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Renal hemodynamic response to ureteral obstruction during converting enzyme inhibition

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Abstract Acute unilateral obstruction (UUO) of the pig kidney is associated with an increased secretion of intrarenally generated angiotensin II (ANG II). In order to clarify the importance of this intrarenal ANG II generation during acute UUO, ipsilateral and contralateral renal blood flow and renal secretion rate of ANG II were determined in pigs during continuous infusion of an angiotensin I converting enzyme (ACE) inhibitor. Pigs were operatively equipped with electromagnetic flow probes and catheters in the renal veins and aorta. Intravenous administration of the ACE inhibitor SQ14 225 (captopril), 1 mg/kg per hour, resulted in a significant increase in renal blood flow in the contralateral kidney from 340 ± 28 ml/min to 435 ± 36 ml/min ($P < 0.01$), whereas renal blood flow in the ipsilateral kidney was significantly reduced from 388 ± 23 ml/min to 248 ± 24 ml/min, similar to the reduction in controls. Captopril reduced mean aortic blood pressure, renal vascular resistance consistently on both sides, and plasma concentrations of ANG II and aldosterone from all sample sites. Renal secretion rate of ANG II showed a clear tendency to be reduced from the ipsilateral kidney. The results suggest that in UUO a compensatory increase in renal blood flow may be inhibited in part due to an enhanced secretion of ANG II in the ipsilateral kidney. However, a captopril-mediated inhibition of bradykinin breakdown may also explain some of the observed changes.

Key words Pigs · Obstructive nephropathy · Renal blood flow · Renal vascular resistance · Blood pressure · Angiotensin II · Angiotensin I converting enzyme inhibition

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Introduction

Following complete unilateral ureteral obstruction (UUO), renal blood flow (RBF) is reduced [27]. This reduction is thought to be caused by active vasoconstrictor mechanisms within the kidney vasculature increasing renal vascular resistance (RVR) [7]. The role of angiotensin II (ANG II) as a mediator of this increased RVR in ureteral obstruction has previously been investigated [2, 21, 30]. Moreover, there is now substantial evidence to indicate that all of the components necessary for the local formation of ANG II exist in the kidney, and they operate in whole or in part, independently of the circulating renin angiotensin system (RAS) [1, 12, 13, 19, 25].

A pig model with acute unilateral complete ureteral obstruction enables us to study renal extraction of hormones from both the obstructed kidney (OK) and the contralateral intact kidney (CLK) together with continuous monitoring of renal blood flow, and in a previous study we demonstrated an increased intrarenal ANG II generation in response to short-term UUO [9]. In addition to its effect on the obstructed kidney, it has been suggested that ANG II also plays a role in the CLK during and after relief of obstruction in the rat [5, 6]. In the neonatal rat, UUO results in a prompt increase in the ipsilateral renal juxtaglomerular granulation index, as well as a delayed increase in the granulation index of the intact kidney [5]. Similar to the results from our recent study [9], El-Dahr et al. found elevated levels of both ANG I and ANG II 1 week after UUO [6]. In addition, renal angiotensin-converting enzyme (ACE) activity was elevated in both the OK and CLK during prolonged UUO [6]. Taken together, previous investigations suggest a major role for ANG II during the early phase of development of

obstructive nephropathy and an intimate communication between the two kidneys where endogenous ANG II may participate as a mediator.

The aims of this study were therefore to investigate the effects of ACE inhibition on the renal hemodynamics in the OK and the CLK, as well as renal secretion of endogenous ANG II. Furthermore, the roles of endogenous aldosterone and vasopressin were investigated in acute unilateral obstruction together with changes in urine flow and sodium and potassium excretion from the contralateral kidney.

Material and methods

Preparation of pigs

Female pigs of the Danish Landrace breed (Yorkshire-Lancaster) weighing between 27 and 37 kg were studied. Before the study the pigs were fed a normal diet. From the day prior to any experimental procedures, the animals had free access to water but were deprived of food.

The pigs were operated on 48–72 h prior to any experimental procedure and instrumented as described previously [9, 10]. Briefly, the animals were equipped with silastic catheters in both renal veins and in the abdominal aorta. Electromagnetic flow probes were implanted on both renal arteries proximal to any bifurcation. On the day of the experiment the left ureter was isolated and a ureteral catheter was guided up with side and end holes in the left pelvis. A suture was placed around the ureter and the catheter at the proximal part of the ureterostomy, and another suture was placed around the distal part. A second catheter was placed in the bladder for collection of urine. During the experiments urine was collected every hour either from the CLK in UUO animals or from the right kidney in sham-operated animals. Volume was determined and urine frozen for later analysis.

Prior to ureteral occlusion, at least 1 h of basal observation and urine collection from the UUO animals were done. At time zero the ureteral catheter was connected to a Statham Gould pressure transducer (No. 4523551), thereby totally occluding the left ureter for the subsequent 15 h. Sham-operated animals were monitored for 15 h. At 0, 2, 6, 10, and 15 h blood samples were simultaneously taken from both renal veins and the aorta for measurement of immunoreactive ANG II, aldosterone, and vasopressin. Blood samples were volume replaced by an equal volume of saline. Additionally, the following parameters were measured continuously over the subsequent 15 h: bilateral renal blood flow, arterial blood pressure, pulse rate, central venous pressure, and core temperature. Urine was collected quantitatively every hour from the CLK in UUO pigs and from both kidneys in sham-operated pigs to measure renal electrolyte excretion. However, only clearance data from the right kidney in sham-operated pigs were used for analysis. The pigs were finally killed with an overdose of potassium. Before death the renal pedicles were clamped, and kidneys were taken out and weighed.

Study design

Study 1: captopril infusion during UUO

Captopril (SQ14 225) (provided by The Squibb Institute for Medical Research, Princeton, N.J., USA) was administered intravenously in eight pigs. A bolus of 1 mg/kg body wt. was given 30 min before obstruction followed by a sustained infusion of 1 mg/kg per hour during the remainder of the experiment to block local and systemic renin-angiotensin systems. This group is referred to as UUO + CAPTO. Data from a previous study on ten pigs subjected to the same type of obstruction without the drug served as controls [9].

