Effects of the angiotensin converting enzyme inhibitor benazepril in cats with induced renal insufficiency

Scott A. Brown, VMD, PhD; Cathy A. Brown, VMD, PhD; Gilbert Jacobs, DVM; Jean Stiles, DVM, MS; Rim S. Hendi, BS; Shawn Wilson, BS

Objective—To determine effects of the angiotensin converting enzyme inhibitor benazepril in cats with induced renal insufficiency.

Animals—32 cats.

Procedure—Renal mass was surgically reduced, and cats were assigned to 1 of 4 eight-cat groups. Group 1 received placebo, whereas groups 2, 3, and 4 received benazepril hydrochloride orally once daily for approximately 6.5 months at the following doses: group 2, 0.25 to 0.50 mg/kg of body weight; group 3, 0.50 to 1.00 mg/kg; and group 4, 1.00 to 2.00 mg/kg.

Results—Compared with cats that received placebo, mean systolic arterial blood pressure was significantly less and GFR significantly greater in cats that received benazepril. Glomerular capillary pressure and the ratio of efferent to afferent arteriolar vascular resistance were also significantly less in treated cats. However, histologic differences in renal specimens were not detected.

Conclusions and Clinical Relevance—Treatment with benazepril sustained single nephron GFR in remnant nephrons of cats with induced renal insufficiency. Administration of benazepril was also associated with a small but significant reduction in degree of systemic hypertension and an increase in whole kidney GFR. Benazepril may be an effective treatment to slow the rate of progression of renal failure in cats with renal disease. (Am J Vet Res 2001;62:375–383)

It is generally accepted that chronic renal disease in animals often progresses to end-stage renal failure even when the primary cause of renal disease is eliminated. In rodents, the inherently progressive nature of renal disease has been partly attributed to adaptive changes in remnant nephron structure and function that develop following renal injury. Results of previous studies in our laboratory indicate that cats with induced chronic renal insufficiency develop glomerular hypertension and hypertrophy similar to that observed in rats following partial nephrectomy. In humans, laboratory rodents, and diabetic dogs, a renoprotective effect of angiotensin converting enzyme (ACE) inhibition has been identified and linked to reductions in systemic arterial pressure, glomerular capillary pressure, or glomerular volume.

The goal of this study was to address the hypothesis that ACE inhibition would limit the extent of systemic and glomerular hypertension that develops following partial renal ablation in cats. To achieve this goal, renal clearance, micropuncture, and radiotelemetric blood pressure examinations were performed in cats with induced renal insufficiency treated for 6 months with either benazepril hydrochloride or placebo.

Materials and Methods

Animals—Forty-five 11- to 30-month-old cats (23 sexually intact females; 22 sexually intact males), initially weighing 3.64 ± 0.20 kg (mean ± SEM), were procured from a commercial supplier. Health was assessed by physical examination and determinations of plasma electrolyte, BUN, and creatinine concentrations and the urine protein-to-creatinine concentration ratio. Cats were fed a diet that contained 28% protein on a dry-weight basis. Initially, 70 kcal of food/kg of body weight was offered to each cat each day, and daily food consumption was determined and recorded. Food intake was adjusted on a monthly basis without knowledge of treatment group, with a goal of maintaining a stable body weight.

Cats were entered into the study in 2 groups. The first group was entered into the protocol approximately 4 months before the second group. All research was conducted in accordance with the guidelines from the National Institutes of Health after approval by the Institutional Animal Care Committee at the University of Georgia.

Animal preparation—Radiotelemetric implants for blood pressure measurements were surgically placed as described. Briefly, a radiotelemetric implant was placed in each of the 45 cats by inserting a catheter in the right femoral artery and suturing the implant body in the subcutaneous space in the ipsilateral flank. Approximately 3 weeks later, all cats underwent right nephrectomy and infarction of approximately five sixths of the left kidney by ligation of a variable number of branches of the renal artery, a procedure hereafter referred to as partial nephrectomy. Biopsy specimens were obtained from the left kidney at this time. Seven cats were excluded from the study because they developed anorexia, upper respiratory tract disease, or both after partial nephrectomy.

Experimental protocol—Two to 3 weeks after partial nephrectomy, glomerular filtration rate (GFR) was determined for the remaining 38 cats by measuring the urinary clearance of inulin. The 32 cats (17 sexually intact females;
15 sexually intact males) with the lowest GFR were randomly assigned to 1 of 4 eight-cat groups that subsequently received a vehicle placebo (group 1) or benazepril (groups 2 through 4) orally once daily for 6 to 7 months. The 6 cats with the highest GFR were excluded from the study. Benazepril was administered as the hydrochloride salt in 1.25-mg increments. Doses were selected on the basis of results of a previous study in clinically normal cats. Target daily doses of benazepril were 0.25 to 0.50 mg/kg (group 2), 0.50 to 1.00 mg/kg (group 3), and 1.00 to 2.00 mg/kg (group 4). Doses were adjusted on the basis of monthly measurements of body weight.

