Lack of reflex increase in myocardial sympathetic tone after captopril: potential antianginal effect

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ABSTRACT Many vasodilators have been tried as antianginal agents, but the reflex increase in sympathetic tone produced by these drugs necessitate their use with caution in patients with angina. In the first part of this study, captopril was given to 14 patients with angina and systolic arterial pressures of greater than 120 mm Hg. Over the short term, captopril decreased arterial blood pressure (from 110 ± 18 to 98 ± 18 mm Hg, p < .01) without increasing heart rate (75 ± 15 vs 74 ± 15 beats/min), arterial concentrations of epinephrine (0.38 ± 0.28 vs 0.34 ± 0.25 nM) or norepinephrine (2.7 ± 2.1 vs 2.8 ± 2.1 nM), or transmyocardial norepinephrine balance (216 ± 254 vs 146 ± 170 p mol/min). Captopril decreased average myocardial oxygen consumption (9.7 ± 4.1 to 8.2 ± 2.7 ml/min, p < .01). Given over the long term (mean 5.5 months), captopril decreased the severity of angina from NYHA classification 3.0 ± 0.8 to 1.6 ± 0.8. In the second part of this study, captopril was given in a prospective, randomized, double-blind, placebo-controlled study to 21 patients with stable exercise-induced angina and systolic arterial pressures greater than 120 mm Hg. Captopril increased exercise time (309 ± 137 vs 374 ± 142 sec, p < .05) without changing anginal threshold (rate-pressure product 17.0 ± 6.0 vs 17.1 ± 5.6 × 10⁻²). We conclude that captopril decreases mean arterial pressure without causing a reflex increase in myocardial sympathetic tone. By decreasing myocardial oxygen consumption, captopril may prove to be a useful adjunct to the antianginal drug regimens of patients with systolic arterial pressures greater than 120 mm Hg.


Most vasodilators decrease arterial pressure and thus myocardial work, but their antianginal efficacy is limited by reflex tachycardia.¹ ² Use of captopril has the advantage that it does not cause reflex tachycardia and in previous work we have shown that the drug decreased myocardial oxygen consumption when given to patients with congestive heart failure and coronary artery disease.³ We have recently shown that captopril decreases myocardial oxygen consumption when given to hypertensive patients with coronary artery disease.⁴ These effects may be the result of decreased myocardial sympathetic tone.⁵–¹² If this is true, captopril might prove useful in the treatment of patients with coronary artery disease.

To measure myocardial sympathetic activation in vivo in man, it is important to measure arterial concentra-

trations of epinephrine and norepinephrine and to measure myocardial norepinephrine balance (arterial–coronary sinus concentration times coronary sinus flow).¹³ Myocardial norepinephrine balance is the convergence of norepinephrine uptake and release in the heart and has been shown to more closely reflect myocardial sympathetic tone than levels of circulating catecholamines.¹³

In this study, arterial and coronary sinus epinephrine and norepinephrine concentrations were measured before and after giving captopril to 14 patients with moderate-to-severe exercise-induced angina. Also, the effects of captopril on exercise-induced angina were assessed in a further 21 patients.

Materials and methods

Part I — hemodynamic protocol. Fourteen patients (six women and eight men) with stable angina who responded poorly to treatment with calcium-entry blockers and with β-blockers and nitrates were selected for the study. Exclusion criteria included creatinine level of greater than 2 mg/dl, proteinuria of greater than 1 g/day, or presence of any immunologic disease. To avoid induction of hypotension, only patients with systolic arterial pressures greater than 120 mm Hg were enrolled in the study. The patients ranged in age 48 to 79 years and had experienced angina for 4 months to 14 years. Five patients had sig-
nificant obstructive lesions (≥50% stenosis) of the left anterior descending, left circumflex, and right coronary arteries; three had obstructive lesions of the left anterior descending and right coronary arteries and a single obstruction of the left anterior descending artery was present in three patients. All four patients who refused to undergo coronary arteriography had documented myocardial infarctions and stable angina. Six of the 14 patients had received β-blockers, nine had taken calcium-entry blockers, and 11 had been on nitrates. Diuretics, β-blockers, and calcium-entry blockers were discontinued at least 24 hr before the study, and nitrates were discontinued 12 hr before the study. Each patient gave informed written consent.

