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Hemodynamic effects of enalapril on neonatal chronic partial ureteral obstruction

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Hemodynamic effects of enalapril on neonatal chronic partial ureteral obstruction (CPUO). To evaluate the role of angiotensin II (ANG II) in renal vasoconstriction due to ipsilateral CPUO, guinea pigs were subjected to incomplete left ureteral stenosis within the first 48 hr of life, and were given enalapril from the 14th day of life until study at 23 ± 3 days or 8 weeks of age. Renal blood flow (RBF) was measured using radioactive microspheres, and glomerular filtration rate (GFR) was derived from inulin extraction. The number of perfused glomeruli per kidney was determined following in vivo India ink perfusion. Enalapril treatment resulted in an 83% rise in RBF of the obstructed kidney, from 2.58 ± 0.26 to 4.73 ± 0.48 ml/min ($P < 0.001$), which was associated with a 26% increase in number of perfused glomeruli ($P < 0.01$). Mean GFR of the hydronephrotic kidney increased from 0.13 ± 0.02 to 0.37 ± 0.10 ml/min ($P < 0.05$). Enalapril had no effect on intraureteral pressure of the obstructed left kidney after 7 to 13 days of administration, and did not affect renal mass or ureteral diameter after 6 weeks of treatment. It is concluded that hemodynamic consequences of CPUO in the neonate may be attenuated by ANG converting enzyme inhibition. The primary effect of enalapril is most likely inhibition of intrarenal ANG II formation.

Effets hémodynamiques de l'énalapril sur l'obstruction urétérale chronique partielle (OUCP) néonatale. Afin d'évaluer le rôle de l'angiotensine II (ANG II) sur la vasoconstriction rénale dû à une OUCP controlatérale, des cobayes ont été soumis à une sténose incomplète de l'uretère gauche pendant les premières 48 heures de leur vie, et ont recu de l'énalapril à partir du 14ème jour de vie jusqu'au moment de l'étude, à l'âge de 23 ± 3 jours ou 8 semaines. Le flux sanguin rénal (FSR) a été mesuré en utilisant des microsphères radioactives, et la filtration glomérulaire (FG) a été obtenue par la clearance de l'inuline. Le nombre de glomérules perfusés par rein a été déterminé après une perfusion d'encre de chine in vivo. Le traitement par enalapril a provoqué une augmentation de 83 % du FSR du rein obstrué, de 2,58 ± 0,26 à 4,73 ± 0,48 ml/min ($p < 0.001$), qui était associé avec une augmentation de 26 % du nombre des glomérules perfusés ($p < 0,01$). La FG moyenne du rein hydronéphrotique a augmenté de 0,13 ± 0,02 à 0,37 ± 0,10 ml/min ($p < 0,05$). L'énalapril n'a eu aucun effet sur la pression intra-urétérale du rein gauche obstrué après 7–13 jours d'administration et n'a pas affecté la masse rénale ou le diamètre urétéral après 6 semaines de traitement. Nous concluons que les conséquences hémodynamiques de l'OUCP chez le nouveau-né peuvent être atténuées par l'inhibition de l'enzyme de conversion de l'ANG. L'effet primaire de l'énalapril est très probablement l'inhibition de la formation intra-rénale de l'ANG II.

Although obstructive nephropathy is a major cause of renal insufficiency in infancy and childhood [1], factors contributing to decreased renal function remain incompletely understood. While most previous experimental studies have addressed models of complete ureteral obstruction [2], partial urinary tract obstruction is of greater clinical interest because it is more prevalent and is potentially reversible. Furthermore, because most lesions are congenital, renal damage occurs early in life, at the time of most rapid structural and functional development. We have therefore developed a model of unilateral chronic partial ureteral obstruction (CPUO) in the neonatal guinea pig [3, 4]. In this species, like the human, nephrogenesis is complete at the time of birth, and functional and renal maturation proceeds rapidly during the first four postnatal weeks [5, 6]. Following partial constriction of the left ureter within the first 2 days of life, 23-day-old guinea pigs develop marked vasoconstriction of the ipsilateral kidney and an 80% decrease in glomerular filtration rate (GFR) [3]. This is associated with 34% fewer perfused glomeruli compared to the untouched contralateral kidney [3].

