Association between initial systolic blood pressure and risk of developing a uremic crisis or of dying in dogs with chronic renal failure

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Objective—To determine whether high systolic blood pressure (SBP) at the time of initial diagnosis of chronic renal failure in dogs was associated with increased risk of uremic crisis, risk of dying, or rate of decline in renal function.

Design—Prospective cohort study.

Animals—45 dogs with spontaneous chronic renal failure.

Procedure—Dogs were assigned to 1 of 3 groups on the basis of initial SBP (high, intermediate, low); Kaplan-Meier and Cox proportional hazards methods were used to estimate the association between SBP and development of a uremic crisis and death. The reciprocal of serum creatinine concentration was used as an estimate of renal function.

Results—Dogs in the high SBP group were more likely to develop a uremic crisis and to die than were dogs in the other groups, and the risks of developing a uremic crisis and of dying increased significantly as SBP increased. A greater decrease in renal function was observed in dogs in the high SBP group. Retinopathy and hypertensive encephalopathy were detected in 3 of 14 dogs with SBP ≥ 180 mm Hg. Systolic blood pressure remained high in 10 of 11 dogs treated with antihypertensive drugs.

Conclusions and Clinical Relevance—Results suggested that initial high SBP in dogs with chronic renal failure was associated with increased risk of developing a uremic crisis and of dying. Further studies are required to determine whether there is a cause-and-effect relationship between high SBP and progressive renal injury and to identify the risks and benefits of antihypertensive drug treatment. (*J Am Vet Med Assoc* 2003;222:322–329)

In humans, arterial hypertension has been associated with progression of renal disease and an increased risk of death.[1-3] With the advent of improved methods for indirect measurement of blood pressure, high arterial blood pressures have frequently been observed in dogs with spontaneous chronic renal failure.[4-7,a] However, the clinical importance of these high arterial blood pressures is unclear, as published reports[8-11] of the adverse effects of high blood pressure in dogs have consisted primarily of empirical clinical observations involving a small number of cases. Furthermore, the criteria for determining whether dogs have systemic hypertension have often been derived from statistical analyses of population blood pressures, rather than from epidemiologic data derived from clinical studies linking particular blood pressure values with adverse effects.[12]

Consequences of systemic hypertension in humans include hypertensive retinopathy, coronary heart disease, hypertensive encephalopathy, cerebrovascular accidents, and progression of renal failure.[13-16] Hypertension-related diseases, such as retinopathy, have also been reported in dogs.[8-12,17] However, epidemiologic studies linking retinopathy, cardiomyopathy, CNS lesions, and progressive nephropathy to hypertension in dogs with spontaneous chronic renal failure are lacking.

This prospective cohort study was designed to test the hypothesis that high **systolic blood pressure (SBP)** at the time of initial diagnosis of chronic renal failure in dogs was associated with increased risk of developing a uremic crisis, the risk of dying, or the rate of decline in renal function.

Material and Methods

Dogs—Forty-five dogs with chronic renal failure recruited from the Minneapolis-St Paul metropolitan area were included in the study. Thirty-eight of the 45 dogs were also included in a randomized controlled clinical trial of the efficacy of dietary modification in the management of chronic renal failure.[18] The remaining 7 dogs included in the present study had been excluded from the diet study because initial SBP was ≥ 180 mm Hg.

On the basis of results of medical histories, physical examinations, CBCs, serum biochemical profiles, urinalyses, and indirect blood pressure measurements, the 45 dogs met the following inclusion and exclusion criteria. Dogs that were included were > 1 year of age with stable renal function characterized by serum creatinine concentrations between 2.0 and 8.0 mg/dL. Stable renal function was confirmed by determining that serum creatinine concentrations did not increase or decrease by > 20% within 5 to 15 days of determination of the initial value. Dogs that were excluded were dogs that were expected to die from nonrenal illnesses before the study was completed; dogs with diabetes mellitus or hyperadrenocorticism; dogs with overt signs of uremia (eg, anorexia, vomiting, and lethargy); and dogs being treated with corticosteroids, H_2-blocking drugs, antiemetic drugs, antihypertensive drugs, parenterally administered fluids, vit-

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amin supplements, phosphate binders, alkalinizing agents, potassium supplements, recombinant human erythropoietin, or vitamin D supplements.

Dogs were enrolled in the study between January 1997 and April 1999. All dogs that had not reached 1 of the study endpoints (development of uremic crisis, died of renal disease, or died of any cause) prior to termination of the study in November 1999 were followed up for at least 225 days.

Owners of all dogs included in the study reviewed and signed an informed consent form. The study protocol was approved by the University of Minnesota Institutional Animal Care and Use Committee.

Study protocol—For all dogs, a medical history was obtained and a physical examination (including retinal examination) was performed during the initial visit and 1 and 2 months later. In addition, PCV was measured, along with serum urea nitrogen, creatinine, total CO_2, inorganic phosphorus, and albumin concentrations. Urine protein and creatinine concentrations were also measured. A urinalysis was performed, and indirect blood pressure measurements were obtained.[b,c] Beginning 3 months after the initial visit and continuing for up to 24 months, dogs were scheduled to be similarly reevaluated at 3-month intervals or sooner if clinical signs warranted evaluation. Phone interviews were performed monthly when on-site examinations were not scheduled.

