Response of the Systemic and Pulmonary Circulation to Converting-enzyme Inhibition (Captopril) at Rest and During Exercise in Hypertensive Patients

ROBERT FAGARD, M.D., CHRISTOPHER BULPITT, M.D., PAUL LIJNEN, PH.D., AND ANTOON AMERY, M.D.

SUMMARY Twenty sodium-replete patients with hypertension were allocated either to a placebo or to a captopril treatment group. Each patient was investigated in rest-recumbent (RR) and rest-sitting (RS) positions and during an uninterrupted, graded, submaximal exercise test (up to the anaerobic threshold) before treatment, and with a similar protocol 75 minutes after treatment with captopril or placebo on the same morning. Captopril decreased brachial intraarterial pressure by 7/4 mm Hg at RR, by 16/10 mm Hg at RS, and by 19/10 mm Hg during exercise (p < 0.001), based on a decrease of systemic vascular resistance (p < 0.001). Slight increases of cardiac output and of heart rate were noted at rest; cardiac output was not significantly affected during exercise, but the increase of heart rate of 2.4 beats/min was significant (p < 0.01). Captopril decreased pulmonary artery (p < 0.05) and capillary wedge pressures (p < 0.001), with unchanged pulmonary vascular resistance.

The data indicate that the action of captopril is characterized by arteriolar and possibly venous dilatation both at rest and during exercise. Pulmonary vascular resistance, however, is not affected.

INTERFERENCE with the renin-angiotensin system by either angiotensin II antagonists or converting-enzyme inhibitors indicates that the role of angiotensin II in maintaining arterial pressure depends on the prevailing plasma levels of renin or angiotensin II, which vary with sodium state and physical activity. The role of angiotensin appears to be insignificant in recumbent, sodium-replete normotensive persons,1-8 but angiotensin II does seem to contribute to the arterial pressure of some normal subjects in the sitting position,4 and during exercise.1 During sodium restriction of sufficient degree, angiotensin II antagonists and converting-enzyme inhibitors lower arterial pressure at any level of physical activity.2-8

In hypertensive patients, plasma renin levels vary widely and do determine the response to angiotensin antagonists and converting-enzyme inhibitors, which is enhanced by sodium depletion.8-11 The hypotensive effect of these agents is based on a decrease of systemic vascular resistance in most subjects;12-19 cardiac output usually is not changed, but increases with converting-enzyme inhibitors16-18 and decreases with angiotensin antagonists14 have been reported. These effects have not been studied during exercise.

We report the hemodynamic effects of captopril1 (2-D-methyl-mercaptopropionyl-L-proline; SQ 14225; Squibb Institute for Medical Research) at rest and during exercise in hypertensive patients. The study was restricted to sodium-replete patients because a single dose of sodium may produce adverse hypotension after sodium depletion.4, 22
Patients and Methods

Patients

Twenty patients with hypertension were studied and allocated to either a placebo or a captopril treatment group after stratification for age, sex, type of hypertension and control brachial intraarterial pressure at rest-recumbent (RR). Their characteristics are given in table 1. Each patient gave informed consent. The diagnosis was based on history, physical examination, appropriate laboratory tests and an i.v. pyelogram. A renal arteriogram and renal vein blood sampling for measurement of plasma renin activity were performed when indicated. All patients were admitted to the hospital and had not taken antihypertensive drugs for at least 3 weeks. They were on a diet that contained approximately 110 mEq of sodium per day.