One cat assigned to group 3 in the first group of cats entered into the study developed rapidly progressive neurologic disease and died during the first month of treatment. Necropsy revealed acute cerebral edema and cerebellar herniation of unknown cause. This cat was replaced by the cat in the second group with the closest matching GFR.

Prior to partial nephrectomy, at the time cats were assigned to treatment groups but before drug administration (baseline), and at monthly intervals throughout the treatment period, plasma concentrations of BUN, creatinine, and electrolytes were measured, blood pressures were determined by use of radiotelemetry, and GFR and renal plasma flow (RPF) were determined by measuring the clearance of inulin and para-aminophippuric acid (PAH), respectively. Ophthalmic examinations and echocardiography were performed before nephrectomy and at months 3 and 6 of the treatment period. Micropuncture examinations for determination of renal hemodynamics were performed and renal biopsy specimens collected at the end of the treatment period. Cats were euthanatized immediately following the micropuncture studies by IV injection of an overdose of sodium pentobarbital.

Radiotelemetry—The radiotelemetry system has been described. The noncompressible fluid within the catheter transmits pressure changes to a pressure transducer in the implant body. Pressure information is then converted to a radio signal, which is acquired by a receiver within the animal’s cage. The receiver is connected to a computer that converts the radio signal modulations into waveform data and the radio signal, which is acquired by a receiver within the animal’s cage, is transmitted to a computer that converts the radio signal modulations into waveform data and determines systolic, diastolic, and mean blood pressures and heart rate, using a data acquisition program.

Radiotelemetry measurements were obtained from ambulatory undisturbed cats by continuous recording for 10 seconds every 5 minutes for approximately 24 hours. Unless otherwise specified, reported values for blood pressure and heart rate represent an average of values recorded over a 24-hour period. We allowed at least 2 weeks after partial nephrectomy before obtaining baseline radiotelemetry measurements. In 1 cat in group 4, the blood pressure implant ceased functioning prior to month-1 measurements; radiotelemetry data from this cat were excluded from statistical analyses.

Biochemical and renal clearance measurements—Blood was obtained by venipuncture and collected into tubes containing approximately 5 U of heparin/ml of blood for subsequent measurement of plasma concentrations of BUN, creatinine, and electrolytes. For determination of GFR and RPF, cats were lightly anesthetized by administration of sodium pentobarbital (30 mg/kg, IV), and indwelling urinary and saphenous venous catheters were placed. Cats received water equal to 2% of body weight (w/vol) by gavage. Following collection of blood into a heparinized tube, 7.5% inulin and 0.375% PAH were administered subcutaneously at doses sufficient to maintain stable plasma concentrations of each compound during urine collections. Two urine samples were obtained beginning 50 minutes after administration of inulin and PAH. Urine was collected for 30 minutes, and concentrations of inulin and PAH were determined. Blood was collected into heparinized tubes at the beginning and end of each 30-minute urine collection period for determination of plasma inulin and PAH concentrations.

Ophthalmic examinations—For ophthalmic examinations, pupils were dilated with 1% tropicamide. Approximately 15 minutes later, cats were sedated with xylazine (0.2 mg/kg, IV) and ketamine (5 mg/kg, IV). The anterior segment was examined with a biomicroscope, and the fundus was examined by use of indirect ophthalmoscopy.

Echocardiography—For echocardiography, cats were sedated with tiletamine/zolazepam (3 mg/kg, IM). Hair over the right thoracic wall at the third to fifth intercostal space near the sternum was clipped, and examinations were performed with cats positioned in right lateral recumbency. Simultaneous 2-dimensional and M-mode echocardiograms were obtained from the right parasternal imaging position, with a 7.5-MHz phased array transducer coupled to an ultrasonograph. Heart rate, left ventricular free wall thickness in diastole and systole, left ventricular chamber dimension in diastole and systole, maximal left atrial dimension, and aortic root dimension were determined as the average of 3 sequential measurements of each variable.

