Dose Effect of Captopril on Renal Hemodynamics and Proteinuria in Conscious, Partially Nephrectomized Rats (42863)

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Abstract. **The effect of varying doses of captopril, an angiotensin I-converting enzyme inhibitor, on renal hemodynamics, systemic arterial pressure, and the progression of chronic renal disease in conscious, three-quarter nephrectomized adult male Sprague-Dawley rats was studied. Six weeks following nephrectomy (Week 0), rats were randomly divided into five groups. Groups 2 ($n = 8$), 3 ($n = 8$), 4 ($n = 9$), and 5 ($n = 5$) were given 5, 10, 20, and 40 mg/kg captopril, respectively, daily in drinking water. Group 1 ($n = 7$) and sham-operated controls ($n = 7$) were given water only. On Weeks −6, 0, 2, and 4, renal function was assessed by 24-hr urinary protein excretion and plasma creatinine. Systolic blood pressure was measured at these times by the tail cuff method. Following Week 4, glomerular filtration rate and effective renal plasma flow were measured in conscious rats by single injection clearance of [^{3}H]inulin and [^{14}C]tetraethylammonium bromide, respectively. Group 1 had significantly higher ($P < 0.05$) 24-hr urinary protein excretion, plasma creatinine, and systolic pressure compared with Group 5 and controls by Week 4, whereas values for these parameters for Groups 2–4 ranged between these extremes. Although systolic pressures were not significantly different ($P > 0.05$), Group 2 had significantly lower proteinuria than Group 1 ($P < 0.05$) at Week 4. Total kidney glomerular filtration rate was similarly decreased in Groups 1–5 compared with control rats. Total kidney effective renal plasma flow was higher in captopril-treated groups than in Group 1, whereas systolic blood pressure was similar or lower, indicating that captopril reduced renal vascular resistance. Furthermore, unlike Groups 1–3, the groups receiving higher doses of captopril (4 and 5) did not develop anemia associated with chronic renal disease. In conclusion, captopril attenuated renal functional deterioration in a dose-related manner. The effect on proteinuria was evident at low doses of captopril which did not significantly reduce systemic blood pressure and was accompanied by an increase in effective renal plasma flow and a decrease in renal vascular resistance.**
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Systemic and intraglomerular hypertension have been implicated as factors contributing to the progressive deterioration of renal function in chronic renal disease (1–3). Intraglomerular hypertension is accompanied by increases in single nephron glomerular filtration rate (SNGFR) and capillary plasma flow rate (4). Antihypertensive therapeutic regimes with propranolol (5), clonidine (6), guanethidine-hydralazine (2), reserpine-hydrochlothiazide-hydralazine (7), or angiotensin-converting enzyme (ACE) inhibitors (8, 9) have proven variably efficacious in retarding the progression of experimental chronic renal disease. The ACE inhibitors, enalapril and captopril, attenuate the progression of renal disease in the renal ablation model (8, 9). However, captopril appears to be superior to either clonidine or propranolol in lessening the severity of morphologic lesions that develop in partially nephrectomized rats (5, 6, 9). The differences in retarding progression are not directly correlated with control of the systemic hypertension in all cases. For example, compared with untreated hypertensive controls, treatment with propranolol decreases the severity of proteinuria and delays the onset of hypertension in partially nephrectomized rats (5). This difference in proteinuria is maintained even after the propranolol-

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treated rats eventually develop hypertension. Enalapril is also more effective than the reserpine-hydralazine-hydrochlorothiazide combination despite equivalent systemic blood pressure control (7). However, dissociation of the relative contribution of the systemic antihypertensive effects of ACE inhibition to the slowing of renal functional deterioration has not been shown using subpressor doses of ACE inhibitors.

Micropuncture studies in anesthetized, partially nephrectomized rats have shown that the beneficial effects of ACE inhibitors are associated with a decrease in systemic hypertension and transcapillary hydrostatic pressure, while SNGFR is maintained (8). Barbiturate anesthesia is associated with decreases in systemic arterial pressure, glomerular filtration rate (GFR), and effective renal plasma flow (ERPF; 10–12). Pretreatment with an ACE inhibitor prevents the reductions in GFR and ERPF, indicating that an anesthesia-induced activation of the renin-angiotensin system may increase renal vascular resistance. Consequently, anesthesia may alter the measured relationship between renal hemodynamics and systemic arterial pressure.

