Renal Vasodilation by Converting Enzyme Inhibition
Role of Renal Prostaglandins

JUAN A. OLIVER, M.D., ROBERT R. SCIACCA, ENG.SC.D. AND PAUL J. CANNON, M.D.

SUMMARY The present study was designed to determine whether renal prostaglandins are involved in the renal vasodilation evoked by angiotensin II inhibition in sodium depletion. The converting enzyme inhibitor (CEI) captopril was administered to sodium-depleted control dogs and sodium-depleted dogs that had previously received the inhibitors of prostaglandin synthesis, indomethacin or meclofenamate. CEI in control dogs increased renal blood flow (RBF) from a mean value of 220 to 309 ml/min (p < 0.01) and decreased renal vascular resistance (RVR) from 0.64 to 0.38 arbitrary resistance units (ru) (p < 0.01). Renal venous prostaglandin E2 (PGE2) concentration also increased from 52 to 85 pg/ml (p < 0.01). In the dogs that received inhibitors of prostaglandin synthesis, RBF fell from 214 to 168 ml/min (p < 0.01), RVR increased from 0.61 to 0.82 ru (p < 0.05), and renal venous PGE2 fell from 114 to 20 pg/ml (p < 0.01). The subsequent administration of captopril increased RBF from 168 to 221 ml/min (p < 0.01), lowered RVR from 0.82 to 0.43 ru (p < 0.01), but failed to significantly increase renal venous PGE2 (20 to 25 pg/ml). The decrease in RVR induced by captopril was not significantly different in the control dogs and in the dogs with prostaglandin synthesis inhibition. However, in the control dogs RBF after captopril was significantly higher than during the control period; this was not the case in the dogs with prostaglandin synthesis inhibition. RBF after captopril and prostaglandin inhibition was not significantly different from RBF during the control period. The results indicate that the acute renal vasodilator effect of captopril in sodium depletion does not require renal prostaglandins; however, the level of RBF after captopril is dependent upon renal prostaglandins, suggesting that endogenous prostaglandins increase renal blood flow when angiotensin II is inhibited. The results confirm previous studies indicating that captopril increases renal PGE2 synthesis. (Hypertension 5: 166-171, 1983)

KEY WORDS • captopril • renal blood flow • sodium depletion

In sodium depletion, inhibitors of the converting enzyme (CEI) decrease the plasma concentration of angiotensin II and markedly increase renal blood flow (RBF). Since angiotensin II is a potent renal vasoconstrictor, the renal vasodilation evoked by its inhibition during sodium depletion has been postulated to be due to elimination of its renal vasoconstrictor action. However, in previous studies from this laboratory and other laboratories, RBF in animals with moderate sodium depletion with increased plasma renin activity (PRA) has not been found to be different from that of sodium-replete animals with suppressed PRA.

It has been shown that RBF during sodium depletion is maintained by enhanced renal prostaglandin synthesis which attenuates the effect of vasoconstrictor mechanisms. Accordingly, the renal vasodilator evoked by blockade of the generation of angiotensin II in sodium depletion could be mediated, at least in part, by vasodilator prostaglandins. This possibility was explored in the present study in which the effect of captopril upon RBF was examined in sodium depleted dogs during control conditions and after inhibition of prostaglandin synthesis.

Methods

Experimental Preparation

The experiments were performed in 31 mongrel dogs of either sex in which dietary sodium depletion was induced by the administration of 10 mg of furose-
The RBF was measured with an electromagnetic flow-tance units (ru).

Inhibition of Converting Enzyme by Captopril

Blood samples were collected. Each animal was then catheterized into the right atrium for the collection. In all instances aortic and renal vein bloods were obtained in triplicate as previously described. The RBF was determined with an electromagnetic flow probe of appropriate diameter (Carolina Medical Electronics, King, North Carolina). The RBF was measured with an electromagnetic flow-meter as previously described. Through a right jugular vein, a catheter was introduced into the right atrium for the administration of indocyanine dye solution. Cardiac output was determined in triplicate as previously described. Through a left flank incision and retroperitoneal dissection, the left renal artery was dissected and fitted with a flow probe of appropriate diameter (Carolina Medical Electronics, King, North Carolina). The RBF was measured with an electromagnetic flow-meter as previously described. Through a left ovarian/testicular vein, a small catheter was introduced in retrograde fashion into the left renal vein for blood collection. In all instances aortic and renal vein bloods were obtained simultaneously.