Protocol

The hemodynamic studies were performed in the morning, after a light breakfast, in a laboratory where room temperature was 18–22°C and humidity 40–60%. The brachial artery was punctured to measure intraarterial pressure (BAP) and to sample arterial blood. A 6F venous catheter (Swan-Ganz) was introduced in the antecubital vein and positioned in the pulmonary artery to sample mixed venous blood. The venous catheter was positioned so that pulmonary capillary wedge pressure (PCWP) was measured when the balloon near its tip was inflated, and pulmonary artery pressure (PAP) when the balloon was deflated. Pressures were registered on a recorder (Mingograph 81) using Elema-Schönander EMT 34 pressure transducers. Uptake of oxygen (\(\text{VO}_2\)) and carbon dioxide output (\(\text{VCO}_2\)) were measured continuously by the open-circuit method; minute-volume (\(\dot{V}_E\)), oxygen and carbon dioxide levels were determined with a pneumotachograph, a paramagnetic oxygen analyzer and an infrared carbon dioxide analyzer (Siregnost FD 84, Siemens). The ventilatory equivalent for oxygen (\(\text{V}^{*}_E/\text{VO}_2\)) and the respiratory gas exchange ratio (R) were monitored continuously. Cardiac output (CO) was determined by the direct-oxygen Fick method. Systemic vascular resistance (SVR) was calculated from mean brachial arterial pressure (MBAP), obtained by electrical damping, and CO, and pulmonary vascular resistance (PVR) from mean pulmonary artery (MPAP) and capillary wedge pressures (MPCWP) and CO. Heart rate (HR) was recorded from the ECG. Stroke volume (SV) was calculated from CO and HR.

After catheters were inserted, the patients remained recumbent and a first set of measurements was obtained after 45 minutes (RR). The patients were seated on the bicycle and measurements were performed 10 minutes later (rest-sitting [RS]). A graded, uninterrupted exercise test was then started at a work load of 20 W for 4 minutes. The load was increased by 30 W every 4 minutes until \(\dot{V}_E/\text{VO}_2\) increased, i.e., one step above the anaerobic threshold;\(^2\) pressures and HR were recorded at every step, but CO was determined every other step and at the final work load.

After the first exercise test (control), the patients regained the recumbent position. Ten patients were given a placebo and 10 were given 25 mg of captopril orally. The RR measurements were obtained 75 minutes later. The patients were again seated on the bicycle for 10 minutes (RS) and performed an identical exercise test. The final work load averaged 101 ± 6 W in the placebo treated group and 104 ± 9 W in the captopril group, with R values of 1.01 ± 0.03 and 0.98 ± 0.02 respectively.

Biochemical determinations were done on arterial blood. Plasma renin activity (PRA) was determined by the method of Fyhrquist and Puutula\(^24\) and plasma catecholamines were determined according to a radioenzymatic method.\(^25\)

Statistical Analysis

To compare the data after treatment (placebo or captopril) with the control data within each of the two

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of Patients</th>
<th>Captopril-treated</th>
<th>Placebo-treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>41.3 ± 4.5</td>
<td>43.1 ± 3.9</td>
</tr>
<tr>
<td>Sex: male/female (n)</td>
<td>7/3</td>
<td>8/2</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>71.3 ± 4.0</td>
<td>77.2 ± 3.0</td>
</tr>
<tr>
<td>Recumbent blood pressure on admission to hospital (mm Hg)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>177.8 ± 7.9</td>
<td>179.8 ± 10.9</td>
</tr>
<tr>
<td>Diastolic</td>
<td>110.2 ± 4.2</td>
<td>110.5 ± 7.6</td>
</tr>
<tr>
<td>ECG (n)</td>
<td>Normal 9</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Left ventricular hypertrophy 1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Left bundle branch block 0</td>
<td>1</td>
</tr>
<tr>
<td>Cardiothoracic ratio on chest x-ray (%)*</td>
<td>46.4 ± 0.7</td>
<td>46.6 ± 1.6</td>
</tr>
<tr>
<td>Eye-fundus (Keith-Wagener-Barker grade) (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)*</td>
<td>100.0 ± 10.6</td>
<td>117.1 ± 8.9</td>
</tr>
<tr>
<td>Type of hypertension (n)</td>
<td>Essential 8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal parenchymal disease 0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Renal artery stenosis 2</td>
<td>1</td>
</tr>
<tr>
<td>Urinary sodium excretion (mEq/24 hr)*</td>
<td>103 ± 17</td>
<td>113 ± 22</td>
</tr>
</tbody>
</table>

*Mean ± SEM.
There were no significant differences for any of the characteristics between the two groups.
groups, three-way analysis of variance** was used, considering levels of physical activity, subjects, and treatment, and their interactions as sources of variance. Only the effects of treatment and interactions between treatment and levels of physical activity are discussed.

