# Regulation of papillary plasma flow by angiotensin II

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**Regulation of papillary plasma flow by angiotensin II.** We examined in anesthetized dogs the effects of left (L) intrarenal artery infusion of angiotensin II (AII) on renal hemodynamics, urinary concentration and Na excretion, and papillary plasma flow (PPF) (measured by the albumin accumulation technique) in both kidneys. Following AII infusion (0.5 ng/kg/min) into the L renal artery, urinary Na excretion decreased and osmolality increased slightly ipsilaterally, whereas Na excretion did not change significantly and osmolality decreased in the right (R) kidney. PPF was significantly lower in the L compared to the R kidney. When saline loading was superimposed on L intrarenal AII infusion, there was a blunted natriuretic response ipsilaterally with a significantly smaller decrease in urine osmolality compared with the R kidney. PPF increased significantly in the R, but not in the L kidney. Finally, AII blockade with saralasin prior to AII infusion and saline loading prevented the differences between the two kidneys, including PPF. In all groups GFR and renal blood flow did not differ between the two kidneys before or after AII. These data suggest that AII regulates regional blood flow in the medulla, and that the exogenously administered AII induces papillary ischemia, which serves to preserve medullary hypertonicity, preventing an increase in PPF during saline loading, and possibly contributing to the diminished natriuretic response.

It is now widely recognized that angiotensin II (AII) plays a pivotal role in the regulation of renal hemodynamics, salt and water balance, and arterial pressure [1]. Employing various techniques, including micropuncture [2] and microperfusion of isolated tubules [3] or arterioles [4], a number of studies have clearly characterized the effects of AII on the glomerular microcirculation and fluid transport in the proximal tubule. In contrast, the issue of whether AII affects the medullary circulation has been largely neglected.

In previous studies examining inner medullary hemodynamics in various canine models of chronic sodium retention, we have observed that activation of the renin-angiotensin system is associated with markedly reduced papillary plasma flow (PPF) [5–7]. We further examined in normal dogs the effects on PPF of furosemide, ethacrynic acid and chlorthiazide, since the loop diuretics increase renal blood flow (RBF) but also stimulate renal renin release, whereas chlorothiazide decreases RBF but has no significant effect on renin release [8]. During euvolemic diuresis furosemide and ethacrynic acid produced a marked decrease in PPF despite a significant rise in RBF, whereas chlorothiazide did not alter PPF despite a significant fall in

RBF. Furthermore, the decrease in PPF produced by furosemide was prevented by saralasin, a specific AII inhibitor, without altering the other effects of this agent. In addition to these functional relationships, morphological studies of the dog kidney have demonstrated a medullary vascular architecture compatible with regional regulation of medullary blood flow [9]. Thus, evidence appears compelling for a role of AII in the regulation of medullary blood flow. The present study was, therefore, undertaken to examine the effects of intrarenal infusion of AII, at a dose not affecting glomerular filtration rate (GFR) and RBF on PPF, urinary concentration and sodium excretion during hydropenia, and after saline loading in normal dogs.

## Methods

Experiments were performed in mongrel dogs of either sex. The animals were maintained on a daily diet containing 60 mEq of sodium and 40 mEq of potassium and allowed free access to water. Prior to the acute experiments the animals were placed in metabolic cages for five days. After sodium balance was achieved, the animals were anesthetized with sodium pentobarbital (30 mg/kg i.v.) and surgery was performed. Through a midline suprapubic incision both ureters were isolated 6 cm below the renal pelvis, and a small longitudinal incision was made in each ureter. Through the incision, each ureter was catheterized with a 19-gauge polyethylene tube (Deseret Co., Sandy, Utah, USA) which was secured by sutures. The right and left side of the rectum was then punctured with a 14-gauge needle and a guide wire threaded through the needle on each side and passed out of the anus. The distal end of each ureteral catheter was passed into the guide wire and fastened by a ligature. Aided by the guide wire, the ureteral catheters were pulled through and their tips placed just outside the anus. This arrangement allowed for shorter preparation time and accurate collection of urine from each kidney during the acute experiment. Finally, a loop was loosely placed around the right renal artery and vein with a nonreacting Teflon suture impregnated with braided polyester fiber (Tevdek 5, Deknatel Co., Queens Village, New York, USA). The ends of the loop were exteriorized through a right flank puncture. After free flow of urine was demonstrated from each ureteral catheter, the suprapubic incision was closed. During surgery the dogs received 500 ml of 0.9% saline to replace fluid losses and were allowed water ad libitum after recovering from anesthesia.