Previous studies have implicated angiotensin II (ANG II) as a mediator of vasoconstriction during or following relief of complete urinary tract obstruction [7–10], but others have not confirmed this [11–13]. To our knowledge, the only published report of vasoactive substances in CPUO was performed in adult rats with mild ureteral obstruction [14]. Because infusion of prostaglandin synthesis inhibitors resulted in increased arteriolar resistances of obstructed kidneys, the authors postulated the action of a vasoconstrictor such as ANG II [14]. Since renal vascular resistance (RVR) is normally higher [15], and circulating ANG II levels are increased in early postnatal life [16], hemodynamics may differ in the neonate. The present study was therefore designed to investigate the role of ANG II in the observed vasoconstriction of unilateral severe CPUO in the neonatal guinea pig. In view of its superior activity and lack of nephrotoxicity, the new ANG II converting enzyme inhibitor, enalapril, was used as a probe to block endogenous ANG II formation in animals with CPUO. To minimize artifactual changes due to relief of intraureteral pressure, hemodynamic measurements were made without release of the ureteral constriction. Changes in the hydronephrotic kidney due to enalapril administration were compared with those in the contralateral intact kidney, as well as with sham-operated animals receiving enalapril.

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Methods

Fifty-seven Hartley guinea pigs (male:female ratio 1:1) were anesthetized with halothane within the first 48 hr of life, and the left ureter was exposed through a midline abdominal incision. A 2 mm length of sterilized polyethylene tubing (PE5O, Clay Adams, Parsippany, New Jersey, USA) was slit longitudinally and placed around the distal one-third of the ureter, after which the incision was sutured and coated with collodion. Animals were returned to their mothers until weaning at 14 days, after which they were fed standard guinea pig chow (No. 5025, Purina, St Louis, Missouri, USA). From the 14th day until the time of study at 21 to 27 days of age, tap water was supplied to animals in individual cages, and the volume consumed was measured each day. Each litter was divided equally into two groups: the first group received tap water alone (control), while enalapril maleate (MK-421, Merck, Sharp & Dohme, Rahway, New Jersey, USA) was added to the drinking water of the other group. The enalapril was mixed freshly each day to provide a concentration of 0.2 mg/ml. Angiotensin converting enzyme activity of enlapril in aqueous solution is not diminished after 48 hr (SWEET CS, personal communication).

Animals were fasted with free access to drinking water the night before study. On the day of study, guinea pigs were anesthetized with intraperitoneal sodium pentobarbital, 3 mg/100 g body wt and placed on a thermostatically controlled heating table to maintain rectal temperature at 39 ± 0.5°C. Tracheostomy was performed and a jugular vein was cannulated for infusion of 0.9% saline containing [^{3}H]inulin (New England Nuclear, Boston, Massachusetts, USA) in a concentration of 10 μCi/ml, at a rate of 0.3 ml/100 g body wt/hr. To replace surgical fluid losses, the contralateral jugular vein was cannulated for infusion of donor guinea pig plasma at a rate of 0.9 ml/hr. A polyethylene catheter was threaded down the right carotid artery so that the tip lay at the aortic root. Mean arterial pressure (MAP) was continuously recorded from this catheter by means of a Statham 23ID pressure transducer coupled to a Hewlett-Packard 7754B recorder. In four animals receiving enalapril, teprotide, 0.2 mg was infused intravenously to maximally inhibit converting enzyme activity.

The left kidney and ureter were exposed through an abdominal incision, and were kept moist throughout the experiment by covering them with saline-soaked cotton. External diameter of the left ureter was measured halfway between kidney and bladder using calipers, and intraureteral pressure was measured proximal to the stenosis in 14 animals using an 8-10-μm micropipette (containing 2 M NaCl) connected to a servo-nulling apparatus. A polyethylene catheter was then inserted in the abdominal aorta at the aortic bifurcation for collection of a reference blood flow sample during microsphere injection. Because urine flow rates from the obstructed kidney were previously found to be too low to be accurately measured [3], urine was not collected. However, urine collected distal to the stenosis from animals prepared in identical fashion contained significant [^{3}H] activity in each case, demonstrating patency of the ureter [3]. Blood samples (100 μl) were drawn from the carotid artery catheter at the beginning of the experiment and after a 1-hr equilibration period for measurement of hematocrit in heparinized tubes. The left renal vein was carefully dissected free of perirenal fat and a 27G needle was inserted between the adrenal vein and renal hilum after ligation of the gonadal vein. One-hundred μl of blood was withdrawn from the renal vein into a heparinized syringe at a rate of 0.1 ml/min, while a similar sample was obtained simultaneously from the carotid artery catheter for determination of inulin extraction. Blood was not obtained from the right renal vein because its access was prevented by the bulky viscera in this species. All blood withdrawn was replaced with an equal volume of donor guinea pig blood.