For comparison between the two groups, the effects of captopril were compared with the effects of placebo. When a significant interaction was present between treatment and levels of physical activity, the results are presented separately according to whether the subjects were resting or exercising. If there was no significant interaction, the effects of placebo and of captopril are compared for all data.

Results

Hemodynamic Data

Analysis of Data Within Each Group

The data (mean ± SEM) for systolic and diastolic BAP, CO, SVR, SV and HR of both the placebo and the captopril-treated group are given in figures 1–3 at RR, RS and the various work loads. The figures indicate the significance of the effect of treatment and of the interaction between treatment and levels of activity.

Captopril significantly reduced systolic BAP and diastolic BAP ($p < 0.001$), SVR ($p < 0.001$) and SV ($p < 0.01$), did not change CO, and slightly increased HR ($p < 0.05$). Placebo significantly reduced systolic BAP ($p < 0.001$), CO ($p < 0.001$), SV ($p < 0.05$) and HR ($p < 0.001$), did not change diastolic BAP and increased SVR ($p < 0.001$). There were significant interactions between treatment and physical activity for systolic BAP ($p < 0.05$) and diastolic BAP ($p < 0.01$) in the captopril-treated group and for CO ($p < 0.05$), SVR ($p < 0.01$) and HR ($p < 0.05$) in the placebo group.

Overall MBAP decreased from 125 to 112 mm Hg ($p < 0.001$) with captopril and from 124 to 122 mm Hg ($p < 0.001$) with placebo. The interaction between treatment and levels of activity was not significant for the placebo group, but it was for captopril ($p < 0.001$). MBAP during exercise was 13 ± 0.4 mm Hg greater than the sitting pressure during captopril, which was significantly different from the 16-mm Hg rise for the control data ($p < 0.001$); in the placebo group, the increase during placebo was not different from the control measurements ($p > 0.2$).

MPAP and PCWP (fig. 4) did not change in the placebo group, but significantly decreased in the captopril-treated group ($p < 0.001$). PVR increased significantly in the placebo group (from 1.45 to 1.61 mm Hg/l/min; $p < 0.001$) and in the captopril-treated group (from 1.32 to 1.52 mm Hg/l/min; $p < 0.001$). There were no significant interactions between treatment and activity for MPCWP, MPAP and PVR, except for PVR in the captopril-treated group ($p < 0.05$).

Comparison of Data Between Groups

The comparison of the effects of captopril with those of placebo is shown in table 2. A separate analysis of resting and exercise data was done for systolic and diastolic BAP, MBAP, SVR, CO, HR and PVR because interactions between treatment and activity were significant in at least one of the two groups; the interactions were not significant for resting or exercise data taken separately. The comparison was performed on all data combined for SV, MPAP and MPCWP because the effects of captopril and of placebo on these variables were independent of levels of activity.

This comparison indicates that the reductions of systolic and diastolic BAP, MBAP and SVR during
captopril are significantly different \( p < 0.001 \) from the changes of these variables during placebo, both at rest and during exercise. In resting conditions, the reduction of CO during placebo was less pronounced \( p < 0.05 \) during captopril, but CO behaved similarly in both groups during exercise. While the effects on SV did not differ between the two groups, HR was statistically higher during captopril both at rest \( p < 0.001 \) and during exercise \( p < 0.01 \), though the differences were very small.

Both MPAP \( p < 0.05 \) and MPCRWP \( p < 0.01 \) show greater decreases during captopril than during placebo treatment, while PVR behaved similarly in both groups of patients.

**Biochemical Data**

Figure 5 is a summary of the data for PRA and for plasma noradrenalin levels. Captopril significantly increased PRA \( p < 0.001 \), while placebo had no effect; the changes during captopril were significantly different from those during placebo \( p < 0.001 \). Plasma noradrenalin levels were not different from control in either group.