In each patient the right side of the heart was catheterized with a flow-directed, balloon-tipped No. 7 Swan-Ganz thermocatheter inserted percutaneously through the right subclavian vein to record right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP). With the same catheter, cardiac output (CO) was determined in triplicate by the thermocatheter technique. Arterial pressure was recorded directly by cannulating the radial artery. The hemodynamic variables were calculated as follows: SV = CO/HR, where SV = stroke volume and HR = heart rate; SWI = SVI × (MAP – PCWP) × 0.0136, where SWI = stroke work index, SVI = stroke volume index, and MAP = mean arterial pressure; SVR = (MAP – RAP)/CO × 80, where SVR = systemic vascular resistance.

Under fluoroscopic guidance, a No. 8 thermocatheter coronary sinus flow catheter (Wilton Webster Co., Altadena, CA) was placed in the coronary sinus through the left subclavian vein. To minimize coronary sinus reflex, the catheter was positioned under fluoroscopic control near the great cardiac vein. Coronary sinus flow was measured by the constant-infusion thermocatheter technique, and was calculated as (Tb – Ti/Tb – Tm) – 1 × 1.08 × 46 ml/min, where Tb = temperature of blood, Ti = temperature of injectate, Tm = temperature of mixture of blood and injectate, 1.08 = a constant accounting for specific heat and density of both blood and injectate, and 46 ml/min is the injection rate of the injectate (5% dextrose in water) through the Harvard constant-infusion pump. Arterial and coronary sinus blood samples were drawn simultaneously for the determination of oxygen saturation, oxygen content, and lactate concentration.

Lactate concentration was measured by the enzymatic fluorometric method of Loomis. Renin levels were measured by the New England Nuclear radioimmunoassay, and epinephrine and norepinephrine concentrations were measured by the radioenzymatic assay of Peuler and Johnson. Oxygen content was calculated as oxygen saturation times hemoglobin times 1.34. The arterial–coronary sinus oxygen difference (myocardial oxygen extraction, ART-CS DO₂) was calculated as arterial oxygen content – coronary sinus oxygen content. Myocardial oxygen consumption was calculated as (ART-CS DO₂) × CSF (ml/min) × 10, where CSF is coronary sinus flow. Myocardial lactate extraction was calculated as (ART lactate – CS lactate)/ART lactate × 100, where ART lactate = arterial lactate concentration (mg/100 ml) and CS lactate = coronary sinus lactate concentration (mg/100 ml). The myocardial norepinephrine and epinephrine balance was calculated as (arterial – coronary sinus concentrations) × CSF, and transmyocardial norepinephrine and epinephrine extractions were calculated as (arterial – coronary sinus concentrations)/arterial concentrations.

Once the baseline measurements were obtained, the patients received captopril in increasing doses of 6.25, 12.5, 25, 50, 100, 200, and 200 mg every hour until there was a greater than 10 mm Hg decrease in mean arterial pressure or until the second dose of 200 mg of captopril was given. At this time, systemic and coronary hemodynamic measurements along with arterial and coronary sinus blood sampling were repeated.

On completion of the study, catheters were removed and patients were allowed to become ambulatory gradually. During the remainder of the hospital stay, arterial pressures were measured before and at 30 and 60 min after administration of captopril. After discharge from the hospital, each patient was followed monthly in the cardiac clinic and received captopril in addition to his or her prestudy medications.

Part II — stress test protocol.