Indirect blood pressure measurement—An oscillometric method[b] was used for indirect measurement of blood pressure in 43 of the 45 dogs. In the remaining 2 dogs, unsatisfactory results (ie, discrepancy between heart rate recorded by the monitor and heart rate determined concurrently by means of auscultation and inability to obtain blood pressure values) were obtained with this method, and an ultrasonic Doppler[c] method was used to measure blood pressure in these dogs.

Blood pressure measurements were obtained before any other diagnostic procedures were performed. One technician consistently performed all blood pressure measurements, and all measurements were performed in the same quiet environment. Dogs were allowed to adapt to the environment for 5 to 10 minutes before blood pressure measurements were obtained. Neonatal cuffs with a width that was 40% of the limb circumference were used.[19,20] Thick hair at the site of cuff placement was clipped from 1 dog during the initial visit. In this dog, SBP was 109 mm Hg after the hair was clipped and 118 mm Hg when the dog was reexamined 1 month later. For measurement of blood pressure, dogs were placed in left lateral recumbency, and cuffs were positioned on the right hind limb distal to the hock, with the cuff held at the level of the heart. Cuffs were placed so the arrow on the cuff was positioned over the right metatarsal artery with the index falling in the range printed on the cuff. During indirect blood pressure measurements, the heart rate was monitored by means of cardiac auscultation and compared with heart rate indicated on the oscillometric monitor. When a discrepancy was noted, the cuff was repositioned, and blood pressure measurements were repeated. During each session, 5 to 7 measurements of systolic, mean, and diastolic blood pressures (oscillometric method) or SBP (ultrasonic Doppler method) were obtained over a 5- to 10-minute period. Blood pressures were measured until 5 to 7 consecutive measurements that did not vary by > 10 mm Hg from one another were recorded. Results were then averaged, and the mean value was recorded.

Laboratory testing—Owners were instructed not to feed their dogs for 12 hours prior to each examination. During each examination, a blood sample was collected from the jugular vein; serum was obtained within 30 minutes. Serum samples were analyzed the same day they were collected or were stored at 4°C and analyzed the next day. Packed cell volume was measured, and serum biochemical analyses were performed with standard equipment.[d,e]

Urine was collected by means of cystocentesis. Urine samples were stored at 4°C until analyzed; all samples were analyzed within 24 hours. Urine protein concentration was determined by means of Coomassie brilliant blue dye precipitation[f] and spectrophotometry.[21] Urine creatinine concentration was determined with an automatic analyzer on the basis of the kinetic Jaffe reaction.[22]

Patient management—With the exception of diet and administration of antihypertensive drugs, standard treatment protocols[18] were used to manage chronic renal failure and treat associated conditions other than uremia. Because some of the dogs were also part of a controlled study designed to evaluate the efficacy of dietary modification in the management of chronic renal failure,[18] some dogs were fed a diet designed for dogs in renal failure, and others were fed an adult maintenance diet.

In a study[12] of healthy dogs evaluated at the University of Minnesota Veterinary Teaching Hospital, mean ± SD SBP, determined by use of oscillometric techniques, was 125 ± 29 mm Hg. On the basis of results of this study, treatment to reduce blood pressure (enalapril, amlodipine, or diltiazem) was given to dogs in the present study when SBP was ≥ 180 mm Hg during at least 2 consecutive hospital visits 5 to 14 days apart. Antihypertensive drugs were also given if SBP was ≥ 180 mm Hg during a single visit and clinical signs of hypertension (eg, retinal detachment or seizures) were detected. The goal of antihypertensive treatment was to reduce SBP to < 160 mm Hg.

Diagnosis of uremic crisis—A diagnosis of uremic crisis was made if the owner reported observing 2 or more clinical signs consistent with uremia. These signs included, but were not limited to, depression, lethargy, anorexia, vomiting, uriniferous breath odor, and uremic stomatitis, and an increase in SUN concentration of 20% or greater than the concentration measured during the previous visit when signs of uremia were absent. Further, no other plausible explanation for these clinical signs and the increase in SUN concentration could be identified, as determined by medical history, physical examination, a limited serum biochemical profile, PCV, urinalysis, aerobic bacterial culture of a urine sample, abdominal radiography, and indirect blood pressure measurement.

Establishing cause of death—For dogs that died during the study period, the medical history and results of physical examinations, laboratory tests, and necropsy (when available) were used to establish the cause of death. The cause of death was categorized as definitely not renal, possibly renal, probably renal, or definitely renal. Dogs in which cause of death was classified as definitely not renal or possibly renal were considered to have died of a nonrenal cause. Dogs in which cause of death was classified as probably or definitely renal were considered to have died of a renal cause.

Detection of hypertension-associated organ damage—Prior to each retinal examination, topical tropicamide solution was used to induce mydriasis. An antemortem diagnosis of hypertensive retinopathy was made on the basis of detection of typical ocular lesions (eg, tortuous vessels, focal hemorrhage, and bilateral or unilateral serous retinal detachment). Ophthalmic findings were confirmed by a board-certified veterinary ophthalmologist.

Hypertensive encephalopathy was suspected on the basis of the owner's observation of typical neurologic signs (eg, seizures, dementia, and vocalization) and results of a neurologic examination and, when available, necropsy.