On the following morning (approximately 20 hr after the surgery) after blood was obtained for measurement of plasma

renin activity (PRA), the dogs were anesthetized with pento-barbital, an endotracheal tube was inserted and light anesthesia was maintained throughout. Through a left flank incision the left renal pedicle was gently dissected to fully expose the renal artery. The right renal artery was also isolated by blunt tunneling through the retroperitoneal space posterior to the aorta. An electromagnetic flow probe (model EP-408, Carolina Medical Electronics, King, North Carolina, USA) was placed around the left and right renal artery and total RBF was measured by electromagnetic flow meters (model 501, Carolina Medical Electronics). A 25-gauge curved needle was inserted into the left renal artery distal to the flow probe and maintained patent with 0.9% saline infused at 0.3 ml/min. After the flow probes were in place, an umbilical tape was passed around the left renal pedicle and a knot loosely tied. Both the Teflon loop and umbilical tape were placed so that the renal artery and vein of both kidneys could be simultaneously occluded at the time when PPF was determined. Zero renal blood flow was determined by brief occlusion of each renal artery distal to the probe. The flow probe was calibrated by in situ perfusion of the renal artery at the conclusion of the experiment.

Initial blood and urine samples were obtained and a priming dose of inulin was administered followed by a sustaining infusion of inulin and 10% mannitol at 0.8 ml/min to induce a mild diuresis. After 60 minutes of equilibration time, two to three 10-minute control clearance periods and control hemodynamic measurements were obtained. Thereafter, four groups of experiments were performed:

### Group I. Control during hydropenia (N = 5)

In order to examine the effects of renal artery manipulation on renal hemodynamics and PPF, and to compare the function of the two kidneys, the infusion of 0.9% NaCl into the left renal artery at the rate of 0.3 ml/min was continued following the control measurements. After 20 minutes, two 10-minute (experimental) clearance periods were obtained along with repeat hemodynamic measurements.

### Group II. Unilateral AII infusion during hydropenia (N = 5)

The dogs were prepared as in group I except that after control measurements were taken AII was added to the intrarenal artery infusion to deliver 0.5 ng/kg/min. After 20 minutes, two 10-minute clearance periods were obtained along with repeat hemodynamic measurements.

### Group III. Saline loading superimposed on unilateral AII infusion (N = 6)

Ten minutes after starting the unilateral AII infusion (0.5 ng/kg/min) into the left renal artery, acute saline loading was achieved with 0.9% NaCl infused at 2 ml/kg/min for 15 minutes, followed by a constant infusion of 0.2 ml/kg/min. After establishing a steady state, two 10-minute clearance periods and hemodynamic measurements were obtained.

### Group IV. AII blockade with saralasin plus saline loading superimposed on unilateral AII infusion (N = 5)

After the initial 60 minute equilibration period, saralasin was infused intravenously at 2 mg/kg/min and continued throughout

the experiment. After a steady state was achieved (approximately 30 min), the experiment proceeded as in Group III.

Immediately after the two experimental periods in each group, PPF was determined in each kidney by the ^{125}I-albumin accumulation technique as previously described [5]. PRA, osmolality, inulin and sodium were determined as previously described [5] and clearances calculated by standard methods.

All results are expressed as mean ± SE. The data were treated statistically with one–way analysis of variance when comparisons were made among the four groups. Student's *t*-test for paired comparisons was used to determine the statistical significance of a difference between two means in the same group of animals. *P* < 0.05 was considered significant.

## Results

### Balance studies

The mean daily intake and urinary output of sodium for five days before the acute experiment were averaged in each group of dogs. The mean sodium intake and output were similar in the four groups and were, respectively, 55 ± 5 mEq/24 hr and 56 ± 6 mEq/24 hr in group I, 55 ± 4 mEq/24 hr and 56 ± 3 mEq/24 hr in group II, 63 ± 3 mEq/24 hr and 63 ± 3 mEq/24 hr in group III, and 65 ± 2 mEq/24 hr and 65 ± 4 mEq/24 hr in group IV. PRA was 5.3 ± 0.9 in group I, 5.5 ± 1.5 in group II, 4.5 ± 1.2 in group III, and 6.1 ± 1.6 ng/ml/hr in group IV with no significant difference among the four groups.