Study 2: captopril infusion to sham-operated pigs

To study the hemodynamic effects of captopril, five pigs were monitored during 10 h after administration of a captopril bolus (1 mg/kg body wt.) followed by a sustained infusion (1 mg/kg per hour). This group is referred to as SHAM + CAPTO, and data from ten sham-operated pigs used in a previous study were used for comparison [9].

Flow measurements

An electromagnetic flow probe (HMS 1000, HQ 3.0 or HQ 3.5, Howell Instruments, Camarillo, Calif., USA) was mounted on each renal artery proximal to any bifurcation. Following each experiment flow probe calibration was carried out by an in vivo method. The flow probe was inserted on the femoral artery proximal to the arterial line. Blood was allowed to flow from the artery after the zero point had been determined. When flow was stabilized, the amount of blood collected during 1 min was measured. This procedure was done 3 times and the mean volume of blood determined. Using this number in milliliters and the flowmeter recording during 1 min of stable flow, the sensitivity of the probe was determined.

Analytical methods

p-ANG II

Blood samples were drawn in glass vials containing ethylenediaminetetracetate (EDTA) and *o*-phenanthroline. Immunoreactive angiotensin II was determined by a slight modification of the method described by Kappelgaard et al. [14]. Radioimmunoassay was performed after plasma extraction by means of Sep-pack cartridges using methanol/water. Separation was performed on Sephadex G25 microcolumns. Recovery was 80 ± 3%. The coefficients of variations were 12% (interassay) and 8% (intraassay) (in 15 double determinations). Lower detectable level was 2.0 pmol/l plasma.

p-Aldosterone

Blood samples were drawn in EDTA-glass vials. Immunoreactive aldosterone was measured by a slight modification of a previously described method [23]. Using a rabbit-anti-aldosterone antibody (International CIS, France) and ^{3}H-aldosterone (NEN, USA), radioimmunoassay was performed on a residue from plasma prepared by extraction with dichloromethane and purification on silica gel columns. Separation was performed on Sephadex G25 fine microcolumns. Recovery was 80%. The coefficients of variation were 13% (interassay) and 9% (intraassay). Minimum detection level was 42 pmol/l.

p-Vasopressin

Blood samples were drawn in heparin plast vials. Immunoreactive vasopressin was measured as previously described [22]. Radioimmunoassay was performed after extraction on Sep-pack cartridges, using methanol/trifluoracetic acid/water. Separation was performed by charcoal. Recovery was 90%. The coefficient of variations were

13% (interassay) and 9% (intraassay). Lower detectable limit was 0.5 pmol/l.

Electrolytes

Blood and urine samples for measurement of serum and urine electrolyte concentration were taken every hour. The analysis was done in a continuous flow system (SMAC, Technicon).

Other calculations included:

Renal vascular resistance was calculated as:

$$RVR = MAP/RBF,$$

where MAP is mean aortic blood pressure. The renal vein pressure was considered to be zero.

Renal secretion rates for i-ANG II were calculated according to

$$RS_{ANG} = (C_V - C_A) \times RPF,$$

where $RPF = RBF \times (1 - Hct)$ and Hct is hematocrit.

Endogenous creatinine clearance was calculated from:

$$Cl_{Creatinine} = (U_{Creatinine} \times D)/P_{Creatinine},$$

where $P_{Creatinine}$ is the concentration of creatinine in plasma at the end of each clearance period.

Statistics

The mean values and the standard error of the mean (SEM) were calculated for all measurements. The following analyses were performed. To ascertain whether changes occurred between groups and with time a univariate analysis of variance (ANOVA) with repeated measurements was performed on every parameter. Comparison of data between groups at selected time points was made by the *t*-test for unpaired data. Analysis of the i-ANG II, i-vasopressin and i-aldosterone measurements was also based on a univariate repeated measurements analysis of variance (ANOVA) model. The ANOVA model included one between animals factor (study group) and two within animals factors (site and sample time). Analysis of each study separately using a similar model was also performed. A probability of 0.05 or less was considered significant.

Results

Renal blood flow

Obstructed kidney

In Fig. 1 the normalized RBF values (changes relative to RBF level at the start of the experiment) are depicted. Obstruction of the ureter resulted in a significant reduction in ipsilateral RBF, which did not differ between groups. Infusion of captopril 30 min before obstruction resulted in an immediate increase in RBF from 356 ± 25 to a maximum of 401 ± 24 ml/min 45 min after onset of obstruction. Similarly, in the untreated UUO animals the ipsilateral RBF was transiently increased from 319 ± 35 ml/min to a maximum of 339 ± 26 ml/min 45 min following onset of obstruction, whereafter RBF declined to 246 ± 39 ml/min after 15 h of obstruction [9].

Contralateral kidney

Captopril administration consistently resulted in increases in contralateral RBF (Fig. 1). Following captopril infusion the contralateral RBF increased from 341 ± 29 to 435 ± 36 ml/min 4 h after onset of obstruction ($P < 0.01$). Subsequently, RBF declined slowly to 346 ± 20 ml/min after 15 h. In contrast, contralateral RBF did not change significantly in the untreated UUO animals.

Sham-operated animals

Administration of captopril to sham-operated animals resulted in a significant RBF increase in both kidneys (Fig. 4). In untreated sham-operated animals no significant changes were found. The reason for the pronounced difference in absolute RBF between the sham-operated animals receiving captopril and the other groups is not clear. It may be related to a small number in that particular group. Additionally, depth of anesthesia, differences in anesthetic susceptibility, and differences in hydration are well known to influence the magnitude of RBF.

Pelvic pressure

Comparing the two groups, there were no significant differences between the maximum pelvic pressure, the pelvic pressure increase rate, and the pelvic pressure after 15 h of UUO. Pelvic pressure increased 8 times from 7.1 ± 0.5 cmH_2O to 55.6 ± 4.5 cmH_2O during the first 2.5 h after onset of obstruction in the captopril-treated group (Fig. 1). A decline to 43.6 ± 8.2 cmH_2O was seen until 8 h after onset of obstruction, whereafter pelvic pressure stabilized at this level during the rest of the experiment. Linear regression of the pelvic pressure during the 1 h after obstruction showed an increase rate of 0.421 ± 0.011 cmH_2O per minute, similar to that of the untreated UUO group (0.450 ± 0.011 cmH_2O per minute).

