Renal Effects of Angiotensin II Inhibition During Increases in Renal Venous Pressure

Mary J. Fiksen-Olsen, David M. Strick, Hope Hawley, and Juan Carlos Romero

Increases in renal venous pressure have been shown to consistently increase renal interstitial pressure; however, not until renal interstitial pressure is increased threefold is a natriuresis noted in normal animals. Since the intrarenal angiotensin II (Ang II) concentration has been postulated to increase with increasing renal venous pressure, the antinatriuretic action of Ang II could override the natriuretic effect of increased renal interstitial pressure. Therefore, the role of Ang II in the natriuretic response to increased renal venous pressure was examined in 10 pentobarbital-anesthetized dogs. Mean arterial pressure, renal blood flow, renal interstitial pressure, glomerular filtration rate, urinary sodium excretion, plasma renin activity, and prostaglandin E$_2$ excretion were measured at renal venous pressures of 3, 15, and 30 mm Hg. The measurements were repeated after the administration of captopril (1 mg/kg i.v. bolus, n=5) or [Sar$^2$,Ile$^5$]Ang II (50 μg/kg i.v. bolus+50 μg/kg/hr infusion, n=5). Under control conditions, mean arterial pressure, renal blood flow, plasma renin activity, and prostaglandin E$_2$ excretion remained unchanged when renal venous pressure was increased. The elevations in renal venous pressure increased renal interstitial pressure from 7±2 to 12±2 and 22±4 mm Hg, while sodium excretion remained unchanged until renal venous pressure was 30 mm Hg. In the captopril-treated group, increasing renal venous pressure increased renal interstitial pressure as under control conditions; however, sodium excretion (23±4, 19±4, and 27±6 μeq/min) was not significantly increased even at the highest renal venous pressure. In the presence of [Sar$^2$,Ile$^5$]Ang II, increasing renal venous pressure increased renal interstitial pressure as before administration of the antagonist while sodium excretion did not change significantly (7±3, 7±2, and 16±4 μeq/min), even at the highest renal venous pressure. The withdrawal or inhibition of Ang II failed to potentiate the natriuretic effect of increased renal interstitial pressure at renal venous pressures of 15 and 30 mm Hg. The inability of the kidney to maintain the glomerular filtration rate at high venous pressures may have contributed to the lack of natriuresis. (Hypertension 1992;19[suppl II]:II-137-II-141)
accurately reflected by measurements of systemic plasma renin activity (PRA), may inhibit natriuresis. This study, therefore, was undertaken to determine if suppression of intrarenal Ang II generation by a converting enzyme inhibitor (captopril) or blockade of Ang II receptors with an Ang II antagonist ([Sar''Ile'']Ang II) would facilitate the natriuresis at small to moderate elevations of RVP.

Methods

Ten dogs (body weight 16–20 kg) of either sex were anesthetized with 30 mg/kg i.v. pentobarbital sodium, intubated, and mechanically ventilated with room air by a respirator (Harvard Apparatus, South Natick, Mass.); the minute volume was selected by reference to the nomogram of Kleinman and Radford. A femoral artery was cannulated for continuous measurement of mean arterial pressure (MAP) using a pressure transducer (Pd23ID, Statham, Hato Rey, Puerto Rico) connected to a polygraph (2600, Gould, Cleveland, Ohio). A femoral vein was cannulated for infusion of inulin (a 2% solution in saline) at 1 ml/min and supplemental anesthesia as necessary. The dog was then placed in a metal frame that held it in a position approximating the normal standing position. The left kidney was exposed through a flank incision. A noncannulating electromagnetic flow probe (Carolina Medical Electronics, Inc., King, N.C.) was placed on the renal artery at its origin from the aorta. A Blalock clamp was placed on the renal vein for controlling RVP, and a 21-gauge curved needle connected to polyethylene (PE) tubing and a pressure transducer (8750, Micro Switch, Freeport, Ill.) was inserted into the renal vein between the clamp and the kidney for measurement of RVP. The ureter was cannulated with PE-200 tubing to facilitate urine collection. A polyethylene-matrix capsule was placed in the middle cortex and attached to a pressure transducer (8750, Micro Switch) for measurement of renal cortical interstitial hydrostatic pressure.

The animals were allowed to equilibrate for 1 hour before control clearances were measured at normal RVP and RVP of 15 and 30 mm Hg. At each pressure a 15-minute stabilization period preceded two consecutive 15-minute clearance periods. After the last measurement, the clamp was released and RVP was allowed to return to normal. Five dogs received captopril (1 mg/kg bolus) administered intravenously, and the remaining five animals received an intravenous infusion of the Ang II receptor blocker [Sar''Ile'']Ang II (50 μg/kg bolus followed by a continuous infusion of 50 μg/kg/hr). After a 30-minute stabilization period, two 15-minute clearance periods were again obtained at normal RVP and RVP of 15 and 30 mm Hg.

