Evaluation of the effects of inhibition of angiotensin converting enzyme with enalapril in dogs with induced chronic renal insufficiency

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Objective—To determine whether the angiotensin converting enzyme inhibitor enalapril would lower systemic arterial and glomerular capillary pressure and reduce the magnitude of renal injury in a canine model of renal insufficiency.

Animals—18 adult dogs that had renal mass reduced by partial nephrectomy.

Procedure—After surgical reduction of renal mass and baseline measurements, dogs in 2 equal groups received either placebo (group 1) or enalapril (0.5 mg/kg, PO, q 12 h; group 2) for 6 months.

Results—Values for systemic mean arterial blood pressure determined by indirect and direct measurement after 3 and 6 months of treatment, respectively, were significantly lower in group 2 than in group 1. During treatment, monthly urine protein-to-creatinine ratios were consistently lower in group 2 than in group 1, although values were significantly different only at 3 months. At 6 months, significant reduction in glomerular capillary pressure in group 2 was detected, compared with group 1, but glomerular filtration rate in group 2 was not compromised. Glomerular hypertrophy, assessed by measurement of planar surface area of glomeruli, was similar in both groups. Glomerular and tubulointerstitial lesions were significantly less in group 2, compared with group 1.

Conclusions and Clinical Relevance—Data suggest that inhibition of angiotensin converting enzyme was effective in modulating progressive renal injury, which was associated with reduction of glomerular and systemic hypertension and proteinuria but not glomerular hypertrophy. Inhibition of angiotensin converting enzyme may be effective for modulating progression of renal disease in dogs. (Am J Vet Res 2003;64:321–327)

Progressive renal disease is a leading cause of death in dogs. It has been proposed that systemic and glomerular changes that are observed in affected animals are responsible for the genesis or progression of renal injury.1,2 The most frequently implicated changes are increased systemic arterial pressure (systemic hypertension), intraglomerular pressure (glomerular hypertension), and glomerular enlargement (glomerular hypertrophy). This hypothesis is supported by results of studies with rodent models of renal failure in which systemic hypertension, glomerular hypertension, and hypertrophy have been associated with pathologic changes in renal tissue.1,3 Similar to these results in rats, the remnant kidney model of renal failure in dogs is inherently progressive4 and is associated with marked glomerular hypertension and hypertrophy.7

Several lines of evidence suggest that angiotensin converting enzyme inhibitors (ACEIs) preserve glomerular structure and function in renal disease. Mechanistic studies of the effects of administration of ACEIs to rats with reduced renal mass reveal that renoprotection is associated with a lowering of glomerular capillary pressure (Pgc),8 blood pressure (BP),9 and glomerular size.7 A study of the long-term effects of the ACEI lisinopril in a canine model of diabetic nephropathy revealed beneficial effects on renal structure and proteinuria that were linked to reductions of glomerular and systemic hypertension and glomerular hypertrophy.10 Furthermore, studies of omega-3 polyunsaturated fatty acid supplementation in the canine remnant kidney model have suggested a causal link between the renoprotective effects of this supplementation and the effect of these fatty acids in reducing the magnitude of glomerular hypertension and hypertrophy.11 In extending these findings to dogs with spontaneous nondiabetic renal diseases, evidence was recently presented that the use of the ACEI enalapril in dogs with primary glomerulopathies leads to reduced proteinuria and systemic arterial BP.12 Similarly, a renoprotective effect of converting enzyme inhibition has been proposed in a genetic model of renal disease in dogs.13

Although evidence is accumulating that ACEIs are renoprotective in dogs with chronic renal insufficiency, little is known about the response of glomerular hemodynamics and glomerular growth to ACEIs in dogs with renal insufficiency. The purpose of the study reported here was to determine the effects of chronic administration of enalapril on glomerular and systemic hypertension, glomerular hypertrophy, and the structural progression of renal disease in a canine model of chronic renal insufficiency.

Materials and Methods
Dogs—Experiments were performed on 18 adult Beagles of both sexes that weighed (mean ± SD) 9.7 ± 0.4 kg. In all dogs, renal mass was reduced by right nephrectomy and infarction of approximately five-sixths of the left kidney.
Diet—All dogs were provided free access to a low-protein diet that contained 14.6% protein, 19.5% fat, 0.3% sodium, 0.4% potassium, 0.8% calcium, and 0.3% phosphorus on a dry matter basis.

