Association of Systemic Hypertension with Renal Injury in Dogs with Induced Renal Failure

Delmar R. Finco

Systemic hypertension is hypothesized to cause renal injury to dogs. This study was performed on dogs with surgically induced renal failure to determine whether hypertension was associated with altered renal function or morphology. Mean arterial pressure (MAP), heart rate (HR), systolic arterial pressure (SAP), and diastolic arterial pressure (DAP) were measured before and after surgery. Glomerular filtration rate (GFR) and urine protein : creatinine ratios (UPC) were measured at 1, 12, 24, 36, and 56–69 weeks after surgery, and renal histology was evaluated terminally. The mean of weekly MAP, SAP, and DAP measurements for each dog over the 1st 26 weeks was used to rank dogs on the basis of MAP, SAP, or DAP values. A statistically significant association was found between systemic arterial pressure ranking and ranked measures of adverse renal responses. When dogs were divided into higher pressure and lower pressure groups on the basis of SAP, group 1 (higher pressure, n = 9) compared with group 2 (lower pressure, n = 10) had significantly lower GFR values at 36 and 56–69 weeks; higher UPC values at 12 and 56–69 weeks; and higher kidney lesion scores for mesangial matrix, tubule damage, and fibrosis. When dogs were divided on MAP and DAP values, group 1 compared with group 2 had significantly lower GFR values at 12, 24, 36, and 56–69 weeks; higher UPC values at 12 and 56–69 weeks; and higher kidney lesion scores for mesangial matrix, tubule damage, fibrosis, and cell infiltrate. These results demonstrate an association between increased systemic arterial pressure and renal injury. Results from this study might apply to dogs with some types of naturally occurring renal failure.

Key words: Canine; Indirect blood pressure; Page–remnant kidney.

Hypertension is a risk factor for progressive renal damage in humans. Naturally occurring chronic renal disease in dogs sometimes is associated with systemic hypertension, and an association between initial systolic blood pressure and risk of mortality has been reported. Dogs with the remnant kidney model of renal failure have normal to mildly increased systemic arterial pressure. However, they have impaired ability to autoregulate renal perfusion, and consequently, glomerular capillary pressure is increased. Increased glomerular capillary pressure has been incriminated as a cause of renal damage in rats. When blood pressure was increased in remnant kidney dogs by giving a nitric oxide synthase inhibitor or desoxycorticosterone pivalate and excess salt, an increase in proteinuria and decline in glomerular filtration rate (GFR) were observed. These findings suggest that systemic hypertension can lead to adverse changes in renal function, but an association between hypertension and severity of renal lesions was not examined.

The Page model of hypertension was discovered serendipitously when it was found that applying a wrap to an intact kidney resulted in systemic hypertension. A combination of the Page model and the remnant kidney model was reported to result in both systemic hypertension and renal failure. In this study, the Page–remnant kidney model was used to test the hypothesis that systemic hypertension was associated with adverse effects on renal function and renal morphology.

Materials and Methods

Dogs and Dog Care

Male and female Beagle dogs were purchased from commercial suppliers. Dogs were housed individually in inside runs in compliance with US Department of Agriculture regulations for dog care. Temperature and light-dark intervals were controlled, and dogs had free access to water at all times. Before a 2-stage surgical procedure, dogs were fed a commercially available dry ration that was formulated to fulfill nutritional requirements of normal adult dogs. Between surgical stages, the diet was gradually changed to a commercially available canine diet formulated for dogs with renal failure. Food intake was measured by weighing food offered and food declined for each 24-hour period. Body weight of dogs was measured at ~3-mo intervals throughout the study.