Renal vascular resistance

In the ipsilateral kidneys the overall variation differed significantly between the two groups ($P = 0.032$). Compared with control animals, captopril administration resulted in a significant RVR reduction in both the ipsilateral and the contralateral kidney (Fig. 1). Administration of captopril resulted in an immediate decrease in ipsilateral RVR, from 31.9 ± 2.4 mmHg/ml $\times \min^{-1}$/g to 27.4 ± 1.6 mmHg/ml $\times \min^{-1}$/g. After onset of obstruction, ipsilateral RVR slowly increased by 11.6% to a maximum of 35.6 ± 4.7 mmHg/ml $\times \min^{-1}$/g after 15 h of UUO. In the control animals

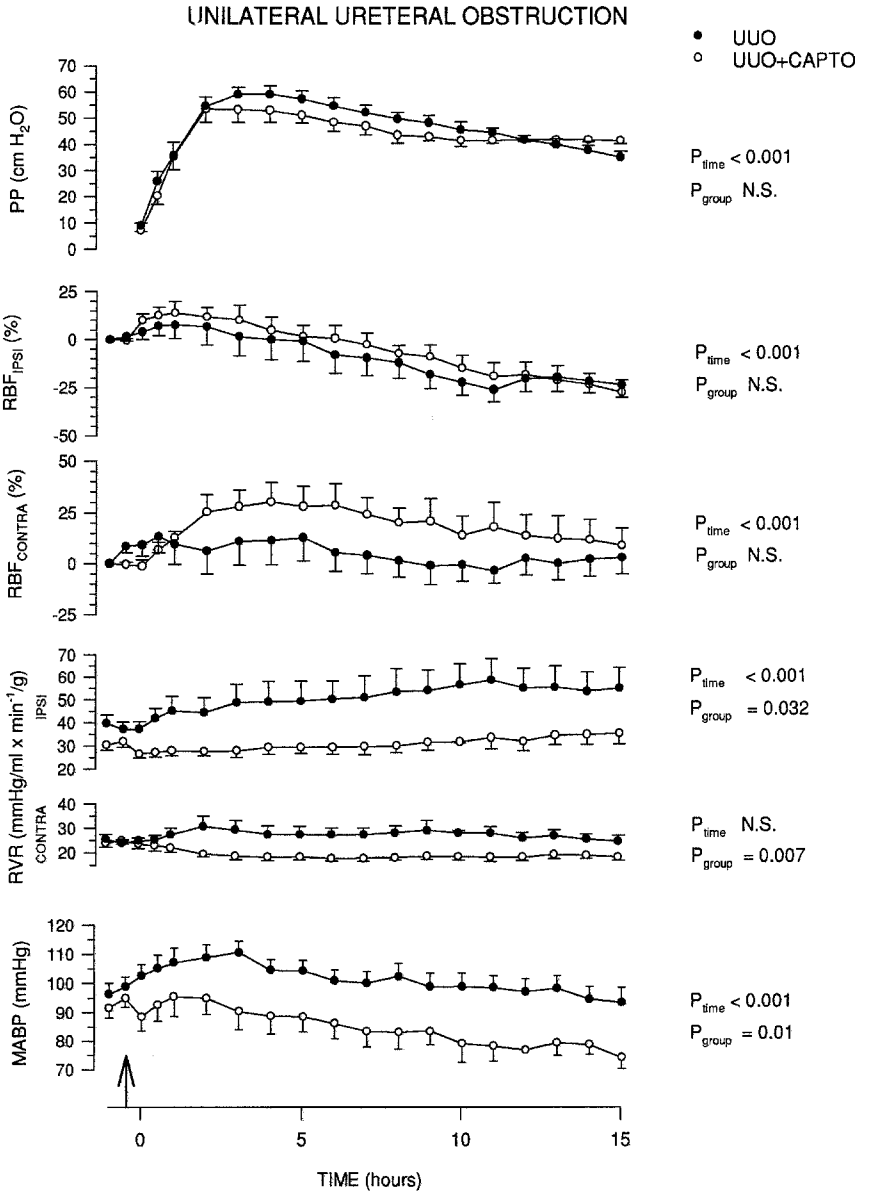

Fig. 1 After onset of unilateral ureteral obstruction, pelvic pressure (*PP*) increased equally in both groups. Relative changes in RBF after administration of captopril (1 mg/kg) and in control pigs during 15 h of complete ureteral obstruction are given for ipsilateral (RBF_{IPSI}) and contralateral (RBF_{CONTRA}) kidneys. Captopril administration did not change the overall response in RBF to ureteral obstruction in the ipsilateral kidney. However, RBF_{CONTRA} increased significantly after captopril infusion. Captopril administration resulted in a steady reduction in mean aortic blood pressure (*MABP*), which differed significantly compared with control animals. In control animals there was a significant increase in MABP 3 h after onset of obstruction in the control animals. Renal vascular resistance (*RVR*) differed significantly between groups for both kidneys. Data are means ± SEM

the ipsilateral RVR increased significantly from 37.4 ± 3.2 mmHg/ml × min^{-1}/g to 55.1 ± 9.2 mmHg/ml × min^{-1}/g. In the contralateral kidneys there was a significant difference in the variation between the two groups ($P = 0.007$). RVR was 24.9 ± 1.4 mmHg/ml × min^{-1}/g before and 22.8 ± 1.6 mmHg/ml × min^{-1}/g after captopril infusion started (Fig. 1). During the rest of the experiment a significant (20.2%) decrease in contralateral RVR was observed to18.3 ± 1.3 mmHg/ml × min^{-1}/g after 15 h of obstruction. In the control animals no changes were found in contralateral RVR.

Angiotensin II

The changes in plasma i-ANG II concentrations are shown in Figs. 2 and 5. Compared with the UUO control animals, captopril administration resulted in a relative decrease in i-ANG II, which differed significantly at all three sample sites. Arterial p-i-ANG II concentration was 10.9 ± 4.9 pmol/l at the start of captopril infusion and increased almost 3 times to 29.2 ± 5.0 pmol/l after 15 h of captopril infusion (Fig. 2A). The p-ANG II concentrations in the renal veins were the same at the start. On the contralateral side p-i-ANG II increased to 23.5 ± 7.5 pmol/l, and on the ipsilateral side p-i-ANG II increased to 38.8 ± 5.7 pmol/l. In the control animals arterial p-i-ANG II in the control animals increased almost 9 times from 9.60 ± 2.31 pmol/l to 80.9 ± 15.9 pmol/l. In the ipsilateral renal vein p-ANG II increased 15 times from 6.8 ± 1.2 pmol/l to 95.4 ± 17.5 pmol/l.