Micropuncture examination—Prior to micropuncture examination, food was withheld from all cats for 16 to 20 hours, and a blood sample was obtained for determination of plasma concentrations of protein, creatinine, and BUN. Cats were anesthetized by administration of sodium pentobarbital (60 mg/kg, IV) and prepared for micropuncture and renal clearance studies as described. An endotracheal tube was inserted, and respiration was regulated mechanically. A catheter was placed in the left femoral vein, and a solution of inulin and PAH (3% inulin and 0.2% PAH in saline [0.9% NaCl] solution) was infused at a rate sufficient to maintain a plasma inulin concentration of approximately 0.8 mg/ml. The renal perfusion pressure (RPP) was measured through a catheter inserted into the femoral artery and advanced into the aorta to the level of the left renal artery. This catheter was connected to a pressure transducer, and output was recorded on a polygraph. Blood samples were also collected through this catheter. The left kidney was exposed through a flank incision, and the renal artery and vein and the ureter were dissected free of adjacent tissue. The ureter was catheterized to allow timed urine collections.

The left kidney was positioned on a lucite holder and prepared for micropuncture by removal of approximately 3 cm2 of renal capsule. This area was continuously bathed with warm (39 C), heparinized, isotonic saline solution dripped through a quartz rod that was used to illuminate the micropuncture field. Flexible tape was placed around the micropuncture field to assist in stabilization. An agar well was placed around the micropuncture field to maintain an isotonic saline solution pool. The remainder of the kidney was covered with warm, saline-soaked gauze and was loosely surrounded with plastic wrap.

Hydrostatic pressures were determined by use of a micropressure servo-null system. Free-flow proximal tubular pressure (Prf), stop-flow proximal tubular pressure (Psr), and peritubular capillary pressure (Prc) were measured at least 3 times in each cat. Free-flow proximal tubular pressure and Prc were measured at the earliest accessible site on the cortical surface of the kidney.

During each procedure, mean arterial pressure was continuously monitored. Two or three timed urine collections of 15 to 30 minutes each were performed during micropuncture examinations for determination of GFR and RPF. A blood
sample was collected at the beginning and end of each timed urine collection for determination of plasma inulin and PAH concentrations.

**Histologic examination**—After micropuncture studies, kidney tissue was excised, stripped of surrounding tissue and capsule, and blotted dry. The scar from the experimentally infarcted area was removed from each remnant kidney by sharp dissection under stereoscopic magnification. The viable portion of the remnant kidney was weighed and fixed in neutral-buffered 10% formalin.

Formalin-fixed tissue specimens obtained at the time of partial nephrectomy and following micropuncture examinations were processed by use of routine histologic methods, and sections were stained with hematoxylin and periodic acid-Schiff or H&E. Fifteen glomeruli in each of 2 sections of renal cortex were examined by a pathologist (CAB) blinded to treatment group. Glomeruli were scored for degree of mesangial matrix expansion, using a numerical scoring system (0 = normal; 1 = mild expansion; 2 = moderate expansion; 3 = severe expansion). For each cat, an overall glomerular score was determined as the mean of these 30 individual glomerular scores. Two sections from each kidney were also evaluated for severity of tubular lesions, interstitial fibrosis, and interstitial cellular infiltrate. A numerical score was assigned (0 = normal; 1 = mild; 2 = moderate; 3 = severe), with the mean score taken as the overall score for that kidney. The planar area of 25 randomly selected glomerular capillary tufts was measured in PAS-stained sections of renal tissue, using a planar morphometry image analysis system as described. Glomerular volumes were calculated according to the formula:

$$V = \beta k \text{area}^{2.57}$$

where $\beta = 1.38$ (the shape coefficient for spheres), $k = 1.1$ (the size distribution coefficient for glomerular profiles), and area = mean glomerular profile planar area. Glomerular counts, expressed as number of glomeruli per kidney, were obtained after acid digestion of the kidney as described.

**Calculations**—Inulin and PAH concentrations in urine and plasma were measured by use of standard chemical methods. Whole kidney GFR and RPF were calculated by use of standard clearance formulas. Whole kidney filtration fraction (FF) was determined from GFR and RPF. Plasma colloid osmotic pressure was measured with a membrane osmometer. The single nephron glomerular filtration rate (SNGFR) was determined as the quotient of GFR divided by total glomerular count. Glomerular blood flow (GBF) and glomerular plasma flow (GPF) were computed from whole kidney FF, SNGFR, and Hct as follows:

$$\text{GBF} = \text{SNGFR}/(1 – \text{Hct})$$
$$\text{GPF} = \text{SNGFR}/\text{FF}$$