Baseline Studies

Dogs were acclimated for hemodynamic measurements by placing them in a quiet room adjacent to their kennels and simulating blood pressure measurements with dogs resting in Pavlov slings. The acclimation procedure was performed on 5 different days. After acclimation, mean arterial pressure (MAP), heart rate (HR), systolic arterial pressure (SAP), and diastolic arterial pressure (DAP) were measured on each dog with an apparatus that uses the indirect oscillometric principle. A pressure cuff of recommended size was applied around the base of the tail, and at least 5 measurements of MAP, HR, SAP, and DAP were made. The mean of measurements for each variable was accepted as the result for each dog on that day. Measurements were repeated presurgically on at least 6 days at approximately the same time each day.

Surgical Procedures

Surgical protocol was approved by the Institutional Animal Care and Use Committee and entailed use of aseptic techniques. After overnight fasting, acepromazine (0.1 mg/kg SC) and atropine (0.05 mg/kg SC) were administered as preanesthetic medications. Anesthesia was induced by IV injection of thiopental sodium and was maintained by halothane inhalation. Morphine (0.3 mg/kg SC) was administered as an analgesic at the conclusion of each surgical procedure.
During the 1st stage, the left kidney was exposed by making a paracostal incision through the skin and separating each underlying muscle along the long axis of its fibers. Once exposed, the left kidney was exteriorized and reduced in mass by approximately three-fourths, either by ligating branches of the renal artery and resecting infarcted tissue or by resecting the kidney poles after polar ligation. Residual tissue was wrapped in sterilized bands of silk cloth approximately 2 cm in width and 20 cm long. Care was taken to avoid impinging on the ureter. Silk sutures were used to hold the wraps in place. Ethanol-sterilized Parafilm was stretched over the kidney wrap. During the 2nd stage (1–2 weeks later), the right paracostal approach was used to expose the right kidney, and it was subjected to 15/16 infarction by selectively ligating appropriate branches of the renal artery.

Post-surgical Grouping of Dogs and Data Analysis

One week after the 2nd surgical procedure, GFR was measured by determining urinary clearance of exogenously administered creatinine. The GFR measurements were repeated at approximately 12-week intervals after the 2nd surgery for 36 weeks and then terminally. Before each GFR procedure, urine was obtained and protein and creatinine concentrations (mg/dL) were measured to calculate the urine protein:creatinine ratio (UPC).

After the 2nd surgical procedure, MAP, HR, SAP, and DAP were measured weekly on each dog for 26 weeks and at 2–4-week intervals thereafter in dogs studied beyond 26 weeks. During the study, dogs were not treated for hypertension unless clinical signs attributable to its presence were judged to endanger the life of the dog. At 12-week intervals during the study, the accuracy of the blood pressure apparatus was determined as directed by the manufacturer.

Results

Grouping of Dogs

Arrangement of dogs in descending order for MAP, SAP, and DAP values gave similar but not identical dog sequences for the 3 pressure measurements. Thus, the association between magnitude of systemic pressure and renal changes was analyzed separately for MAP, SAP, and DAP.

In generating groups 1 and 2, the 9 dogs with the highest MAP also had the highest DAP. Consequently, data analyzed and reported as MAP/DAP applies to both. Seven of the 9 dogs with the highest MAP/DAP had the highest SAP, but because 2 dogs were not common to the groups by these rankings, results from dogs ranked by SAP were analyzed separately from MAP/DAP.

Clinical Observations

One dog with marked hypertension (mean SAP = 188 mm Hg) was euthanized at 185 days because of progressive azotemia and uremia but was retained in the data analysis. Three of 8 dogs in group 1 by both SAP and MAP/DAP assignment had transient clinical signs attributed to hypertension (e.g., lethargy, anorexia, scleral injection, exophthalmos, retinal hemorrhages). These dogs were treated with antihypertensive agents. (One dog was treated with hydralazine [20 mg PO bid] and enalapril [6 mg PO bid] for 7 days then amlodipine [2.5 mg PO OD] for 10 days. Another dog was treated with hydralazine [20 mg PO bid] and enalapril [5 mg PO bid] for 5 days then hydralazine [10 mg PO bid] for 8 days. A 3rd dog was treated with labetalol [50 mg PO OD] for 28 days.) Drugs were discontinued when clinical signs abated. The remaining dogs completed the period of observation without development of major abnormalities referable to either hypertension or renal failure. Groups 1 and 2 were similar in body weight and in food intake whether assigned by MAP/DAP or SAP.