### Clearance and hemodynamic experiments

Table 1 summarizes the results of the clearance and hemodynamic measurements in group I. During the control period urine volume, osmolality and sodium excretion were similar in the two kidneys. During the experimental period urine volume and sodium excretion did not change significantly in either kidney; however, a similar slight, but significant, decrease in urine osmolality was noted in both kidneys, reflecting the effect of mannitol infusion. GFR and RBF were similar in the two kidneys during the control period and remained stable during the experimental period; in addition, similar PPF values were observed in the two kidneys.

Table 2 summarizes the results of the clearance and hemodynamic measurements in group II before and after intrarenal infusion of AII. During the control period urinary volume, osmolality and sodium excretion were similar in the right and the left kidney. After AII infusion into the left kidney urine volume did not change in either kidney; however, sodium excretion decreased significantly ipsilaterally but did not change in the right kidney. As a result of the mild mannitol–induced diuresis, urinary osmolality decreased significantly in the right kidney but was unchanged ipsilaterally. GFR and RBF were similar in the right and left kidney before AII infusion and remained stable throughout the experiment as did the mean arterial pressure (MAP).

Figure 1 depicts the changes in urinary osmolality and sodium excretion in both kidneys in group II. Urine osmolality decreased 72 ± 29 mOsm/kg/$H_2O$ in the right kidney, significantly different from the change in the left kidney (increased 18 ± 17 mOsm/kg/$H_2O$). The decrement in sodium excretion in the left kidney was 11.4 ± 4.7 mEq/min, significantly greater than that in the right kidney (4.0 ± 3.1 mEq/min).

**Table 1.** Function of the right and left kidney during hydropenia (Group 1)[a]

| | V | | Uosm | | $U_{Na}V$ | | FE Na | | $C_{In}$ | | RBF | | MAP | HCT | PPF | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | R | L | R | L | R | L | R | L | R | L | R | L | | | R | L |
| | *ml/min* | | *mOsm/kg H₂O* | | *μEq/min* | | *%* | | *ml/min* | | *ml/min* | | *mm Hg* | *%* | *ml/min/100g* | |
| C | 0.6 | 0.7 | 768 | 859 | 29 | 27 | 0.6 | 0.4 | 42 | 40 | 211 | 213 | 123 | 45 | | |
| | ± 0.1 | ± 0.2 | ± 109 | ± 178 | ± 9 | ± 8 | ± 0.2 | ± 0.1 | ± 6 | ± 5 | ± 11 | ± 12 | ± 6 | ± 2 | | |
| E | 0.6 | 0.7 | 706 | 799 | 32 | 28 | 0.7 | 0.5 | 38 | 37 | 211 | 215 | 123 | 44 | 23.8 | 23.1[b] |
| | ± 0.1 | ± 0.1 | ± 102 | ± 172 | ± 10 | ± 9 | ± 0.3 | ± 0.2 | ± 6 | ± 4 | ± 10 | ± 13 | ± 6 | ± 2 | ± 3.2 | ± 3.2 |
| P | NS | NS | < 0.05 | < 0.05 | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | | |

[a] Values are mean ± SEM; $N = 5$. Abbreviations are: R, right kidney; L, left kidney; V, urine volume; Uosm, urine osmolality; $U_{Na}V$, absolute sodium excretion; FE Na, fractional sodium excretion; $C_{In}$, inulin clearance; RBF, renal blood flow; MAP, mean arterial pressure; Hct, hematocrit; PPF, papillary plasma flow; C, control; E, experimental; P, probability value; NS, statistically not significant.
[b] Statistically not significant when compared with R

