrial natriuretic peptide [ANP] and brain natriuretic peptide [BNP]) at rest and at maximal exercise. During this second test, exercise time had to be within 15% of the first test; results of the second test were taken as baseline. Patients were then randomized to 10 mg enalapril bid or placebo bid for 12 weeks. Patients visited the outpatient clinic after three and 12 weeks. ANP and BNP were determined as previously described in detail (10). Normal values for ANP were 1 to 15 pmol/l and for BNP 1 to 10 pmol/L. All measurements were performed in one batch at the core laboratory at the Erasmus University Rotterdam.

**Statistical analysis.** Values are given as the mean value ± SD. The primary end point, time to 0.1 mV ST-segment depression at 12 weeks, was evaluated by analysis of covariance (ANCOVA), by including the time to 0.1 mV ST-segment depression as additional covariate. Baseline values of all end points were analyzed by one-way ANOVA. If no 0.1 mV ST-segment depression was attained for the end point time to 0.1 mV ST-segment depression, the total exercise time was substituted. Comparison between the two treatment groups for remaining continuous normally distributed variables was analyzed by one-way ANOVA and/or skewed distributed variables by the Wilcoxon two-sample test. Categorical variables were analyzed by the chi-square test with continuity correction or Fisher exact test if appropriate. A p-value <0.05 was considered statistically significant.

**RESULTS**

Forty-four patients (mean age 63 ± 8 years) were included (Table 1). All patients were treated with the beta blocker metoprolol, except for one patient in the placebo and one patient in the enalapril group who were treated with atenolol. Twenty-three patients completed treatment with enalapril; 20 patients with placebo. One patient in the placebo group withdrew informed consent. The two groups were well matched for all clinical parameters (Table 1).

<table>
<thead>
<tr>
<th>Abbreviations and Acronyms</th>
<th>ANP = atrial natriuretic peptide</th>
<th>BNP = brain natriuretic peptide</th>
<th>CAD = coronary artery disease</th>
<th>LV = left ventricular</th>
<th>RPP = rate pressure product</th>
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<tr>
<th>Table 1. Patients’ Characteristics</th>
<th>Placebo</th>
<th>Enalapril</th>
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</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 ± 8</td>
<td>62 ± 9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173 ± 7</td>
<td>178 ± 6</td>
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<tr>
<td>Weight (kg)</td>
<td>79 ± 12</td>
<td>85 ± 9</td>
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<tr>
<td>Prev. MI</td>
<td>4</td>
<td>3</td>
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<tr>
<td>PTCA</td>
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<td>5</td>
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<tr>
<td>CABG</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>AP (NYHA)</td>
<td>I</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>12</td>
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<tr>
<td>Blood pressure (mm Hg)</td>
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<tr>
<td>systolic</td>
<td>139 ± 18</td>
<td>132 ± 14</td>
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<tr>
<td>diastolic</td>
<td>78 ± 9</td>
<td>77 ± 9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>62 ± 6</td>
<td>62 ± 5</td>
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<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.1 ± 0.9</td>
<td>5.1 ± 0.8</td>
</tr>
<tr>
<td>Long-acting nitrate</td>
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<td>3</td>
</tr>
<tr>
<td>ANP rest (pmol/ml)</td>
<td>12.4 ± 7.2</td>
<td>13.8 ± 8.0</td>
</tr>
<tr>
<td>ANP exercise (pmol/ml)</td>
<td>23.5 ± 18.2</td>
<td>30.5 ± 17.5</td>
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<tr>
<td>BNP rest (pmol/l)</td>
<td>15.0 ± 14.6</td>
<td>8.9 ± 8.3</td>
</tr>
<tr>
<td>BNP exercise (pmol/l)</td>
<td>18.2 ± 17.2</td>
<td>12.3 ± 11.9</td>
</tr>
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</table>

ANP = atrial natriuretic peptide; AP = angina pectoris; BNP = brain natriuretic peptide; CABG = coronary artery bypass graft; MI = myocardial infarction; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty.
Results after three weeks (Table 2). Heart rate and blood pressure were not affected after three weeks and there were no differences between the groups. Time to 0.1 mV ST-segment depression slightly increased in both groups (p = NS vs. baseline), but there was no difference between the groups (Fig. 1).