Total peripheral and renal vascular resistances (RVR) were calculated as the ratio of mean arterial pressure (mm Hg) to cardiac output (liter/min) or RBF (ml/min) respectively, and expressed in arbitrary resistance units (ru).

Specific Protocols

Inhibition of Converting Enzyme by Captopril

Sixteen sodium-depleted dogs were utilized for this protocol. At least 1 hour after surgery was allowed for equilibration of the preparation before control measurements of cardiac output, arterial blood pressure, and RBF were made and arterial and renal venous blood samples were collected. Each animal was then given an intravenous injection of 0.4 mg/kg of captopril dissolved in 10 ml of 0.9% saline followed by a continuous infusion of 0.4 μg.kg⁻¹.min⁻¹ for the remainder of the experiment. This dose of captopril has been previously shown to effectively block the blood pressure and RBF effect of an intravenous bolus of 200 ng/kg of angiotensin I. After stabilization of the blood pressure and RBF recordings (20 to 30 minutes later), hemodynamic measurements and blood collections were repeated.

Inhibition of Converting Enzyme by Captopril During Prostaglandin Synthesis Inhibition

Fifteen dogs with dietary sodium depletion were utilized in this experiment. After baseline hemodynamic determinations and blood collections, 5 mg/kg of indomethacin (n = 10), prepared as previously described, or 4 mg/kg of meclofenamate (n = 5) dissolved in 0.9% saline, was administered intravenously as a bolus injection. Twenty to 30 minutes later, hemodynamic measurements and blood collections were repeated. Finally, a bolus intravenous injection of 0.4 mg/kg of captopril dissolved in 10 ml of 0.9% saline was administered followed by a continuous infusion of 0.4 μg.kg⁻¹.min⁻¹ for the remainder of the experiment. Final hemodynamic measurements and blood collections were performed 20 to 30 minutes later. Since the results for all quantities measured were similar with both prostaglandin inhibitors, the data were pooled for statistical evaluation.

Statistical Analysis

All values are expressed as means ± SEM. Data were analyzed by analysis of variance or by paired t test. Differences were termed significant if the F or t value exceeded the critical value for the 5% level.

Results

Effect of Inhibition of the Converting Enzyme During Sodium Depletion

Table 1 depicts the systemic and renal hemodynamic responses to blockade of the converting enzyme by captopril in a group of sodium-depleted dogs. Administration of captopril resulted in a significant decrease in mean arterial pressure from 131 to 111 mm Hg (p < 0.01) and a decrease in total peripheral vascular resistance.

\[
\begin{array}{cccccc}
\text{Period} & \text{MAP (mm Hg)} & \text{CO* (liter/min)} & \text{TPVR* (ru)} & \text{RBF (ml/min)} & \text{RVR (ru)} & \text{PRA (ng ml⁻¹ hr⁻¹)} \\
\text{Control} & 131 ± 3 & 3.55 ± 0.29 & 40.9 ± 3.6 & 220 ± 15 & 0.64 ± 0.06 & 26.4 ± 4.6 \\
\text{CEI} & 111 ± 3 & 3.90 ± 0.39 & 31.9 ± 4.5 & 309 ± 15 & 0.38 ± 0.03 & 54.7 ± 9.2 \\
\hline
\text{p} & <0.01 & \text{ns} & <0.05 & <0.01 & <0.01 & <0.01 \\
\end{array}
\]

\(n = 16\) except * where \(n = 9\). Values are mean ± SEM. CEI = converting enzyme inhibition with captopril; MAP = mean arterial pressure; CO = cardiac output; TPVR = total peripheral vascular resistance in arbitrary resistance units (ru); RBF = renal blood flow; RVR = renal vascular resistance in arbitrary resistance units (ru); PRA = plasma renin activity.
Effect of Inhibition of Converting Enzyme During Sodium Depletion and Inhibition of Prostaglandin Synthesis