**Table 2.** Effects of intrarenal infusion of angiotensin II into the left kidney during hydropenia (Group 2)[a]

| | V | | Uosm | | $U_{Na}V$ | | FE Na | | $C_{In}$ | | RBF | | MAP | HCT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | R | L | R | L | R | L | R | L | R | L | R | L | | |
| | *ml/min* | | *mOsm/kg H₂O* | | *μEq/min* | | *%* | | *ml/min* | | *ml/min* | | *mm Hg* | *%* |
| C | 0.5 | 0.6 | 1027 | 953 | 31 | 24 | 0.50 | 0.36 | 40 | 35 | 231 | 247 | 149 | 38 |
| | ± 0.1 | ± 0.1 | ± 277 | ± 159 | ± 19 | ± 10 | ± 0.26 | ± 0.10 | ± 6 | ± 6 | ± 18 | ± 17 | ± 7 | ± 1 |
| E | 0.5 | 0.5 | 955 | 971 | 27 | 14 | 0.51 | 0.23 | 38 | 32 | 230 | 241 | 149 | 38 |
| | ± 0.1 | ± 0.1 | ± 263 | ± 143 | ± 16 | ± 6 | ± 0.18 | ± 0.10 | ± 5 | ± 4 | ± 17 | ± 17 | ± 7 | ± 1 |
| P | NS | NS | < 0.05 | NS | NS | < 0.05 | NS | < 0.02 | NS | NS | NS | NS | NS | NS |

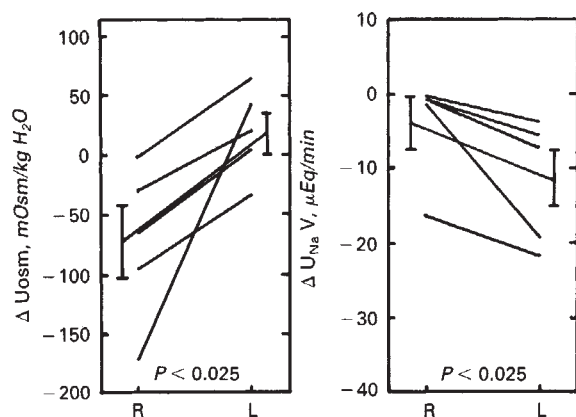[a] Values are mean ± SEM. $N = 5$. For abbreviations, see Table 1.



**Fig. 1.** *Changes in urine osmolality (Δ Uosm) and sodium excretion (Δ $U_{Na}V$) in the right (R) and left (L) kidney after intrarenal AII infusion into the L kidney under hydropenia.* Bars indicate means ± SE.



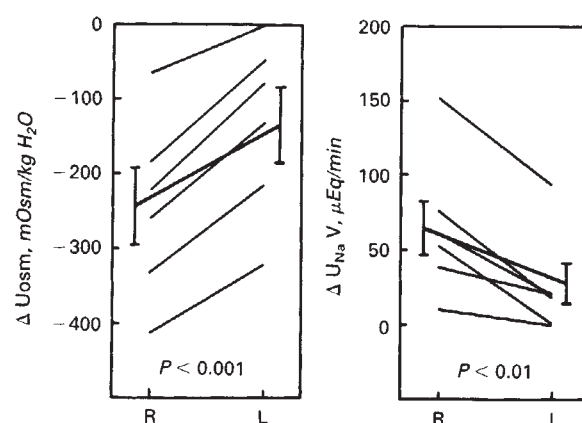**Fig. 2.** *Changes in urine osmolality (Δ Uosm) and sodium excretion (Δ $U_{Na}V$) in the right (R) and left (L) kidney during acute saline loading superimposed on intrarenal AII infusion into the L kidney.* Bars indicate means ± SE.

Table 3 summarizes the clearance and hemodynamic measurements in group III before and after acute saline loading superimposed on left intrarenal infusion of AII. During the control period, urinary volume, osmolality and sodium excretion as well as GFR and RBF were similar in both kidneys. After acute saline loading, urinary volume and sodium excretion increased significantly in both kidneys; however, the response in the left kidney was blunted. GFR and RBF did not change after acute saline loading in either kidney. MAP remained stable and hematocrit decreased significantly.

Figure 2 depicts the decrease in urinary osmolality and the increase in sodium excretion in both kidneys in group III. The

decrement in urine osmolality in the right kidney was 247 ± 50 mOsm/kg/H₂O, significantly greater than that in the left kidney (133 ± 49 mOsm/kg/H₂O). The increment in sodium excretion in the right kidney was 65 ± 20 μEq/min, significantly greater than that in the left kidney (29 ± 14 μEq/min).