Patient population (Table 1). Twenty-two patients (two women and 20 men) with a mean age 58 ± 6 years (range 51 to 70) and with stable NYHA class II to III angina were selected for the study. Exclusion criteria included a creatinine level of greater than 2 mg/dl, proteinuria of greater than 1 g/day, and presence of any immunologic disease. To avoid induction of hypotension, only patients with systolic arterial pressures greater than 120 mm Hg were enrolled in the study. To ensure that each patient had angina that could be precipitated by exercise testing and to minimize the training effect, each patient underwent an exercise test after administration of vasodilators was discontinued for 48 hr and just before the study began. Of the 22 patients included in the study, only 21 completed the study because one patient could not tolerate the placebo. Before entering the study, 14 patients had received β-blockers, six had been on diuretics, 13 had taken long-acting nitrates, and six had received calcium-entry blockers. The mean resting systolic arterial pressure in the group was 142 ± 21 mm Hg and the mean resting heart rate was 72 ± 12 beats/min while off all medications except β-blockers and diuretics.

Medication and stress testing. Each patient gave informed, written consent. All vasodilators had been discontinued for at least 48 hr, and each patient received one-half of a tablet from bottle A, which contained either placebo or 12.5 mg doses of captopril. The patients then received one half tablet daily for 1 week. On day 7, if systolic arterial pressure remained greater than 100 mm Hg and if there had been no clinical deterioration, a full tablet from bottle A was given daily for 7 days. Seventeen of the 21 patients received full tablets of captopril and 20 of 21 patients received the full placebo tablets. On day 14, 45 min

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
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<tbody>
<tr>
<td>Patient characteristics: exercise stress test</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>Responders</td>
</tr>
</tbody>
</table>

Patients that had decreased systolic arterial pressure while on captopril of at least 10 mm Hg at rest and during exercise when compared with placebo.
after receiving medication A, each patient underwent a symptom-limited, modified Bruce exercise stress test during which heart rate and blood pressure were measured every minute until anginal threshold. The same protocol was followed during administration of medication B, and once the last patient completed the study, the code was broken. All stress tests were completed between 10 and 11 A.M., at least 3 hr after a light breakfast.

Statistical analysis. The data obtained before and after captopril were compared by a two-tailed paired t test. The data from the responders and nonresponders to captopril were compared by a two-tailed unpaired t test. The correlation between serum renin and the decrease in arterial pressure was assessed by linear regression. All reported values are mean ± SD unless otherwise specified.

Results

Hemodynamic protocol

Patient response. The patients received between 12.5 and 594 mg of captopril (mean 328 ± 235 mg). The responders (>10 mm Hg decrease in mean arterial pressure) received 127 ± 86 mg of captopril and the nonresponders 518 ± 142 mg. As expected, the decrease in arterial pressure was directly proportional to baseline renin value (figure 1). During the short-term study, no patient developed signs or symptoms of hypotension or cardiac ischemia. All 14 patients are still alive and their conditions are improved at a mean follow-up of 5.5 months (range 4 to 8 months) and only one patient has been readmitted for cardiac ischemia (nocturnal angina). At last follow-up, the mean NYHA class of the patients had improved from 3.0 ± 0.8 to 1.6 ± 0.8 (figure 2). Captopril therapy has been discontinued in only two patients, in one because of hypertensive symptoms and in one because of 5 g proteinuria that had been underestimated before captopril was administered. The long-term daily dose of captopril was 50 to 125 mg/day.

Systemic hemodynamics (table 1). The control mean arterial pressure in the patients we chose for study was slightly elevated because we wanted to avoid induction of hypotensive symptoms (inclusion criteria systolic arterial pressure >120 mm Hg). Captopril decreased mean arterial pressure without causing reflex tachycardia. As a result, the decrease in rate-pressure product was proportional to the decrease in arterial pressure.

After captopril stroke work index and the cardiac index were both slightly decreased, but pulmonary capillary wedge pressure was in the high normal range (14 ± 9 mm Hg). Captopril decreased systemic vascular resistance and stroke work index, but did not change cardiac index or pulmonary capillary wedge pressure.