In both groups ANOVA of the plasma i-ANG II data demonstrated a highly significant difference

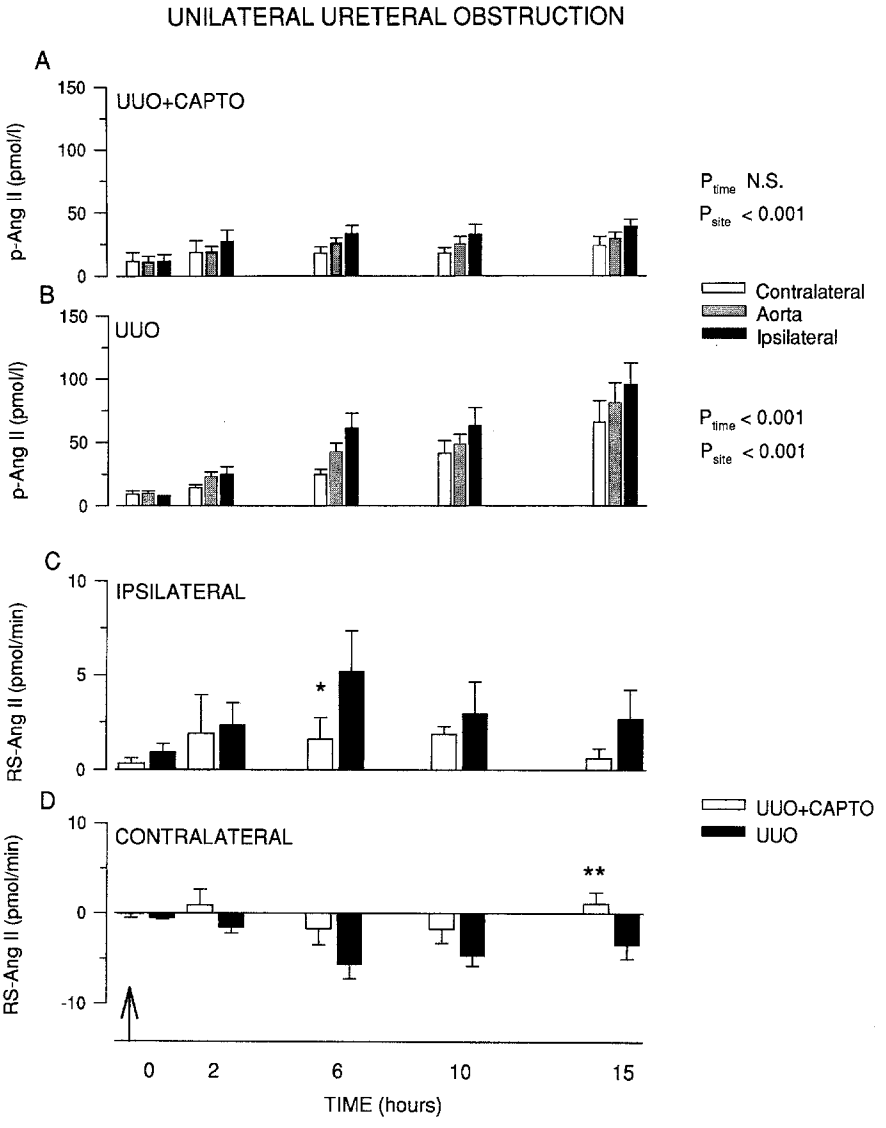

Fig. 2 Plasma concentration of immunoreactive angiotensin II (*p-Ang II*) during 15 h of complete ureteral obstruction. *A*, effects of captopril (1 mg/kg) on changes in p-Ang II concentration; *B*, changes in control animals during 15 h of obstruction; *C*, changes in ipsilateral renal secretion rate of immunoreactive angiotensin II, RS-Ang II, are shown for the UUO + CAPTO and the UUO group. $*P = 0.06$. *D*, changes in contralateral renal secretion rate of immunoreactive angiotensin II, $**P < 0.05$. *Bars* are means ± SE

between the five sampling times ($P < 0.001$). In contrast to the control animals, there was no significant interaction between sampling time and sampling site in the captopril-treated animals. However, in both groups i-ANG II depended significantly on the sampling site ($P < 0.001$), where the left renal vein concentration differed significantly from the arterial concentration ($P = 0.01$).

To compare the findings in the two groups, an ANOVA of the combined data was performed. There was a significant difference between sampling sites ($P < 0.001$), which did not differ between the two groups ($P = 0.099$). Furthermore, there was a significant time trend in each group ($P < 0.001$), which was significantly higher in the control (UUO) group ($P = 0.036$).

In the sham-operated animals ANOVA of the i-ANG II data demonstrated a significant difference between the four sampling times (Fig. 5). Arterial p-i-ANG II increased from 9.1 ± 2.7 pmol/l to 23.5 ± 6.6 pmol/l after 10 h, similar to the increase during the first 10 h in the UUO + CAPTO. Furthermore, in the sham-operated animals there was a significant interaction between sampling time and sampling site ($P = 0.049$).

Renal secretion of angiotensin II

The renal secretions of i-ANG II are depicted in Fig. 2C, D. After 6 h RS-ANG II in the UUO + CAPTO group was 1.65 ± 1.12 pmol/min vs 5.18 ± 2.17 pmol/min in the UUO pigs ($P = 0.06$) (Fig. 2C). In the contralateral kidney RS-ANG II was significantly higher in the captopril-treated animals after 15 h (Fig. 2D). In the sham-operated animals there was no difference in RS-ANG II between the two groups (Fig. 5C, D).