Study protocol—Two weeks after partial nephrectomy, serum concentrations of creatinine and urea nitrogen, urine protein-to-creatinine ratio, and urinary clearance of creatinine (CcR) that was exogenously administered were determined. Dogs were paired on the basis of rank order of values for serum creatinine concentration, and 1 dog from each pair was randomly assigned to receive either placebo (vehicle only; group 1) or enalapril maleate (group 2) twice daily, starting 10 days after reduction of renal mass. Dogs that received enalapril received 1.0 mg/kg twice daily for the initial 2 weeks, followed by 0.5 mg/kg twice daily for the remainder of the treatment period (approx 6 months). Investigators were unaware of treatment group assignments. During the treatment period, urine protein-to-creatinine ratio and plasma concentrations of creatinine, urea nitrogen, and electrolytes were determined monthly. The remainder of the treatment period (approx 6 months).

Renal clearance and BP studies—Before clearance studies, food was withheld from dogs for 12 to 20 hours. While restrained in slings, dogs were given water equal to 3% of their body weight (vol/wt) by gavage. A bolus injection of creatinine, followed by a continuous infusion of creatinine delivered in physiologic saline (0.9% NaCl) solution at an infusion rate of 2.0 mL/min, was used to maintain plasma creatinine concentration at a constant concentration with a target concentration of 8 to 14 mg/dL. Urine was collected by use of an indwelling bladder catheter, and CcR was determined as the mean of 3 consecutive clearance periods of approximately 20 minutes each.

After the urinary clearance procedure, BP (systolic, diastolic, and mean) was estimated as the mean of 5 measurements by use of indirect oscillometry with a commercially available apparatus. For these measurements, dogs were standing quietly in slings with cuffs placed on the tail or forelimb.

Renal micropuncture studies—Before hemodynamic studies, food was withheld from dogs for 12 to 20 hours. Dogs were anesthetized with sodium pentobarbital (30 mg/kg, IV) 2 to 3 hours after treatment and were prepared for micropuncture and renal clearance studies, as described. The trachea was intubated, and respiration was regulated mechanically. A catheter was placed in the left femoral vein. A solution containing 0.9% NaCl and 3.0% inulin was infused at a rate sufficient to maintain plasma concentrations of approximately 0.8 mg of inulin/mL. Arterial pressure was measured through a catheter inserted into the femoral artery. The catheter was connected to a Statham pressure transducer. Output was recorded on a polygraph, and blood samples were collected through the arterial catheter.

The left kidney was exposed through a flank incision, and the proximal portion of 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 placed on a plastic holder and prepared for micropuncture by removal of a portion of the renal capsule (approx 3 cm²). This area was continuously bathed with warm (39°C) heparinized isotonic saline solution dripped through a hollow quartz rod, which 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 loosely wrapped with plastic wrap.

Forty-five minutes later, micropuncture collections and micropressure measurements were made. Mean systemic arterial pressure (MAP), renal arterial blood pressure (RAP), and renal blood flow (RBF) were continuously monitored, and 2 or 3 timed ureteral collections of 15 to 20 minutes each were made during these micropuncture studies for determination of inulin clearance (CIn). A blood sample was collected at the midpoint of each timed urine collection. For single nephron glomerular filtration rate (SNGFR) determination, a sharpened pipette (12- to 18-μm tip) was filled with Sudan black-stained castor oil. The pipette tip was inserted into a proximal tubule, and an oil column of at least 5 tubule diameters was inserted. Gentle aspiration was applied to initiate the collection and to maintain the oil block in a constant position. Timing was started at the initiation of collection and continued for 1 to 2 minutes. After removal, the pipette was stored in mineral oil before determining the volume and inulin concentration of the collection. Hydraulic pressures were determined by use of a micropressure servo-null system. At least 3 free-flow proximal tubular pressures (Ppa), stop-flow proximal tubule pressures (Psf), and peritubular capillary pressures (Ppc) were measured for each dog. The Ppc measurements were taken from the earliest accessible site on the cortical surface of the kidney.