Maximal ST depression, total exercise time and RPP were also unaffected. Atrial natriuretic peptide and BNP at rest were not affected by enalapril. During peak exercise, however, the increase of both ANP and BNP tended to be blunted by enalapril (p = 0.08 for ANP and p = 0.24 for BNP vs. placebo) (Table 2).

Results after 12 weeks (Table 2). During prolonged treatment, heart rate and blood pressure remained unaffected. In contrast, time until 0.1 mV ST-segment depression further increased in the enalapril group, whereas it returned to baseline in the placebo group (p = 0.036 between groups) (Fig. 1).

Rate pressure product was again unaffected by study medication. Total exercise and maximal ST-segment depression were also unchanged. Plasma ANP and BNP at rest were again unaffected while slight, but again nonsignificant, decreases in peak values were observed.

DISCUSSION

The main finding of the present study is that enalapril reduced exercise-induced myocardial ischemia in normoten-
sive patients with normal LV function who had symptomatic angina despite optimal beta blockade. Enalapril increased time to 0.1 mV ST-segment depression whereas RPP was not affected. In addition, the increase of the natriuretic peptides (ANP and BNP) during exercise tended to be blunted during enalapril administration. Although this effect did not reach statistical significance, this finding may explain the observed decrease in exercise-induced ischemia. The finding that most patients did not experience angina during the exercise test may be explained by the fact that patients stop before they experience angina pectoris.

Anti-ischemic effects of enalapril. Short-term studies with angiotensin-converting enzyme inhibitors in normotensive patients with stable, exercise-induced angina pectoris and normal LV function have shown disappointing results (6–8). In some of these studies, the observed absence of a favorable effect was explained by a decrease in blood pressure, leading to a reduction in coronary perfusion pressure. These results are in contrast with the beneficial effects described after long-term administration in patients with CAD and LV dysfunction (3,11). In the latter studies, the anti-ischemic properties of angiotensin-converting enzyme inhibition were not observed within 3–6 months of treatment. This delayed onset of action may suggest that, rather than direct hemodynamic effects on the myocardial supply/demand ratio, other (indirect) effects, possibly on the tissue/cellular level, are responsible for the long-term anti-ischemic properties of angiotensin-converting enzyme inhibitors. By inhibition of angiotensin-converting enzymes, these drugs not only prevent generation of the vasoconstrictor angiotensin II, but also stimulate prostanoid and nitric oxide formation through local bradykinin accumulation, thereby enhancing vasodilation (12–13). In addition, both prostacyclin and nitric oxide prevent platelet aggregation by increasing cyclic adenosine monophosphate in platelets. These local effects may be attributable to the protective properties of angiotensin-converting enzyme inhibitors in CAD, which may lead to a better endothelial function (14).

Recently, the results of the Heart Outcomes Prevention Evaluation (HOPE) study (15) showed that the angiotensin-converting enzyme inhibitor ramipril reduced the incidence of cardiovascular events and overt nephropathy in people with diabetes. This cardiovascular benefit was already on a single agent, the sample size to demonstrate benefit of a second agent has to be large, and therefore this study, because of its small sample size, cannot exclude a type II statistical error (1).

Conclusions. In patients with stable CAD and normal LV function who were symptomatic despite optimal beta blockade, angiotensin-converting enzyme inhibition by enalapril reduced exercise-induced myocardial ischemia after prolonged treatment. Further (larger) studies will be needed to examine underlying mechanisms.

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REFERENCES


Anti-Ischemic Effects of ACE Inhibition