Association between Systemic Pressure Measurements and Renal Changes

Regression analysis of blood pressure rank for each of the 3 systemic pressure measurements and GFR rank identified a statistically significant relationship between GFR and each pressure measurement (MAP, $R^2 = .351$, $P = .008$; SAP, $R^2 = .372$, $P = .006$ [Fig 1]; DAP, $R^2 = .331$, $P = .010$). Likewise, a statistically significant association existed between mean UPC and each pressure measurement (MAP, $R^2 = .384$, $P = .005$; SAP, $R^2 = .269$, $P = .023$; DAP, $R^2 = .399$, $P = .004$). For microscopic renal lesions, a statistically significant association was found between score ranks for all lesions (mesangial matrix accumulation, tubule lesions, fibrosis, and cell infiltration) and SAP rank. For DAP and MAP rank, values were statistically signifi-
cific for all lesion score ranks except mesangial matrix accumulation, which approached but did not reach significance (DAP, \( P = .062 \); MAP, \( P = .077 \)).

The GFR rank of dogs was significantly associated with average UPC rank (\( R^2 = .376, P = .005 \)) and with score ranks for some renal lesions (fibrosis, \( R^2 = .293, P = .017 \); mesangial matrix accumulation, \( R^2 = .384, P = .005 \)), but not with others (tubule lesions, \( R^2 = .178, P = .072 \); cell infiltrate, \( R^2 = .173, P = .076 \)). The UPC rank was significantly associated with score ranks for fibrosis (\( R^2 = .736, P = .000 \)), tubule lesions (\( R^2 = .520, P = .000 \)), and cell infiltrate (\( R^2 = .610, P = .000 \)), but not with mesangial matrix accumulation (\( R^2 = .074, P = .260 \)).

**Group Comparisons**

Results from presurgical measurements of MAP, HR, SAP, and DAP indicated no statistically significant difference between groups when dogs were assigned on the basis of either SAP or MAP/DAP ranking (Table 1). Values 1 week postsurgically were not significantly different between groups for MAP, SAP, or DAP regardless of SAP or MAP/DAP assignment (group 1 by SAP ranking: MAP = 114 ± 17, SAP = 158 ± 28, and DAP = 94 ± 16 mm Hg; group 2 by SAP ranking: MAP = 114 ± 8, SAP = 155 ± 11, and DAP = 94 ± 8; group 1 by MAP/DAP ranking: MAP = 117 ± 17, SAP = 155 ± 28, and DAP = 95 ± 16 mm Hg; group 2 by MAP/DAP ranking: MAP = 113 ± 11, SAP = 155 ± 13, and DAP = 92 ± 10.2 mm Hg). When assigned by SAP value, the SAP of both group 1 and group 2 increased after 1 week, but the magnitude of increase in group 2 never attained the level of group 1 (Fig 2). When assigned by MAP/DAP values, the increase in DAP was similar in both groups 1 and 2 at 4 weeks, but groups diverged thereafter (Fig 3). With both SAP and DAP measurements, pressures decreased moderately with time from their peak levels (Figs 2, 3).