Coronary hemodynamics (table 2; figure 3). Captopril decreased rate-pressure product (a major determinant of myocardial oxygen consumption), coronary sinus blood flow, and myocardial oxygen consumption. These changes were independent of whether or not the patients had been on β-blockers. The decrease in coronary sinus flow was not accompanied by a change in average myocardial oxygen extraction or in global myocardial lactate extraction (figure 3). Although captopril tended to improve lactate extraction in most patients, in two it seemed to cause reduced lactate extraction. In one of these two patients lactate extraction changed to production. This patient, whose angina was originally NYHA class II, underwent symptom-limit-
ed Naughton exercise stress test 4 days after starting captopril therapy. It was clinically and electrocardiographically negative up to 12 min when the patient had to stop because of leg fatigue. In the other patient myocardial lactate extraction decreased from 14% to 1%. He has had no effort-induced angina since the study but was readmitted after 4 months because of nocturnal angina that improved with the addition of 60 mg oral diltiazem three times a day to his drug regimen.

Transmyocardial catecholamine levels (table 3). Although captopril decreased arterial pressure, it did not cause a reflex increase in sympathetic tone. Captopril did not increase arterial epinephrine or norepinephrine concentrations, and more importantly it did not change myocardial norepinephrine balance. Myocardial epinephrine balance and extraction also remained unchanged.

Responders vs nonresponders (table 4; figure 4). In our study, patients with a decrease of greater than 10 mm Hg in mean arterial pressure were defined as responders to captopril; seven patients were responders and seven were nonresponders. The responders had higher renin values compared with the nonresponders (Fig. 4). The control arterial blood pressures (111 ± 23 vs 108 ± 17 mm Hg) and the heart rates (76 ± 15 vs 75 ± 11 beats/min) were the same in both groups and there was no difference with respect to any of the other control systemic or coronary hemodynamic variables in the two groups. The responders tended to have higher resting myocardial sympathetic tone than did the nonresponders. Myocardial norepinephrine balance was higher in the responders and coronary sinus norepinephrine concentrations also tended to be higher in this group (p < .1) (table 4).

With the addition of captopril, there was a decrease in systemic vascular resistance in the responders (671 ± 408 dynes-sec-cm⁻²) as well as an increase in cardiac index (0.3 ± 0.1 liter/min/m²); these effects were not noted in the nonresponders. Captopril decreased rate-pressure product and myocardial oxygen consumption in responders, but not in nonresponders. The response of all other variables to the addition of captopril was the same in both groups. It should be noted, however, that the difference in net transmyocardial concentration of norepinephrine observed before captopril became insignificant after the drug (table 5).

A persistent decrease in arterial pressure of greater
than 10 mm Hg was noted in both groups within 48 hr of reinstituting diuretics and/or vasodilators. This may explain why the addition of captopril had long-term antianginal effects in both groups.

**Stress test protocol.** Twelve patients received captopril as tablet A, and 10 patients received captopril as tablet B. Captopril increased exercise tolerance (309 ± 137 vs 374 ± 142 sec, p < .05) but did not change anginal threshold (rate-pressure product 17.0 ± 6.0 vs 17.1 ± 5.6 × 10^{-3}).

The increase in exercise tolerance was limited to those patients in whom captopril decreased systolic arterial pressure greater than 10 mm Hg at rest and throughout the stress test (responders) (figures 5 and 6). The concomitant use of β-blockers or a decrease in resting systolic arterial pressure only did not predict which patients would improve their exercise tolerance while on captopril, but as expected four of the six patients receiving diuretics responded favorably to captopril.