Morphologic studies—A portion of the infarcted section of the left kidney was removed and preserved in neutral-buffered 10% formalin solution at the time of infarction. After euthanasia following the micropuncture studies, renal tissue was removed, excised, stripped of surrounding tissue and capsule, and blotted dry. The scar from the area previously infarcted was removed from each kidney remnant by sharp dissection, and the viable portion of the remnant was weighed. A single 2- to 3-mm-thick midsagittal section was placed in neutral-buffered 10% formalin solution for subsequent processing for examination by light microscopy. Formalin-fixed tissue was processed by routine histologic methods, and sections were stained with hematoxylin and periodic acid-Schiff (PAS) dyes. For glomerular morphologic analyses, only glomeruli from the outer third of the cortex were evaluated. A minimum of 25 outer cortical glomeruli were examined by 4 individuals (CAB, SAB, DRF, and WAC) without the knowledge of the group of origin and scored for the presence of mesangial matrix expansion with a numeric scoring system (0 = normal, 1 = minimal expansion, 2 = moderate expansion, 3 = severe expansion). Tubular lesions, interstitial fibrosis, and interstitial inflammatory cell infiltrate were scored by a similar qualitative scoring system (0 = normal, 1 = minimal change, 2 = moderate change, and 3 = severe change).

Planar area of 20 randomly selected outer cortical glomerular capillary tufts was measured in PAS-stained, formalin-fixed sections of renal tissue obtained at the time of nephrectomy (initial) and at the time of the renal hemodynamic studies (final) with the aid of a planar morphometry image analysis system, as described. A single mean planar area was determined for each dog at each time point.

Analyses and calculations—Routine plasma biochemical analyses (creatinine, urea nitrogen, electrolytes) and urine protein-to-creatinine ratio were measured by use of an automated analyzer. Inulin and para-aminohippuric acid (PAH) concentrations in ureteral urine and plasma collected as described. All research was conducted in accordance with the National Institute of Health Guide for Care and Use of Laboratory Animals.
during micropuncture studies were measured by use of routine chemical methods. The Ccr and clearance of inulin (Cin) were calculated by use of the standard clearance formula. Microhematocrit (Hct) measurements were performed on all arterial blood samples obtained during micropuncture. The renal plasma flow (RPF) was measured as CprA. Whole kidney filtration fraction (FF) was determined from RPF and either Ccr or Cin. Plasma colloid osmotic pressure was measured with a membrane osmometer.

Tubular fluid inulin concentration was determined in duplicate by use of an ultramicrofluorometric method. The SNGFR was determined from the product of flow rate and the tubular fluid-to-plasma inulin ratio. Glomerular blood flow (GBF) and glomerular plasma flow (GPF) were computed from the FF, SNGFR, and Hct:

\[
GBF = \frac{SNGFR}{FF(1 - Hct)}; \quad \text{and} \quad GPF = \frac{SNGFR}{FF}
\]

Whole kidney FF values were used for these calculations because efferent arteriolar blood samples could not be obtained routinely during the study. The PGc was estimated from the sum of PSF and plasma colloid osmotic pressure (πa). Single-nephron afferent arteriolar resistance (RA), efferent arteriolar resistance (RE), and total arteriolar resistance (RT) were estimated by the expressions:

\[
RA = \frac{\text{mean BP} - \text{PGc}}{\text{GBF}}; \quad RE = \frac{\text{PGc} - \text{Pc}}{\text{GBF} - \text{SNGFR}}; \quad \text{and} \quad RT = \text{mean BP}/\text{GBF}
\]

The glomerular ultrafiltration coefficient (Kf) was calculated by use of the integrated solution to the general differential equation:

\[
Kf = \frac{\text{SNGFR}/\text{AP}}{\left(1 - a \times \ln(1 - B)\right)}, \quad \text{where} \quad A = \frac{R \times \pi_a}{(FF \times \Delta P) [R + \pi_a]}, \quad \text{and} \quad B = \frac{FF \times \Delta P [R + \pi_a]}{(R \times \Delta P - \pi_a)}
\]

In these equations, ΔP is the glomerular transcapillary hydraulic pressure gradient, πa is the afferent colloid osmotic pressure, and R is a constant that relates πa to FF and efferent colloid osmotic pressure (πc). This approach is particularly useful in dogs because the value of R (43) is affected only slightly by variations in albumin-to-globulin ratios, which are substantial in this species.