MAP, RVP, renal cortical interstitial hydrostatic pressure, and renal blood flow (RBF) were continuously recorded. The zero reference point for MAP was the midheart level. The zero reference points for RVP and RIP were the levels of the renal vein needle and capsule, respectively. Urine was collected during each clearance period for measurement of flow rate and the sodium, inulin, and prostaglandin E2 (PGE2) concentrations. Blood was withdrawn from the femoral artery catheter at the midpoint of each clearance period for measurement of plasma sodium and inulin concentrations, hematocrit, and PRA. UNaV, fractional sodium excretion, and urinary excretion of PGE2 were calculated.

Sodium concentrations were measured using a flame photometer (IL 943, Instrumentation Laboratories, Inc., Lexington, Mass.). Inulin concentrations were analyzed using the anthrone method, and the clearance of inulin was used to calculate the glomerular filtration rate (GFR). Urinary PGE2 concentrations were measured using a commercial radioimmunoassay kit (Du Pont, Billerica, Mass.). PRA was determined by the generation of angiotensin I (NEA-105, Du Pont).

The data are expressed as mean±SEM for each maneuver. A randomized-block analysis of variance followed by the Newman-Keuls test when appropriate was used to evaluate the statistical significance of the results. Results were considered significant at p<0.05.

Results

During control conditions neither MAP nor RBF in either group of animals was affected by increasing RVP to 15 or 30 mm Hg (Figure 1). GFR was
unaltered by changes in RVP in one group; however, GFR decreased approximately 36% in the second group when RVP was increased to 30 mm Hg (Figure 1). Renal cortical interstitial hydrostatic pressure increased in a virtually identical manner in both groups of animals in response to RVP reaching 15 and 30 mm Hg. The parallel and nearly equal increases in RIP in animals showing no change or even a decrease in GFR suggest that the observed increases in RIP are primarily the result of increasing venous congestion and not renal tubule dilation (Figure 2). UNaV was unaffected by a RVP of 15 mm Hg but increased significantly by the same magnitude in both groups when RVP was increased to 30 mm Hg despite the decreased GFR in one group. Urinary PGE₂ excretion did not change in response to the increased RVP, nor was PRA altered in either group (Table 1) by these maneuvers.

After administration of either compound neither captopril nor [Sar¹, Ile⁸]Ang II had any effect on MAP at normal RVP, and MAP was not altered as RVP was increased (Figure 1). RBF was increased significantly by administration of [Sar¹, Ile⁸]Ang II; however, RBF was not altered further by renal venous constriction. GFR remained depressed in the group of dogs treated with [Sar¹, Ile⁸]Ang II, even at normal RVP. In contrast to control conditions, GFR remained unaltered as RVP increased. Administration of captopril tended to increase GFR slightly at normal RVP and RVP of 15 mm Hg. However, the most profound effect was observed when increasing RVP to 30 mm Hg decreased GFR by approximately 50%. In both groups, RIP returned to baseline after the renal venous occlusion was released (Figure 2). Increasing RVP increased RIP in a parallel manner in animals treated with captopril or [Sar¹, Ile⁸]Ang II, and the increases at elevated pressures were similar to the responses observed before administration of the drugs. UNaV, which had returned to the respective baseline levels in each group after release of the control renal venous occlusions, was unaffected by increasing RVP in the presence of either antagonist. The administration of either captopril or [Sar¹, Ile⁸]Ang II decreased the excretion rate of PGE₂ (Table 1), which remained depressed in response to the venous congestion. PRA increased in the [Sar¹, Ile⁸]Ang II-treated group (Table 1) when RVP reached 30 mm Hg, while no changes were observed in the captopril-treated group.

Discussion

The results of the present study show that increasing RVP causes pressure-dependent increases in RIP and UNaV in the presence of constant renal perfusion pressure and autoregulated RBF. Blockade of the renin-angiotensin system during increasing RVP

Table 1. Effect of Changes in Renal Venous Pressure on Plasma Renin Activity and Urinary Excretion of Prostaglandin E₂

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=5)</th>
<th>Inhibitor present (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal venous pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Captopril</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA (ng Ang I/ml/hr)</td>
<td>1.8±0.4</td>
<td>2.2±0.6</td>
</tr>
<tr>
<td>UPGE₂ (ng/min)</td>
<td>5.4±2.1</td>
<td>5.3±2.2</td>
</tr>
<tr>
<td>[Sar¹, Ile⁸]Ang II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA (ng Ang I/ml/hr)</td>
<td>3.3±1.3</td>
<td>6.9±3.1</td>
</tr>
<tr>
<td>UPGE₂ (ng/min)</td>
<td>4.3±2.4</td>
<td>3.5±2.2</td>
</tr>
</tbody>
</table>

PRA, plasma renin activity; Ang I, angiotensin I; UPGE₂, urinary excretion of prostaglandin E₂; Ang II, angiotensin II.

* p<0.05 compared with previous value.
had no effect on RIP; however, UNaV was significantly depressed, showing that it can be altered independently of changes in RIP and suggesting that intrarenal Ang II may be necessary for renal sodium excretion under some physiological conditions.