The purpose of this study was to examine the effects of varying low doses of captopril on renal hemodynamics in conscious, unrestrained, partially nephrectomized rats. This was done to attempt to dissociate the systemic depressor effects of ACE inhibition from effects on intrarenal hemodynamics and to eliminate the potentially confounding effects of anesthesia.

Materials and Methods

Fifty-four male Sprague-Dawley rats (Charles River Laboratories, Inc., Wilmington, MA) weighing 322–450 g were used. They were housed in pairs and were provided with standard rat chow (Wayne Lab-Blocks; Allied Mills Inc., Chicago, IL) and drinking water *ad libitum* for the duration of the study. The rats were allowed a 2-week acclimation period, after which time they were placed in metabolic cages for a 24-hr sampling period (Week −6). At the end of the sampling period, the rats were weighed and 24-hr urine output and water intake were measured. The rats were lightly anesthetized with ether and a heparinized blood sample was obtained by amputation of the tail tip. Plasma creatinine concentrations were measured by an alkaline picrate method (Beckman creatinine analyzer II; Beckman Instruments Inc., Fullerton, CA). Urinary protein concentrations were determined by the Coomassie brilliant blue dye-binding technique (Bio-Rad protein assay; Bio-Rad Laboratories, Richmond, CA).

After baseline data were obtained, 45 rats underwent surgical ablation of approximately three-quarters of their renal mass. The rats were anesthetized with 130 mg/kg ketamine hydrochloride and 0.05 mg/kg acepromazine maleate, given intramuscularly. The left kidney was exteriorized through a flank incision, and a purse string suture was placed around the poles of the kidney so that approximately one-quarter of the kidney's mass was distal to each ligature. Renal parenchyma distal to the ligatures was excised and wet weight of the removed tissue was determined. The rats were allowed to recover for 48 hr, after which they were again anesthetized using acepromazine and ketamine. The right kidney was exteriorized through a flank incision and was removed following placement of a ligature around the renal artery and vein. The right kidney was weighed, and the percentage of renal parenchyma removed was calculated by dividing the total renal parenchymal mass excised by two times the weight of the right kidney and multiplying by 100. Nine rats (controls) underwent sham operations in which the kidneys were exposed by a flank incision and replaced in the abdominal cavity.

The rats were allowed to recover for 6 weeks, at which time the 24-hr metabolic cage studies were repeated as previously described (Week 0). Five groupings of nine partially nephrectomized rats, matched by similar levels of proteinuria were formed, and rats with these five groups were then randomly assigned to five different treatment groups ($n = 9$ for each treatment group). Groups 2–5 were given 5 mg/kg, 10 mg/kg, 20 mg/kg, and 40 mg/kg captopril, respectively, in the drinking water for a total of 4 weeks. Captopril solutions were prepared fresh daily, and dose was adjusted for weight gain and water intake on a weekly basis. Group 1 and control rats were given water only. Metabolic cage studies were repeated on Weeks 2 and 4. Blood samples were not obtained on Week 2. Systolic blood pressure was measured by the tail cuff method (13) on Weeks −6, 0, 2, and 4. Blood pressure determinations were separated from other manipulations by a minimum period of 2 days.

At the end of the treatment period, GFR and ERPF were determined using a single injection, double isotope method as described previously (14). The technique, in brief, is as follows. The day before the clearance studies were performed, the rats were anesthetized with ketamine (130 mg/kg) and acepromazine (0.05 mg/kg), given intramuscularly. A carotid artery and jugular vein were catheterized using 20-cm lengths of PE50 and PE90 polyethylene tubing, respectively. The catheters were tunneled subcutaneously to the top of the head and were secured out of the rat's reach by suture. The rats were allowed to recover for 24 hr, during which time free access to food and water was allowed and all rats were observed to eat and drink.

[*methoxy*-^{3}H]Inulin with a specific activity of 4.2 μCi/g for the determination of GFR and [1-^{14}C]tetraethylammonium bromide with a specific activity of 47 μCi/mmol for determination of ERPF were obtained in preweighed, sealed vial lots of 250 μCi each (New England Nuclear, Boston, MA). Sterile normal saline was added to obtain a solution of 2.0 μCi/ml. Both stock solutions were stored at 5°C. Infusate was pre-

pared by mixing equal volumes of each stock solution. Each rat received a dose of 1.0 μCi/kg of each isotope or a bolus of 1.0 ml/kg infusate.