Serial serum creatinine concentrations were transformed into reciprocals to estimate the rate of decline in renal function.[23]

Statistical analyses—For purposes of analysis, dogs were assigned to 1 of 3 groups on the basis of initial SBP (ie, the first SBP obtained in this study). For this assignment, initial SBPs were divided into tertiles, because there is no generally accepted definition of systemic hypertension in dogs. Dogs with SBP equal to the cutoff between tertiles were assigned to the lower tertile, even if > 1 dog had this value. Thus, groups did not have equal numbers of dogs. Dogs assigned to the **high SBP (HSBP)** group (n = 14) had initial SBP ranging from 161 to 201 mm Hg. Dogs assigned to the **intermediate SBP (ISBP)** group (n = 15) had initial SBP ranging from 144 to 160 mm Hg. Dogs assigned to the **low SBP (LSBP)** group (n = 16) had initial SBP ranging from 107 to 143 mm Hg.

Because of the possibility of a "white coat effect" on SBP measured during the initial examination, we also assigned dogs to groups on the basis of the mean value for SBPs measured during the initial examination and the first follow-up examination 1 month later.[3] Systolic blood pressure values obtained during subsequent visits were not suitable for statistical analysis, because differences in dates of enrollment and death of some dogs during the study precluded collection of data from all dogs at the intervals specified by the study design. With this method, 13 dogs with SBP ranging from 164 to 217 mm Hg were assigned to the HSBP group, 15 dogs with SBP ranging from 147 to 163 mm Hg were assigned to the ISBP group, and 17 dogs with SBP ranging from 109 to 145 mm Hg were assigned to the LSBP group. Overall, 3 of the 45 dogs changed from 1 group to another when assigned on the basis of mean SBP for the first 2 examinations versus SBP at the initial examination. Two dogs assigned to the HSBP group on the basis of SBP at the initial examination were assigned to the ISBP and LSBP groups on the basis of mean SBP for the first 2 examinations. One dog assigned to the ISBP group on the basis of SBP at the initial examination was assigned to the HSBP group on the basis of mean SBP for the first 2 examinations.

Clinical, biochemical, and hematologic findings during the first examination were compared among the HSBP, ISBP, and LSBP groups by means of ANOVA.[24] Although clinical outcome differed between diet groups,[18] the association between SBP and clinical outcome was similar within each diet group in the present study. Thus, for analyses of the association of SBP with clinical outcome, data for the diet groups were combined.

Kaplan-Meier analysis with the Mantel-Cox logrank test[25] was used to determine whether initial SBP was associated with time to development of a uremic crisis and time to death (death attributable to renal causes and death attributable to any cause). The same methods were used to determine whether mean SBP during the first 2 examinations was associated with time to development of a uremic crisis or time to death.

The Cox proportional hazard model was used to determine the **relative risk (RR)** that dogs in the LSBP, ISBP, and HSBP groups would develop a uremic crisis or die, and to evaluate the effect of diet on development of uremic crises and death among groups.[26] Using the same method, we evaluated the effect of other covariates measured during the initial examination (ie, age, weight, PCV, and serum creatinine, urea nitrogen, phosphorus, total CO_2, and albumin concentrations) on outcomes of interest. Because HSBP can lead to proteinuria,[g] the urine **protein-to-creatinine ratio (P:C ratio)** was not included as a covariate in the statistical model.

Relationships between outcomes of interest and initial SBP were also evaluated by using SBP as a continuous variable in Cox proportional hazard models. We chose to express the RR as the risk associated with a 20 mm Hg increment in SBP.

Whether SBP was associated with progression of renal failure was determined by calculating the mean of the reciprocal of serum creatinine concentration for dogs in each of the 3 groups (HSBP, ISBP, and LSBP) at each sampling interval (initial visit and 30, 60, 90, 180, 270, and 360 days after the initial visit). For each group, a best-fit line was then calculated with the least-square method[h] to illustrate the pattern of change in renal function. For each dog, the reciprocal of the serum creatinine concentration measured at the initial visit and the mean of the reciprocal of serum creatinine concentrations measured at each sampling interval were recorded. Then, in each blood pressure group, paired *t*-tests were used to test the hypothesis that the reciprocal of the serum creatinine concentration progressively decreased. Because of the high mortality rate in dogs with HSBP, only data collected up to 12 months after the initial examination were used in these analyses.

The decrease in renal function in each blood pressure group was also estimated by calculating, for each dog, the difference between the mean of the reciprocal of serum creatinine concentrations obtained at each sampling interval and the reciprocal of the serum creatinine concentration obtained during the initial visit. The change in the reciprocal of serum creatinine concentrations was then compared among blood pressure groups with ANOVA. Data obtained at the time of a uremic crisis were not included in any of these analyses.

Statistical analyses were performed with the aid of standard software.[i,j] For all analyses, a value of $P < 0.05$ was considered significant.

Results

Baseline characteristics—Values for demographic (age, weight), serum biochemical (SUN, creatinine, phosphorus, total CO_2, and albumin concentrations), and hematologic (PCV) data collected at the time of the initial examination were not significantly different among blood pressure groups (**Table 1**). However, urine P:C ratio for dogs in the HSBP group was significantly ($P = 0.009$) higher than ratios for dogs in the ISBP and LSBP groups.

Six of the 14 dogs in the HSBP group were fed a therapeutic renal food, and 8 were fed a maintenance food. Eleven of the 15 dogs in the ISBP group were fed a renal food, and 4 were fed a maintenance food. Nine of the 16 dogs in the LSBP group were fed a renal food, and 7 were fed a maintenance food.