Figure 3 illustrates the results of PPF measurements in both kidneys during group II and group III experiments. After AII infusion during hydropenia PPF was 8.6 ± 2.9 ml/min/100 g in the left, significantly lower than 27.9 ± 1.8 ml/min/100 g in the right kidney. Following AII infusion and saline loading PPF was still significantly lower in the left (17.4 ± 2.6 ml/min/100 g) compared to the right kidney, 40.8 ± 4.3 ml/min/100 g. An

**Table 3.** Effects of saline loading superimposed on intrarenal angiotensin II infusion into the left kidney (Group 3)[a]

| | V | | Uosm | | $U_{Na}V$ | | FE Na | | $C_{In}$ | | RBF | | MAP | HCT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | R | L | R | L | R | L | R | L | R | L | R | L | | |
| | *ml/min* | | *mOsm/kg H₂O* | | *μEq/min* | | *%* | | *ml/min* | | *ml/min* | | *mm Hg* | *%* |
| C | 0.6 | 0.5 | 733 | 694 | 17 | 13 | 0.25 | 0.23 | 39 | 41 | 228 | 237 | 145 | 37 |
| | ± 0.1 | ± 0.1 | ± 81 | ± 126 | ± 7 | ± 4 | ± 0.08 | ± 0.08 | ± 8 | ± 8 | ± 15 | ± 19 | ± 8 | ± 3 |
| E | 1.5 | 0.9 | 485 | 545 | 82 | 42 | 0.99 | 0.53 | 45 | 42 | 237 | 242 | 143 | 27 |
| | ± 0.2 | ± 0.1 | ± 56 | ± 90 | ± 25 | ± 16 | ± 0.22 | ± 0.06 | ± 5 | ± 6 | ± 14 | ± 20 | ± 8 | ± 2 |
| P | < 0.005 | < 0.05 | < 0.005 | < 0.025 | < 0.025 | < 0.05 | < 0.005 | < 0.01 | NS | NS | NS | NS | NS | < 0.001 |

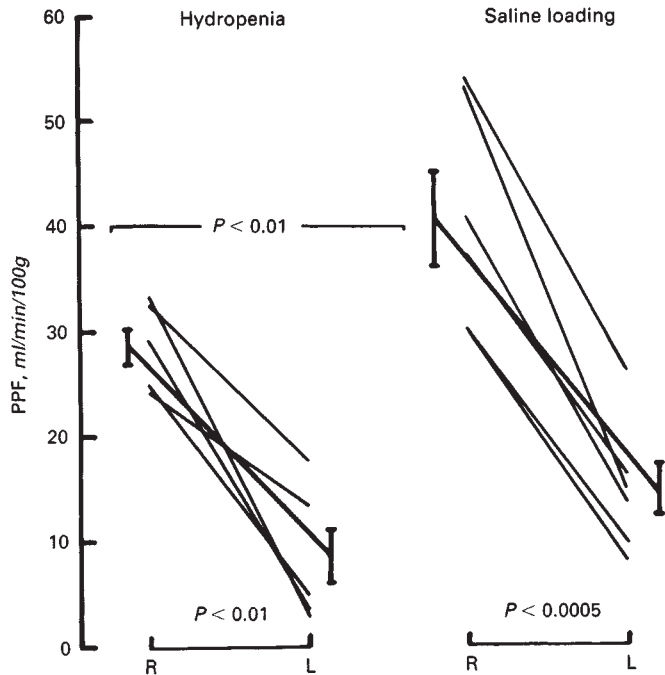[a] Values are means ± SEM. $N = 6$. For abbreviations, see Table 1.



**Fig. 3.** *Papillary plasma flow (PPF) in the right (R) and left (L) kidney after AII infusion into the left kidney during hydropenia and after saline loading.*
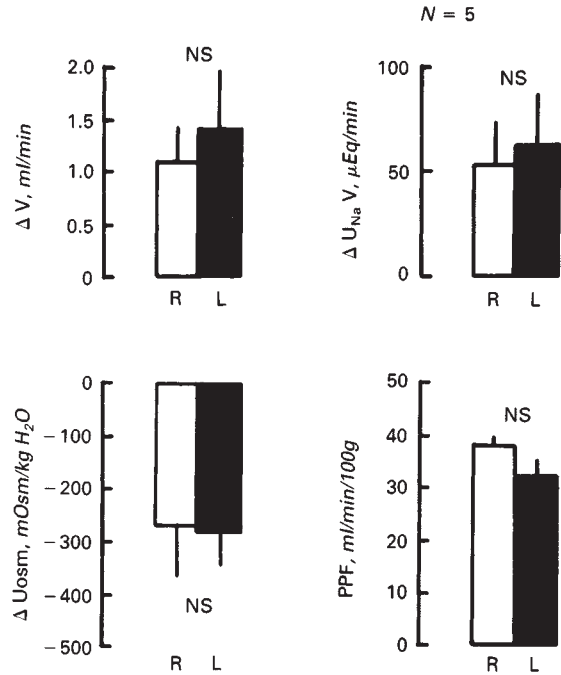