Statistical analyses—Values are reported as mean ± SEM. Numeric data were compared between groups by use of ANOVA with a randomized block design. Morphologic data for fibrosis score, cellular infiltrate score, and tubular lesion score were compared by use of the Wilcoxon signed rank test on the basis of differences between observations paired by pathologist and replicates. The glomerular lesion scores were compared by use of the Cochran-Mantel-Haenszel test, using 4 response categories (0 to 3) and using 2 response categories that were defined as mild (score of 0 or 1) and marked (score of 2 or 3). Values of P < 0.05 were considered significant.

Results

Following reduction of renal mass, before administration of treatment or placebo, there were no significant differences between groups in body weight, measures of renal function, degree of proteinuria, plasma concentrations of creatinine, urea nitrogen, or electrolytes, MAP, or pulse rate (Table 1).

The dogs received either enalapril or placebo for 6 months. During this treatment period, there were no significant differences between groups in body weight, RPF, Ccr, or measured plasma biochemical parameters. Results for indirect osmometric measurement of mean and diastolic BP were significantly lower in group 2 at 3 months, compared with group 1 (Fig 1). Systolic blood pressure at 3 months and all 3 blood pressure parameters at 6 months were somewhat lower in group 2, although not significantly, compared with group 1. Proteinuria, as assessed by the urine protein-to-creatinine ratio, was significantly different between groups only at 3 months.

During the renal micropuncture studies conducted at the end of the study, there were no differences in

Table 1—Systemic and renal parameters (mean ± SEM; n = 9/group) in dogs 2 weeks after reduction of renal mass (before treatment) and 3 and 6 months after initiation of treatment with placebo (group 1) or enalapril (group 2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before treatment</th>
<th>3 Months</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 1</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>9.4 ± 0.3</td>
<td>9.9 ± 0.7</td>
<td>10.0 ± 0.3</td>
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<tr>
<td>Ccr (mL/min/kg)</td>
<td>1.38 ± 0.21</td>
<td>1.84 ± 0.18</td>
<td>2.0 ± 0.11</td>
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<tr>
<td>Filtration fraction (%)</td>
<td>28.1 ± 2.0</td>
<td>29.4 ± 1.6</td>
<td>22.2 ± 1.0</td>
</tr>
<tr>
<td>Scr (mg/dL)</td>
<td>4.4 ± 0.53</td>
<td>4.7 ± 0.52</td>
<td>2.37 ± 0.24</td>
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<tr>
<td>Urea nitrogen (mg/dL)</td>
<td>79.2 ± 7.8</td>
<td>78.8 ± 11.2</td>
<td>35.9 ± 4.5</td>
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<tr>
<td>Urine protein-to-creatinine ratio</td>
<td>1.63 ± 0.17</td>
<td>2.74 ± 0.89</td>
<td>1.29 ± 0.33</td>
</tr>
<tr>
<td>Na+ (mEq/L)</td>
<td>155.9 ± 0.8</td>
<td>155.8 ± 1.0</td>
<td>150.8 ± 0.3</td>
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<tr>
<td>K+ (mEq/L)</td>
<td>3.49 ± 0.14</td>
<td>3.55 ± 0.19</td>
<td>4.52 ± 0.14</td>
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<td>Cl- (mEq/L)</td>
<td>121.6 ± 0.6</td>
<td>120.5 ± 1.7</td>
<td>116.9 ± 0.4</td>
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<td>HCO3- (mEq/L)</td>
<td>16.9 ± 0.7</td>
<td>17.2 ± 1.1</td>
<td>19.6 ± 0.5</td>
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<td>Anion gap (mEq/L)</td>
<td>20.9 ± 0.7</td>
<td>21.6 ± 0.7</td>
<td>18.9 ± 0.3</td>
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<tr>
<td>SBP (mm Hg)</td>
<td>161.2 ± 7.3</td>
<td>157.3 ± 9.9</td>
<td>140.4 ± 4.8</td>
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<tr>
<td>MBP (mm Hg)</td>
<td>124.2 ± 6.0</td>
<td>122.4 ± 7.8</td>
<td>115.0 ± 3.6</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>108.1 ± 5.4</td>
<td>104.9 ± 7.6</td>
<td>99.9 ± 3.6</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>99.8 ± 5.7</td>
<td>114.7 ± 6.2</td>
<td>104.0 ± 7.6</td>
</tr>
</tbody>
</table>

*Significant (P < 0.05) difference from value for group 1.

