Effect of captopril on renal vascular tone in patients with essential hypertension

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Summary

1. The effect of acute inhibition of angiotensin-converting enzyme by captopril (50 mg) on renal haemodynamics and function was assessed in nine patients with essential hypertension on unrestricted sodium intake (n = 8) or low sodium diet (n = 1).

2. Captopril induced a rapid and significant decrease in arterial pressure, which was maximal within 60 min.

3. Effective renal plasma flow (ERPF) increased, glomerular filtration rate (GFR) did not change and filtration fraction (FF) decreased after captopril. No change in sodium excretion and a decrease in urinary potassium occurred.

4. In the patient on low sodium diet, captopril induced striking increases in GFR and ERPF (64 and 106% respectively).

5. The logarithm of baseline plasma renin activity was positively correlated with the change in ERPF and negatively correlated with changes in FF and renal resistance.

6. The results indicate that in patients with essential hypertension angiotensin participates actively in the maintenance of renal vascular tone at the efferent arteriolar level. A possible influence of kinins remains to be defined.

Key words: captopril, essential hypertension, renal blood flow, renin.

Abbreviations: ERPF, effective renal plasma flow; FF, filtration fraction; GFR, glomerular filtration rate; MAP, mean arterial pressure; PRA, plasma renin activity.

Introduction

The relationship between the renin concentration and renal haemodynamics is unclear. Whereas some groups found an inverse relationship between renal blood flow and renin secretion (Blaufax, Fromowitz, Lee, Meng & Elkin, 1970), a positive correlation between renin concentration and renal blood flow as obtained by others (Schalekamp, Schalekamp-Kuyken & Birkenhäuser, 1970; Pedersen & Kornerup, 1976).

The availability of angiotensin inhibitors has made it possible to study the role of renin in the regulation of renal function in animals (Mimran, Guiod & Hollenberg, 1974) and man (Hollenberg, Williams, Taub, Ishikawa, Brown & Adams, 1977). Recently the orally active angiotensin-converting enzyme inhibitor SQ 14 225 (captopril) was shown to be effective in long-term treatment of hypertension (Brunner, Gavras, Waeber, Kershaw, Turini, Vukovich, McKinstry & Gavras, 1979).

The purpose of this study was to assess the effect of captopril on renal haemodynamics and function in patients with essential hypertension.

Patients and methods

Patients

Studies were conducted in nine patients, eight women and one man, aged 17–56 years. After usual laboratory and radiological investigations (arteriography was performed in seven patients and was within normal limits), it was established that they had essential hypertension. All had minimal or no retinal abnormality, normal renal function and no sign of heart failure. The known duration of hypertension ranged from 7 to 120 months.
Hypertension was permanent in five patients and labile in four.

All antihypertensive therapy was withdrawn at least 2 weeks before the study and the patients were maintained on an unrestricted sodium intake, except in one patient who was given a sodium restricted diet for 4 days before the investigation.

**Protocol**

The patients were kept recumbent throughout the study, which started at 08.00 hours. Arterial pressure was measured every 2 min with an Arteriosonde Roche (model 1217) and heart rate was continuously recorded with an ECG monitor.

Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were estimated by a constant-infusion technique, employing as reference substance $\text{o}^{-111}\text{I}$iodohippurate and $\text{I}^{-125}$ labelled sodium iothalamate (Amersham Radiochemicals). Timed urine collections were obtained via a bladder catheter.

After determination of two 20 min control clearances, one 50 mg tablet of captopril (SQ 14 225, Squibb Laboratories, Princeton, NJ, U.S.A.) was given and a 20 min period was allowed for absorption of the compound. It has been previously shown that after swallowing one 20 mg captopril tablet, nearly complete inhibition of the effect of exogenous angiotensin I on arterial pressure was produced at 15 min, which lasted for more than 2 h (Ferguson, Turini, Brunner & Gavras, 1977).

Subsequently, renal clearances were determined during four periods of 20 min each between the minutes 20 and 100 after captopril administration. Sodium and potassium were determined in each urine collection. Plasma renin activity (PRA) was measured before, 60 min and 100 min after captopril.

**Analytical methods**

The two control renal clearances were averaged (control value) as well as the two determinations obtained between minutes 20 and 60 (E$_1$) and minutes 60 and 100 (E$_2$) after captopril administration. Clearances were proportioned by conversion into 1.73 m$^2$ body surface area.

Filtration fraction (FF) was expressed as GFR/ERPF. Renal resistance was calculated as the ratio of mean arterial pressure (MAP) to renal blood flow [ERPF/(1 − packed cell volume)].

PRA was estimated by radioimmunoassay (Brunner et al., 1979) (normal range in recumbent subjects on unrestricted sodium diet: 0.40–1.9 pmol h$^{-1}$ ml$^{-1}$).

Results are expressed as means ± SEM.

**Results**

The effects of captopril on arterial pressure, and renal haemodynamics of the eight patients maintained on an unrestricted sodium intake are shown in Table 1.

Arterial pressure progressively decreased by 2.3 ± 0.9, 5.2 ± 0.9, 6.8 ± 1.2 and 8.8 ± 1.8% (range 1.1–17.3%) at 20, 40, 60 and 100 min respectively after captopril administration. Heart rate was 87 ± 4 beats/min before captopril and 93 ± 5 beats/min (N.S.) at the end of the study. PRA rose from a control value of 1.2 ± 0.4 to 13.9 ± 6.9 pmol h$^{-1}$ ml$^{-1}$ (P < 0.05).

