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. 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 hypertrophy, and hypertrophy have been associated with pathologic changes in renal tissue. Similar to these results in rats, the remnant kidney model of renal failure in dogs is inherently progressive and is associated with marked glomerular hypertension and hypertrophy.

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), blood pressure (BP), and glomerular size. 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. 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. 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. Similarly, a renoprotective effect of converting enzyme inhibition has been proposed in a genetic model of renal disease in dogs.

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.
as described. All research was conducted in accordance with the National Institute of Health Guide for Care and Use of Laboratory Animals.

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 were 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 Ccr and BP ratio and plasma concentrations of creatinine, urea nitrogen, and the proximal portion of the renal artery and vein and the remainder of the treatment period (approx 6 months). The trachea was intubated, and respiration was regulated mechanically. A catheter was placed in the left femoral vein. The left kidney was exposed through a flank incision, 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.

Fourty-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 insulin 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 insulin concentration of the collection. Hydraulic pressures were determined by use of a micropressure servo-null system. At least 3 free-flow proximal tubular pressures (Ptp), 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 midcortical 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, DRE, 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 infiltration 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
during micropuncture studies were measured by use of routine chemical methods.\textsuperscript{2,3} 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 CPAH. Whole kidney filtration fraction (FF) was determined from RPF and either Ccr or Cin. Plasma colloid osmotic pressure was measured with a membrane osmometer.\textsuperscript{4} Tubular fluid inulin concentration was determined in duplicate by use of an ultramicrofluorimetric method.\textsuperscript{5} The SNGFR was determined from the product of volume 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:

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

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:

\[
RA = (\text{mean BP} - \text{Pgc})/\text{GBF}; \quad \text{RE} = (\text{Pgc} - \text{Pcr})/(\text{GPF} - \text{SNGFR}); \quad \text{and} \quad \text{RT} = \text{mean BP}/\text{GBF}
\]

The glomerular ultrafiltration coefficient (Kf) was calculated by use of the integrated solution to the general differential equation:\textsuperscript{6}

\[
Kf = \left(\frac{\text{SNGFR}}{\Delta P}\times (1 - A \times \ln[1 - B])\right)
\]

In these equations, Α 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 (Πe). 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.\textsuperscript{7}

**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 replicate. 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 oscillometric 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>
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<th>Parameter</th>
<th>Before treatment</th>
<th>3 Months</th>
<th>6 Months</th>
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<td>Group 1</td>
<td>Group 2</td>
<td>Group 1</td>
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<tr>
<td>Body weight (kg)</td>
<td>9.4 ± 0.3</td>
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<td>Ccre (mL/min/kg)</td>
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<td>Filtration fraction (%)</td>
<td>28.1 ± 2.0</td>
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<td>Scr (mg/dL)</td>
<td>4.43 ± 0.53</td>
<td>4.54 ± 0.52</td>
<td>2.37 ± 0.24</td>
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<td>Urea nitrogen (mg/dL)</td>
<td>79.2 ± 7.8</td>
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<td>Urine protein-to-creatinine ratio</td>
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<td>2.74 ± 0.89</td>
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<td>Na+ (mEq/L)</td>
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<td>K+ (mEq/L)</td>
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<td>Cl- (mEq/L)</td>
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<td>HCO3- (mEq/L)</td>
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<td>Anion gap (mEq/L)</td>
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<td>99.8 ± 5.7</td>
<td>114.7 ± 6.2</td>
<td>104.0 ± 7.6</td>
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*Significant (P < 0.05) difference from value for group 1.

Ccre = 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. MBPdirect = Mean arterial blood pressure indirectly estimated by oscillography. MBPdirect = Mean arterial blood pressure indirectly estimated by oscillography.
Table 1—Serial values for urine protein-to-creatinine ratio (solid lines) and systolic arterial blood pressure measured by indirect oscilloscopy (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).

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.

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 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. *Significantly (P < 0.05) different from value determined at the beginning of the treatment period within the same group. *Significantly (P < 0.05) different from the value in group 1 for the same time period. NA = Not applicable.

Figure 3—Prevalence of moderate to severe glomerular lesions (scores 2 and 3; %) at baseline and after 6 months (6 mon) in placebo (open bars) and enalapril (closed bars) treated dogs. *Significant (P < 0.05) difference between groups.

Table 5—Cortical and interstitial fibrosis scores in dogs treated with placebo (open bars [n = 9]) or enalapril (closed bars [9]) for 6 months following partial nephrectomy.
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 PCG 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. Results of our study indicate that remnant nephrons in dogs with renal insufficiency respond similarly. Taken in concert with previous experimental studies in rodent and feline models of renal insufficiency, results of our study support the assertion that this hemodynamic effect is widespread amongst the ACEIs and occurs in several mammalian species over a range of renal diseases.