CprA = Renal plasma flow determined by urinary clearance of para-aminohippuric acid. Ccr = Glomerular filtration rate determined as urinary clearance of exogenously administered creatinine. Scr = Serum concentration of creatinine. MBP = Mean blood pressure. DBP = Diastolic blood pressure. BP = Systolic arterial blood pressure. PP = Systolic blood pressure.
Table 2—Systemic and renal parameters (mean ± SEM) measured during micropuncture studies at the end of a 6-month treatment period in dogs with reduced renal mass treated with placebo (group 1) or enalapril (group 2).

Table 3—Single nephron parameters measured at the time of micropuncture studies in dogs with reduced renal mass treated with placebo (group 1) or enalapril (group 2) for 6 months following partial nephrectomy.

Table 4—Morphologic parameters at the beginning (pre) and end (post) of a 6-month treatment period in dogs with reduced renal mass treated with placebo (group 1) or enalapril (group 2).

Figure 1—Serial values for urine protein-to-creatinine ratio (solid lines) and systolic arterial blood pressure measured by indirect oscillometry (dashed lines) in dogs treated with placebo (open symbols [n = 9]) or enalapril (closed symbols [9]) for 6 months following partial nephrectomy. At 3 months, differences between groups for both parameters were significant (P < 0.05).

Figure 2—Proportion of glomeruli scored as having moderate to severe lesions (scores 2 and 3) in dogs receiving placebo (closed bars [n = 9]) or enalapril (open bars [9]) for 6 months following partial nephrectomy. *Significant (P < 0.05) difference between groups.

CraH = Renal plasma flow as determined by urinary clearance of para-aminohippuric acid. CPAH = Glomerular capillary pressure as determined by the stop-flow technique. MPAP = Mean systemic arterial blood pressure measured by direct arterial cannulation. CN = Glomerular filtration rate as determined by urinary clearance of inulin. GFR = Glomerular filtration rate. SNGFR = Single nephron glomerular filtration rate. PPT = Free-flow proximal tubular pressure. Ptc = Peritubular capillary hydraulic pressure. PSF = Stop-flow proximal tubular pressure. Na = Plasma colloid osmotic pressure. AFR = Afferent arteriolar vascular resistance. EffF = Effluent arteriolar vascular resistance.

Data are expressed as mean ± SEM. *Significant (P < 0.05) difference between groups.
Morphologic studies revealed no difference between groups in kidney weight (Table 4) or mean volume of cortical glomeruli. At the end of the study, the cellular infiltrate score and tubular lesion score were significantly higher in group 1, compared with baseline values and with group-2 values. Baseline glomerular lesion score was slightly, albeit significantly, lower in the enalapril group when each score (0, 1, 2, 3) was considered a separate response category. However, there was no significant difference at baseline between groups for glomerular lesions scored as mild (the 2 lower scores, 0 and 1) or marked (the 2 higher scores, 2 and 3). At the end of the study, glomerular lesions scored as marked were significantly more prevalent in group 1, compared with group 2 (Fig 2).

Discussion

Long-term administration of the ACEI, enalapril, altered glomerular hemodynamics and BP in the remnant kidney model of canine chronic renal failure. Associated with these hemodynamic effects of enalapril were significant differences in the magnitude of proteinuria and scores for renal lesions, compared with placebo-treated dogs.

At 6 months, the group mean for PGC in dogs that received placebo exceeded values reported for clinically normal dogs from our laboratory by 10 mm Hg, consistent with previous observations that glomerular hypertension is present following partial nephrectomy in dogs, and that it persists despite moderate dietary protein restriction. Glomerular volume at 6 months in group 1 was more than 2-fold greater than initial values for these dogs, indicating a substantial hypertrophic response as well. Treatment with enalapril significantly altered glomerular hemodynamics, but not glomerular growth, through site-specific effects on renal vascular resistance. Glomerular capillary pressure in dogs receiving enalapril was similar to values obtained from clinically normal dogs with intact renal function. In particular, enalapril administration led to preferential dilatation of the efferent arterioles.