**Discussion**

Despite significantly decreasing arterial blood pressure, captopril did not cause reflex tachycardia or increase myocardial sympathetic activation. These results contrast with those of other commonly used vasodilators, such as hydralazine, that cause a marked reflex tachycardia and can worsen angina.1,2 Even the calcium-entry blockers nifedipine and verapamil have recently been shown to increase myocardial sympathetic activation while decreasing arterial pressure.21 In our study, the antianginal efficacy of captopril resulted from a decrease in myocardial oxygen consumption.

### TABLE 3

**Changes in coronary hemodynamics after captopril**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Response to Captopril</th>
<th>HR × BP (mm Hg/min × 10^{-3}) Control</th>
<th>HR × BP (mm Hg/min × 10^{-3}) Captopril</th>
<th>CSF (ml/min) Control</th>
<th>CSF (ml/min) Captopril</th>
<th>MVO_2 (ml/min) Control</th>
<th>MVO_2 (ml/min) Captopril</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>R</td>
<td>19.2</td>
<td>13.3</td>
<td>117</td>
<td>78</td>
<td>15.5</td>
<td>9.6</td>
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<tr>
<td>2</td>
<td>NR</td>
<td>15.5</td>
<td>14.9</td>
<td>142</td>
<td>91</td>
<td>13.5</td>
<td>7.5</td>
</tr>
<tr>
<td>3</td>
<td>NR</td>
<td>13.4</td>
<td>13.0</td>
<td>144</td>
<td>142</td>
<td>12.1</td>
<td>12.9</td>
</tr>
<tr>
<td>4</td>
<td>R</td>
<td>11.6</td>
<td>8.8</td>
<td>81</td>
<td>76</td>
<td>8.1</td>
<td>7.9</td>
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<tr>
<td>5</td>
<td>NR</td>
<td>9.4</td>
<td>11.2</td>
<td>45</td>
<td>51</td>
<td>4.3</td>
<td>5.0</td>
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<tr>
<td>6</td>
<td>NR</td>
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<td>7.5</td>
<td>40</td>
<td>43</td>
<td>4.7</td>
<td>4.8</td>
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<tr>
<td>7</td>
<td>NR</td>
<td>14.8</td>
<td>12.5</td>
<td>126</td>
<td>126</td>
<td>11.4</td>
<td>11.4</td>
</tr>
<tr>
<td>8</td>
<td>R</td>
<td>20.3</td>
<td>18.4</td>
<td>144</td>
<td>142</td>
<td>16.0</td>
<td>16.0</td>
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<tr>
<td>9</td>
<td>R</td>
<td>12.2</td>
<td>11.6</td>
<td>114</td>
<td>115</td>
<td>10.1</td>
<td>10.2</td>
</tr>
<tr>
<td>10</td>
<td>NR</td>
<td>12.4</td>
<td>11.4</td>
<td>107</td>
<td>93</td>
<td>10.1</td>
<td>9.0</td>
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<tr>
<td>11</td>
<td>R</td>
<td>13.3</td>
<td>10.1</td>
<td>203</td>
<td>137</td>
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<td>11.2</td>
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<tr>
<td>12</td>
<td>R</td>
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<td>8.8</td>
<td>74</td>
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<td>8.4</td>
<td>7.9</td>
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<tr>
<td>13</td>
<td>NR</td>
<td>10.6</td>
<td>10.2</td>
<td>50</td>
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<td>9.1</td>
<td>9.8</td>
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<tr>
<td>14</td>
<td>R</td>
<td>10.4</td>
<td>8.7</td>
<td>68</td>
<td>53</td>
<td>7.0</td>
<td>5.3</td>
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<tr>
<td>Mean</td>
<td></td>
<td>13.0</td>
<td>11.5</td>
<td>98</td>
<td>84</td>
<td>9.7</td>
<td>8.2</td>
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<tr>
<td>±SD</td>
<td></td>
<td>±3.5</td>
<td>±2.9</td>
<td>±47</td>
<td>±39</td>
<td>±4.1</td>
<td>±2.7</td>
</tr>
</tbody>
</table>

R = responders to captopril (> 10 mm Hg decrease in mean arterial pressure); NR = nonresponders to captopril; HR × BP = rate — pressure product; CSF = coronary sinus flow; ART-CS DO_2 = myocardial oxygen extraction; MVO_2 = myocardial oxygen consumption.