Table 2 depicts the systemic and renal hemodynamic responses to inhibition of prostaglandin synthesis and subsequent administration of captopril in a group of sodium-depleted dogs. Administration of prostaglandin synthesis inhibitors had no significant effect on mean arterial pressure, cardiac output, or total peripheral vascular resistance. Prostaglandin synthesis inhibition, however, significantly reduced RBF from 214 to 168 ml/min ($p < 0.01$) and increased RVR from 0.61 to 0.82 RU ($p < 0.05$). The subsequent administration of captopril lowered mean arterial pressure from 129 to 105 mm Hg ($p < 0.01$) and total peripheral vascular resistance from 54.9 to 37.0 RU ($p < 0.05$). Captopril also induced a marked renal vasodilation with RBF increasing from 168 to 221 ml/min ($p < 0.01$) and RVR falling from 0.82 to 0.43 RU ($p < 0.01$). The RBF and RVR after captopril were not significantly different than their corresponding control values. Table 2 also shows that following captopril administration there was a significant increase in arterial PRA.

Figure 2 depicts the change in plasma concentration of PGE$_2$ in arterial and renal venous blood in this group of sodium-depleted dogs. During control conditions, the plasma concentration of PGE$_2$ in renal venous blood was significantly greater than that in arterial blood (114 ± 42 vs 30 ± 9 pg/ml; $p < 0.05$). Administration of inhibitors of prostaglandin synthesis sig-

Table 2. Effect of Converting Enzyme Inhibition with Captopril in Sodium Depletion During Prostaglandin Synthesis Inhibition

<table>
<thead>
<tr>
<th>Period</th>
<th>MAP (mm Hg)</th>
<th>CO* (liter/min)</th>
<th>TPVR* (RU)</th>
<th>RBF (ml/min)</th>
<th>RVR (RU)</th>
<th>PRA (ng/ml⁻¹·hr⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>128 ± 3</td>
<td>2.77 ± 0.27</td>
<td>51.1 ± 5.5</td>
<td>214 ± 10</td>
<td>0.61 ± 0.03</td>
<td>38.0 ± 7.4</td>
</tr>
<tr>
<td>PGSI</td>
<td>129 ± 3</td>
<td>2.62 ± 0.25</td>
<td>54.9 ± 6.4</td>
<td>168 ± 13</td>
<td>0.82 ± 0.09</td>
<td>34.0 ± 7.0</td>
</tr>
<tr>
<td>CEI</td>
<td>105 ± 5</td>
<td>3.05 ± 0.32</td>
<td>37.0 ± 4.6</td>
<td>221 ± 13</td>
<td>0.43 ± 0.03</td>
<td>133 ± 18.1</td>
</tr>
<tr>
<td>$p$ (PGSI vs control)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>ns</td>
</tr>
<tr>
<td>$p$ (CEI vs PGSI)</td>
<td>&lt;0.01</td>
<td>ns</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>ns</td>
</tr>
<tr>
<td>$p$ (CEI vs control)</td>
<td>&lt;0.01</td>
<td>ns</td>
<td>&lt;0.05</td>
<td>ns</td>
<td>ns</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

n = 15 except * where n = 8. Values are mean ± SEM. PGSI = prostaglandin synthesis inhibition. All other abbreviations as in table 1.
significantly lowered renal venous PGE$_2$ to 20 ± 3 pg/ml ($p < 0.01$). Figure 2 also shows that administration of captopril during blockade of prostaglandin synthesis had no significant effect on the plasma concentration of PGE$_2$ in arterial (19 ± 3 pg/ml) or renal venous blood (25 ± 6 pg/ml).

Table 3 depicts the changes in mean arterial pressure, RBF, and RVR induced by captopril during control conditions and during blockade of renal prostaglandin synthesis. The acute blood-pressure-lowering effect of captopril was unaffected by inhibition of prostaglandin synthesis. Mean arterial blood pressure fell by 20 mm Hg after captopril in the control dogs while it fell by 24 mm Hg in the dogs receiving prostaglandin synthesis inhibitors. The increase in RBF induced by captopril in the control dogs (88 ml/min) was significantly greater than that produced during inhibition of prostaglandin synthesis (58 ml/min). However, this difference was not apparent when the increase in RBF was expressed as a percentage change. Moreover, as also shown in table 3, the decrease in RVR induced by captopril was not significantly different in the two groups of animals.