In each animal, 50 to 80 × 10^3 latex microspheres 14 ± 1 μm in diameter, labeled with ^{85}Sr (3M, St. Paul, Minnesota, USA) were suspended in 10% dextran and Polysorbate 80 by vigorous agitation (Vortex Genie, Scientific Industries, Bohemia, New York, USA) and ultrasonication (Bransonic 12, Branson Co., Shelton, Connecticut, USA). During withdrawal of a reference blood sample from the abdominal aorta at 0.7 ml/min using a precision withdrawal pump (Harvard Apparatus, Millis, Massachusetts, USA), the microspheres were injected into the carotid catheter and flushed with 0.5 ml 0.9% saline. After replacement of blood withdrawn with an equal volume of donor blood and equilibration of MAP, ANG I (Sigma, St Louis, Missouri, USA), 1 μg/kg body wt (approximately 0.2 μg in 0.2 ml 0.9% NaCl) was infused intravenously in 16 animals. After MAP had stabilized (2 to 3 min), a second bolus of 50 to 80 × 10^3 14 μm spheres (labeled with ^{141}Ce) was injected during withdrawal of a reference sample. In eight animals, ANG II (Sigma) (1 μg/ml saline) was injected intravenously at 0.1 μg/min, and a second bolus of microspheres was injected after MAP had equilibrated (2 to 4 min). After replacement of blood withdrawn, 1 ml India ink (Higgins No. 4465, Newark, New Jersey, USA) was infused in the carotid catheter, followed by infusion of saturated potassium chloride solution to sacrifice the animal.

Blood from renal vein and carotid artery was diluted in PCS solubilizer (Amersham, Arlington Heights, Illinois, USA) and radioactivity measured in a beta scintillation counter (Beckman Instruments, Irvine, California, USA). Kidneys were removed, drained, decapsulated, bisected, weighed, and fixed in 10% formalin solution. Radioactivity of the reference blood samples and kidneys was measured in a gamma scintillation counter (Beckman Instruments). In 16 animals, one-half of the kidney was digested in 25% hydrochloric acid and the number of perfused glomeruli was counted as described previously [5]. Remaining kidney tissue was weighed before and after drying at 40°C for 10 days for calculation of dry/wet ratio.

To evaluate the long-term effects of CPUO and enalapril administration on somatic and renal growth, ten additional guinea pigs (five receiving water, and five receiving enalapril) were sacrificed at 8 weeks of age, and body wt, kidney wts, and ureteral diameter were measured. To assess the effects of chronic enalapril administration on normal growth and renal function, 11 sham-operated guinea pigs were given enalapril in the drinking water starting at 14 days of age, and were studied at 22 to 26 days of age.

Calculations

Filtration fraction was given by the renal inulin extraction ratio. Cardiac output, total vascular resistance (TVR), RBF, and RVR were calculated from microsphere data and GFR was calculated from RBF and inulin extraction ratio as described previously [3, 17].

Table 1. Characteristics of guinea pigs with partial left ureteral obstruction

	Age *days*	Birth wt	Body wt	L kidney wt	R kidney wt	Water intake *ml/day*	Hct, pre *%*	Hct, post *%*	L ureter diameter *mm*	Lureter pressure *mm Hg*	L kidney FF *%*	L kidney GFR *ml/min*
		g										
Water	23.2	106.0	213.8	1.07[a]	1.53	37.3	41.3[a]	39.1	4.3	6.6	10.6	0.13
SE	0.3	2.9	6.8	0.03	0.07	1.7	0.4	0.8	0.1	0.9	2.0	0.02
N	23	22	23	23	23	23	21	21	22	7	11	11
Enalapril	23.5	101.6	204.9	1.13[a]	1.37	34.8	38.0	38.0	4.2	5.9	11.2	0.37
SE	0.4	2.6	7.6	0.04	0.05	1.6	0.4	0.5	0.1	0.6	1.9	0.10
N	24	23	24	24	23	24	23	23	22	7	12	12
P	NS	NS	NS	NS	NS	NS	< 0.001	NS	NS	NS	NS	< 0.05

Abbreviations are: L, left; R, right; Hct, hematocrit on day of physiologic study; pre, beginning experiment; post, end of experiment; FF, filtration fraction; GFR, glomerular filtration rate; SE, standard error; *N*, number of animals; NS, not signficant.
[a] $P < 0.01$.

Table 2. Characteristics of 8-week-old guinea pigs with left partial ureteral obstruction

	Age *days*	Body wt	L kidney wt	R kidney wt	L ureter diameter *mm*
		g			
Water	57.8	402.4	1.09	2.35	5.0
SE	0.8	30.1	0.18	0.14	0.3
N	5	5	5	5	5
Enalapril	58.4	384.4	1.05	2.34	4.8
SE	1.0	27.6	0.16	0.11	0.2
N	5	5	5	5	5

Statistical analysis

The effects of enalapril, age, and CPUO of morphometric and hemodynamic measurements were evaluated by means of the Student's *t* test for unpaired data. Comparisons between left and right kidneys were made using Student's *t* test for paired data. The effects of CPUO and enalapril on number of perfused glomeruli, shown in Figure 4, were evaluated for each kidney by one-way analysis of variance. Statistical significance was defined as $P < 0.05$.