The rats were placed in metabolic cages and the catheters were attached to extension tubing and three-way valves to facilitate handling. The infusate was administered via the jugular catheter over 15 sec, and the catheter was flushed with a similar volume of sterile heparinized saline. Blood samples (200 μl) were collected from the carotid artery catheter at 2, 5, 10, 15, 20, 30, 40, 50, and 60 min into 1.5-ml lithium-heparinized polyprolene microsample tubes. The catheter was flushed with 200 μl of heparinized saline to clear the blood from the catheter and to replace blood volume after each sampling. Samples were centrifuged at 700*g* for 2 min.

A 20-μl aliquot of infusate and 100-μl aliquots of plasma were counted for 10 min each using a two-channel dual-label automatic-quench correction program (Beckman model LS1801; Beckman Instruments Inc.). Quench corrected disintegrations per minute were used for all calculations. A computer program using the method of least-squares analysis was used to construct a plasma radioactivity disappearance curve. Using a modified single-exponential, one-compartment mathematical model, the area under the disappearance curve was calculated as described previously (15). Clearance rate of each isotope-labeled solute was then calculated as the dose of the appropriate isotope administered divided by the area under the curve.

Prior to beginning the clearance studies, a 1.5-ml blood sample, anticoagulated with EDTA, was collected on ice from the carotid artery catheter for hematocrit (Hct), plasma protein, and plasma renin activity (PRA) determinations. Plasma protein was determined by refractometry (AO TS meter; American Optical Co., Keene, NH). For PRA measurement, blood samples were centrifuged at 1200*g* for 15 min at 4°C and plasma was immediately frozen and stored at −20°C until the PRA was assayed using a commercial radioimmunoassay (RIANEN Assay System; New England Nuclear), a modification of a technique by Haber *et al.* (16).

Following the clearance studies, rats were euthanatized with an overdose of pentobarbital. The kidneys, right ventricle, and left ventricle plus interventricular septum were weighed and the organ weight/100 g body wt ratios were calculated. Renal plasma flow/g kidney (RPF/g kidney) was calculated.

Group and time effects for the functional data and group effects for isotope clearance data, PRA, and organ weight/100 g body wt ratios were analyzed by multiple analysis of variance and Fisher's least significant difference test for mean separation.

Results

There were no differences ($P > 0.05$) in percentage of renal parenchyma removed between groups (68.9 ± 1.1, 67.1 ± 1.3, 69.0 ± 3.1, 67.7 ± 0.6, 67.9 ± 0.8% for Groups 1–5, respectively). Five rats died due to renal failure during the last week of the study (one each from Groups 1–3, two from Group 4). One Group 1 rat was eliminated due to urinary calculi formation and bladder obstruction. Two rats each from Group 5 and controls were eliminated due to technical difficulties during the clearance studies. There were no significant differences ($P > 0.05$) in any parameter, including 24-hr urinary protein excretion, measured between groups for baseline data (Week −6) or between Groups 1, 2, 3, 4, or 5 at the time of randomization (Week 0) for either the survivors or all members of the respective groups. Only data from rats that completed the study are presented in the following sections and tables (n = 7, 8, 8, 9, 5, and 7 for Groups 1, 2, 3, 4, and 5 and controls, respectively). Although changes in the numbers of rats in the groups due to death appeared to skew the data, there were no significant differences ($P > 0.05$) in 24-hr urinary protein excretion between Groups 1, 2, 3, 4, and 5 when treatment began.