*Patients on β-blockers before the study

*Values are mean ± SD.

### TABLE 4

**Changes in transmyocardial catecholamine balance**

<table>
<thead>
<tr>
<th>Arterial norepinephrine (nM)</th>
<th>Coronary sinus norepinephrine (nM)</th>
<th>Myocardial norepinephrine balance (pmol/min)</th>
<th>Arterial epinephrine (nM)</th>
<th>Coronary sinus epinephrine (nM)</th>
<th>Myocardial epinephrine balance (pmol/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.7±2.1</td>
<td>4.5±2.9</td>
<td>216±254</td>
<td>0.38±0.28</td>
<td>0.25±0.22</td>
</tr>
<tr>
<td>Captopril</td>
<td>2.8±2.1</td>
<td>4.2±2.7</td>
<td>146±170</td>
<td>0.34±0.25</td>
<td>0.28±0.19</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
due to a decrease in arterial pressure and a lack of reflex myocardial sympathetic activation.

We found a linear relationship between circulating renin levels and the decrease in arterial pressure caused by captopril. In the short-term hemodynamic study, the average dose of captopril given was higher than that normally given for two reasons. First, the nonresponders received large doses of captopril to ensure that they were truly nonresponders, and second, although the dose given to the responders was much smaller (127 ± 86 mg), it would have been even smaller if our end point of a 10 mm Hg decrease in mean arterial pressure had not been strictly enforced. Most responders had a decrease in mean arterial pressure of at least 5 mm Hg after 25 mg of captopril, but we continued to double the dose until a 10 mm Hg decrease in mean arterial pressure was achieved.

After the short-term study, when captopril was added to the antianginal drug regimen of patients with low or normal renin levels, it caused a significant (>10 mm Hg) decrease in arterial pressure. By withholding diuretics and vasodilators before the study, we may have artificially decreased circulating renin below prestudy levels and when these drugs were reintroduced, captopril may have inhibited restimulation of the renin-angiotensin system. This would also explain why patients with low renin levels and minor changes in arterial pressure during the short-term study also improved with the addition of captopril during the long-term study. In the stress test study, the frequencies of use of β-blockers (14 of 21 patients) and diuretics (six of 21 patients) may help explain why only 10 of 21 patients had significant decreases in systolic arterial pressure.

In the hemodynamic study our patients improved significantly when captopril was added to their drug regimens. Although antianginal efficacy was only assessed by a subjective NYHA classification, the apparent improvement was remarkable and probably represents a true beneficial effect. Although we could not measure regional coronary blood flow or metabolism after captopril, myocardial oxygen consumption decreased overall and myocardial metabolism did not deteriorate. In the stress test study, only those patients in whom rate-pressure product decreased had improved exercise tolerance, suggesting that a decrease in myocardial oxygen consumption is the major antianginal mechanism of captopril. Indeed, of all the antianginals, captopril was the only one to show a marked decrease in myocardial oxygen consumption. 

### TABLE 5
Comparison of transmyocardial catecholamine balance in responders and nonresponders

<table>
<thead>
<tr>
<th></th>
<th>Arterial epinephrine (nM)</th>
<th>Arterial norepinephrine (nM)</th>
<th>Coronary sinus Norepinephrine (nM)</th>
<th>Myocardial norepinephrine balance (pmol/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>control</td>
<td>0.37 ± 0.19</td>
<td>2.9 ± 1.6</td>
<td>5.7 ± 3.1</td>
<td>362 ± 291&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>captopril</td>
<td>0.39 ± 0.26</td>
<td>3.2 ± 1.7</td>
<td>5.3 ± 3.1</td>
<td>187 ± 176</td>
</tr>
<tr>
<td><strong>Nonresponders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>control</td>
<td>0.40 ± 0.47</td>
<td>2.4 ± 1.3</td>
<td>3.3 ± 2.3</td>
<td>69 ± 68</td>
</tr>
<tr>
<td>captopril</td>
<td>0.39 ± 0.26</td>
<td>2.4 ± 1.2</td>
<td>3.7 ± 2.3</td>
<td>79 ± 132</td>
</tr>
</tbody>
</table>