Glomerular capillary pressure (Pgc) was calculated as the sum of Psc and arterial plasma colloid osmotic pressure. Mean glomerular colloid osmotic pressure (\(\pi_m\)) was calculated as the mean of initial (\(\pi_a\)) and final (\(\pi_f\)) values for \(\pi\) determined from the afferent colloid osmotic pressure, FF, and the relation between plasma protein concentration and \(\pi\) in cats. The final glomerular plasma protein concentration (Ce) was calculated from FF and the initial glomerular plasma protein concentration (Ca) as follows:

$$\text{Ce} = \text{Ca} \left(\frac{100}{100 – \text{FF}}\right)$$

Glomerular transcapillary hydrostatic pressure and colloid osmotic gradients (\(\Delta P\) and \(\Delta \pi\), respectively), mean effective filtration pressure (EFPm), and glomerular ultrafiltration coefficient (KI) were determined as follows:

$$P = \text{Pgc} \pm \text{Ptr}$$
$$\Delta P = \text{Ppi} – \text{Psci}$$
$$\text{EFPm} = \frac{\Delta P}{\beta \kappa}$$
$$\text{KI} = \frac{\text{SNGFR}}{\text{EFPm}}$$

Vascular resistance, determined as the quotient of pressure gradient along the length of a vessel divided by blood flow through the vessel, was determined for single nephron vascular resistances (ie, afferent arteriolar [Ra] and efferent arteriolar [Re]) as follows:

$$\text{Ra} = \frac{\text{RPP} – \text{Psci}}{\text{GPF}}$$
$$\text{Re} = \frac{\text{Psci} – \text{Psci}}{(\text{GPF} – \text{SNGFR})}$$

**Statistical analyses**—Values were reported as mean ± SEM. Statistical analyses were performed with the aid of a commercial software package. Values were compared among and within groups by use of ANOVA. Statistical models included treatment, time, and interaction of treatment and time. If a significant treatment effect was observed, pairs of group means were compared by use of a Fisher protected least significant difference test to determine whether a group effect was present. Significance was set at $P < 0.05$.

**Results**

Effects of induced renal insufficiency—Compared with values obtained prior to renal mass reduction, cats with induced renal insufficiency developed mild azotemia (ie, increased plasma creatinine and BUN concentrations) at the time of assignment to treatment groups (Table 1). Partially nephrectomized cats developed systemic hypertension without significant changes in mean heart rate. Mean values for systemic arterial pressures were approximately 35 to 50 mm Hg greater in cats with renal insufficiency than in cats prior to renal mass reduction. The urine protein-to-creatinine concentration ratio also increased after partial nephrectomy, but this increase was not significant. Plasma potassium concentration decreased significantly in cats after partial nephrectomy. Plasma sodium and chloride concentrations also decreased in these cats.

**Treatment period**—Significant differences were not detected in mean baseline body weight, urine protein-to-creatinine concentration ratio, RPF, GFR, blood pressure, and plasma electrolyte, BUN, and creatinine concentrations among treatment groups.

Mean daily doses of benazepril were 0.0 ± 0.0 mg/kg in group 1, 0.43 ± 0.02 mg/kg (range, 0.30 to 0.56 mg/kg) in group 2, 0.72 ± 0.02 mg/kg (0.63 to 0.92 mg/kg) in group 3, and 1.63 ± 0.05 mg/kg (1.11 to 1.85 mg/kg) in group 4. The duration of the treatmenTable 1—Status of 32 young adult cats before and 2 to 3 weeks after surgery to reduce renal mass

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before surgery</th>
<th>After surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma creatinine (mg/dl)</td>
<td>1.15 ± 0.04</td>
<td>2.69 ± 0.13*</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>22.1 ± 2.0</td>
<td>44.0 ± 2.1*</td>
</tr>
<tr>
<td>Urine protein/creatinine</td>
<td>0.38 ± 0.07</td>
<td>0.49 ± 0.06</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>179.9 ± 3.1</td>
<td>164.5 ± 3.5</td>
</tr>
<tr>
<td>systolic BP (mm Hg)</td>
<td>122.5 ± 2.1</td>
<td>171.8 ± 0.9*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>85.5 ± 1.8</td>
<td>122.5 ± 3.3*</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>101.8 ± 1.3</td>
<td>143.8 ± 3.4*</td>
</tr>
</tbody>
</table>

Data reported as mean ± SEM. Urine protein/creatinine = Urine protein-to-creatinine concentration ratio. BP = Blood pressure. *Significantly ($P < 0.05$) different from value determined before surgery.
Table 2—Renal status of cats with induced renal insufficiency following treatment with placebo or benazepril hydrochloride