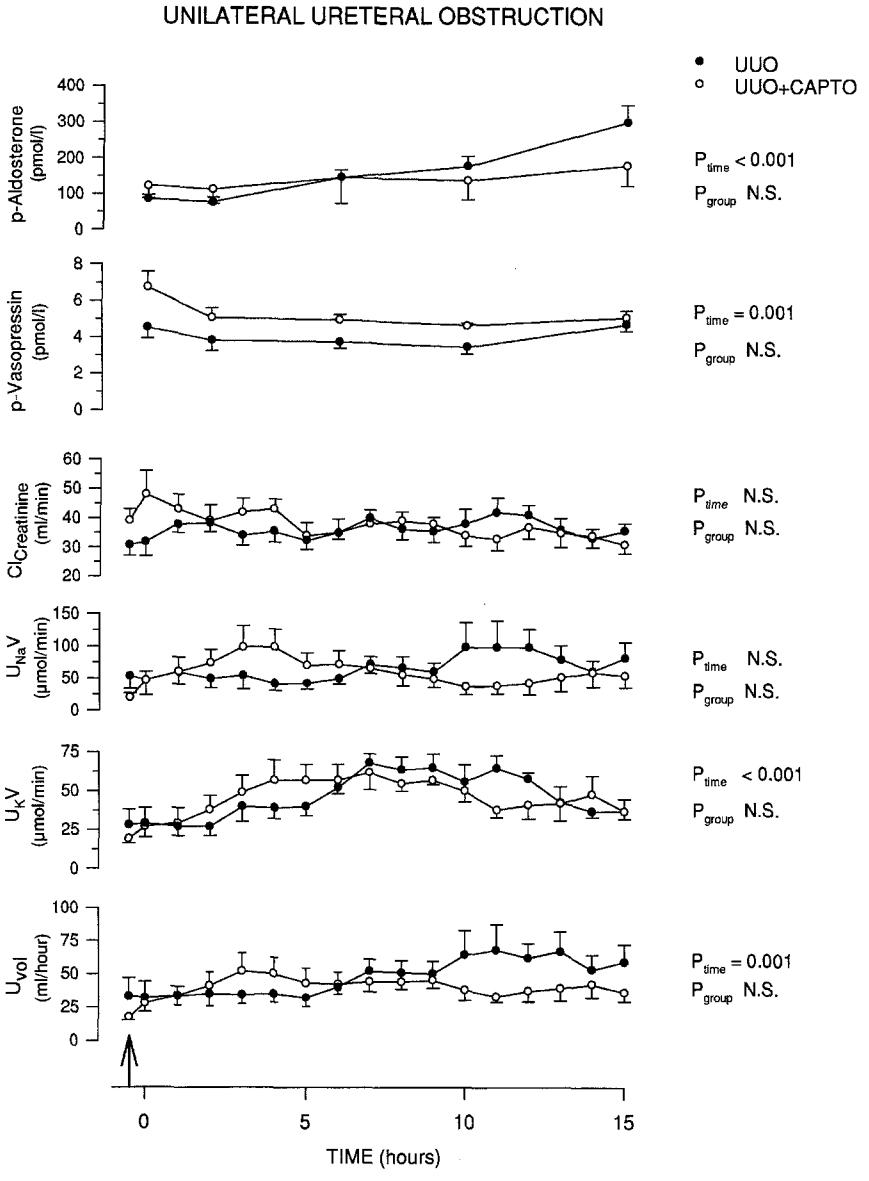

Fig. 3 Changes in arterial plasma concentrations of immunoreactive aldosterone and vasopressin 0, 2, 6, 10, and 15 h after complete unilateral ureteral obstruction in UUO and UUO + CAPTO animals. Data on endogenous creatinine clearance ($Cl_{Creatinine}$), urinary sodium ($U_{Na}V$), urinary potassium excretion (U_KV), and diuresis (U_{vol}) are given every hour after onset of obstruction in the UUO and UUO + CAPTO animals. $Cl_{Creatinine}$ from the CLK was not affected by captopril administration, and there was no difference compared with controls. $U_{Na}V$ increased from 19.6 ± 7.3 to 99.0 ± 32.1 µmol/min 3 h after captopril administration. In control animals sodium excretion showed a more extended increase from 46.8 ± 19.9 to 98.6 ± 39.9 ml/h after 10 h of obstruction. Potassium excretion increased significantly in both groups and did not differ between groups. Urine flow from the contralateral kidney increased by 184% from 17.4 ml/h to 49.6 ml/h. However, this response was temporary, and at the end of the experiment urine production (U_{vol}) was 35.9 ± 6.6 ml/h. In the control animals the contralateral urine flow showed a moderate and more extended increase from 33.2 ± 13.7 ml/h to 68.0 ± 19.3 ml/h 11 h after onset of obstruction. Data are means ± SEM

Aldosterone

In the UUO groups p-aldosterone concentrations were similar at the start of the experiment. The overall variation did not differ between the two groups. However, there was a significant time trend in each group ($P < 0.001$), which differed between the two groups ($P < 0.002$). In the untreated UUO animals there was a significant increase in plasma aldosterone during the 15 h of obstruction (Fig. 3). Plasma aldosterone increased from 86 ± 10 pmol/l to 300 ± 44 pmol/l in the aorta. Almost similar increases were seen in p-aldosterone from the ipsi- and contralateral renal veins. Captopril administration inhibited to some extent this increase in plasma aldosterone concentration, being significantly lower after 15 h of UUO. Plasma aldosterone in the aorta was 122 ± 34 pmol/l at onset of obstruction and 180 ± 58 pmol/l after 15 h of obstruction. In the sham-operated animals p-aldosterone did not differ between the two groups (Fig. 6).

Vasopressin

The plasma concentrations of vasopressin in the UUO groups are depicted in Fig. 3 and in Fig. 6 for the sham-operated animals. There was a significant difference in the vasopressin concentrations between the UUO + CAPTO and UUO animals at the onset of obstruction ($P < 0.05$) (Fig. 3). However, during the course of obstruction this difference was eliminated. In the sham-operated animals there was a significant time trend during 10 h of observation, and the 10-h sample p-vasopressin was significantly higher in the SHAM + CAPTO animals (Fig. 6).