As would be expected on the basis of method of group generation, group 1 dogs had significantly higher values than group 2 dogs for MAP, SAP, and DAP, but not for HR (Table 1). The weeks of observation for dogs assigned by SAP was 47.1 ± 15.9 for group 1 and 50.5 ± 15.2 for group 2. The weeks of observation for dogs assigned by MAP/DAP assignment (group 1 by SAP ranking: MAP = 114 ± 17, SAP = 158 ± 28, and DAP = 94 ± 16 mm Hg; group 2 by SAP ranking: MAP = 114 ± 8, SAP = 155 ± 11, and DAP = 94 ± 8; group 1 by MAP/DAP ranking: MAP = 117 ± 17, SAP = 155 ± 28, and DAP = 95 ± 16 mm Hg; group 2 by MAP/DAP ranking: MAP = 113 ± 11, SAP = 155 ± 13, and DAP = 92 ± 10.2 mm Hg). When assigned by SAP value, the SAP of both group 1 and group 2 increased after 1 week, but the magnitude of increase in group 2 never attained the level of group 1 (Fig 2). When assigned by MAP/DAP values, the increase in DAP was similar in both groups 1 and 2 at 4 weeks, but groups diverged thereafter (Fig 3). With both SAP and DAP measurements, pressures decreased moderately with time from their peak levels (Figs 2, 3).

| Table 1. Hemodynamic values in dog groups before and after surgical procedures.\(^a\) |
|------------------|--------|--------|--------|--------|--------|--------|
|                  | Assignment by SAP |                  | Assignment by MAP/DAP |
|                  | MAP    | HR     | SAP    | DAP    | MAP    | HR     | SAP    | DAP    |
| Presurgical      |        |        |        |        |        |        |        |        |
| 1                 | 101 ± 6 | 136 ± 23 | 143 ± 6 | 81 ± 6 | 103 ± 6 | 138 ± 19 | 143 ± 6 | 83 ± 7 |
| 2                 | 105 ± 7 | 138 ± 15 | 143 ± 9 | 86 ± 7 | 103 ± 7 | 136 ± 19 | 143 ± 9 | 84 ± 7 |
| 1–26 weeks       |        |        |        |        |        |        |        |        |
| 1                 | 128 ± 6 | 118 ± 18 | 169 ± 10 | 107 ± 8 | 128 ± 7 | 119 ± 17 | 168 ± 11 | 108 ± 6 |
| 2                 | 112 ± 7* | 122 ± 15 | 150 ± 7* | 92 ± 8* | 112 ± 7* | 121 ± 16 | 151 ± 8* | 92 ± 7* |
| 1–68 weeks       |        |        |        |        |        |        |        |        |
| 1                 | 125 ± 8 | 117 ± 16 | 166 ± 11 | 105 ± 8 | 125 ± 8 | 117 ± 16 | 164 ± 13 | 106 ± 8 |
| 2                 | 112 ± 6* | 120 ± 12 | 149 ± 6* | 92 ± 6* | 112 ± 6* | 120 ± 13 | 151 ± 8* | 92 ± 6* |

MAP, mean arterial pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure (mm Hg); HR, heart rate (beats/min).

\( ^a \) An asterisk (*) denotes statistically significant differences between groups for each time within assignment.
MAP/DAP was 49.5 ± 15.9 for group 1 and 48.2 ± 15.2 for group 2. The blood pressure monitoring device was accurate at all times tested when compared with a mercury manometer that was used as the standard.

At 1 week after surgery, GFR was not significantly different between groups assigned by either SAP or MAP/DAP (Table 2). However, at this time, dogs had a marked reduction in renal function when compared with the GFR of normal dogs (3–4 mL/min/kg) measured in the same laboratory by the same method.11 By 12 weeks, GFR increased as a result of renal compensatory hypertrophy.13 However, the increase in GFR was significantly less in group 1 than in group 2 at 36 and 50–68 weeks in dogs ranked by SAP and at 12, 24, 36, and 50–68 weeks in dogs ranked by MAP/DAP (Table 2).

For both SAP and MAP/DAP assignments, level of azotemia increased between 12 and 24 weeks in group 1 but diminished in group 2. Serum creatinine concentration (mg/dL) was: group 1 SAP ranking 0.94 ± 0.09 at baseline, 2.73 ± 1.09 at week 12, and 3.33 ± 2.05 at week 24; group 2 SAP ranking 0.92 ± 0.08 at baseline, 2.17 ± 0.05 at week 12, and 1.99 ± 0.57 at week 24; group 1 MAP/DAP ranking 0.93 ± 0.10 at baseline, 2.81 ± 1.00 at week 12, and 3.42 ± 1.97 at week 24; group 2 MAP/DAP ranking 0.93 ± 0.08 at baseline, 2.10 ± 0.58 at week 12, and 1.91 ± 0.59 at week 24.