Over the course of the study, 14 dogs were considered candidates for antihypertensive therapy because their SBP was ≥ 180 mm Hg. Seven dogs were detected during the initial examination, and 7 dogs with initial

Table 1—Initial characteristics of dogs with chronic renal failure; dogs were assigned to a low systolic blood pressure (LSBP; n = 16), intermediate systolic blood pressure (ISBP; 15), or high systolic blood pressure (HSBP; 14) group on the basis of systolic blood pressure at the time of initial diagnosis

Variable	LSBP	ISBP	HSBP	*P* value
Age (y)	7.3 ± 5.1	7.8 ± 3.5	8.9 ± 2.8	0.54
Weight (kg)	21.3 ± 13.8	21.7 ± 11.8	19.3 ± 9.9	0.85
Urea nitrogen (mg/dL)	60 ± 29	70 ± 30	58 ± 17	0.41
Creatinine (mg/dL)	3.2 ± 1.2	3.9 ± 1.8	3.2 ± 0.8	0.20
Phosphorus (mg/dL)	5.2 ± 1.1	4.7 ± 1.8	2.8 ± 2.1	0.25
Total CO_2 (mmol/L)	21.2 ± 2.3	19.7 ± 3.8	21.2 ± 2.8	0.34
Albumin (mg/dL)	3.2 ± 0.3	3.1 ± 0.3	3.0 ± 0.4	0.87
PCV (%)	36.7 ± 8.1	36.4 ± 9.1	39.9 ± 10.3	0.52
Urine P:C ratio	0.80 ± 1.03[a]	1.52 ± 1.04[a]	3.47 ± 3.84[b]	0.009

Data are given as mean ± SD.
[a,b]Values with different superscript letters are significantly different.
Urine P:C ratio = Urine protein-to-creatinine ratio.

SBP < 180 mm Hg subsequently developed sustained SBP ≥ 180 mm Hg. Three of 14 dogs (1 in the ISBP group and 2 in the HSBP group) with elevated SBP were not treated because their owners were unable or unwilling to give medications. The remaining 11 dogs were given antihypertensive drugs. Amlodipine besylate[k] (dosage range, 0.05 to 0.75 mg/kg [0.02 to 0.34 mg/lb], PO, q 12 to 24 h), diltiazem hydrochloride[l] (0.5 mg/kg [0.23 mg/lb], PO, q 8 h), and enalapril maleate[m] (dosage range, 0.25 to 0.75 mg/kg [0.11 to 0.34 mg/lb], PO, q 12 to 24 h) were used to reduce SBP. Initially, lower dosages were used, and dosage was increased incrementally on the basis of serial SBP measurements. Two dogs (1 in the LSBP group and 1 in the HSBP group) were treated with enalapril alone, 5 dogs (1 in the LSBP group, 1 in the ISBP group, and 3 in the HSBP group) were treated with amlodipine alone, and 4 dogs (all in the HSBP group) were treated with a combination of enalapril and amlodipine (n = 3) or enalapril and diltiazem (1). Following initiation of antihypertensive drug treatment, SBP was < 160 mm Hg in only 1 of these 11 dogs.

After 225 days of follow-up, 8 of the 14 dogs in the HSBP group were alive, compared with 13 of the 15 dogs in the ISBP group and 12 of the 16 dogs in the LSBP group.

Association between SBP and outcome—Associations between initial SBP and outcomes of interest (ie, development of a uremic crisis, death from renal causes, and death from any cause) were similar to associations between mean SBP during the first 2 visits and outcomes of interest (**Tables 2 and 3**). When Cox's proportional hazard model was used to adjust for the effect of baseline covariates (ie, age, weight, PCV, and serum creatinine, urea nitrogen, phosphorus, total CO_2, and albumin concentrations) on outcomes of interest, RRs were significantly higher for dogs in the HSBP group than for dogs in the other 2 groups.

Association between SBP and development of a uremic crisis—Kaplan-Meier analysis indicated that time to development of a uremic crisis (initial SBP, P = 0.023; mean SBP for first 2 visits, P = 0.006) was significantly shorter for dogs in the HSBP group, compared with dogs in the 2 other groups (**Fig 1**), and dogs in the HSBP group had a significantly higher RR of developing a uremic crisis than did dogs in the other

Table 2—Association between initial SBP and development of a uremic crisis or death in dogs with chronic renal failure

Outcome and group	No. of events/ No. of dogs	Median time to events (d)	Unadjusted			Adjusted		
			RR	95% CI	*P* value	RR	95% CI	*P* value
Development of a uremic crisis								
LSBP	7/16	599	1.0	NA	NA	1.0	NA	NA
ISBP	6/15	624	1.2	0.4–3.1	0.75	1.1	0.3–3.4	0.80
HSBP	8/14	289	3.3	1.1–10.2	0.032	3.3	1.0–10.1	0.046
Death from renal causes								
LSBP	7/16	599	1.0	NA	NA	1.0	NA	NA
ISBP	8/15	624	1.1	0.4–3.1	0.89	1.2	0.4–3.7	0.73
HSBP	8/14	281	3.5	1.2–11.8	0.027	3.4	1.1–10.8	0.036
Death from any cause								
LSBP	10/16	425	1.0	NA	NA	1.0	NA	NA
ISBP	11/15	348	0.9	0.4–2.1	0.77	1.4	0.6–3.5	0.43
HSBP	11/14	154	3.2	1.3–7.9	0.01	3.0	1.2–7.4	0.02

Dogs were grouped according to systolic blood pressure (SBP) at the time of diagnosis of chronic renal failure. For this assignment, initial SBP was divided into tertiles, and dogs were assigned to a high SBP (HSBP; initial SBP ranged from 161 to 201 mm Hg), intermediate SBP (ISBP; initial SBP ranged from 144 to 160 mm Hg), or low SBP (LSBP; initial SBP ranged from 107 to 143 mm Hg) group.