Results

As shown in Tables 1 and 2, there was no difference in somatic growth as a result of chronic enalapril administration, even after 8 weeks of age. Body wt of sham-operated animals (Table 3) was not different from that of guinea pigs with CPUO receiving enalapril (Table 1). Wet kidney wt was unaffected by enalapril administration, and mass of the obstructed left kidney did not change from 3 to 8 weeks of age (Tables 1 and 2). In each case, the left kidney surface was irregular, with dilatation of the renal pelvis, and the left ureter was uniformly distended and tortuous to the point of obstruction. Mass of the unobstructed right kidney was significantly greater than the left, and increased more than 50% from 3 to 8 weeks of age (Tables 1 and 2). Compared to animals with CPUO receiving enalapril (Table 1), left kidney wt of sham-operated guinea pigs was not different, while that of the right kidney was less ($P < 0.001$) (Table 3). The ratio of dry/wet kidney wt for 3-week-old animals receiving water was 0.178 ± 0.004 and 0.204 ± 0.004 for left and right kidneys, respectively ($N = 10$). This did not differ from the ratio for animals receiving enalapril, which averaged 0.188 ± 0.003 and 0.213 ± 0.004 for left and right kidneys ($N = 9$). In each group, the ratio for the right kidney was greater than for the left ($P < 0.001$). Diameter of the left ureter in guinea pigs with CPUO was greater than that of the normal right ureter, (which remained 1.0 ± 0.0 mm) and increased further from 3 to 8 weeks of age ($P < 0.025$) (Tables 1 and 2). There was no effect of enalapril on intraureteral hydrostatic pressure (Table 1).

Daily water intake was unaffected by CPUO or enalapril administration (Tables 1 and 3). The daily enalapril dose was 7.0 ± 0.3 mg for animals with CPUO, and 6.7 ± 0.3 mg for sham-operated guinea pigs studied at 23 days of age. This amounted to approximately 30 mg/kg/day. Hematocrit at the beginning of the experiment on the day of study was lower in animals receiving enalapril than in control littermates (Tables 1 and 3), and decreased by 2 volumes % during the experiment in controls ($P < 0.01$), but did not change in those receiving enalapril (Table 1).

As shown in Table 4, enalapril administration resulted in a 17% decrease in MAP. Infusion of a bolus of ANG I resulted in a rise of MAP to 88.6 ± 2.0 mm Hg in the group receiving water, and to 66.6 ± 2.0 mm Hg in the animals reciving enalapril ($P < 0.001$). Increment in MAP due to ANG I infusion was not correlated with RBF of the left kidney in animals with CPUO receiving enalapril ($r^2 = 0.05$, P = NS). Infusion of ANG II caused a similar increase in MAP in both groups: resultant MAP was 82.8 ± 2.5 mm Hg and 78.4 ± 2.4 mm Hg for water and enalapril groups, respectively (P = NS). Four animals receiving teprotide in addition to enalapril showed no difference in left kidney blood flow (Fig. 1), and results were therefore combined with those receiving enalapril only. As shown in Table 4, enalapril administration had no significant effect on cardiac output or right kidney RBF, but mean RBF of the obstructed left kidney increased 83% from 2.58 to 4.73 ml/min. As shown in Figure 1, left kidney RBF was not increased in all animals receiving converting enzyme inhibitor, but there was no relationship between RBF and duration of enalapril administration. Mean left kidney RBF of animals with CPUO receiving enalapril was not different from that of sham-operated animals treated with the drug, while right kidney RBF was 71% higher ($P < 0.005$) (Tables 3 and 4). As shown in Figure 2, ANG I and II decreased RBF of both kidneys in control animals with CPUO by approximately 50%, and resulting RBF was not different after ANG I and II. For animals receiving enalapril, RBF of left and right kidneys following ANG II infusion was

Table 3. Data for sham-operated guinea pigs receiving chronic enalapril

	Age	Body wt	L kidney wt	R kidney wt	Water intake	Hct, pre	Hct, post	L ureter diameter
	days	*g*			*ml/day*	*%*	*%*	*mm*
Mean	23.7	220.7	1.16	1.10	33.6	38.6	37.1	1.0
SE	0.3	7.9	0.05	0.04	1.7	0.9	0.8	0.0
N	11	11	11	11	11	9	9	11

	MAP	Cardiac output	L kidney RBF	R kidney RBF	TVR	L kidney RVR	R kidney RVR
	mm Hg	*ml/min*			*mm Hg/ml · min*		
Mean	50.9	94.8	5.74	5.81	0.60	9.26	9.79
SE	2.9	14.7	0.76	0.86	0.09	0.85	1.37
N	11	7	9	9	7	9	9