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Benazepril treated*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (n = 8)</td>
<td>Group 2 (8)</td>
</tr>
<tr>
<td>Plasma creatinine (mg/dl)</td>
<td>2.57 ± 0.09</td>
<td>2.88 ± 0.20</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>46.5 ± 1.4</td>
<td>49.2 ± 3.1</td>
</tr>
<tr>
<td>RPF (ml/min)</td>
<td>9.36 ± 0.88</td>
<td>8.53 ± 0.80</td>
</tr>
<tr>
<td>Corrected (ml/min/kg)</td>
<td>2.63 ± 0.20</td>
<td>2.85 ± 0.39</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>2.79 ± 0.20</td>
<td>2.93 ± 0.24</td>
</tr>
<tr>
<td>Corrected (ml/min/kg)</td>
<td>0.81 ± 0.06</td>
<td>0.99 ± 0.11</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>0.33 ± 0.03</td>
<td>0.39 ± 0.02</td>
</tr>
<tr>
<td>Urine protein:creatinine</td>
<td>0.18 ± 0.02</td>
<td>0.20 ± 0.02</td>
</tr>
</tbody>
</table>

Data reported as mean ± SEM of values determined throughout the 6-month treatment period.

*Dosages of benazepril: group 2, 0.25 to 0.50 mg/kg of body weight/d; group 3, 0.50 to 1.00 mg/kg/d; group 4, 1.00 to 2.00 mg/kg/d. †Significant (P < 0.05) different.

Within a row, values with different superscripts are significantly (P < 0.05) different.

Table 3—Blood pressure and heart rate determined by use of radiotelemetry in cats with induced renal insufficiency following treatment with placebo or benazepril hydrochloride

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Benazepril treated*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (n = 8)</td>
<td>Group 2 (8)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>147.4 ± 3.1</td>
<td>138.0 ± 3.6</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>104.2 ± 2.1</td>
<td>98.1 ± 2.7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>179.9 ± 2.3</td>
<td>172.9 ± 2.8</td>
</tr>
</tbody>
</table>

See Table 2 for key.

Effects of benazepril—Dose of benazepril did not have a significant effect on body weight or food intake. Mean food intake was 15.5 ± 0.2 g/kg/d during the treatment period. Given that the food used in this study contained 4.46 kcal/g, cats ingested a mean of 69.3 ± 0.9 kcal of metabolizable energy/kg/d during the treatment period. Dose of benazepril also did not affect plasma concentrations of creatinine, electrolytes, or BUN. An antiproteinuric effect of benazepril was not apparent.

Mean overall values for GFR during the treatment period were significantly affected by treatment (Table 2). Compared with group 1, GFR was significantly higher in groups 3 and 4. However, when GFR was factored by body weight, this difference was not significant (P = 0.07). Filtration fraction was not significantly different among groups treated with benazepril.

Benazepril had a significant antihypertensive effect in cats with induced renal insufficiency (Table 3). However, blood pressure decreased during the 6-month treatment period in all groups (Fig 1). Although treatment had a significant effect on blood pressure, we did not detect significant differences in blood pressures averaged throughout the treatment period between groups 2 or 4 and group 1. One cat in group 4 had a high blood pressure at baseline; blood pressure in this cat remained high throughout the treatment period. Systolic blood pressure in this cat was persistently > 185 mm Hg.
was not affected by treatment, exceeded systolic blood pressure for all other cats during the treatment period by > 20 mm Hg, and exceeded the 90th percentile for systolic blood pressure during the treatment period by > 25 mm Hg. When data from this cat were excluded from blood pressure analyses, mean systolic blood pressure in groups 2, 3, and 4 was significantly less than in group 1 (group 1, 147.4 ± 3.1 mm Hg; group 2, 138.0 ± 3.6 mm Hg; group 3, 131.1 ± 2.5 mm; group 4, 132.6 ± 3.7 mm Hg). Similarly, compared with group 1, diastolic blood pressure was significantly less in groups 3 and 4 (group 1, 87.3 ± 2.2 mm Hg; group 2, 115.5 ± 3.0 mm Hg; group 3, 109.5 ± 3.0 mm Hg; group 4, 132.6 ± 3.7 mm Hg), and mean blood pressure was significantly less in all benazepril-treated groups (group 1, 122.8 ± 2.5 mm Hg; group 2, 115.3 ± 3.0 mm Hg; group 3, 109.5 ± 2.3 mm Hg; group 4, 110.8 ± 2.9 mm Hg). When blood pressure data obtained during the pretreatment period from the cat in group 4 with high blood pressure were excluded from analyses, mean group 4 baseline blood pressure values did not change (systolic, 171 ± 4.5 mm Hg; diastolic, 124.1 ± 6.6 mm Hg; mean, 145.0 ± 5.2 mm Hg).