RR = Relative risk. CI = Confidence interval.

Table 3—Association between mean SBP during the initial visit and 1 month later and development of a uremic crisis or death in dogs with chronic renal failure

Outcome and group	No. of events/ No. of dogs	Median time to events (d)	Unadjusted			Adjusted		
			RR	95% CI	*P* value	RR	95% CI	*P* value
Development of a uremic crisis								
LSBP	8/17	599	1.0	NA	NA	1.0	NA	NA
ISBP	5/15	521	0.8	0.3–2.5	0.71	0.9	0.3–3.0	0.92
HSBP	8/13	281	4.0	1.3–12.2	0.01	3.5	1.1–11.1	0.031
Death from renal causes								
LSBP	8/17	599	1.0	NA	NA	1.0	NA	NA
ISBP	7/15	521	0.9	0.3–2.8	0.93	1.1	0.4–3.4	0.84
HSBP	8/13	281	4.4	1.4–13.3	0.01	3.9	1.2–12.2	0.02
Death from any cause								
LSBP	11/17	532	1.0	NA	NA	1.0	NA	NA
ISBP	10/15	334	0.9	0.4–2.1	0.64	1.2	0.5–2.9	0.64
HSBP	11/13	154	3.2	1.3–7.9	0.003	3.8	1.6–9.4	0.003

Dogs were grouped according to the mean of SBP measurements obtained at the time of diagnosis of chronic renal failure and during a re-examination 1 month later. Systolic blood pressure was divided into tertiles, and dogs were assigned to an HSBP (mean SBP ranged from 164 to 217 mm Hg), ISBP (mean SBP ranged from 147 to 163 mm Hg), or LSBP (mean SBP ranged from 109 to 145 mm Hg) group.

See Table 2 for key.

groups, regardless of whether the RRs were or were not adjusted for the effect of diet.

When SBP values were evaluated as a continuous variable in a Cox proportional hazards model, initial SBP was not significantly associated with risk of developing a uremic crisis (RR, 1.4 [ie, risk associated with a 20-mm Hg increment in SBP]; 95% **confidence interval [CI]**, 0.93 to 2.2); $P = 0.097$). However, the mean SBP for the first 2 visits was significantly associated with risk of developing a uremic crisis (RR, 1.6; 95% CI, 1.0 to 2.4; $P = 0.038$).

Association between SBP and death from renal causes—Kaplan-Meier analysis indicated that time to death from renal causes was significantly (initial SBP, $P = 0.024$; mean SBP for first 2 visits, $P = 0.006$) shorter for dogs in the HSBP group, compared with dogs in the 2 other groups (**Fig 2**). Cox proportional hazards analysis indicated that the risk of death from renal causes was significantly higher for dogs in the HSBP than for dogs in the LSBP and ISBP groups, regardless of whether the RRs were or were not adjusted for the effect of diet.

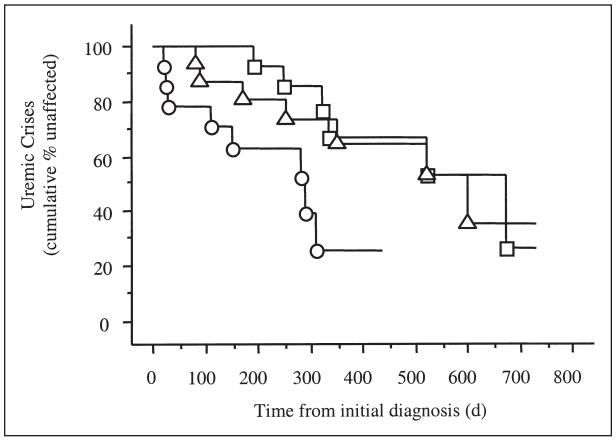

Figure 1—Kaplan-Meier graph of time to development of a uremic crisis in dogs with chronic renal failure. Dogs were grouped according to systolic blood pressure (SBP) at the time of diagnosis of chronic renal failure. For this assignment, initial SBP was divided into tertiles, and dogs were assigned to a high SBP (circles; initial SBP ranged from 161 to 201 mm Hg; n = 14), intermediate SBP (squares; initial SBP ranged from 144 to 160 mm Hg; 15), or low SBP (triangles; initial SBP ranged from 107 to 143 mm Hg; 16) group.

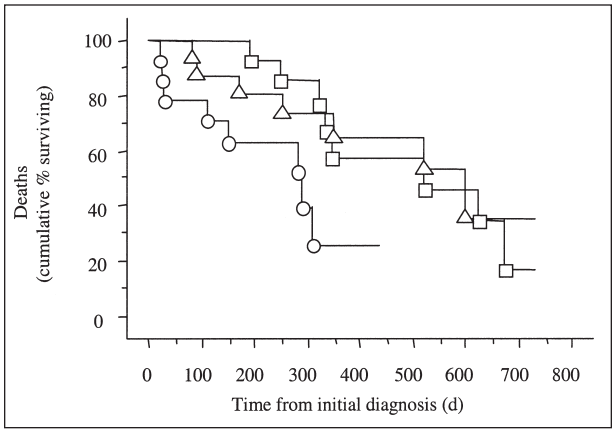

Figure 2—Kaplan-Meier graph of time to death from renal causes in dogs with chronic renal failure. *See* Figure 1 for key.