Table 4. Hemodynamic measurements of guinea pigs with partial left ureteral obstruction

	MAP	Cardiac output	L kidney RBF	R kidney RBF	TVR	L kidney RVR	R kidney RVR	L RVR/TVR	R RVR/TVR
	mm Hg	*ml/min*			*mm Hg/ml · min*				
Water	66.7	81.4	2.58	7.96	1.02	31.7	9.7	33.6	10.2
SE	1.5	9.4	0.26	0.68	0.13	4.2	1.2	3.9	0.8
N	23	18	19	19	18	19	19	18	18
Enalapril	55.4	95.5	4.73	9.93	0.61	13.4	5.9	22.8	10.2
SE	1.6	8.7	0.48	0.91	0.05	1.4	0.5	2.2	0.8
N	24	20	20	20	20	20	20	20	20
P	< 0.001	NS	< 0.001	NS	< 0.01	< 0.001	< 0.01	< 0.025	NS

Additional abbreviations: MAP, mean arterial pressure; RBF, renal blood flow; TVR, total vascular resistance; RVR, renal vascular resistance.

more than 50% lower than RBF of respective kidneys following ANG I, but the difference was of borderline significance ($0.05 < P < 0.1$)

Total vascular resistance and right kidney RVR were reduced by 40% as a result of enalapril treatment (Table 4). However, RVR of the obstructed left kidney was reduced by 60%. The ratio of left kidney RVR to total vascular resistance therefore deceased from 33.6 ± 3.9 to 22.8 ± 2.2 ($P < 0.025$) due to enalapril, while the ratio for the right kidney remained unchanged at 10.2 ± 0.8. Thus, while enalapril decreased resistance in all vascular beds, the effect on the obstructed left kidney was significantly greater. Compared to sham-operated guinea pigs receiving enalapril, left kidney RVR was higher in animals with CPUO receiving enalapril ($P < 0.025$), while resistance of the right kidney was lower in those with contralateral obstruction ($P < 0.005$) (Tables 3 and 4). As shown in Figure 3, ANG I and II had a similar effect on left and right RVR in animals receiving water, while RVR was more than twofold greater following ANG II than ANG I in the group receiving enalapril ($P < 0.025$). There was no significant difference in the ratio of left to right kidney RVR before or after ANG I or ANG II for either group. Thus CPUO caused no difference in vasoconstrictor response to similar pharmacologic doses of ANG I or ANG II.

The number of glomeruli containing identifiable India ink in each kidney is shown in Figure 4. Included for comparison are data from sham-operated animals receiving ordinary drinking water, reported previously [3]. There was no difference between number of perfused glomeruli in left compared to right kidneys except for the group with CPUO not receiving drug. In animals with CPUO compared to sham-operated controls, there was no difference in number of perfused glomeruli in the left obstructed kidney, while the number in the contralateral right kidney increased by 33%. Enalapril treatment had the effect of increasing the number of perfused glomeruli of both kidneys in sham-operated animals, and of the left kidney in animals with CPUO. There was no further increase in number of perfused glomeruli of the unobstructed right kidney in guinea pigs with left CPUO receiving enalapril.

Filtration fraction for the obstructed kidney was not affected by enalapril, but mean GFR was significantly increased as a result of enalapril administration (Table 1). As shown in Figure 5, RBF of the obstructed kidney was not increased in all animals receiving enalapril. However, GFR was elevated in all those with RBF greater than 5 ml/min. In control animals, GFR did not change over the measured range of RBF (1 to 5 ml/min).

Discussion

The major finding of this study is that chronic enalapril administration results in significant vasodilation of the neonatal guinea pig kidney subjected to CPUO. This is associated with a 26% increase in number of perfused glomeruli identified by India ink. It is likely that the observed effects of enalapril on renal hemodynamics are largely due to inhibition of conversion of ANG I to ANG II [18, 19]. Compared to captopril, which contains a sulfhydryl group, enalapril has a greater absolute affinity for ANG converting enzyme [20]. However, additional effects must also be considered. By stimulating arachidonic acid release, captopril may stimulate prostaglandin synthesis [21], but enalapril does not share in this effect [22]. Because ANG