Before administration of either antagonist, MAP and RBF were well regulated over the range of experimental RVP. The maintenance of constant RBF during decreasing effective renal perfusion pressures demonstrates efficient renal vasodilation (i.e., decreasing renal vascular resistance) under these conditions. GFR, however, decreased in one group of animals when a RVP of 30 mm Hg was achieved. Several previous studies have shown that GFR is autoregulated until RVP exceeds 30 mm Hg.3,4,11,12 It is conceivable, however, that 30 mm Hg is actually at or above the upper limit of GFR autoregulation in some animals. The cause of the decreased GFR is unclear; however, increasing RIP secondary to increasing venous congestion may have compressed renal tubules, thereby increasing tubular hydrostatic pressure. Despite this, RIP and UNaV showed nearly equal changes in both groups, suggesting a compensatory decrease in sodium reabsorption in the group of animals in which GFR decreased and a possible correlation between RIP and UNaV.

The return of RVP to normal and the administration of captopril or [Sar'1,Ile8]Ang II increased RBF slightly, although this change was significant only at normal RVP and only in the group that received [Sar'1,Ile8]Ang II. The observed increases suggest a possible withdrawal of angiotensin-mediated renal vasoconstriction; nevertheless, RBF was not altered further by changes in RVP.

The return of RVP to normal and the administration of either drug did not alter GFR from the previous clearance period values. Increasing RIP in captopril-treated animals, however, decreased GFR at the highest pressure. In the presence of the converting enzyme inhibitor, the decline in GFR presumably cannot be attributed to preglomerular vasoconstriction. Rather, it is more likely to be caused by withdrawal of efferent tone. This appears to be supported by the observation that total RBF remained unaltered. It is conceivable, however, that tubular hydrostatic pressure increased secondary to venous congestion and increased RIP and contributed to the decline in GFR. In contrast, GFR was unaltered over the range of RVP after the administration of [Sar'1,Ile8]Ang II, although the rate remained depressed to the level achieved when RVP was initially increased to 30 mm Hg under control conditions. It is unclear why, unlike during the control period, GFR did not decrease further even at the highest RVP, unless the receptor blocker has a partial agonistic effect at postglomerular arterioles that serves to defend GFR.

Increasing RVP during administration of either drug increased RIP in a pressure-dependent manner, nearly identical to the response seen during the control period. Under these conditions, however, UNaV did not increase; that is, there was a clear dissociation of RIP and UNaV. We predicted that in the absence of the antinatriuretic effect of Ang II, the elevation of RVP to 15 mm Hg would result in an increase in UNaV; however, this was not the case. The elevation of RVP to 20 mm Hg has been shown to increase proximal tubular sodium reabsorption independently of intrarenal angiotensin levels.13 Together these results suggest that the unaltered UNaV at RVP of 15 mm Hg under control conditions was independent of intrarenal angiotensin levels. Despite the fact that after administration of captopril at RVP of 30 mm Hg RIP was elevated; however, UNaV did not increase. This lack of natriuresis may have been due to the decreased GFR. In the [Sar'1,Ile8]Ang II-treated group, UNaV remained unaltered; this, too, may have been due to the depressed GFR over the range of RVP. These results appear to contrast with studies showing that inhibition of Ang II formation facilitates natriuresis during increases in renal arterial pressure and with the direct antinatriuretic effect of intrarenal Ang II infusion.14,15 These results suggest, however, that the modulatory role of intrarenal Ang II on UNaV may not be the same during alterations in renal arterial pressure as during changes in RVP.

It is generally accepted that UNaV is controlled by multiple and complex interactions, stimulatory as well as inhibitory, between intrarenal hormones, including those of the renin-angiotensin system and the prostaglandin system.3 It may be the nature of these relations that determines UNaV under any given condition. For example, in a previous study3 we showed that increasing RIP increased urinary excretion of PGE2, a prostaglandin considered to be natriuretic, as well as the fractional sodium excretion. Inhibiting prostaglandin synthesis, however, had no effect on PRA and increased the fractional sodium excretion. These results suggest that PGE2 is not necessary for RVP natriuresis and show that, despite the inhibition of a natriuretic hormone, natriuresis could still be evoked in the presence of (presumably) unaltered renin-angiotensin system activity. Similarly, in the present study RVP natriuresis occurred only when the renin-angiotensin system was intact. Although administration of either captopril or [Sar'1,Ile8]Ang II also tended to decrease urinary excretion of PGE2, it was not determined under these conditions if replacing the prostaglandin would have restored the natriuretic response.

Although the apparent importance of angiotensin as a sodium-conserving hormone has been demonstrated previously,14 the results of the present study suggest that blocking the renin-angiotensin system does not facilitate increases in UNaV in response to increased RVP; however, a functional renin-angiotensin system is essential for the maintenance of GFR and UNaV under these conditions.

References


KEY WORDS • renal circulation • glomerular filtration rate • captopril • sodium excretion
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