Mean values for echocardiographic variables measured during the treatment period were not significantly different among groups. In addition, intraocular lesions attributable to systemic hypertension were not observed in any cat.

Results of the micropuncture examinations at the end of the treatment period revealed that, although RPF and GFR were greater in benazepril-treated cats, compared with placebo-treated cats, differences were not significant (Table 4). Mean arterial blood pressure also was not significantly different among groups at this time.

Arteriolar resistances varied among cats; mean Ra and Re for all 32 cats was 0.48 ± 0.08 and 0.94 ± 0.25 mm Hg • min/nl, respectively. Arteriolar resistances were not significantly different among groups (Ra: group 1, 0.32 ± 0.06 mm Hg • min/nl; group 2, 0.67 ± 0.24 mm Hg • min/nl; group 3, 0.93 ± 0.22 mm; group 4, 0.39 ± 0.15 mm Hg • min/nl). However, the ratio of Re to Ra, an index of relative vasodilation, was significantly less in the 3 benazepril-treated groups, compared with the placebo-treated group (Fig 2). Consequently, compared with group 1, PGC was significantly less in each of the benazepril-treated groups. Mean decrease in PGC, compared with the placebo-treated group, was 12 to 14 mm Hg.

We did not detect significant differences in pi or Δπ among groups. The difference in EFPm between group 1 and each of the other groups was approximately 10 mm Hg, which represented a decrease of

Table 4—Renal hemodynamics determined for cats with induced renal insufficiency following treatment with benazepril or placebo for 6 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo Group 1 (n = 8)</th>
<th>Benazepril treated&lt;sup&gt;*&lt;/sup&gt; Group 2 (8)</th>
<th>Group 3 (7)</th>
<th>Group 4 (7)</th>
<th>All treated (22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BP</td>
<td>118 ± 7</td>
<td>123 ± 0.9</td>
<td>130 ± 5</td>
<td>124 ± 10</td>
<td>125 ± 5</td>
</tr>
<tr>
<td>RPF (ml/min)</td>
<td>6.2 ± 1.2</td>
<td>5.7 ± 0.9</td>
<td>6.6 ± 1.6</td>
<td>10.6 ± 2.4</td>
<td>7.6 ± 1.2</td>
</tr>
<tr>
<td>Corrected (ml/min/nl)</td>
<td>1.72 ± 0.16</td>
<td>1.94 ± 0.35</td>
<td>1.67 ± 0.32</td>
<td>2.82 ± 0.6</td>
<td>2.13 ± 0.24</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>2.51 ± 0.38</td>
<td>2.90 ± 0.47</td>
<td>3.24 ± 0.65</td>
<td>3.92 ± 0.48</td>
<td>3.33 ± 0.31</td>
</tr>
<tr>
<td>Corrected (ml/min/kg)</td>
<td>0.77 ± 0.10</td>
<td>1.00 ± 0.19</td>
<td>0.84 ± 0.15</td>
<td>1.12 ± 0.15</td>
<td>0.99 ± 0.10</td>
</tr>
<tr>
<td>Filtration factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stop-flow pressure (mm Hg)</td>
<td>62.6 ± 2.78</td>
<td>47.9 ± 2.61</td>
<td>49.4 ± 2.38</td>
<td>46.4 ± 2.55</td>
<td>47.0 ± 1.41</td>
</tr>
<tr>
<td>∆P (mm Hg)</td>
<td>53.3 ± 3.2</td>
<td>38.6 ± 2.4</td>
<td>39.7 ± 2.4</td>
<td>40.3 ± 2.8</td>
<td>39.5 ± 1.61</td>
</tr>
</tbody>
</table>

ΔP = Glomerular transcapillary hydrostatic pressure gradient.
See Table 2 for key.
Although SNGFR increased with increasing dose of benazepril, the difference among groups was not significant. Compared with group 1, Kf was significantly greater in groups 2, 3, and 4.

Kidney weights were not significantly different among groups (group 1, 11.1 ± 2.1 g; group 2, 10.0 ± 1.0 g; group 3, 13.5 ± 2.5 g; group 4, 12.1 ± 1.9 g). Glomerular counts (ie, number of glomeruli per kidney) were not significantly different among groups (group 1, 51.4 ± 5.4 X 10^3; group 2, 51.4 ± 5.3 X 10^3; group 3, 51.4 ± 5.3 X 10^3; group 4, 57.1 ± 5.9 X 10^3). Although there were significant increases in scores for glomerular and tubulointerstitial lesions during the course of the study, changes were considered mild, and there were no observable treatment effects.