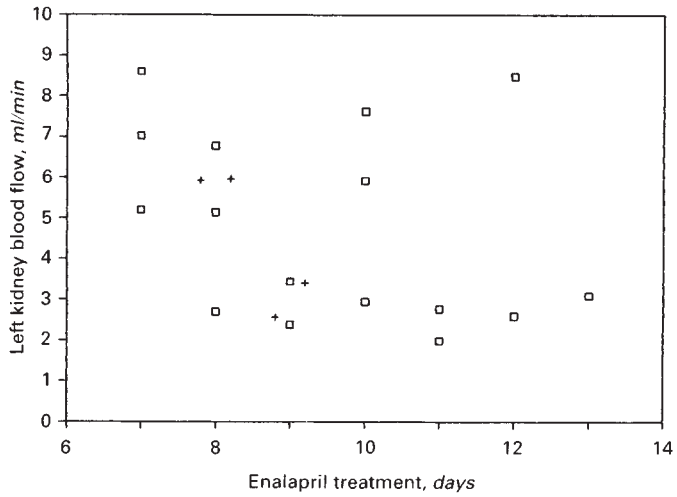

Fig. 1. *Relationship of renal blood flow to days of enalapril treatment for left hydronephrotic kidney of 23 ± 3-day-old guinea pigs.* Each point represents one animal. □ denote animals receiving enalapril alone, and + indicate animals also receiving teprotide. There was no significant correlation between renal blood flow and days of enalapril treatment (r^2 = 0.11).

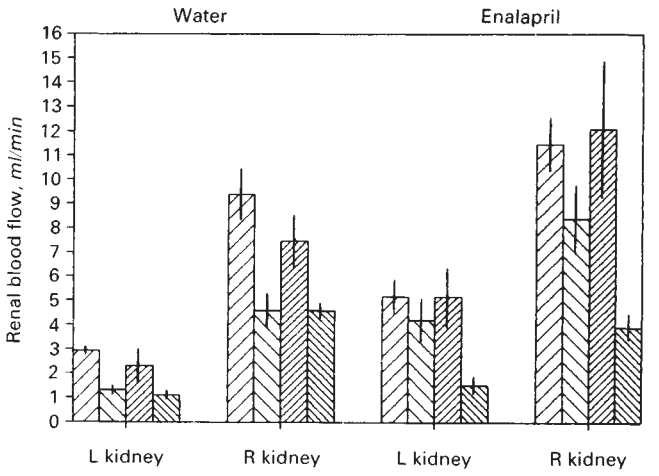

Fig. 2. *Renal blood flow for left (L) hydronephrotic and right (R) unoperated kidney of guinea pigs receiving ANG I or ANG II intravenously.* Symbols are: ▨, pre ANG I; ▧, post ANG I; ▨, pre ANG II; ▧, post ANG II. For each group (water and enalapril), eight animals received ANG I and four received ANG II. Values are mean ± SE.

converting enzyme cleaves vasodilator kinins to inactive fragments, converting enzyme inhibitors may also increase circulating kinin levels [23]. Although potentiation of kinins may be significant in vascular beds other than the kidney [24], some observations of circulating kinins may have been subject to experimental artifact [19], and enalapril does not appear to have any consistent effect on plasma bradykinin levels [22]. Furthermore, Yarger, Schocken, and Harris [8] have shown that captopril increased inulin and para-aminohippuric acid clearance in the rat kidney after release of 24 hr complete ureteral obstruction, an effect which was not diminished by administration of agents known to inhibit kinin synthesis or to degrade kinins. Taken together, the bulk of current evidence thus favors a primary role of converting enzyme inhibition on ANG II formation.

The lower initial hematocrit of enalapril-treated compared to control animals with CPUO may have been due to slight volume expansion in the former group, resulting from sodium retention secondary to prolonged vasodilatation with enalapril. However, hematocrit was not different at the time of microsphere injections, and increase of RBF by converting enzyme inhibition has been shown in salt-loaded or -depleted animals [18]. It is therefore unlikely that the observed variation in RBF was due to differences in volume status of the animals.

Persistence of a vasopressor response to ANG I following enalapril (and teprotide) administration in the neonatal guinea pig suggests incomplete converting enzyme inhibition. However, it appears that ANG II formation may be effectively suppressed regardless of the depressor response, which is less specific [18]. While not all guinea pigs receiving enalapril demonstrated a significant increase in RBF of the obstructed kidney compared to controls, this could not be correlated with a lack of a depressor response to ANG I in these animals. Furthermore, there was no correlation of the number of days of enalapril administration with left kidney blood flow. The variability in response to enalapril may therefore result from vasoconstrictors acting independently from ANG II.