**Discussion**

To avoid repetitive introduction of catheters, the study was performed in one session. But the long terminal half-life of captopril implied that the control observations had to precede the observations during captopril. Therefore, the exercise test was kept submaximal, i.e., at one level of 30 W above the anaerobic threshold,\(^a\) and a placebo-treated group was included to consider any daytime variation in hemodynamics, any effect of the first exercise test on subsequent observations, e.g., by extravasation of fluid and further adaptation of the patient to the

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**Table 2. Means (± SEM) of the Differences Between the Averages Before and After Treatment for the Captopril- and Placebo-treated Groups**

<table>
<thead>
<tr>
<th>Measurements where the effects of captopril or of placebo differ according to levels of activity</th>
<th>At rest</th>
<th>During exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Captopril</td>
<td>Placebo</td>
</tr>
<tr>
<td>( \Delta SBAP ) (mm Hg)</td>
<td>-16.6 ± 2.2</td>
<td>-5.1 ± 2.0</td>
</tr>
<tr>
<td>( \Delta DBAP ) (mm Hg)</td>
<td>-7.2 ± 0.8</td>
<td>-0.1 ± 0.4</td>
</tr>
<tr>
<td>( \Delta MBAP ) (mm Hg)</td>
<td>-9.9 ± 1.1</td>
<td>-2.3 ± 1.1</td>
</tr>
<tr>
<td>( \Delta SVR ) (mm Hg/l/min)</td>
<td>-1.50 ± 0.73</td>
<td>+2.55 ± 0.46</td>
</tr>
<tr>
<td>( \Delta CO ) (l/min)</td>
<td>-0.18 ± 0.20</td>
<td>-0.92 ± 0.27</td>
</tr>
<tr>
<td>( \Delta HR ) (beats/min)</td>
<td>+1.42 ± 0.68</td>
<td>-5.53 ± 0.93</td>
</tr>
<tr>
<td>( \Delta PVR ) (mm Hg/l/min)</td>
<td>+0.25 ± 0.08</td>
<td>+0.23 ± 0.04</td>
</tr>
</tbody>
</table>

**Measurements where the effects of captopril and of placebo are independent of levels of activity**

<table>
<thead>
<tr>
<th></th>
<th>All data</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Captopril</td>
<td>Placebo</td>
<td>( p )</td>
</tr>
<tr>
<td>( \Delta SV ) (ml/beat)</td>
<td>-3.83 ± 1.30</td>
<td>-3.26 ± 1.38</td>
<td>NS</td>
</tr>
<tr>
<td>( \Delta MPAP ) (mm Hg)</td>
<td>-0.71 ± 0.20</td>
<td>-0.05 ± 0.28</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>( \Delta MPWP ) (mm Hg)</td>
<td>-1.86 ± 0.22</td>
<td>-0.42 ± 0.24</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviations: \( \Delta \) = change; SBAP = systolic brachial artery pressure; DBAP = diastolic brachial artery pressure; MBAP = mean brachial artery pressure; SVR = systemic vascular resistance; CO = cardiac output; HR = heart rate; PVR = pulmonary vascular resistance; SV = stroke volume; MPAP = mean pulmonary artery pressure; MPWP = mean pulmonary capillary wedge pressure.
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It is not possible to determine which factors were responsible for these hemodynamic changes at rest after placebo. However, arterial pressure was held rather constant in the face of a decreased CO by a raised SVR. The mechanism of the latter is not clear; neither plasma noradrenaline nor plasma renin had increased. Whatever the cause of these differences, the hemodynamic pattern of the hypotensive effect of converting enzyme inhibition at rest is difficult to interpret. Several studies have been performed at rest and consistently report a reduction of SVR, 14-16 in accordance with our present data. The acute or short-term effects of converting enzyme inhibition on CO indicate no change, 14-16 or an increase. 4 The present data are compatible with a slight increase. Its effects on HR are controversial; in some studies, 4, 11, 27 it has increased and in others it has not changed. 4, 18, 19, 27, 29 possibly related to the magnitude of the hypotensive effect. 29 The present study suggests a slight increase of HR at rest.

When the data at RR are taken separately, allowing for the changes during placebo, captopril decreased arterial pressure by 7/4 mm Hg. This could suggest that the renin angiotensin system has a small role in the maintenance of arterial pressure in sodium-replete hypertensive patients with average normal renin levels. However, captopril may have other hypotensive effects; indeed, the converting enzyme is responsible not only for the conversion of angiotensin I to angiotensin II, but also for the degradation of bradykinin, the accumulation of which may decrease arterial pressure.