**Discussion**

Chronic treatment with the ACE inhibitor benazepril decreased PGC, increased Kf, and sustained SNGFR in remnant nephrons of cats with induced renal insufficiency. Administration of benazepril was associated with a small but significant reduction in degree of systemic hypertension and either no significant change or an increase in whole kidney GFR in these mildly azotemic cats.

Previously, we found that cats with intact renal function have mean PGC of approximately 58 to 63 mm Hg and SNGFR of approximately 28 to 30 nl/min. Compared with these values, cats with renal insufficiency in the present study that received placebo for 6 months had glomerular hypertension (PGC, 74.8 mm Hg) and hyperfiltration (SNGFR, 52.7 nl/min). In a previous study, cats with renal insufficiency for 1 month had a comparable degree of glomerular hypertension (PGC, 74.2 mm Hg) and hyperfiltration (SNGFR, 56 nl/min). Taken in concert, these results suggest that glomerular hypertension and hyperfiltration are sustained for at least 6 months following the development or induction of renal insufficiency in cats.

Glomerular hypertension in cats with renal insufficiency has been attributed to preferential afferent arteriolar vasodilation. In cats of the present study that received placebo, it is likely that a similar degree of afferent arteriolar vasodilation coupled with an increase in systemic arterial blood pressure led to glomerular hypertension. Chronic treatment with benazepril led to preferential efferent arteriolar vasodilation coupled with a modest decrease in systemic arterial blood pressure. Compared with values for placebo-treated cats, the decrease in mean blood pressure during treatment with benazepril was 8.5 mm Hg. If arteriolar tone had remained unchanged after benazepril treatment, the expected decrease in PGC would have been approximately 5 mm Hg. However, compared with values for placebo-treated cats, the mean PGC decrease was 13.4 mm Hg in benazepril-treated cats, indicating that the arteriolar vascular effect of benazepril was the primary factor contributing to the decrease in glomerular hypertension.

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Single nephron glomerular filtration rate is equivalent to the product of Kf and EFp. Single nephron glomerular filtration rate was not adversely affected by treatment with benazepril. Our results...
indicate that benazepril treatment decreased EFPm but increased Kf to a similar extent. Thus, on a single nephron and whole kidney level, hyperfiltration was maintained because of this increase in Kf, and GFR was sustained or increased in cats that received benazepril. Results of investigations of glomerular hemodynamics in clinically normal and partially nephrectomized cats, dogs, and some strains of rats indicate that changes in Kf contribute substantially to alterations in SNGFR. Further, similar increases in Kf have been observed in diabetic dogs in response to chronic treatment with the ACE inhibitor lisinopril. The Kf is determined by glomerular hydraulic conductivity and glomerular capillary surface area. Angiotensin II can cause mesangial cell contraction in vitro, an effect that may decrease glomerular filtration surface area. Our histologic data, however, indicate that mesangial expansion or glomerulosclerosis probably did not contribute to the increase in Kf. Because we did not assess surface area or hydraulic conductivity of glomerular capillaries, further studies will be required to elucidate the relative contribution of each to changes in Kf in remnant nephrons of cats treated with ACE inhibitors.

Systemic hypertension has been reported in cats with chronic renal failure. In the present study, cats with reduced renal mass developed systemic hypertension. The antihypertensive effects of chronic administration of benazepril were mild, although significant. There was no evidence for an added antihypertensive effect at dosages of benazepril greater than 0.5 to 1.0 mg/kg/d. Our results are similar to results of another report in which enalapril had limited antihypertensive efficacy in cats with naturally occurring renal disease. Activation of the renin-angiotensin-aldosterone system was not common in that study. The data are somewhat conflictive on this issue, however, as other studies have provided evidence for activation of the renin-angiotensin-aldosterone system in cats with renal failure and systemic hypertension. It seems likely that there is a heterogeneity in the degree of involvement of the renin-angiotensin-aldosterone system in cats with naturally occurring renal disease and, thus, in the responsiveness of systemic blood pressure to ACE inhibition. Plasma constituents of the renin-angiotensin-aldosterone system were not directly assessed in the present study, although the modest effects of ACE inhibition would argue against a primary role for this system in maintenance of systemic hypertension. Although the reduction in systemic arterial blood pressure during ACE inhibition in the present study contributed little to the decrease in Pgc, benazepril had significant intrarenal hemodynamic effects. This is presumably a result of the effects of benazepril on the intrarenal renin-angiotensin system, which can generate exceedingly high concentrations of angiotensin II within the kidneys of rats.