**Fig. 4.** *Effects of intravenous saralasin administration on the saline loading induced changes in urine volume (ΔV), urine osmolality (Δ Uosm), sodium excretion (Δ $U_{Na}V$) and papillary plasma flow (PPF) during unilateral AII infusion into the left kidney. R, right kidney; L, left kidney; NS, not significant.*

**Table 4.** Effects of angiotensin II blockade with saralasin plus saline loading superimposed on unilateral angiotensin II infusion[a]

| | V | | Uosm | | $U_{Na}V$ | | FE Na | | $C_{In}$ | | RBF | | MAP | HCT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | R | L | R | L | R | L | R | L | R | L | R | L | | |
| | *ml/min* | | *mOsm/kg H₂O* | | *μEq/min* | | *%* | | *ml/min* | | *ml/min* | | *mm Hg* | *%* |
| C | 0.5 | 0.6 | 860 | 835 | 3 | 4 | 0.13 | 0.06 | 38 | 36 | 238 | 236 | 124 | 42 |
| | ± 0. | ± 0.2 | ± 94 | ± 162 | ± 1 | ± 1 | ± 0.09 | ± 0.02 | ± 4 | ± 5 | ± 17 | ± 16 | ± 9 | ± 2 |
| E | 1.6 | 2.0 | 591 | 564 | 57 | 67 | 0.76 | 0.83 | 49 | 56 | 306 | 304 | 120 | 31 |
| | ± 0.5 | ± 0.8 | ± 151 | ± 166 | ± 21 | ± 27 | ± 0.33 | ± 0.34 | ± 10 | ± 8 | ± 24 | ± 23 | ± 8 | ± 1 |
| P | < 0.05 | < 0.05 | < 0.05 | < 0.01 | <0.05 | < 0.05 | < 0.05 | < 0.05 | < 0.05 | < 0.025 | < 0.01 | < 0.025 | NS | < 0.005 |

[a] Values are mean ± SEM. $N = 5$. For abbreviations, see Table 1.

increase in PPF occurred after saline loading in both kidneys but was statistically significant in the right kidney only.

Table 4 summarizes the clearance and hemodynamic measurements in group IV. Urinary volume, osmolality and sodium excretion were similar in the two kidneys during saralasin infusion. After AII infusion and superimposed acute saline

loading, urinary volume, sodium excretion, GFR and RBF increased similarly and significantly in both kidneys. Urinary osmolality decreased similarly and significantly in both kidneys. MAP remained stable and hematocrit decreased significantly with saline loading.

Figure 4 depicts the changes in urinary volume, osmolality,

sodium excretion and PPF in both kidneys in group IV. The increment in urinary volume and sodium excretion in the left kidney was 1.4 ± 0.7 ml/min and 63 ± 28 μEq/min, similar to 1.1 ± 0.4 ml/min and 54 ± 21 μEq min in the right kidney, respectively. The decrement in urinary osmolality in the left kidney was 271 ± 68, similar to 268 ± 102 mOsm/kg/H$_2$O in the right kidney. During AII blockade with saralasin, PPF in the left kidney was 31.7 ± 2.9 ml/min/100 g, similar to 38.0 ± 1.6 ml/min/100 g in the right kidney following intrarenal AII infusion.

## Discussion

The results of the present study demonstrate that intrarenal infusion of AII during hydropenia significantly decreases PPF ipsilaterally without altering GFR or RBF. This reduction in PPF is associated with preservation of urinary concentration (despite a mild diuresis induced by mannitol) and decreased sodium excretion compared to the contralateral control kidney. In addition, when a saline load was superimposed, there was a blunted diuretic and natriuretic response and less of a decrease in urinary osmolality in the AII infused kidney compared to the control kidney. Moreover, PPF did not increase as in the control kidney. These effects of AII in the experimental kidney were abolished by prior saralasin infusion, a specific AII inhibitor.