Group 1 had a significant increase ($P < 0.05$) in systolic pressure from Week 0 to Week 4 (Table I). On Week 4, systolic pressure for Group 1 was significantly higher than that of Groups 3–5 and the controls ($P < 0.05$), but was not significantly different from that of Group 2. Group 5 also had a significantly lower systolic pressure than that of Group 1 on Week 2. Systolic pressure for Group 2 at Week 4 was significantly higher than its value at Week 2 ($P < 0.05$). There was no significant ($P < 0.05$) increase in systolic pressure between Weeks 0 and 4 in Groups 3–5 and the controls. Group 1 had significantly elevated ($P < 0.05$) 24-hr urinary protein excretion (Table II) compared with Group 5 and controls on Weeks 2 and 4. Values for urinary protein excretion of Groups 2–4 ranged between Groups 1 and 5. Only Group 1 had significantly ($P < 0.05$) greater proteinuria on Week 4 compared with its own value on Week 0. Plasma creatinine concentrations were significantly ($P < 0.05$) increased in

Table I. Effect of Partial Nephrectomy and Captopril on Systolic Blood Pressure (mm Hg) in Rats

Group	Week			
	−6	0	2	4
Control (n = 7)	130 ± 7	140 ± 6	136 ± 7[a,b]	150 ± 8[a,b]
1 (n = 7)	123 ± 5	148 ± 11	157 ± 17[a]	189 ± 19[c]
2 (n = 8)	129 ± 5	157 ± 12	147 ± 14[a,b]	178 ± 14[a,c]
3 (n = 8)	114 ± 9	150 ± 10	146 ± 14[a,b]	149 ± 17[b]
4 (n = 9)	128 ± 4	152 ± 6	138 ± 8[a,b]	138 ± 6[b]
5 (n = 5)	131 ± 6	158 ± 4	123 ± 2[b]	130 ± 4[b]

Note. Data expressed as mean ± SEM. Group 1, no treatment; Group 2, 5 mg/kg; Group 3, 10 mg/kg; Group 4, 20 mg/kg; Group 5, 40 mg/kg of captopril daily. Treatments began at Week 0 which was 6 weeks after partial nephrectomy.

[a,b,c] At a given time, treatment groups marked with different letters are significantly different ($P < 0.05$).

partially nephrectomized groups compared with controls on Week 0 (Table III) and compared with their Week −6 values. On Week 4, plasma creatinine concentration in Group 1 was significantly greater ($P < 0.05$) than that of Group 5 and controls. Values for Groups 2–4 ranged between these two extremes. Control rats showed no change in plasma creatinine concentration during the study and only Group 1 of the partially nephrectomized rats had significantly ($P < 0.05$) increased plasma creatinine concentrations compared with its own Week 0 values.

There were no significant differences ($P > 0.05$) in plasma protein concentrations between groups at the beginning of the clearance studies (Table IV). Groups 1–3 were significantly ($P < 0.05$) anemic compared with control rats (Table IV). There were no significant differences in Hct between controls and Groups 4 and 5. Total kidney GFR and ERPF were decreased significantly ($P < 0.05$) in all nephrectomized groups compared with control rats (Table IV). Although GFR tended to increase with increasing captopril dose, there were no significant differences ($P > 0.05$) in GFR between Groups 1, 2, 3, 4, and 5. Group 5 had a significantly greater ($P < 0.05$) ERPF than Group 1 and the other values ranged in between. There was no significant difference ($P > 0.05$) in filtration fraction between Group 1 and controls. All captopril-treated groups had lower filtration fractions than either the Controls or Group 1, but the differences were statistically significant for Groups 2 and 3 only (Table IV). RPF/g kidney was significantly decreased ($P < 0.05$) in Group 1 compared with Group 5 and controls. PRA values for all captopril-treated groups were higher than those of controls or nontreated nephrectomized rats, but the only statistically significant differences were between nontreated nephrectomized rats and rats receiving 20 or 40 mg/kg of captopril (Table IV).

Body weight increased in all groups over time. At Week 4, there were no significant differences in body weight between control rats and any group treated with captopril (Table V). There were no significant differences in kidney weight/100 g body wt or right ventricle weight/100 g body wt between Groups 1, 2, 3, 4, and 5 (Table V). Controls had significantly greater total kidney weight/100 g body wt than any nephrectomized group. There were no significant differences in right ventricle weight/100 g body wt between controls and Groups 1–5 (Table V). Group 1 had significantly greater

Table II. Effect of Partial Nephrectomy and Captopril on Urinary Protein Excretion (mg/24 hr) in Rats