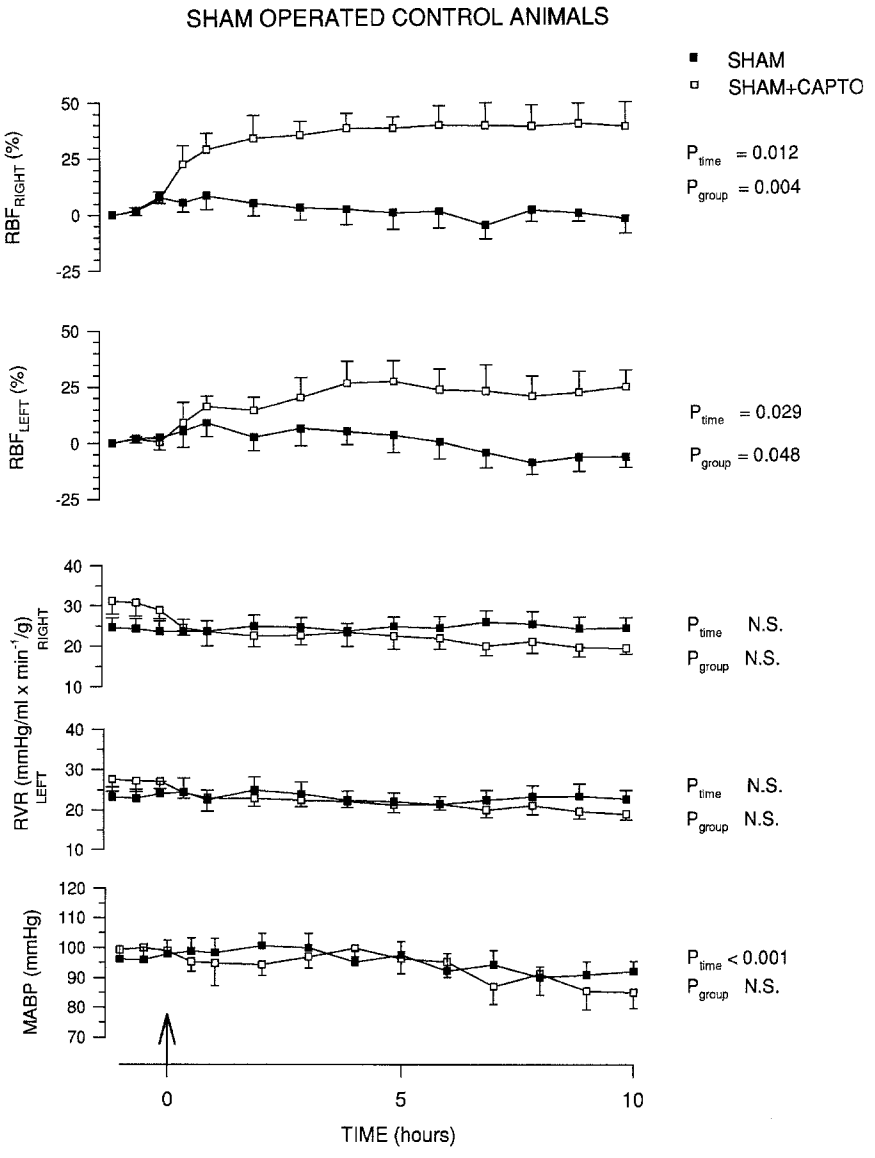

Fig. 4 Changes in renal blood flow (*RBF*), renal vascular resistance (*RVR*), and mean aortic blood pressure (*MABP*) in sham-operated control animals. RBF differed significantly between captopril-treated pigs and control pigs. In the right kidney RBF increased from 246 ± 25 ml/min to 344 ± 42 ml/min, and in the left kidney from 288 ± 27 ml/min to 352 ± 28 ml/min after captopril administration. RVR and MABP did not differ between groups. Data are means ± SEM

Discussion

The results of the present study demonstrate that administration of captopril results in a significant increase in contralateral RBF, whereas ipsilateral RBF decreases significantly. In addition captopril administration resulted in significant reductions in mean aortic blood pressure, renal vascular resistance on both sides, and plasma concentrations of ANG II and aldosterone from all sample sites. Renal secretion rate of ANG II showed a clear tendency to be reduced from the ipsilateral kidney. Urinary output increased from the contralateral kidney. Furthermore, the study suggests that captopril administration may not be able to block intrarenal ANG II generation momentarily in pigs with unilateral ureteral obstruction where the intrarenal renin-angiotensin system is activated.

The renal hemodynamic response to acute UUO is a decrease in ipsilateral renal blood flow due to an increased renal vascular resistance [7, 20, 27, 30]. Numerous attempts have been made to clarify the role of ANG II as a mediator of renal vasoconstriction during obstruction. During acute unilateral obstruction of the dog kidney, infusion of saralasin, an ANG II receptor blocker, had no effect on hemodynamic parameters [21]. However, saralasin may itself act as a renal vasoconstrictor as a result of its angiotensin agonistic properties. Therefore, it is more relevant to use ACE inhibitors to study the involvement of ANG II in obstructive nephropathy. Indeed, blockade of the conversion of ANG I to its active form ANG II by ACE inhibitors has provided evidence for a definite role of ANG II in the increased RVR during obstruction in different models [2, 30]. Carmines and Tanner examined glomerular blood flow using microspheres and