Because enalapril was administered systemically to the guinea pigs in the present study, both intrarenal and extrarenal converting enzyme were inhibited. Since there was no difference in RVR following ANG II compared to ANG I in control animals with CPUO, it is unlikely that the observed vasoconstriction of the obstructed kidney in animals receiving water was due to increased intrarenal converting enzyme activity. This observation is in agreement with Zimmerman et al [25], who found that intrarenal converting enzyme plays a minor role in the renal vasodilator response to captopril and teprotide. However, it has been shown that intrarenal ANG I conversion is approximately 22% in a single pass through the kidney of the anesthetized dog, and is independent of RBF [26, 27]. Since enalapril decreased RVR of the obstructed kidney more than that of the contralateral kidney or resistance of other vascular beds, ureteral obstruction resulted in specific intrarenal effects in addition to any systemic alterations in the renin-angiotensin system. Recent studies indicate that locally produced ANG II contributes significantly to regional vascular tone [28, 29]. Possibilities include increased renin release, decreased degradation of ANG II by the obstructed kidney, or increased sensitivity to ANG II (increased ANG II receptor number or binding affinity). Increased "pressor material" has been identified in the kidney subjected to prolonged ureteral ligation [30], and the juxtaglomerular granulation index of both obstructed and contralateral unobstructed kidneys was found to be increased 7 and 14 days following unilateral ureteral ligation [31]. However, kidneys of animals with congenital bilateral hydronephrosis were found to have decreased renin content [32]. It is, therefore, difficult to predict which mechanism is responsible for ANG II-mediated vasoconstriction in CPUO, although the response may be localized to a single obstructed nephron [10].

While the present experiments do not permit localization of the site of vasoconstriction within the obstructed kidney, an increase in number of glomeruli containing India ink following

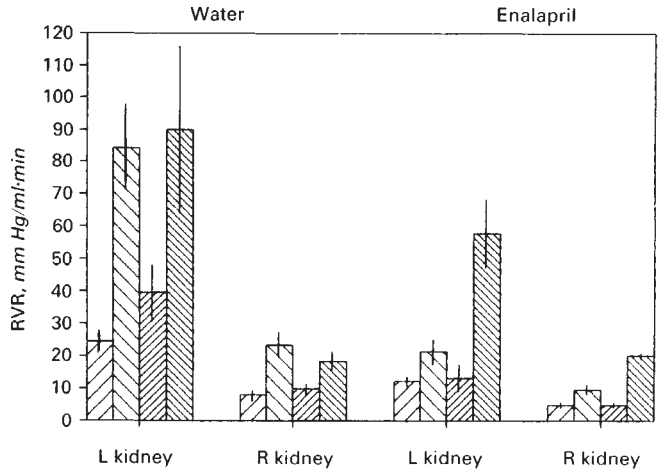

Fig. 3. *Renal vascular resistance (RVR) for each kidney of guinea pigs in Figure 2 receiving ANG I or ANG II intravenously.* Symbols same as Figure 2.

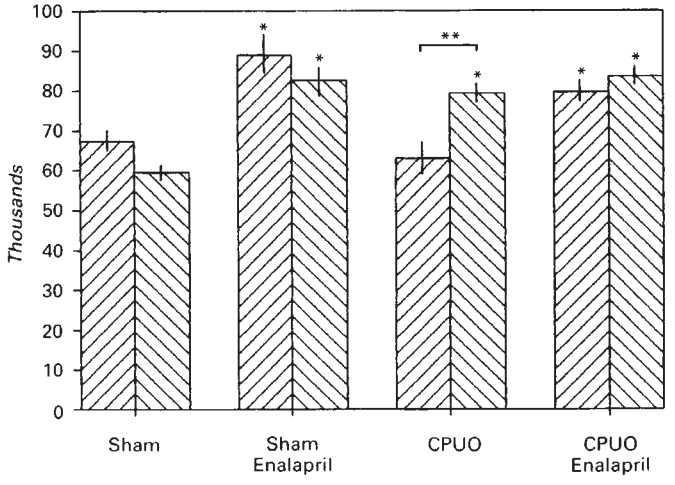

Fig. 4. *Number of perfused glomeruli in left (▨) or right (▧) kidney in each group.* Data for sham-operated animals not receiving enalapril are from [3]. Number of animals in each group: sham, 8; sham-enalapril, 6; CPUO, 9; CPUO-enalapril, 7. $*P < 0.01$ vs. same kidney of animals in sham group not receiving enalapril. $**P < 0.01$ left vs. right kidney.

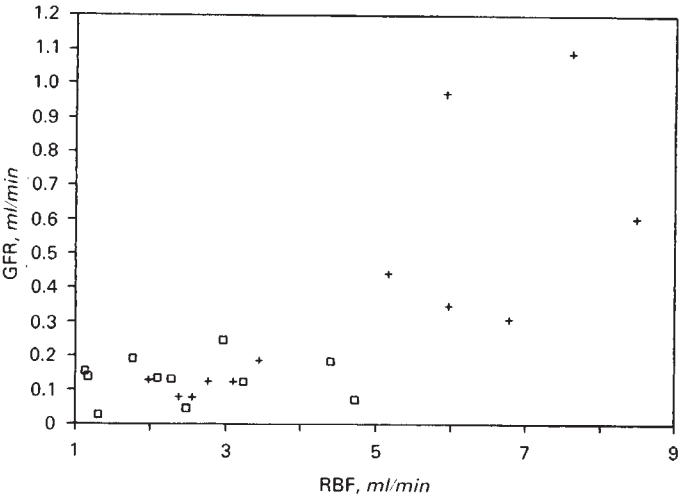

Fig. 5. *Glomerular filtration rate (GFR) as a function of renal blood flow (RBF) for the left (hydronephrotic) kidney of water-drinking (□) and enalapril (+) groups.* Each point represents one animal.