Administration of enalapril significantly reduced BP, compared with control dogs, as measured by indirect oscillometry at 3 months. Direct measurement of BP during micropuncture at the end of the study revealed a significant antihypertensive effect for enalapril. Although not directly investigated in the present study, the mechanism of the antihypertensive effects of enalapril is presumed to be secondary to vasodilation and reduction of extracellular fluid volume. However, ACEIs inhibit kinin degradation, and it is not possible to eliminate a role for kinin accumulation in the systemic or renal effects of ACEI observed in our study.

The sites of activity responsible for observed effects of enalapril were not determined. It is known, however, that all components of the renin-angiotensin system are present within the kidney. Intrarenal generation of angiotensin II may be responsible for high concentrations of angiotensin II measured intrarenally. Enalapril’s effects on renal hemodynamics may be attributable to inhibition of intra- or extra-renal converting enzyme activity or both.

Mechanisms operative within clinically normal canine kidneys adjust renal vascular resistance in order to maintain RBF and GFR at healthy values, despite variations in BP. This property, referred to as renal autoregulation, is compromised in dogs with reduced renal function. Thus, reduction in BP might be expected to reduce RBF and GFR of dogs in our study. Acute exacerbation of azotemia has been observed in humans receiving an ACEI. Similarly, in a multicenter study of ACEIs conducted in 211 dogs with heart failure, 2 dogs were excluded from the study because of adverse effects associated with azotemia. Interestingly, administration of enalapril was not associated with a difference between groups for whole-kidney or SNGFR, despite PCG and BP being lower in group 2. Glomerular hemodynamic studies revealed that enalapril-treated dogs had higher glomerular ultrafiltration coefficient than the placebo-treated dogs. This was presumably caused by 2 separate mechanisms. First, glomeruli in dogs of group 2 had less extensive lesions. It is 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 GFR, 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 preexist-
tubulointerstitial lesions.34 Because proteinuria and lar fluid activates tubular cells and interstitial cells, proposed that the presence of protein within the tubu-mechanisms.35 Angiotensin II alters growth of renal lesions were worse in dogs in our study receiving placebo, our results are consistent with this hypothe-sis. 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 pro-gression of chronic renal disease. 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. Angiotensin II alters growth of glomeruli, extracellular matrix degradation, and mitogenesis of mesangial cells and renal interstitial cells. Evidence for an effect of angiotensin II on interstitial infiltrate has also been revealed in a model of rodent nephropathy. Glomerular size was not signifi-cantly affected by enalapril in our study, but we cannot eliminate the possibility of a role for ACEI to protect renal structure by modulating renal growth. We did not study other nonhemodynamic mechanisms and cannot quantify the importance of their contribution to the results of our study.

Although there was structural injury in remnant nephrons in the group receiving a placebo, there was no evidence of progressive decline of GFR in our study. This was not surprising, because previous studies in our laboratory revealed that a progressive decline in GFR is usually not detected in this model in dogs until 12 to 18 months after reduction of renal mass. However, our study did reveal evidence of developing structural renal lesions. Although there were no signif-icant differences between groups in tubular lesions, interstitial fibrosis, or cellular infiltrate at the begin-ning of the study, dogs in the placebo group had sig-nificantly worse tubular lesion and cellular infiltrate scores at the end of the study. Despite randomization, there was a small but significant difference between group means for dogs receiving enalapril versus place-bo with respect to glomerular lesion scores at the beginning of the study when each score was taken as a unique response category. However, when the analysis was repeated with scores of 0 or 1 combined as a single category (mild lesions) and scores of 2 or 3 combined into another category (marked lesions), the initial values were not different. These results indicate that the difference between groups at baseline was a difference between the frequency of scores 0 and 1, which both indicated mild lesions. Scores of 2 or 3 were uncommon in both groups at baseline. However, for the post-treatment data, the differences were signif-icant regardless of whether 2 or 4 response categories were used. This suggests that the treatment difference observed at study termination was of a greater magni-tude than merely a shift between adjacent scores; that is, there was a significantly greater likelihood of marked glomerular lesions in the placebo group. The differing nature of the treatment effect observed at baseline and at study termination suggests that the post-treatment difference was not a carryover of pre-existing difference. We accept, however, that the slight differences in renal structure in the beginning of the study do somewhat cloud the firmness of this conclu-sion.

Although we did not measure the degree of converting enzyme inhibition in dogs of this study, the dosage chosen (0.5 mg of enalapril/kg, PO, q 12 h) and the presence of renal insufficiency likely increased the exposure of the dogs to the active metabolite, enalapril-
lat. The effects of increased exposure are unknown. Converting enzyme activity is generally measured in plasma, but different tissue converting enzyme activi-ties are likely to be differentially sensitive to ACEIs. Increased exposure to an ACEI may enhance hemody-namic 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 insuffi-ciency.

References