**Discussion**

The purpose of the present study was to determine whether the renal vasodilation induced by inhibition of angiotensin II generation during sodium depletion is mediated by renal prostaglandins. Accordingly, the inhibitor of the angiotensin-converting enzyme, captopril, was administered to sodium-depleted dogs under control conditions and following administration of indomethacin or meclofenamate. In agreement with a previous study from this laboratory, indomethacin and meclofenamate significantly decreased the concentration of PGE$_2$ in renal vein plasma (see fig. 2), suggesting effective inhibition of renal prostaglandin synthesis.

In the present study, acute converting-enzyme inhibition with captopril markedly increased RBF and decreased RVR in sodium-depleted dogs (table 1). These results are in agreement with previous work in sodium-depleted rats and with studies with teprotide. In the dogs that received indomethacin or meclofenamate, captopril evoked similar renal hemodynamic changes; RBF was increased and RVR decreased (table 2). Comparison of the renal vascular effects of captopril between the control dogs and the dogs with inhibition of prostaglandin synthesis revealed a decrease in RVR of similar magnitude (see table 3). The absolute increase in RBF evoked by captopril was slightly but significantly greater in the control dogs than in the dogs with prostaglandin synthesis inhibition (table 3). However, immediately prior to the administration of captopril, the dogs with prostaglandin inhibition had a lower RBF than the dogs that only received captopril (see tables 1 and 2); when the increase in RBF induced by captopril was expressed as a percentage change, no difference was seen in the RBF responses between the two groups (table 3). In the aggregate, these results indicate that the acute renal vasodilator effect of captopril during sodium depletion is not dependent upon renal prostaglandins. These results are in agreement with previous observations by Wong and coworkers; and Tobia and Giardino who demonstrated that administration of prostaglandin synthesis inhibitors had no significant effect on the renal vasodilation caused by captopril in dogs with nonhypotensive hemorrhage and in normal dogs.

Administration of angiotensin II antagonists or of inhibitors of angiotensin II generation consistently elicits increases in RBF in sodium-depleted animals, but has little or no effect in sodium repletion. These observations have been taken as evidence that angiotensin II-induced renal vasconstriction is characteristic of sodium depletion and that the level of RBF after angiotensin II inhibition in sodium depletion reproduces the RBF that existed during the sodium replete state (with suppressed renin-angiotensin system). However, in previous studies from this and other laboratories, RBF in animals with moderate sodium depletion (with increased PRA) was found to be not significantly different from that of sodium-replete ani-

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**Table 3. Changes in Mean Arterial Pressure, Renal Blood Flow, and Renal Vascular Resistance Induced by Captopril in Control Dogs and Dogs with Prostaglandin Synthesis Inhibition**

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 16)</th>
<th>PGSI (n = 15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>−20 ± 3</td>
<td>−24 ± 3</td>
<td>ns</td>
</tr>
<tr>
<td>%</td>
<td>−15 ± 2</td>
<td>−19 ± 2</td>
<td>ns</td>
</tr>
<tr>
<td>RBF (ml/min)</td>
<td>+88 ± 11</td>
<td>+58 ± 8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>%</td>
<td>+44 ± 6</td>
<td>+45 ± 12</td>
<td>ns</td>
</tr>
<tr>
<td>RVR (ru)</td>
<td>−0.26 ± 0.04</td>
<td>−0.39 ± 0.09</td>
<td>ns</td>
</tr>
<tr>
<td>%</td>
<td>−37 ± 4</td>
<td>−40 ± 4</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. For number of experiments and abbreviations, see tables 1 and 2.
mals with suppressed PRA. In the present study, although captopril increased RBF and decreased RVR in the dogs with inhibited prostaglandin synthesis, the level of RBF after captopril was not significantly different from that during the control period, prior to the administration of indomethacin and meclofenamate (see fig. 3). This contrasts markedly with the situation in the control dogs where RBF after captopril was significantly higher than RBF during the control period (see table 1 and fig. 3). The simplest explanation for these results is that the increase in RBF above the control value during angiotensin II blockade in sodium depletion is due to a vasodilator action of renal prostaglandins that is only evidenced during inhibition of angiotensin II. Since renal prostaglandin synthesis is increased during sodium depletion and was further increased by captopril, the augmentation of RBF after administration of captopril observed in the present study may reflect the vascular effect of prostaglandins in response to both these stimuli.