Caution should be used when extrapolating the results of the present study to anticipated effects of ACE inhibition in cats with concurrent diseases such as heart failure or volume depletion. In these cats, maintenance of GFR may be dependent on high efferent arteriolar tone induced by angiotensin II. Transient, reversible decreases of GFR may develop in some cats in response to efferent arteriolar vasodilation during treatment with ACE inhibitors.

Increases in Pgc, often referred to as glomerular hypertension, play a role in the progressive renal injury that develops in rodents with experimentally induced renal failure. As a result, dietary and pharmacologic treatments designed to limit changes in glomerular hemodynamic function have been studied in animals with progressive renal disease. Results support a renoprotective role for treatments that limit the extent of glomerular hypertension. The use of ACE inhibitors has been shown to decrease Pgc and offer structural renoprotection in rodents and diabetic dogs with renal disease. In humans with renal disease, chronic administration of benazepril slows the rate of progression of renal failure. Results of the present study indicate that chronic treatment with the ACE inhibitor benazepril blunted or prevented development of glomerular capillary hypertension in cats with renal insufficiency and suggest that chronic ACE inhibition may delay progression of renal failure in cats.

Increases in glomerular size, referred to as glomerular hypertrophy, appear to play a role in progressive glomerulosclerosis that develops in certain strains of rats. Studies in animals with experimentally induced renal disease indicate that some treatments can exert differential effects on glomerular hypertension and hypertrophy. Although chronic treatment with an ACE inhibitor ameliorated glomerular capillary hypertension in the cats of the present study, there was no apparent effect on glomerular hypertrophy. The relative benefits of treatments that reduce glomerular hypertension but not hypertrophy, as observed in the present study, remain controversial.

The benefits of antihypertensive therapy in cats with renal insufficiency and modest systemic hypertension remain to be characterized. Because renal disease and systemic hypertension frequently coexist in cats, it is tempting to suggest a cause-effect relation. However, the nature of this association has not been well characterized, and the specific renoprotective effect of decreasing systemic arterial blood pressure remains to be established in cats with experimentally induced or naturally occurring renal disease. Although systemic hypertension can lead to cardiovascular alterations such as left ventricular hypertrophy, echocardiographic changes were not observed in the cats of the present study. Similarly, ocular manifestations of severe systemic hypertension have been reported in cats, but we did not detect retinal changes in these cats. Because ocular changes have most commonly been associated with severe increases in systemic arterial blood pressure, the absence of detectable intraocular lesions in the cats of the present study probably reflects the moderate degree of systemic hypertension that developed. In cats with moderate systemic hypertension, hypertensive retinopathy may not develop or it may require more than 6 months to become grossly detectable.

Although results of the present study did not provide evidence of protection of renal structure or func-
tion by ACE inhibition, this study was designed to address the effects of ACE inhibition in cats with a moderate degree of renal insufficiency over a 6-month treatment period. Accordingly, proteinuria and renal structural lesions were minimal in cats that received placebo; these cats were only modestly azotemic. In contrast to rodents, in which a rapid course of progressive renal injury develops after a similar degree of partial nephrectomy, renal structure and function is stable in cats for at least 12 months after moderate to prolonged reduction of functional renal mass.40,41 Similarly, renal function is stable for prolonged periods in cats with naturally occurring renal disease.42 Our results suggest that benazepril has potentially beneficial effects on systemic and intrarenal hemodynamics in cats with renal insufficiency, but it remains to be established whether renal structure and function will be protected by chronic treatment with this drug.

Liberty Research Inc, Waverly, NY.
1Prescription Diet Feline K/D Dry Ration, Hill’s Pet Products, Topeka, Kan.
2Model TA11PA-C40, Data Sciences International, St Paul, Minn.
3Forterox 5, Novartis Animal Health, Basel, Switzerland.
4Model RLA-2000, Data Sciences International, St Paul, Minn.
5LabPRO, version 3.10, Data Sciences International, St Paul, Minn.
Spectrum CXX, Abbott Diagnostics, Irving, Tex.
6Ultrascan, Sigma Chemical Co, St Louis, Mo.
Para-aminohippuric acid, Sigma Chemical Co, St Louis, Mo.
7EUB-555, Ultrasound Scanner, Hitachi Medical Corp, Tokyo, Japan.
P23b Transducer, Statham Laboratories, Hato Rey, Puerto Rico.
8Model 7B Polygraph, Grass Instruments, Quincy, Mass.
10Model 5A Servo-Nulling Pressure System, Instrumentation for Physiology and Medicine, San Diego, Calif.
11DIAS, C Squared Corp, Tamarac, Fla.
Model 4400 Colloid Osmometer, Wescor, Logan, Utah.
Statview 4.1, Abacus, Berkeley, Calif.

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