Group	Week			
	−6	0	2	4
Control ($n = 7$)	18 ± 1	22 ± 2^{a}	21 ± 2^{a}	17 ± 3^{a}
1 ($n = 7$)	19 ± 2	112 ± 49^{a,b}	195 ± 60^{b}	282 ± 84^{c}
2 ($n = 8$)	19 ± 2	107 ± 36^{a,b}	105 ± 33^{a,b}	142 ± 50^{b}
3 ($n = 8$)	19 ± 1	94 ± 27^{a,b}	117 ± 48^{a,b}	153 ± 60^{b}
4 ($n = 9$)	21 ± 1	144 ± 54^{b}	108 ± 30^{a,b}	113 ± 38^{a,b}
5 ($n = 5$)	19 ± 1	56 ± 18^{a,b}	38 ± 7^{a}	45 ± 6^{a,b}

Note. Data expressed as mean ± SEM. Group 1, no treatment; Group 2, 5 mg/kg; Group 3, 10 mg/kg; Group 4, 20 mg/kg; Group 5, 40 mg/kg of captopril daily. Treatments began at Week 0 which was 6 weeks after partial nephrectomy.

^{a,b,c} At a given time, treatment groups marked with different letters are significantly different ($P < 0.05$).

Table III. Effect of Partial Nephrectomy and Captopril of Plasma Creatinine (mg/dl) in Rats

Group	Week		
	−6	0	4
Control ($n = 7$)	0.26 ± 0.03	0.24 ± 0.02^{a}	0.33 ± 0.02^{a}
1 ($n = 7$)	0.30 ± 0.02	0.67 ± 0.07^{b}	1.09 ± 0.27^{b}
2 ($n = 8$)	0.26 ± 0.02	0.74 ± 0.09^{b}	0.88 ± 0.26^{b,c}
3 ($n = 8$)	0.31 ± 0.04	0.69 ± 0.06^{b}	0.70 ± 0.05^{c}
4 ($n = 9$)	0.26 ± 0.02	0.79 ± 0.10^{b}	0.70 ± 0.07^{c}
5 ($n = 5$)	0.22 ± 0.02	0.60 ± 0.04^{b}	0.64 ± 0.07^{a,c}

Note. Data expressed as mean ± SEM. Group 1, no treatment; Group 2, 5 mg/kg; Group 3, 10 mg/kg; Group 4, 20 mg/kg; Group 5, 40 mg/kg of captopril daily. Treatments began at Week 0 which was 6 weeks after partial nephrectomy.

^{a,b,c} At a given time, treatment groups marked with different letters are significantly different ($P < 0.05$).

Table IV. Renal Hemodynamics in Conscious, Partially Nephrectomized Rats Given Various Doses of Captopril for 4 Weeks

	Group					Control ($n = 7$)
	1 ($n = 7$)	2 ($n = 8$)	3 ($n = 8$)	4 ($n = 9$)	5 ($n = 5$)	
Hct (%)	35.1 ± 3.3^{a}	39.8 ± 0.9^{a,b}	38.8 ± 0.8^{a,c}	43.9 ± 0.9^{d}	41.8 ± 1.7^{b,c,d}	45.3 ± 1.4^{d}
PP (g/dl)	6.0 ± 0.5	6.2 ± 0.2	6.5 ± 0.3	6.1 ± 0.2	5.9 ± 0.3	6.7 ± 0.3
GFR (ml/min/kg)	2.69 ± 0.36^{a}	2.77 ± 0.38^{a}	2.86 ± 0.36^{a}	3.16 ± 0.30^{a}	3.61 ± 0.39^{a}	6.00 ± 0.32^{b}
ERPF (ml/min/kg)	7.02 ± 0.90^{a}	8.55 ± 0.95^{a,b}	8.66 ± 0.69^{a,b}	8.22 ± 0.63^{a,b}	10.97 ± 0.47^{b}	15.66 ± 0.84^{c}
FF	0.39 ± 0.03^{a}	0.32 ± 0.02^{b}	0.32 p m0.02^{b}	0.36 ± 0.02^{a,b}	0.33 ± 0.02^{a,b}	0.39 ± 0.02^{a}
RPF/g kidney (ml/min/g)	1.48 ± 0.22^{a}	2.06 ± 0.24^{a,b}	2.07 ± 0.25^{a,b}	2.03 ± 0.22^{a,b}	2.58 ± 0.17^{b}	2.63 ± 0.21^{b}
PRA (ng/ml/hr)	6.02 ± 1.76^{a}	19.82 ± 9.30^{a,b}	16.42 ± 4.30^{a,b}	22.50 ± 3.60^{b}	26.87 ± 2.75^{b}	14.81 ± 4.20^{a,b}

Note. Data expressed as mean ± SEM. PP, plasma protein; FF, filtration fraction. Group 1, no treatment; Group 2, 5 mg/kg; Group 3, 10 mg/kg; Group 4, 20 mg/kg; Group 5, 40 mg/kg of captopril daily.