UPC values were higher in group 1 than group 2 at all times after 1 week for both SAP and MAP/DAP assignments, but values reached statistical significance only at 12 and 56–68 weeks (Table 3).

Scores obtained from microscopic examination of stained slides of the unwrapped (right) kidney of dogs were compared for groups 1 and 2 by both SAP and MAP/DAP assignment. For SAP, mesangial matrix accumulation (group 1 = 1.41 ± 0.65, group 2 = 0.90 ± 0.36), tubule lesions (group 1 = 1.20 ± 0.96, group 2 = 0.36 ± 0.11), and fibrosis (group 1 = 1.35 ± 0.95, group 2 = 0.58 ± 0.26) were significantly different between groups, but values for cell infiltration (group 1 = 0.98 ± 0.60, group 2 = 0.55 ± 0.38) did not reach significance (P = .083). For MAP/DAP assignment, mesangial matrix accumulation (group 1 = 1.52 ± 0.55, group 2 = 0.80 ± 0.32), tubule lesions (group 1 = 1.31 ± 0.85, group 2 = 0.29 ± 0.30), fibrosis (group 1 = 1.47 ± 0.81, group 2 = 0.47 ± 0.26), and cell infiltration (group 1 = 1.11 ± 0.47, group 2 = 0.43 ± 0.35) all were significantly greater in group 1 than in group 2.

Discussion

In this study, a single breed of dogs consuming similar quantities of the same diets had a variable blood pressure response, ranging from no change to marked hypertension, after undergoing the same surgical procedures to induce hypertension and renal dysfunction. Evaluation of renal function during the period of study and microscopic examination of kidney tissue obtained at the conclusion of the study provided an opportunity to compare dogs managed identically but with different arterial blood pressure values.

When the association between progressive increase in systemic arterial pressure and deleterious renal effects was examined, a significant adverse effect of systemic pressure on renal changes was documented, regardless of whether MAP, SAP, or DAP was used as the criterion for pressure measurement. For further analysis, renal effects in 9 dogs with highest SAP or MAP/DAP pressures were compared with the remaining 10 dogs with lower pressures. Division in this manner circumvented the need to designate dogs as

Table 2. Glomerular filtration rate (GFR) in dogs of group 1 (higher pressure) and group 2 (lower pressure).

<table>
<thead>
<tr>
<th>Week</th>
<th>Assignment by SAP</th>
<th>Assignment by MAP/DAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>1</td>
<td>0.57 ± 0.29</td>
<td>0.55 ± 0.21</td>
</tr>
<tr>
<td>12</td>
<td>0.86 ± 0.49</td>
<td>1.11 ± 0.28</td>
</tr>
<tr>
<td>24</td>
<td>0.90 ± 0.57</td>
<td>1.24 ± 0.31</td>
</tr>
<tr>
<td>36</td>
<td>0.84 ± 0.50</td>
<td>1.28 ± 0.39*</td>
</tr>
<tr>
<td>56–69</td>
<td>0.57 ± 0.36</td>
<td>1.40 ± 0.44*</td>
</tr>
</tbody>
</table>

* An asterisk (*) denotes a statistically significant difference between groups within assignments.

Table 3. Urine protein : creatinine ratio (UPC) in dogs of group 1 (higher pressure) and group 2 (lower pressure).