The dose of AII used in the present study was similar to that in the study of Johnson and Malvin [10]. Although these investigators found that the reduced urine volume and sodium excretion after intrarenal AII infusion was not associated with changes in GFR, they observed a slight but significant decrease in para-aminohippurate clearance and an increase in filtration fraction. Similar results were reported by Fagard et al [11] with direct measurement of RBF by an electromagnetic flow probe. The absence of a decrease in RBF in the present experiments may be related to the greater stimulation of the renin–angiotensin system resulting from the extensive surgical preparation required for the simultaneous bilateral determination of PPF. In the present study baseline PRA was significantly higher than that in either of the aforementioned studies [10, 11]. A decreased pressor response to AII has been observed in chronic sodium–depleted subjects and cirrhotics, situations in which the renin–angiotensin system is stimulated [12]. In chronic sodium depletion the dose of AII required to elicit a similar degree of renal vasoconstriction is higher than when the system is less activated. A significant correlation has been found between PRA and the response of RBF to varying doses of AII; the higher the PRA, the smaller the decrease in RBF [13]. This diminished vascular sensitivity to AII has been explained by a greater portion of the vascular AII receptors occupied when the system is activated, leaving fewer receptor sites to be bound by the exogenously administered AII.

The finding of a marked decrease in PPF without a change in RBF during AII infusion in normal dogs is similar to our previous finding in chronic caval dogs and salt–depleted dogs with activation of the renin–angiotensin system [5, 6]. Since inner medullary blood flow constitutes only 1% of total RBF in anesthetized dogs [14], changes in RBF may not be detected even though a profound alteration in PPF occurs. However, actual dissociation between total RBF and PPF has been reported in a variety of circumstances. Fadem et al [15]

reported that similar increases in total RBF induced by various vasodilators in normal dogs were associated with disparate responses in PPF. A marked increase in PPF was noted after acetylcholine or bradykinin administration, whereas secretin failed to alter PPF with a similar increase in total RBF. Moreover, after the administration of furosemide or ethacrynic acid in normal dogs, we have observed a low PPF in the presence of a substantial increase in total RBF [8]. Taken together, these data suggest independent regulation of the cortical and inner medullary circulation.

Anatomical studies have revealed differences in the efferent arterioles of the juxtamedullary glomeruli compared to their superficial counterparts. The juxtamedullary efferent arterioles are longer, larger in diameter, and contain more smooth muscle cells [16]. They give way to the descending vasa recta, the proximal portions of which are also enveloped by smooth muscle cells, which are gradually replaced distally by pericytes provided with contractile elements [6]. The possible functional significance of this unique vascular architecture of the renal medulla has recently been uncovered. Fried and Simpson [17] have demonstrated messenger RNA coding for angiotensinogen predominantly in the rat renal medulla. Ingelfinger et al [18] have recently reported that angiotensinogen mRNA is expressed in apparently equal proportions in renal cortex and medulla, and that the mRNA levels are augmented in response to sodium deprivation. Using autoradiographic mapping, Mendelsohn et al [19] demonstrated that AII binding in the rat was far more dense in the outer medulla than the cortex, and has localized this binding to the vasa recta bundles in the outer medulla [20]. Thus, the decrease in PPF induced by AII in the present study most likely reflects a direct effect on the medullary vasculature, as has been recently postulated for arginine vasopressin. Zimmerhackl, Robertson and Jamison [21], using fluorescent videomicroscopy, have demonstrated that a physiological dose of vasopressin reduced vasa recta blood flow in rats without altering total RBF.