When SBP values were entered as a continuous variable in the Cox proportional hazards model, initial SBP was not significantly associated with risk of death from renal causes (RR, 1.4; 95% CI, 0.93 to 2.2; $P = 0.087$). However, mean SBP for the first 2 visits was significantly associated with risk of death from renal causes (RR, 1.6; 95% CI, 1.2 to 2.5; $P = 0.027$).

Association between SBP and death from any cause—Kaplan-Meier analysis indicated that time to death from any cause was significantly (initial SBP, $P = 0.01$; mean SBP for first 2 visits, $P = 0.004$) shorter for dogs in the HSBP group, compared with dogs in the ISBP and LSBP groups (**Fig 3**). Cox proportional hazards analysis indicated that the risk of death from any cause was significantly higher for dogs in the HSBP group, compared with dogs in the ISBP and LSBP groups, regardless of whether the RRs were or were not adjusted for the effect of diet.

When SBP values were entered as a continuous variable in the Cox proportional hazards model, initial SBP was significantly associated with the risk of death from any cause (RR, 1.5; 95% CI, 1.1 to 2.1; $P = 0.02$). Similarly, mean SBP for the first 2 visits was significantly associated with risk of death from any cause (RR, 1.8; 95% CI, 1.2 to 2.5; $P = 0.028$).

Association between SBP and progression of renal failure—The reciprocal of the serum creatinine concentration decreased significantly over time in dogs in the HSBP group, but not in dogs in the other 2 groups (**Fig 4**). Analysis of variance indicated that the change in renal function was significantly higher for dogs in the HSBP group than for dogs in the other groups (**Table 4**).

Retinopathy—Lesions suggestive of hypertensive retinopathy were observed in 3 dogs; none of the 3 had been treated with antihypertensive drugs. At the time lesions were identified, SBP in these dogs ranged from 191 to 201 mm Hg. Bilateral retinal vessel tortuosity was observed in 1 dog, unilateral complete retinal detachment with secondary hyphema was observed in 1 dog, and bilateral, multifocal retinal hemorrhages

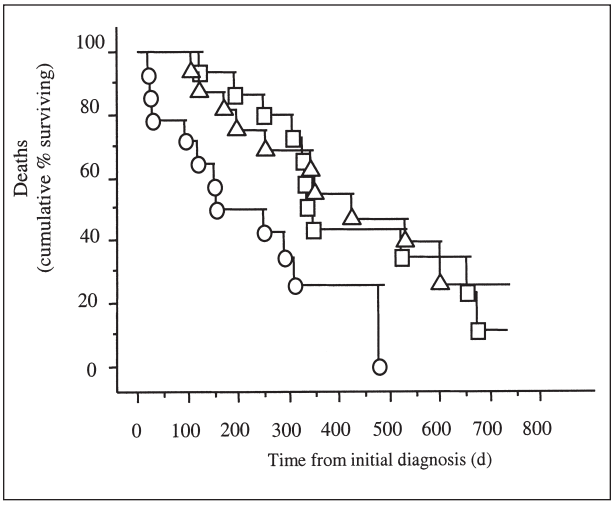

Figure 3—Kaplan-Meier graph of time to death from any cause in dogs with chronic renal failure. *See* Figure 1 for key.

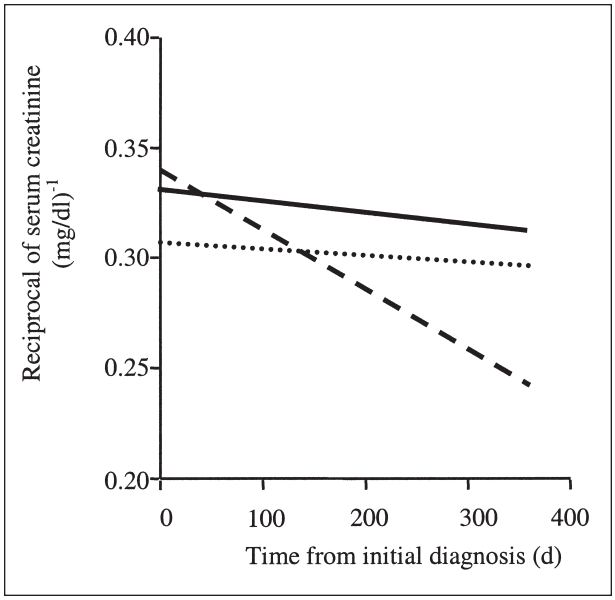

Figure 4—Best-fit graphs of the reciprocal of the serum creatinine concentration in dogs with chronic renal failure. Dogs were grouped on the basis of initial SBP into high SBP (dashed line), intermediate SBP (dotted line), and low SBP (solid line) groups.

were observed in 1 dog. Necropsy of the dog with unilateral retinopathy confirmed complete retinal detachment; light microscopic findings were consistent with retinal detachment secondary to systemic hypertension. Lesions suggestive of hypertensive retinopathy were not detected in the remaining 11 dogs in the HSBP group, 8 of which were treated with antihypertensive drugs. Hypertensive retinopathy was not observed in any of the 31 dogs in the ISBP and LSBP groups.