Responders are patients in whom mean arterial pressure decreased more than 10 mm Hg. Values are mean ± SD.

<sup>a</sup>p < .05 for responders vs nonresponders.
FIGURE 5. Effect of captopril on tolerance to exercise to anginal threshold in patients that responded and did not respond to captopril. Only those patients responding to captopril (decrease in systolic arterial pressure on captopril of at least 10 mm Hg at rest and during exercise as compared with placebo) had an increase in their exercise tolerance. \( \Delta - \Delta = \text{mean exercise time.} \) *p < .05 for placebo vs captopril.

FIGURE 6. Effect of captopril on rate-pressure product (heart rate \( \times \) systolic arterial pressure \( \times 10 \)) at rest, after 3 min of exercise, and at anginal threshold. Captopril decreased the rate-pressure product of the responders to captopril at rest and after 3 min of exercise, but did not change rate-pressure product at anginal threshold. The nonresponders had a decrease in resting rate-pressure product but this decrease disappeared during exercise. *p < .05 for captopril vs placebo; **p < .01 for captopril vs placebo.
into the arterial inflow of vasoically isolated, neurally intact dogs causes a marked pressor effect that is blocked by \( \alpha \)-adrenergic blockers.\(^5\) Also, angiotensin II increases catecholamine release from the adrenal medulla, facilitates norepinephrine release from vascular adrenergic nerve endings, and also may inhibit norepinephrine uptake by these nerve endings.\(^5\) Furthermore, angiotensin-converting enzyme inhibitors have been shown to decrease hypoxia-stimulated norepinephrine release in dogs\(^7\) and captopril has been shown to decrease elevated circulatory catecholamine levels in severely hypertensive patients.\(^6\) Finally, decreased baroreceptor sensitivity, an important modulator of sympathetic tone, could be a possible mechanism.

Captopril may also decrease anginal attacks by improving myocardial oxygen supply. Angiotensin II causes sustained vasoconstriction of the large conductive coronary arteries, but only transient vasoconstriction of the small resistive vessels.\(^8\) In sodium-depleted dogs, Liang and Gavras have shown that during hypoxia the angiotensin-converting enzyme inhibitor teprotide increases coronary blood flow and coronary sinus oxygen content, suggesting that teprotide causes coronary vasodilation. In patients with normal coronary arteries, Faxon et al.\(^9\) found that teprotide could increase coronary sinus flow, but only in patients with elevated renin levels. Because an \( \alpha \)-adrenergic coronary vasoconstricting effect remains despite metabolic vasodilatation,\(^10\) captopril may further improve coronary blood flow to ischemic areas by inhibiting reflex myocardial sympathetic tone. The findings by Ertl et al.\(^11\) that captopril improves regional myocardial blood flow to ischemic areas and decreases the size of experimentally produced myocardial infarctions in dogs suggests that the overall effect of captopril on ischemic areas is beneficial. In our stress test protocol, captopril did not change rate-pressure product at anginal threshold. However, this does not rule out possible beneficial effects of captopril on daily variations of vasomotor tone.

In conclusion, captopril decreases mean arterial pressure without causing a reflex increase in myocardial sympathetic tone. By virtue of the fact that it decreases myocardial oxygen consumption, captopril may prove a useful adjunct to the antiangiinal drug regimen of patients with systolic arterial pressures greater than 120 mm Hg.

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References
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