A significant increase in ERPF of 11.8 ± 4% (range 6–33%) (P < 0.01) occurred after captopril, and calculated renal resistance decreased by 16.4 ± 4.1% (P < 0.01) from a control value of 0.14 ± 0.02 mmHg min$^{-1}$ ml$^{-1}$. GFR and urinary sodium excretion as well as fractional sodium excretion (control value 1.13 ± 0.26%) were not altered by captopril.

**Table 1. Effect of captopril on mean arterial pressure (MAP) and renal function in eight patients with essential hypertension on unrestricted sodium intake**

<table>
<thead>
<tr>
<th></th>
<th>MAP (mmHg)</th>
<th>GFR (ml/min)</th>
<th>ERPF (ml/min)</th>
<th>FF</th>
<th>$U_{Na}V$ (µmol/min)</th>
<th>$U_{e}V$ (µmol/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>119 ± 9</td>
<td>130 ± 4</td>
<td>518 ± 34</td>
<td>0.26 ± 0.02</td>
<td>183 ± 39</td>
<td>70-11</td>
</tr>
<tr>
<td>Period E$_1$</td>
<td>111 ± 8*</td>
<td>122 ± 5*</td>
<td>556 ± 43*</td>
<td>0.23 ± 0.02*</td>
<td>181 ± 42*</td>
<td>49 ± 11**</td>
</tr>
<tr>
<td>(% change)</td>
<td>−6.8 ± 1.2</td>
<td>−6 ± 3.7</td>
<td>+9.8 ± 1</td>
<td>−13.4 ± 3.3</td>
<td>−1.2 ± 10</td>
<td>−32 ± 9</td>
</tr>
<tr>
<td>Period E$_2$</td>
<td>109 ± 8**</td>
<td>129 ± 7**</td>
<td>582 ± 47**</td>
<td>0.23 ± 0.02*</td>
<td>160 ± 30**</td>
<td>40 ± 6**</td>
</tr>
<tr>
<td>(% change)</td>
<td>−8.8 ± 1.8</td>
<td>−1.4 ± 2.9</td>
<td>+11.8 ± 4</td>
<td>−11.3 ± 2.6</td>
<td>−3 ± 13</td>
<td>−38 ± 8</td>
</tr>
</tbody>
</table>
In the patient on restricted sodium intake, MAP decreased by 19% and GFR and ERPF rose by 64 and 106% respectively; urinary sodium excretion and fractional sodium excretion increased from 4 to 16 \(\mu\text{mol/min}\) and 0.04 to 0.10% respectively. PRA rose from 4.5 to 28.7 pmol h\(^{-1}\) ml\(^{-1}\). In this patient the response to captopril was markedly enhanced compared with the responses in the group of subjects on normal sodium intake. No significant correlation between the logarithm of pretreatment PRA and induced change in mean arterial pressure was obtained \((r = -0.64, P < 0.10)\). However, when the results obtained in patients on normal sodium intake were considered \((n = 8)\), there was a significant correlation between log PRA and the percentage change in ERPF \((r = 0.77, P < 0.025)\), the percentage change in renal resistance \((r = -0.70, P < 0.05)\) and the relative variation of FF \((r = -0.69, P < 0.05)\) induced by captopril.

**Discussion**

In patients with essential hypertension maintained on unrestricted sodium intake, acute administration of captopril was associated with an increase in renal plasma flow, the magnitude of which was positively correlated with baseline PRA. In addition, since GFR was not altered, filtration fraction fell in all patients and the relative change in FF was inversely correlated with control PRA. These results suggest that even in patients with normal renin concentrations angiotensin participates in the regulation of renal vascular tone and more precisely at the level of the efferent arterioles of the glomeruli. Our findings contrast with those of Schalekamp et al. (1970) and Pedersen & Kornerup (1976), who found negative correlations between plasma renin concentration and renal plasma flow or filtration fraction. Indeed, the approach of the problem through angiotensin blockade may seem more realistic. However, the role of other factors needs to be evaluated. Captopril induced a significant decrease in arterial pressure and filtration fraction and an increase in renal plasma flow in normal renin patients. So far, no convincing evidence discounts an effect of systemic or intrarenal accumulation of bradykinin secondary to inhibition of kininase II, which is similar to angiotensin-converting enzyme (Erdös, 1976).

Urinary sodium excretion as well as fractional excretion of sodium were not significantly modified after captopril. Since filtration fraction fell, changes in peritubular hydrostatic and oncotic pressures would be expected to result in a decrease in sodium reabsorption. However, the fall of arterial pressure may have blunted this expected consequence. Acute administration (present study) and chronic treatment with captopril (Brunner et al., 1979) did not result in sodium retention, a known consequence of vasodilator therapy.

Of interest is the rapid effect on arterial pressure (significant within 20 min and near maximum within 60 min) and the lack of change in pulse rate after captopril. This observation, which is similar to that made during saralasin-induced systemic vasodilatation, remains unclear.

The main finding of the present study is that angiotensin contributes to the regulation of renal vascular tone in patients with essential hypertension. Renal vasodilatation as well as the lack of sodium retention resulting from captopril administration may be very useful in therapeutic strategy.

**References**