Encephalopathy—Hypertensive encephalopathy was suspected antemortem in 3 of the 14 dogs in which SBP exceeded 180 mm Hg during the study. Two of the 3 dogs with hypertensive encephalopathy were initially assigned to the ISBP group; the third was assigned to the HSBP group. All 3 dogs developed seizures in association with high blood pressure. At the time neurologic signs were observed, SBP ranged from 184 to 208 mm Hg. Necropsies were performed in 2 of the 3 dogs. Light microscopic findings included a focal cerebral lesion consistent with acute hemorrhage and necrosis in 1 dog. In the other dog, hyalinization and thickening of the walls of cerebellar arterioles in the caudate nucleus were observed. Substantial vacuolization of the myelinated tract was also present. None of the remaining 13 dogs assigned to the HSBP group developed signs of hypertensive encephalopathy; however, 8 of the 13 were treated with antihypertensive drugs. Clinical signs of hypertensive encephalopathy were not detected in the remaining 29 dogs; however, multiple microhemorrhages and occasional thrombi were seen in the arterioles of the cerebrum in 1 of 14 dogs that underwent a necropsy. Thrombi were also seen in both atria and the pulmonary vasculature. These lesions likely occurred as a result of thromboembolism and were probably not secondary to systemic hypertension. This dog was assigned to the LSBP group.

Mean SBP—Systolic blood pressure measurements obtained during the initial and second visits were excluded, and mean ± SD SBP for the remainder of the study period was calculated. For the LSBP group, mean ± SD initial SBP was 128 ± 12 mm Hg, and SBP for the remainder of the study period was 130 ± 18 mm Hg. For the ISBP group, mean initial SBP was 155 ± 5 mm Hg, and SBP for the remainder of the study period was 154 ± 12 mm Hg. For the HSBP group, mean initial SBP was 181 ± 14 mm Hg, and SBP for the remainder of the study period was 173 ± 18 mm Hg.

Change in SBP in response to antihypertensive drug treatment—Even though antihypertensive drug dosages were increased and drugs were used in combination in an attempt to achieve an SBP of < 160 mm Hg, SBP was < 160 mm Hg in only 1 of the 11 dogs treated with antihypertensive drugs.

Discussion

Results of the present study support the hypothesis that dogs with chronic renal failure that have a

Table 4—Association between SBP and progression of renal failure in dogs with chronic renal failure

	Reciprocal of serum creatinine concentration (mg/dL)$^{-1}$							
	Baseline*		Overall†			Difference‡		
Group	Mean	95% CI	Mean	95% CI	*P* value§	Mean	95% CI	*P* value‖
Initial SBP								0.015
LSBP	0.310	0.260–0.360	0.317	0.257–0.377	0.77	0.009	–0.051 to 0.069	
ISBP	0.314	0.254–0.374	0.280	0.220–0.340	0.55	–0.01	–0.05 to 0.03	
HSBP	0.365	0.315–0.415	0.270	0.210–0.330	< 0.001	–0.09	–0.13 to –0.05	
Mean SBP for first 2 visits								0.011
LSBP	0.304	0.254–0.354	0.326	0.276–0.376	0.33	0.003	–0.06 to 0.063	
ISBP	0.303	0.243–0.363	0.277	0.217–0.337	0.23	–0.03	–0.08 to 0.02	
HSBP	0.369	0.309–0.429	0.274	0.214–0.334	< 0.001	–0.095	–0.135 to –0.055	

*Mean value and 95% CI for the reciprocal of serum creatinine concentrations measured at the time of initial diagnosis of chronic renal failure. †Mean value and 95% CI for the reciprocal of serum creatinine concentrations measured throughout the study period. ‡Mean value and 95% CI of the difference between the reciprocals of initial serum creatinine concentration and the serum creatinine concentrations measured throughout the study period. §*P* value associated with a paired *t*-test comparing reciprocals of baseline and overall serum creatinine concentrations in each group. ‖*P* value associated with an ANOVA of the difference in reciprocals of serum creatinine concentrations among groups.

Dogs were assigned to LSBP, ISBP, and HSBP groups on the basis of initial SBP at the time of diagnosis of chronic renal failure and on the basis of the mean SBP at the time of initial diagnosis and 1 month later.

See Table 2 for key.

higher SBP at the time of initial diagnosis have a higher risk of having a uremic crisis and of dying from renal causes or from any cause than do dogs with a lower SBP at the time of initial diagnosis and have a faster progression in terms of loss of renal function.

In the present study, renal function was assessed by calculating the reciprocal of the serum creatinine concentration, and a significantly greater decrease in renal function was observed in dogs assigned to the HSBP group, compared with dogs assigned to the ISBP and LSBP groups, regardless of whether group assignment was based on initial SBP or mean SBP during the first 2 visits. These findings are in accord with results from a preliminary study[g] in dogs with experimentally induced renal failure in which marked elevation of SBP was associated with further renal damage, as measured by decreased renal function and increased renal protein excretion. Likewise in humans, uncontrolled systolic hypertension is a major risk factor for chronic irreversible progressive renal failure.[14,15,27-30]

We also found that dogs in the HSBP group were 3 times as likely to develop a uremic crisis and to die as were dogs in the LSBP group. Furthermore, dogs in the HSBP group had a shorter time to development of a uremic crisis and shorter survival time than did dogs in the LSBP and ISBP groups. Our results also indicated that the risks of developing a uremic crisis and of death increased with the degree of elevation in SBP, with risks increasing by a factor of at least 1.4 for every 20 mm Hg increase in SBP.