^{a,b,c,d} Treatment groups marked with different letters are significantly different ($P < 0.05$).

Table V. Body Weight, Organ Weights, Water Intake, and Urine Output at Week 4

	Group					Control ($n = 7$)
	1 ($n = 7$)	2 ($n = 8$)	3 ($n = 8$)	4 ($n = 9$)	5 ($n = 5$)	
Body wt (g)	$498^{a} \pm 31$	$548^{b} \pm 23$	$500^{a,b} \pm 14$	$519^{a,b} \pm 18$	$537^{a,b} \pm 27$	$548^{a,b} \pm 25$
Kidney (g/100 g body wt)	$0.49^{a} \pm 0.02$	$0.42^{a} \pm 0.02$	$0.45^{a} \pm 0.03$	$0.45^{a} \pm 0.03$	$0.43^{a} \pm 0.02$	$0.60^{b} \pm 0.02$
Right vt (g/100 g body wt)	0.07 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.07 ± 0.01	0.06 ± 0.01	0.06 ± 0.02
Left + IVS (g/100 g body wt)	$0.23^{a} \pm 0.02$	$0.21^{a,b} \pm 0.02$	$0.20^{a,b} \pm 0.02$	$0.20^{a,b} \pm 0.02$	$0.17^{b} \pm 0.01$	$0.18^{a,b} \pm 0.01$
24-hr urine (ml/100 g body wt)	$8.0^{a} \pm 1.2$	$6.7^{a,b} \pm 0.7$	$8.4^{a} \pm 0.9$	$6.9^{a,b} \pm 0.8$	$6.0^{a,b} \pm 0.2$	$4.4^{b} \pm 1.0$
24-hr water (ml/100 g body wt)	10.3 ± 1.4	10.5 ± 0.8	11.7 ± 0.9	11.2 ± 0.8	10.4 ± 0.8	8.3 ± 1.4

Note. Data expressed as mean ± SEM. Right vt, right ventricle; left + IVS, left ventricle plus interventricular septum. Group 1, no treatment; Group 2, 5 mg/kg; Group 3, 10 mg/kg; Group 4, 20 mg/kg; Group 5, 40 mg/kg captopril daily.
[a,b] Treatment groups with different letters are significantly different.

left ventricle plus interventricular septum weight/100 g body wt ratios than Group 5 (Table V). However, there were no significant differences in left ventricle plus interventricular septum weight/100 g body wt between Groups 1 or 5 and the other nephrectomized groups or between the controls and any of the nephrectomized groups (Table V). At Week 4, there were no significant differences in 24-hr urine output between any of the nephrectomized groups (Table V). All nephrectomized groups had higher mean values for urine output than the control rats, but the differences were significant for Groups 1 and 3 only. Nephrectomized groups also had higher levels of water intake than control rats, but these differences were not significant.

Discussion

Rats were treated with varying doses of captopril beginning 6 weeks after partial nephrectomy; a time when renal functional deterioration was well established but prior to significant increases in systolic pressure. At appropriate doses, captopril therapy attenuated renal functional deterioration, as manifested by lower plasma creatinine concentrations and a lesser degree of proteinuria, while maintaining systolic pressure near normotensive levels. Concurrent hypertension will accelerate renal functional loss in chronic renal disease (2, 17), and, in this study, the most marked differences in 24-hr urinary protein excretion and plasma creatinine in partially nephrectomized rats occurred between groups with the greatest difference in systolic pressure (Group 1 vs 5 on Week 4). Exposure of Group 1 rats to sustained systemic hypertension probably contributed to their more rapid deterioration in renal function as well as development of cardiac hypertrophy. The lowest dose of captopril (5 mg/kg) also significantly reduced proteinuria as compared with untreated, partially nephrectomized rats, even though systolic pressures for these two groups were not different during treatment. Twenty-four-hour urinary protein excretion tended to decrease with increasing captopril dose in those groups receiving 10, 20, and 40 mg/kg, while systolic pressure was maintained at normotensive levels. The reduction in proteinuria by the lowest dose implies that the mechanism of action of captopril in reducing proteinuria is, at least in part, independent of its action to reduce systemic hypertension.