Captopril has not previously been studied at exercise. Our findings indicate that its hypotensive effect is somewhat more pronounced during exercise than at rest. This suggests that the role of angiotensin II in maintaining arterial pressure becomes more important with physical activity or that accumulation of bradykinin is greater during exercise. However, no information is available on the behavior of bradykinin at exercise; the suggestion on the role of angiotensin seems justified, because similar observations have

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Stroke volume and heart rate at rest-sitting (RS), during graded exercise and at final work load before (control) and during captopril or placebo treatment. Data are mean ± SEM. Statistical analysis was performed by three-way analysis of variance. F = effect of treatment; F = interaction between treatment and levels of activity. *p < 0.05; **p < 0.01; ***p < 0.001.

Laboratory conditions. Several differences did emerge in the placebo-treated group. At the second test, systolic BAP was significantly lower, but only by 5 mm Hg; SVR was higher and CO lower, associated with slight decreases of both HR and of SV. However, these differences were most pronounced in resting conditions and not significant during exercise.

![Figure 4](http://circ.ahajournals.org/)

**Figure 4.** Mean pulmonary artery pressure and capillary wedge pressures at rest-sitting (RR), at rest-sitting (RS), during graded exercise and at the final work load before (control) and during captopril or placebo treatment. Data are mean ± SEM. Statistical analysis was performed by three-way analysis of variance. F = effect of treatment; F = interaction between treatment and levels of activity. *p < 0.05; **p < 0.01; ***p < 0.001.
been done when the renin-angiotensin system was blocked with a different approach, i.e., by the use of the angiotensin II antagonist saralasin in normotensive subjects at rest and during exercise.\(^1\)\(^6\) The hypertensive effect of captopril during exercise was based on a decrease of SVR, in agreement with the data on saralasin.\(^1\)\(^6\) This suggests that the formation of angiotensin II during exercise tends to increase the resistance to blood flow through arteriolar constriction, counteracting to some degree the local vasodilatation in the working muscles or contributing to the observed increased resistance in the nonworking muscles and in other vascular beds. The observations on exercise CO and SV during captopril were not different from the data during placebo. We observed, however, a slight but statistically significant increase of HR, which averaged 2.4 beats/min when the data during placebo are taken into consideration; the physiologic significance of this finding, however, is questionable. Saralasin affected neither CO nor SV or HR.\(^1\)\(^6\) This absence of overt tachycardia in the face of a decreased SVR has intrigued several investigators, and angiotensin II may be required for normal functioning of the baroreceptor reflexes. The peripheral facilitating effects of angiotensin II on the automatic nervous system have been well documented\(^9\) so that blocking the effects of angiotensin II may interfere with normal function of this system. Moreover, saralasin produces blockade of the adrenergic-potentiating effects of angiotensin II.\(^3\)\(^1\) The absence of an increase of plasma noradrenalin in response to arteriolar dilatation may be in agreement with this interpretation. Angiotensin II causes tachycardia,\(^8\) so inhibition of this increase of HR may have contributed to counteracting the reflex baroreceptor-induced tachycardia. Furthermore, a reduction in atrial pressure\(^18\) may have been involved as a result of the Bainbridge reflex.

Captopril reduced PCWP at all levels of physical activity, and this may have been caused by unloading of the left ventricle by the decrease of arterial pressure, pooling of blood by arteriolar or mainly venous dilatation, or both. Venous dilatation might explain the unchanged SV by a reduction of venous return, whereas an increase could be expected in response to the arteriolar dilatation. In contrast to the clear decrease of SVR at rest and during exercise in response to captopril, the behavior of PVR in the captopril group was not different from that in the placebo group. In previous studies at rest, angiotensin II antagonists\(^1\)\(^2\)\(^3\)\(^\) and converting-enzyme inhibition\(^18\)\(^3\) did not affect PVR except for teprotide, which acutely reduced PVR in patients with acute hypertension after coronary bypass surgery.\(^2\)\(^4\)

Converting-enzyme inhibition produced a rise of PRA both at rest, as reported previously, and during exercise. This may be due to the decrease of arterial pressure or to interruption of the negative feedback loop of angiotensin II on renal renin secretion.

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