<table>
<thead>
<tr>
<th>Week</th>
<th>Assignment by SAP</th>
<th>Assignment by DAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>1</td>
<td>2.04 ± 0.77</td>
<td>1.52 ± 0.63</td>
</tr>
<tr>
<td>12</td>
<td>2.44 ± 1.40</td>
<td>0.45 ± 0.15*</td>
</tr>
<tr>
<td>24</td>
<td>1.63 ± 0.95</td>
<td>0.79 ± 0.42</td>
</tr>
<tr>
<td>36</td>
<td>1.77 ± 0.75</td>
<td>1.25 ± 1.25</td>
</tr>
<tr>
<td>56–69</td>
<td>3.42 ± 1.90</td>
<td>1.38 ± 0.11*</td>
</tr>
</tbody>
</table>

* An asterisk (*) denotes a statistically significant difference between group 1 and group 2 for each time within assignments.
hypertensive or nonhypertensive on the basis of published criteria for diagnosis of hypertension in dogs. Although some differences in results were obtained on the basis of whether dogs were separated by SAP or MAP/DAP values, overall, the results support the conclusion that the more hypertensive group had adverse renal changes compared with the less hypertensive group.

In this study, the correlation between SAP and DAP on 26-week mean values from the 19 dogs was statistically significant ($R^2 = .87, P = .000$). This result, and a similar order for dog assignments when ranked by MAP, SAP, or DAP, indicates that in this model of hypertension, an increased SAP usually was accompanied by a corresponding increase in DAP and MAP. Considering the close association between SAP and MAP/DAP measurements, it is doubtful whether the minor difference in pressure values between the groups (Table 1) allows an answer to the question of whether SAP, DAP, or MAP is the best predictor of renal damage. In humans, controversy exists concerning the importance of SAP versus DAP in the pathogenesis of cardiovascular and renal diseases, but in some studies, SAP was considered more important.$^{14-17}$

Different values have been proposed to diagnose hypertension in clinical canine patients. A SAP $\geq 160$ mm Hg, $^{18,19}$ 165 mm Hg, $^{20}$, or 180 mm Hg in trained or untrained dogs $^{21,22}$ has been suggested. It is generally acknowledged that blood pressure readings in untrained, anesthetized animals are more erratic and higher than in trained or anesthetized animals, complicating judgements about a cutoff point for diagnosing hypertension. Another confounding factor is the variation in pressure readings that can occur with instruments that operate on different principles of measurement. $^{23}$ An increase in DAP also has been considered indicative of hypertension in dogs, and cutoff values of more than 90, $^{19}$ 95, $^{18}$ 100, $^{22}$ and 120$^{21}$ mm Hg have been suggested to indicate hypertension.

In addition to lack of agreement on what values constitute hypertension, it is possible that end-organ sensitivity also varies. Loss of autoregulation documented to occur in remnant kidney models has not been studied in dogs with various types of naturally occurring renal diseases. Because glomerular capillary pressure, rather than systemic arterial pressure, is germane to renal injury, $^{6}$ a better marker for glomerular capillary pressure than systemic arterial pressure would be desirable to predict renal damage. In this study, mean postsurgical UPC values had higher $R^2$ values for association with renal lesions than measures of systemic arterial pressure, suggesting that magnitude of UPC might serve as such a marker.

In the Page-infarction model used in this study, renal mass was reduced markedly and rather abruptly. It is well documented that these procedures result in a marked hypertrophy in residual viable nephrons and that the hypertrophy is accompanied by an increase in GFR. $^{13}$ In dogs of group 1, hypertension occurred after about 2 weeks, and renal tissue was exposed to systemic hypertension at a time when hypertrophy was maximal. $^{13}$ This scenario would be expected to be similar to the situation of naturally occurring acute renal failure accompanied by hypertension. Whether results from the present experiment apply to clinical canine patients with chronic renal disease can be questioned because so little is known about the clinical condition. A critical question is whether residual renal tissue undergoing active hypertrophy is more vulnerable to injury than renal tissue in which hypertrophy occurred earlier. In naturally occurring chronic renal failure, it is unknown whether hypertension precedes, is coincident with, or occurs after hypertrophy. Clearly much more must be learned about the biologic behavior of naturally occurring chronic renal failure in order to appropriately extrapolate results from this study.