enalapril administration suggests that nephron response is heterogeneous. India ink has been used to estimate glomerular perfusion in a number of previous studies of functional renal development and response to renal injury [33–36]. Although absence of detectable India ink cannot be interpreted as a total lack of blood flow to a glomerulus, it is reasonable to conclude a significant qualitative difference in perfusion between glomeruli containing and lacking identifiable carbon particles. It is unlikely that India ink would significantly alter the rheologic properties of blood flow to the kidneys, because the amount injected represents only 5% of the blood volume. Since converting enzyme inhibition increased total number of perfused glomeruli of both kidneys of normal animals, it is likely that the previously described maturational increase in number of perfused glomeruli in this species [5] is controlled or modulated by ANG II. Although it is possible that higher levels of circulating ANG II present in early postnatal development [16] may contribute to reduced glomerular perfusion in the normal or hydronephrotic kidney, the accelerated increase in number of perfused glomeruli of the hypertrophic contralateral kidney demonstrates the importance of intrarenal factors in the response to ANG II. Hornych, Beaufils, and Richet [37] have demonstrated previously heterogeneous glomerular vasoconstrictor response to exogenous ANG II in the rat, and others have shown unevenly distributed preglomerular resistance [38] and single nephron GFR [39] after release of unilateral ureteral obstruction. Undetectable perfusion of 26% of glomeruli in the obstructed guinea pig kidney is also consistent with patchy preglomerular vasoconstriction. Although ANG II appears to act preferentially on the efferent glomerular arteriole [40], afferent arteriolar constriction may also develop when systemic or locally formed ANG II levels are increased [41].

Because enalapril administration had no effect on filtration fraction of the obstructed kidney, GFR increased significantly in animals with elevated RBF due to converting enzyme inhibition. Although it is possible that filtration fraction was underestimated in obstructed kidneys due to tubular inulin leakage [42], it is unlikely that enalapril significantly altered tubular permeability to inulin. If by reducing endogenous ANG II formation, enalapril decreased efferent glomerular arteriolar resistance, this effect was masked by afferent arteriolar dilation [41] and/or increased ultrafiltration coefficient [43]. An effect of enalapril on the latter is likely because ultrafiltration coefficient is reduced in rats with mild CPUO [14] and in neonatal guinea pigs with CPUO and contralateral nephrectomy [4].

Despite reduction in MAP due to systemic vasodilation, enalapril administration had no effect on somatic or renal growth up to 8 weeks of age (which represents adulthood in this species). While the obstructed left kidney did not increase in weight after 3 weeks of age, the left ureter continued to dilate, and the right kidney underwent progressive compensatory hypertrophy. Furthermore, there was no effect of converting enzyme inhibition on the severity of hydronephrosis as measured by ureteral diameter and intraureteral hydrostatic pres-

sure. This is remarkable in view of the significant increase in RBF and GFR of the obstructed kidney in animals receiving enalapril, and indicates that impairment of renal function due to CPUO may be reversible despite growth arrest of the kidney. In adult rats subjected to temporary complete unilateral ureteral obstruction and studied 3 months after relief of obstruction, chronic captopril administration resulted in enhanced renal growth as well as improved inulin and para-aminohippurate clearances [9]. It is possible that following release of CPUO, growth of the neonatal kidney would also be promoted by converting enzyme inhibition.

In summary, prolonged ANG converting enzyme inhibition with enalapril selectively increased blood flow to the neonatal kidney with ipsilateral CPUO. Nephron perfusion response to converting enzyme inhibition was heterogeneous, evidenced by an increase in number of glomeruli containing India ink injected in vivo. Glomerular filtration rate of the obstructed kidney was increased in those animals with increased RBF. Despite these hemodynamic effects, the obstructed kidney failed to show enhanced growth, and severity of hydronephrosis was unaltered even after 6 weeks of enalapril treatment. It appears that in the neonatal guinea pig, the proportion of perfused glomeruli in each kidney is modulated by activity of the renin-angiotensin system, as well as by the stimulus of compensatory renal hypertrophy [3, 5]. The marked differences in hemodynamic adaptation of left and right kidneys of animals with unilateral CPUO indicates that the intrarenal milieu is of greater importance than the influence of circulating factors. Although these observations suggest strongly that locally formed ANG II contributes to vasoconstriction in unilateral CPUO of the neonate, additional vasoconstrictors, such as thromboxanes, may also be involved.

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