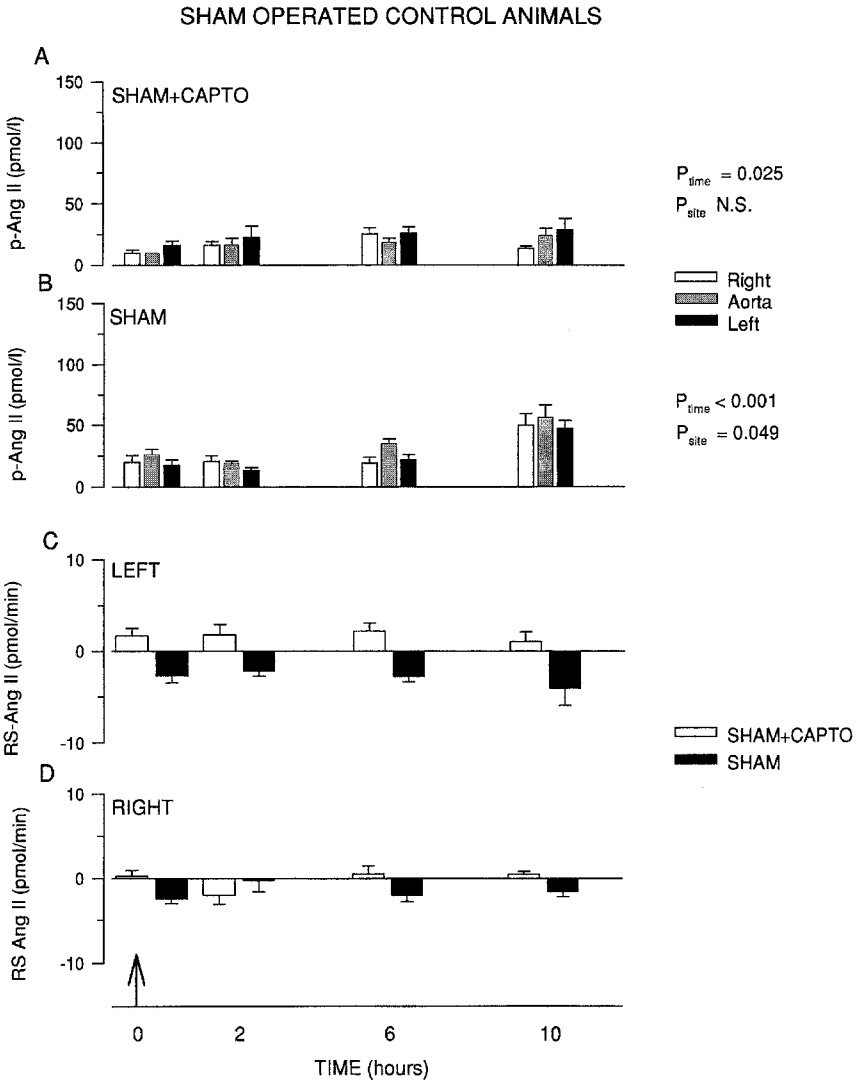

Fig. 5 Plasma concentration of immunoreactive angiotensin II (*p-Ang II*) during 10 h observation in sham-operated control animals with or without captopril administration. *A*, effects of captopril (1 mg/kg) on changes in p-Ang II concentration; *B*, changes in sham-operated animals during 10 h observation; *C* changes in the renal secretion rate of immunoreactive angiotensin II, RS_{ANG}, in the left kidney are shown for the SHAM + CAPTO and for sham-operated animals; *D*, changes in RS_{ANG} in the right kidney. *Bars* are means ± SE

showed that the increase in ipsilateral RVR during blockade of the lumen of single tubules could be prevented by administration of ACE inhibitors [2]. Following release of obstruction, RBF has been shown to improve when rats were treated with captopril [30]. Similar results were obtained during chronic partial ureteral obstruction after treatment of enalapril [3], and during chronic complete obstruction in rats ipsilateral renal function could be maintained by inhibition of ANG II production [18]. However, the results of the above-mentioned studies are difficult to compare with the results of the present study, because the settings are very different (chronic obstruction in rats [18], partial obstruction in the neonatal guinea [4]). Similar to the findings by Vaughan et al. [28], this study showed no changes compared with the control animals. Therefore, these results suggest that a direct ANG II dependent mechanism is not exclusively responsible for the decrease in ipsilateral RBF in this pig model.

In contrast to the ipsilateral RBF reduction, a novel finding in the present study was that RBF in the CLK increased by 29% following captopril administration. In a previous study, Chevalier et al. suggested a role for ANG II in the contralateral kidney in the partially obstructed neonatal guinea pig [4]. In the present study administration of captopril resulted in a marked reduction in contralateral RVR, suggesting an active role for ANG II in the CLK during UUO. However, in sham-operated animals RBF increased similarly after captopril administration indicating a direct effect of ACE inhibition on RBF, an increase which alternatively could be explained by inhibition of the kinin kallikrein system, as suggested in previous studies [6, 8]. In particular, its effects on papillary blood flow and glomerular dynamics may be due to alterations in the intrarenal levels of kinins [8]. Consequently, the RBF increase in the CLK could be due to a bradykinin-determined sustained vasodilation. On the other hand,