Although managed the same, some dogs had marked increases in arterial pressure measurements after surgery, but others had less marked pressure changes. Assessment at postmortem examination indicated that dogs with less change did not have complete enclosure of viable kidney tissue in the wrap or no viable kidney tissue was present within the wrap. Thus, it appears that technical factors as well as biologic variation could have explained why all dogs did not develop the same magnitude of hypertension.

The Page model of producing hypertension without renal failure is produced by wrapping 1 intact kidney and leaving the other kidney intact or removing it. Previous investigation suggested that in the Page model of hypertension in dogs, the wrapped kidney was protected from the harmful effects of hypertension. $^{24}$ Considering that the wrapped kidney remnant might be protected from injury, we chose to compare histologic findings in the unwrapped (right) remnant kidney of group 1 with those in the unwrapped (right) remnant kidney of group 2. An additional reason for comparing unwrapped kidneys was the finding that wrapped kidneys had a marked cellular response to the wrap on the kidney surface, which complicated histologic interpretation.

The pathogenesis of hypertension occurring in the Page model has been studied. In dogs in which 1 kidney was wrapped and the other removed, plasma renin activity was low. $^{25,26}$ Expansion of extracellular volume was documented in hypertensive dogs that was associated with the presence of a sodium-potassium pump inhibitor. $^{26}$ Despite low plasma renin activity, acute experiments determined that a reduction in systemic arterial pressure was achieved by administering angiotensin-converting enzyme (ACE) inhibitors or endothelin inhibitors, suggesting that renin and endothelin might play some role in the genesis of the hypertension. $^{27}$ Because the Page–remnant kidney model differs from the classic Page model in having a reduced renal mass and a remnant unwrapped kidney, it is uncertain whether the pathogenesis of hypertension is the same in both models.

Some dogs in group 1 were treated transiently with antihypertensive agents, raising the question of whether adverse effects of these agents could have been responsible for deterioration of kidney function and morphology. ACE inhibitors might decrease GFR by reducing efferent arteriolar resistance, causing a prerenal azotemia. However, ACE inhibitors are not known to cause renal damage by mechanisms other than those secondary to prerenal effects, and they actually reduced the rate of progression of renal disease in several circumstances. $^{28}$ Amlodipine, a calcium channel blocker, is reported to diminish autoregulation of GFR and to reduce resistance of the afferent glomerular arteriole in dogs. $^{29}$ These changes would increase intrag-
glomerular capillary pressure and potentially aggravate renal injury. An argument against the idea that antihypertensive drugs contribute to the adverse renal effects in group 1 can be made because 5 of 8 dogs were not treated, and the treatment period in the 3 treated dogs was 3, 6, and 15% of total study time.

In conclusion, an association between magnitude of systemic hypertension and adverse renal changes was found. When grouped by magnitude of systemic hypertension, the more hypertensive dogs had significantly lower GFR values, higher UPC scores, and higher renal lesions scores than less hypertensive dogs. These findings provide circumstantial evidence for an adverse effect of systemic hypertension on kidneys of dogs with reduced renal function.

Footnotes

a Dry matter composition reported by the manufacturer was 31% protein and 0.52% sodium, providing 6.55 g of protein and 113 mg of sodium per 418 kJ (100 kcal) of metabolizable energy.

b Dry matter composition reported by the manufacturer was 16% protein and 0.22% sodium, providing 3.61 g protein and 50 mg of sodium per 418 kJ (100 kcal) metabolizable energy.

c Dinanap, Critikon Corp, Tampa, FL

d Parafilm, American National Can, Menasha, WI

Acknowledgments

The authors thank Dawn Sloan for technical assistance, Dr Cathy Brown and Dr John Munday, Department of Veterinary Pathology, for histologic examination of kidney tissue, and Dr A Vidyashankar and Ying Zhao, Department of Statistics, for statistical analyses.

References