During both hydropenia and saline loading, intrarenal AII infusion was associated with relative preservation of urinary concentration in the ipsilateral kidney (Figs. 2 and 3). In dog models of salt retention with activation of the renin–angiotensin system that we have previously studied, a lower PPF was associated with higher urinary osmolality and papillary solute content compared with normal dogs [5–7]. This finding indicates that solutes were added to the papillary interstitium at rates exceeding their egress, which could be due to either enhanced tubular transport or reduced removal, or both. Intrarenal AII infusion increases PGE$_2$ production [22], thereby affecting solute transport. PGE$_2$, however, decreases NaCl reabsorption in the medullary thick ascending limb of Henle [23] and decreases urea reabsorption in the collecting duct [24], events leading to a decrease in medullary solute content and urinary concentration. On the other hand, AII can stimulate norepinephrine release from adrenergic nerve endings, and it is possible that this effect may contribute to preservation of urinary concentration by AII as observed in the present experiments. This possibility is supported by the observations that addition of norepinephrine to the bathing media enhanced chloride absorption in the isolated perfused, mouse medullary, thick ascending limb [26], and that low–frequency renal nerve–stimulation in the rat increases sodium chloride transport in the

loop of Henle of superficial nephrons [25]. Finally, the enhanced urinary concentration may also be related to a direct effect of AII on solute transport in the cortical and medullary thick ascending limb, since AII receptors have been demonstrated in these nephron segments [27].

It is now accepted that an increase in medullary blood flow without a proportionate increase in tubular transport of solutes into the medullary interstitium would result in solute washout and loss of medullary tonicity [5]. A decrease in vasa recta blood flow would, therefore, be expected to enhance medullary solute accumulation insofar as solute transport in the loop of Henle and collecting duct does not decrease proportionately, as formulated by the central core model of Stephenson [29] and the dynamic model of Moore and Marsh [30]. Thus, the finding in the present experiments are consistent with the notion that AII preserves urine concentration by decreasing PPF, particularly if there is an associated increase in loop solute transport.

Intrarenal infusion of AII significantly enhanced ipsilateral sodium reabsorption (Table 2). A systemic release of aldosterone secondary to recirculation of the intrarenally infused AII cannot explain this finding since sodium reabsorption in the contralateral kidney remained unchanged. It is possible that AII potentiated renal nerve norepinephrine release, thereby increasing proximal, tubular sodium reabsorption [31]. However, the antinatriuretic effect of AII has been observed in acutely denervated kidneys [32] as well as in isolated perfused, rabbit proximal tubules [3]. Although experimental evidence for a direct action of a low dose of AII on sodium transport has been limited to the proximal tubule [3], a similar action in a more distal tubular segment cannot completely be ruled out, as noted above.

Previous micropuncture and microcatheterization studies have shown that during acute saline loading, sodium reabsorption in the juxtamedullary nephron is inhibited more than in the superficial nephron, with net addition of sodium between the superficial late distal tubule and the papillary collecting duct [33]. One explanation for this phenomenon is a decrease in passive sodium transport in the thin ascending limb of Henle due to the dissipation of the sodium gradient which normally exists between this nephron segment and ascending vasa recta [34]. The decreased osmotic gradient could result from medullary solute washout secondary to augmented medullary blood flow during acute saline loading in normal animals [5]. There is also evidence for sodium addition to the tubular fluid in the papillary collecting duct during acute saline loading [35]. Ballerman and Brenner [36] have recently suggested that the diuresis and natriuresis induced by atrial natriuretic peptide (which is released during acute saline loading) result, in part, from alterations in papillary hemodynamics. Specifically, after infusion of the peptide in the rat, the hydraulic pressure in the papillary vasa recta was markedly increased, preventing the fluid absorbed from the papillary tubular structures from returning to ascending vasa recta [37]. Thus, it is conceivable that the papillary ischemia induced by AII prevents the rise in the hydraulic pressure in vasa recta after saline loading, thereby leading to a blunted diuretic and natriuretic response.

In the present study, persistent papillary ischemia and a blunted natriuresis accompanied by relative preservation of urinary concentration were observed in the AII-infused kidney during saline loading, and were reversed by specific AII block-ade with saralasin. These actions of AII mimic the findings in dogs with chronic salt retention and activation of the renin–angiotensin system; specifically, in dogs with chronic caval constriction or an aortocaval fistula with avid salt retention, a blunted natriuretic response to acute saline loading is associated with a markedly diminished PPF and conservation of papillary solute content when compared with normal dogs [5, 7]. Thus, the profound medullary ischemia produced by AII may be added to the several efferent mechanisms proposed for chronic salt retention.

In summary, the present data suggest that AII regulates regional blood flow in the medulla and that the AII-induced papillary ischemia serves to preserve medullary hypertonicity during hydropenia and saline loading and prevents an increase in PPF during saline loading, possibly contributing to the diminished natriuretic response.

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