A study of Wong and Zimmerman supports the contention that, during angiotensin II inhibition, endogenous prostaglandins may increase RBF. In their study, moderate hemorrhage in the dog increased PRA and renal prostaglandin synthesis but had no effect on renal hemodynamics. However, when hemorrhage was induced during blockade of angiotensin II with saralasin, along with the increase in renal prostaglandin synthesis, there was an increase in RBF. Thus, in a manner similar to that of angiotensin II (the renal vasoc constriction of which is not fully expressed unless renal prostaglandin synthesis is inhibited), the effect of endogenous prostaglandins to increase RBF is only evidenced during inhibition of angiotensin II.

The present study also shows that administration of captopril in sodium-depleted dogs is associated with a significant increase in the renal venous plasma concentration of PGE, (fig. 1). As the release of prostaglandins reflects de novo biosynthesis, these results suggest that renal PGE, synthesis was increased after captopril administration. This observation is consistent with some previous studies. Vinci et al. showed an increase in the arterial concentration of immunoreactive prostaglandin after administration of teprotide to hypertensive patients. More recently, Swartz et al. and Moore et al. have reported that the peripheral plasma concentrations of 13,14-dihydro-15-keto PGE, a metabolite of PGE, is increased following administration of captopril to normal subjects and to hypertensive patients. In contrast, Olsen and Arrigoni-Martelli and Barr et al. found that administration of captopril to sodium-depleted dogs and teprotide to normal rats, respectively, did not change urinary excretion of PGE,.

Whether the increased renal PGE, synthesis in response to captopril was a direct effect of the drug or an indirect effect is unknown. Recently, Galler et al. showed that captopril enhances the synthesis of PGE, and, to a lesser degree, of PGI, by isolated renal glomeruli. Similarly, in preliminary studies, captopril has been reported to increase the synthesis of PGE, in renomedullary interstitial cells in culture and the synthesis of PGI, in isolated aortic strips. Captopril may also increase renal PGE, synthesis indirectly. One possibility is that captopril may increase renal prostaglandin synthesis by its effect on endogenous kinins. Captopril has been shown to increase plasma and urinary kinins in sodium-depleted dogs, and bradykinin is a potent stimulus for renal prostaglandin synthesis. Another possible stimulus for prostaglandin synthesis is norepinephrine released by renal sympathetic nerves. Renal venous norepinephrine increases markedly after captopril and renal nerve stimulation or norepinephrine may stimulate synthesis of prostaglandins.

In several recent studies, inhibitors of prostaglandin synthesis partially blunted the hypotensive effect of converting-enzyme inhibition with captopril. In the present study, however, captopril acutely lowered blood pressure to a similar extent in the control dogs and in the dogs previously treated with indomethacin or meclofenamate (see table 3). This result is in agreement with the observation of Goldstone et al. that prostaglandin inhibition has no effect in the hypotension induced by captopril in sodium depletion. Moreover, it is possible these different results could be due to dissimilar time sequences used in the different protocols since Provoost has shown that inhibitors of prostaglandin synthesis blunt the late hypotensive effect of captopril but, in agreement with the results of this study, had no effect on its acute action.

In summary, the present study demonstrates that the inhibitor of the converting enzyme captopril induced a decrease in RVR in sodium-depleted dogs that was not significantly altered by blockade of renal prostaglandin synthesis, indicating that the captopril-induced renal vasodilation is not dependent upon renal prostaglandins. However, the level of blood flow following captopril in sodium-depleted dogs is dependent upon intact renal prostaglandin synthesis and appears to be a reflection of the vascular action of an enhanced renal prostaglandin synthesis. The administration of captopril increased renal PGE, synthesis; the significance of this finding remains to be clarified.

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References


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