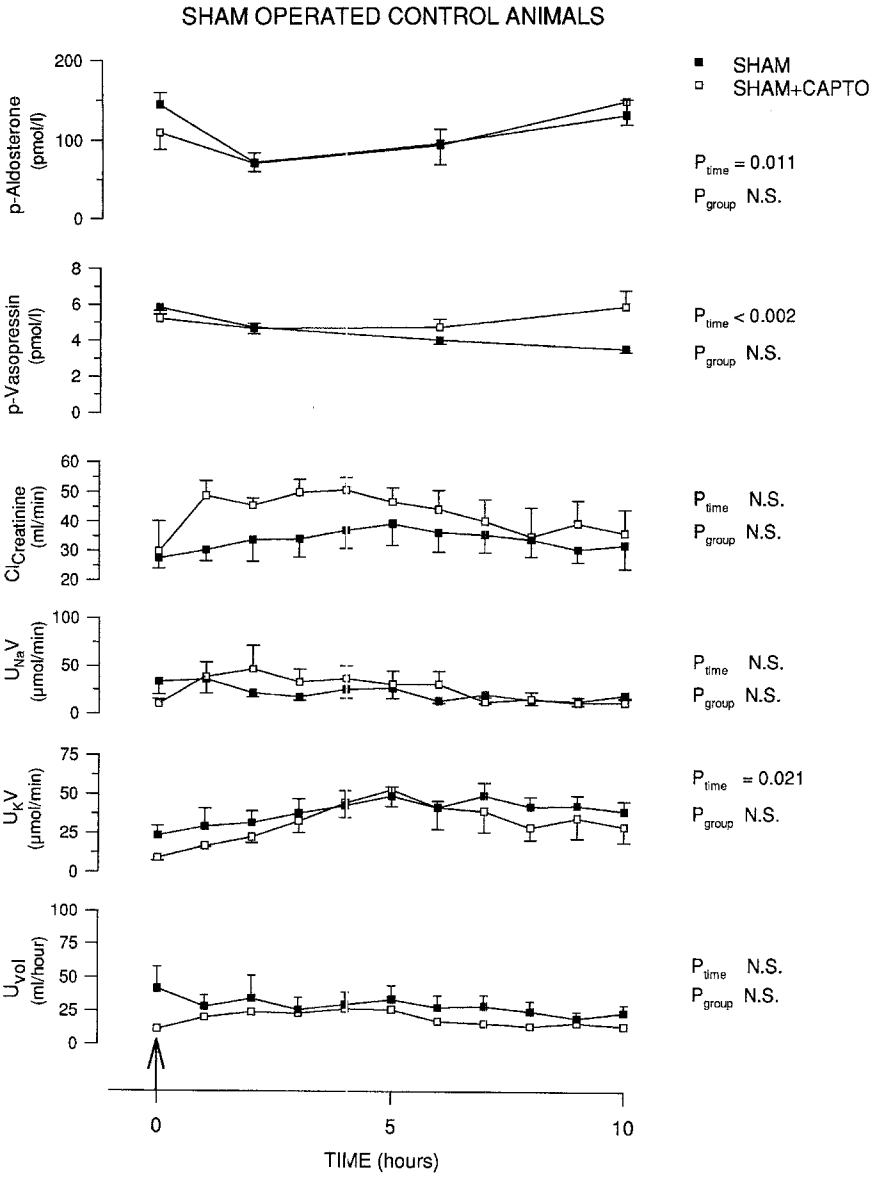

Fig. 6 Changes in arterial plasma concentrations of immunoreactive aldosterone and vasopressin at 0, 2, 6, and 10 h in sham-operated and SHAM + CAPTO animals. Data on endogenous creatinine clearance ($Cl_{Creatinine}$), urinary sodium ($U_{Na}V$), urinary potassium excretion (U_KV), and diuresis (U_{vol}) are given every hour in both groups. $Cl_{Creatinine}$ increased in the first hours after captopril administration. In the SHAM + CAPTO animals $U_{Na}V$ was 10.5 ± 4.8 µmol/min at the start of captopril administration and 46.4 ± 24.9 µmol/min 2 h after captopril administration was started. In the sham-operated animals sodium excretion did not change. In the sham-operated animals U_{vol} did not change. A significant interaction between time and potassium excretion was seen in both sham-operated groups. Data are means ± SEM

El-Dahr et al. suggested in a recent rat study that prolonged unilateral ureteral obstruction resulted in an ipsilateral activation of the renin-angiotensin system and suppression of the kallikrein-kinin system [6]. In addition, they found elevated activity of renal ACE in both the ipsi- and contralateral kidneys compared with sham [6]. However, it is not possible to extrapolate the results from their study to the present study since the models and time course of obstruction are very different.

With the animal preparation we used in this study the arterial concentrations of i-ANG II reflect the overall circulating level to which all vascular beds are exposed. The renal venous ANG II is considered to represent ANG II formed in these vascular beds because approximately 90% of the ANG II presented to the renal vascular bed is metabolized in one passage [25]. In addition to the decline in ipsilateral RBF subsequent to acute UUO in pigs, the ipsilateral kidney showed an enhanced increase in the renal secretion of ANG II from the ipsilateral kidney, which in a recent study we explained by a de novo intrarenal generation of ANG II [9]. Administration of captopril significantly reduced the plasma concentration of i-ANG II, and tended to reduce intrarenal ANG II generation from the ipsilateral kidney, evidenced as a reduction in RS-ANG II. Previously it was shown that the juxtaglomerular (JG) cells contain the whole apparatus to generate ANG II [13]. Administration of ACE inhibitors rapidly inactivates the circulating converting enzyme, but according to the recent hypothesis not the intracellular [13]. Therefore, stimulation of the JG cells to produce ANG II (e.g., by an elevated pelvic pressure) could result in a markedly stimulated ACE activity

which in turn stimulates an increased release of ANG II to the renal interstitium as well as to the renal circulation. The findings in the present study correspond somewhat to what has recently been described in the case of chronic UUO in the rat [6], where intrarenal ANG II levels in the CLK were not suppressed. However, the possibility also exists that ANG II is formed by enzymes other than ACE. Finally, the dose of captopril used in the present study may have been too low to completely block the amount of ACE present in the renal cells. In the sham-operated animals captopril administration resulted in a significant reduction in p-i-ANG II compared with untreated sham animals. However, the circulating i-ANG II levels were not completely blocked. Furthermore, captopril administration did not abolish the ability of renal secretion of ANG II, suggesting that captopril does not momentarily block intrarenal ANG II generation. Alternatively, the remaining low levels of arterial and venous ANG II may represent uninhibited ANG II production, ANG II metabolites, or in vitro generated ANG II [26].

In the present study unilateral occlusion of the ureter resulted in a slight increase in the urine flow and sodium and potassium excretion from the contralateral kidney. This is in accordance with the increased excretion of urine and sodium from the CLK described by Kopp et al. [16]. This was explained by a renorenal reflex mechanism mediated by stimulation of ipsilateral renal pelvic mechanoreceptors [15]. This in turn leads to an increase in efferent renal nerve activity to the contralateral kidney, described as a renorenal reflex mechanism leading to an increase in urine flow and sodium excretion from the contralateral kidney. In addition, stimulation of the mechanoreceptors has recently been suggested to increase plasma vasopressin in the rabbit [29], and bilateral ureteral obstruction has also been accompanied by an increase in plasma vasopressin [24]. However, contrary to the marked changes in plasma i-ANG II and aldosterone in untreated UUO animals and the attenuation of this response in the captopril-treated UUO pigs, there were no significant changes in the vasopressin response in this setting.

Similar to previous results in the normotensive rat and two-kidney one-clip Goldblatt hypertensive rat, captopril administration to UUO pigs reduced mean aortic blood pressure [11]. In addition to inhibiting the conversion of ANG I to ANG II, captopril also blocks the degradation of kinins. Consequently, the immediate contralateral increase in urine production, sodium excretion, and RBF in the UUO + CAPTO and in bilateral RBF in SHAM + CAPTO after captopril administration may be related to a reduction in bradykinin breakdown, as suggested by others [8, 17]. Future studies taking advantage of the selective inhibition of the renin angiotensin with the new generation of non-peptide ANG II receptor antagonists may provide a better understanding of the role of ANG II in the development of obstructive nephropathy and avoid interaction with potential kinin responses.

In conclusion, this study has shown that ACE inhibition during UUO of the pig kidney results in a reduction in systemic p-ANG II concentration and an increase in contralateral RBF. The results also demonstrated that administration of captopril did not block intrarenal ANG II generation momentarily. It is suggested that a compensatory increase in contralateral renal blood flow may in part be inhibited by the enhanced secretion of ANG II in the ipsilateral kidney. However, an inhibition of bradykinin breakdown may also explain some of the observed changes.

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