Total ERPF and RPF/g kidney were the hemodynamic parameters most altered by captopril therapy; both increased with dose. This was in association with a lowering of systolic pressure, indicating that renal vascular resistance was decreased, presumably by vasodilation in the remnant kidney. Total GFR was decreased in all groups of partially nephrectomized rats and tended to increase slightly with increasing dose of captopril. These results are in agreement with micropuncture studies with anesthetized rats demonstrating that administration of an ACE inhibitor, enalapril, in a model of renal parenchymal ablation will decrease systemic arterial pressure and transcapillary hydrostatic pressure while preserving SNGFR and total kidney GFR (8). The decrease in intraglomerular hypertension and palliative effects of ACE inhibition in that study were attributed to normalization of systemic blood pressure and subsequent decrease in transcapillary hydrostatic pressure. Our data in conscious rats suggest that beneficial effects of ACE inhibition may also occur in the absence of significant differences in systolic pressure and renal perfusion pressure. Captopril may exert an effect on glomerular permselectivity possibly by lower intraglomerular pressure, independent of its effects on systemic pressure. This is further supported by studies that indicate that captopril is not as effective in reducing proteinuria and the progression of chronic renal disease in puromycin aminonucleoside and adriamycin nephrosis models in which hyperfiltration does not develop (18, 19).

GFR values, although not significantly different among captopril-treated groups, tended to increase with increasing dose. This might be explained by improved plasma flow and/or increases in ultrafiltration coefficient (K_f). K_f was documented to increase subsequent to ACE inhibition by enalapril, an action that was not

accounted for by increases in glomerular tuft size (8). Administration of angiotensin II will decrease K_f (20) and increases in this parameter by ACE inhibitors may reflect inhibition of angiotensin II formation and action within the glomerulus.

The lower filtration fractions in some captopril-treated groups are similar to reports of reductions in filtration fractions with enalapril treatment of similar duration (8). These differences suggest an effect on the efferent-afferent arteriolar resistance ratio, on K_f, or a combination thereof. The decreased filtration fraction was observed at the lowest dose of captopril (5 mg/kg body wt) which had no significant effect on systemic arterial pressure. This dissociation between renal and systemic hemodynamic effects also supports the conclusion that captopril has an intrarenal effect, independent of its effect on systemic pressure.

There were no significant differences in plasma protein concentrations between groups when the clearance studies were performed. Differences in volume expansion, therefore, probably did not contribute to differences in renal hemodynamics between groups despite variations in PRA between the different groups. PRA values in the controls were somewhat higher than usual when compared with samples obtained by decapitation for other studies in our laboratory (21). This may be due to the environmental setting. However, the renin-angiotensin system behaved as expected when PRA increased with captopril treatment. This increase may be due to inhibition of ACE and feedback within the renin-angiotensin system (22). PRA of untreated, partially nephrectomized rats was lower but not significantly different from values for control rats, indicating that the hypertension seen in this group was not renin dependent.

Rats in the untreated partially nephrectomized group and in those groups receiving the lower doses of captopril had lower Hct. This suggests that overall functional renal parenchyma, as well as glomerular function, is better preserved in those groups receiving long-term, higher doses of captopril. This is in contrast to reports suggesting that captopril therapy may worsen anemia associated with chronic renal disease by decreasing erythropoietin levels (23). Further investigation is needed to clarify the relationship between ACE inhibitors and erythropoiesis. Slower deterioration of functional residual renal parenchyma may also partially explain the slightly greater GFR seen at the end of the study in groups receiving higher doses of captopril.

Captopril attenuated renal functional deterioration and proteinuria in a dose-related manner. Hemodynamic alterations in captopril-treated conscious rats included an increase in ERPF, decrease in renal vascular resistance, decrease in filtration fraction, and maintenance of GFR. At appropriate doses of captopril, changes in filtration fraction and degree of proteinuria may occur without maintaining normotensive systemic blood pressure. These low dose effects of captopril suggest that it has a direct intrarenal effect on the determinants of vascular resistance and glomerular permselectivity in the remnant kidney.

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