Although angiotensin II constricts the afferent and efferent arterioles of kidneys in clinically normal dogs, it has been argued that angiotensin II preferentially constricts efferent arterioles. The sites of activity responsible for observed antihypertensive effect of enalapril appeared to begin within a month of the initiation of treatment. This time course makes it likely that the presence of lesions in group 1 contributed to a reduction in the glomerular ultrafiltration coefficient in that group. Furthermore, enalapril may have raised the glomerular ultrafiltration coefficient in group 2 by relaxing renal mesangial cells. Angiotensin II is believed to reduce glomerular permeability to albumin, in part, as a result of contraction of glomerular mesangial cells, an effect observed in canine mesangial cells in vitro.

Administration of enalapril induced a significant antiproteinuric effect in group 2. Converting enzyme inhibition may reduce proteinuria by several mechanisms. Specifically, antiproteinuric effects of ACEIs may be due to preservation of structural integrity of glomeruli, alteration of glomerular permselectivity, or indirect effects of hemodynamic changes on glomerular protein leakage. The antiproteinuric effect of enalapril appeared to begin within a month of the initiation of treatment. This time course makes it likely that the antiproteinuric effect occurred, at least partially, as a hemodynamic or permselectivity effect of enalapril administration rather than as a result of the differences in glomerular lesions between groups.

Both systemic hypertension and glomerular hypertension appear to be risk factors for progression of renal injury. Although the importance of systemic hypertension as a cause of progressive renal injury in dogs remains to be established, in recent reports it is suggested that severely increased BP can directly damage canine kidneys and lead to increased mortality rate and progressive decline of GFR in dogs with preexis-
tent chronic renal insufficiency. The dogs of our study, however, did not have marked or even moderate systemic hypertension. In spite of this, ACEI administration reduced BP and seemingly offered renoprotection. There is evidence in humans that reduction of BP within reference range may be beneficial for the preservation of renal function.31,32 Consequently, we cannot determine the relative contribution of a reduction in systemic versus intraglomerular blood pressure to effects on renal structure observed in our study. Although structural protection of the kidneys by ACEIs has generally been attributed to hemodynamic effects of these agents, there are a variety of nonhemodynamic effects that might alter progression of renal injury. Proteinuria has been cited as a separate risk factor for the progression of renal disease.33 It has been proposed that the presence of protein within the tubular fluid activates tubular cells and interstitial cells, enhancing the progression of renal disease by causing tubulointerstitial lesions.34 Because proteinuria and renal lesions were worse in dogs in our study receiving placebo, our results are consistent with this hypothesis. However, we cannot determine the cause-effect nature of this relationship. Furthermore, a hypothesis that proteinuria accelerates renal damage cannot be directly supported or refuted by results of our study. In other studies with the remnant kidney model of renal failure in dogs, we have not been able to identify an association between proteinuria and subsequent progression of chronic renal disease.4 The nature of the relationship between proteinuria and renal damage remains to be more fully defined in dogs.

Angiotensin II may participate in progression of renal injury through a variety of nonhemodynamic mechanisms.35 Angiotensin II alters growth of glomeruli,36 extracellular matrix degradation,37 and mitogenesis38,39 of mesangial cells and renal interstitial cells.40 Evidence for an effect of angiotensin II on interstitial infiltrate has also been revealed in a model of rodent nephropathy.41 Glomerular size was not significantly worse in dogs in our study receiving enalapril, but different tissue converting enzyme activity is generally measured in plasma, but different tissue converting enzyme activities are likely to be differentially sensitive to ACEIs. Increased exposure to an ACEI may enhance hemodynamic and nonhemodynamic effects of the agent, whether they are adverse or beneficial.

Long-term administration of enalapril altered glomerular hemodynamics, BP, proteinuria, and structural progression of renal injury in a remnant kidney model of canine chronic renal failure. These data support those of published experimental and clinical trials in dogs and provide insight into the mechanism of the effects of enalapril in dogs with renal insufficiency.

References