In humans with chronic renal failure, there is a strong relationship between the degree of increase in arterial blood pressure and development of ocular lesions. In 1 study,[31] 52% of patients with renal parenchymal hypertension developed ocular lesions. In dogs with chronic renal failure, a relationship between high SBP and hypertensive retinopathy also appears to exist.[9,11] Similarly, whereas none of the dogs in the present study assigned to the ISBP or LSBP group had clinical evidence of retinopathy, ocular lesions consistent with hypertensive retinopathy developed in 3 of 14 dogs in the HSBP group. Conversely, retinal lesions were not detected in the remaining 11 of 14 dogs in the HSBP group, suggesting that ocular signs are not a reliable indicator of high SBP. On the other hand, 8 of these 11 dogs were treated with antihypertensive drugs, and it is possible that the absence of retinal lesions in some of these dogs may be related, at least in part, to intermittent reductions in SBP associated with antihypertensive drug treatment.

Although further studies will be required to determine whether there is a cause-and-effect relationship between higher SBP and progressive renal injury, results of our study suggest that initial measurements of blood pressure in dogs with chronic renal failure may help in refining the prognosis. However, limitations associated with the design of our study should be considered. For example, renal function was assessed by evaluating the reciprocal of serial serum creatinine concentrations. One group of investigators has recommended that caution be used in interpreting isolated measurements of the reciprocal of serum creatinine concentrations, as such values are not a sensitive index of glomerular filtration.[32,33] However, the reciprocal of serial serum creatinine concentrations, as was measured in the present study, is a useful estimate of the trend for changes in glomerular filtration rate.[23]

A criticism of the present study is that the treatment of some dogs with antihypertensive drugs may have influenced the results. In terms of experimental design, it would have been ideal to not treat any dogs with such drugs; however, we believed that the expected standard of care warranted treatment of dogs with SBP > 180 mm Hg.[12] Furthermore, with the exception of 1 dog in which SBP was < 160 mm Hg after treatment with amlodipine besylate, treatment of 11 dogs with antihypertensive drugs did not result in a substantial decrease in SBP. One plausible explanation for this observation is that these dogs died before an effect of antihypertensive drug treatment on hypertension could be observed. Regardless, antihypertensive drug treatment of these dogs, if it had any effect on our results, would likely have reduced the estimated risk of developing a uremic crisis or of dying and the progression in renal failure. The observation that treatment with enalapril reduces the rate of decline in renal function and prolongs survival time in dogs with naturally occurring glomerulonephritis[34] supports our interpretation. The salutatory effect was hypothesized to be related, at least in part, to a significant reduction in SBP.[34] Likewise, treatment of hypertension in humans significantly reduces the risk of cardiovascular and cerebrovascular deaths, hypertensive retinopathy, and progression of renal disease to end-stage renal failure.[35-37] However, because our study was not designed to study the effect of antihypertensive drugs on clinical outcomes, we cannot exclude the possibility that they also may have been associated with adverse effects. For example, in a study[38] of diabetic dogs with induced renal failure, treatment with a calcium-channel blocker was associated with increased intraglomerular pressure. If drug-induced increases in glomerular capillary pressure are sustained, persistent systemic hypertension could cause damage to glomerular capillaries. In this previous study,[38] treatment with an angiotensin converting enzyme inhibitor was associated with decreases in glomerular capillary pressure. Although a decrease in glomerular capillary pressure might reduce the risk of damage to glomerular capillaries, if sustained, it could lead to further reductions in glomerular filtration rate.

The fact that dogs that were fed an adult maintenance food, versus a therapeutic renal failure food, were not equally distributed among groups is also a limitation. As reported elsewhere,[18] diet has been shown to influence the risks of developing a uremic crisis and of dying. However, after adjusting for the effect of diet, dogs in the HSBP group still had significantly higher risks of developing a uremic crisis and dying.

[a]Kallet AJ, Cowgill LD. Hypertensive states in the dog (abstr), in *Proceedings*. Annu Vet Med Forum 1982;79.
[b]Dinamap model 33614, Critikon Inc, Tampa, Fla.
[c]Ultrasonic Doppler flow detector model 811, Park Medical Electronics Inc, Ahoha, Ore.
[d]Astra-8 automated stat/routine analyzer, Beckman Instruments Inc, Fullerton, Calif.

[e]Hematastat II, Separation Technology Inc, Altamante Springs, Fla.
[f]Lancer microprotein rapid stat diagnostic kit, Sherwood Medical, St Louis, Mo.
[g]Brown SA, Brown CA, Hendi R. Does systemic hypertension damage the canine kidney? (abstr). *J Vet Intern Med* 2000;351.
[h]Cricket graph, Computer Associates International Inc, Islandia, NY.
[i]Statview 4.1, Abacus, Berkeley, Calif.
[j]SAS 6.12, SAS Institute Inc, Cary, NC.
[k]Norvasc, Pfizer Labs, New York, NY.
[l]Cardizem, Lederle Laboratories, Pearl River, NY.
[m]Enacard, Merk & Co Inc, Rahway, NJ.

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