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Effect of Control of Systolic Blood Pressure on Survival in Cats with Systemic Hypertension

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Background: Systemic hypertension is a common clinical problem, often occurring in association with renal disease in cats. Limited information is available to assess the effect of blood pressure and the treatment of hypertension on survival.

Hypothesis: That adequacy of blood pressure control is associated with the duration of survival in cats with systolic hypertension.

Animals: One hundred and forty-one client-owned cats with systolic hypertension.

Methods: Hypertensive cats were treated with amlodipine besylate and were followed until death or the study end point. Time-averaged systolic blood pressure (SBPOT) after implementation of antihypertensive medication and stabilization of systolic blood pressure (SBP) was calculated by using the equation (area under the curve/survival [days]). Cats were divided into quartiles based on their SBPOT, representing varying levels of blood pressure control (median [25th, 75th percentile]: Q1 = 137 [132, 141] mm Hg, Q2 = 148 [145, 151] mm Hg, Q3 = 157 [155, 158] mm Hg, Q4 = 170 [164, 175] mm Hg). Survival and clinical variables were compared between the quartiles. Cox proportional hazard regression analysis was used to determine the association of age, renal function, proteinuria, SBPOT, and the presence of hyperthyroidism on survival. Urine protein to creatinine ratio (UP : C) was compared at diagnosis of hypertension and after initiating treatment.

Results: Only UP : C and SBP at diagnosis differed significantly between SBPOT quartiles. Proteinuria was the only variable significantly related to survival in hypertensive cats. A significant decline in UP : C was found in cats treated with amlodipine besylate.

Conclusions and Clinical Importance: Proteinuria before and after treatment of hypertension is strongly associated with survival in cats with systolic hypertension. Treatment with amlodipine besylate can result in a significant reduction in UP : C.

Key words: Amlodipine besylate; Proteinuria.

Systolic hypertension is recognized with increasing frequency in feline practice. Hypertension occurs most commonly in cats in association with either renal disease or hyperthyroidism.[1–3] There are also reports of hypertension in cats with hyperaldosteronism, diabetes mellitus, erythropoietin treatment, and chronic anemia.[4–6] Idiopathic hypertension occurs in cats although definitive measurement of glomerular filtration rate (GFR) is rarely available to fully evaluate renal insufficiency.[a]

Hypertensive retinopathy or choroidopathy is the most common clinical manifestation of hypertension and occurs in 60% of hypertensive cats.[7] However, persistent hypertension can lead to damage of other organs, including kidneys, heart, and central nervous system.[8–10] An association among hypertension, proteinuria, and progression of renal disease has been established in human patients and in dogs.[8,11–13] Such a causal link has not been proven in feline medicine, although systolic blood pressure (SBP) was independently related to severity of proteinuria in a group of cats with variable renal function.[14] However, SBP at diagnosis was not an independent risk factor for survival in cats with renal disease. In that study, 42 of 136 cats (31%) had systemic hypertension in association with renal disease, and these cats were treated for hypertension if it was considered clinically appropriate, which may have confounded the analysis.[14]

Amlodipine besylate is currently the treatment of choice for the control of hypertension in cats. Amlodipine is an effective and safe treatment for hypertension in cats when administered at a dose of 0.625–1.25 mg PO once daily.[15–17] However, there are concerns in human medicine regarding the use of calcium channel blockers as sole antihypertensive agents in patients with proteinuric renal disease.[18]

Adequate blood pressure control or the implications of inadequate blood pressure control on proteinuria, renal disease progression, and survival are poorly defined in cats. Two small-scale studies evaluated survival in hypertensive cats, neither of which detected a significant difference in survival between cats that had a "good" response to treatment and those that had a "poor" response to treatment.[3,7] Target SBP can be related to the American College of Veterinary Internal Medicine (ACVIM) hypertension consensus statement, where the following categories for SBP have been defined and where "risk" infers the possibility of developing hypertensive end organ damage, most commonly hypertensive retinopathy/choroidopathy: <150 mm Hg, minimal risk; 150–159 mm Hg, low risk; 160–179 mm Hg, moderate risk; >180 mm Hg, high risk.[b] However, although these categories provide a useful guideline for studies that evaluate systemic hypertension, their use has yet to be validated.

To date, a large-scale study that examines the association among hypertension, the adequacy of SBP control, and survival is lacking. The aim of this study was to examine the effect of blood pressure control after implementation of

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treatment on survival in a large population of cats with spontaneously occurring hypertension.

Materials and Methods

Cat Selection

Hypertensive cats were recruited from clinics held for geriatric (>9 years) cats at 2 first-opinion practices in central London (Beaumont Animals' Hospital and Peoples' Dispensary for Sick Animals in Bow) between January 1998 and February 2005. Cats were excluded from the study if they were receiving antihypertensive medication, such as a calcium channel blocker, an angiotensin-converting-enzyme (ACE) inhibitor, a diuretic, or a β-blocker. Suspected hypertensive cats were also excluded if they failed to be returned to the clinic for confirmation of the diagnosis. For entry into the study, it was required that all cats had at least 1 SBP measurement while receiving treatment. In all cats presented to these clinics, SPB was measured by means of an indirect Doppler technique[c] by using a standardized method that was previously described.[1,7] Blood pressure was measured with the owner present, after a period of acclimatization during which a history was taken and before the physical examination, to reduce the magnitude of "white coat" hypertension.[19] The cat was allowed to assume its preferred position, most commonly sitting or sternal. A cuff of either 2.5 or 3.3 cm, whichever was closest to 30–40% limb circumference, was applied to the mid antebrachium. A sphygmomanometer was connected to the cuff, and the Doppler probe (9.5 MHz) was placed over the common digital branch of the radial artery on the palmar aspect of the foot. The fur was not clipped, but the region was swabbed with alcohol and an aqueous gel was applied to improve ultrasonic contact. In all cats, the first SBP reading was discarded and a series of 5 consecutive readings were then obtained, and the arithmetic mean was calculated. Systolic hypertension was defined as SBP > 170 mm Hg on 2 or more occasions or SBP > 170 mm Hg on 1 occasion in association with clinical manifestations of hypertension, most commonly hypertensive retinopathy/choroidopathy.

At each visit, a full history was taken and a complete physical examination was performed. A fundic examination was performed on all cats. After the blood pressure measurement, 1 drop of tropicamide 1%[d] was placed in both eyes, and an indirect ophthalmoscopy was performed at the end of the consultation period.

The collection and storage of blood and urine samples was performed with the informed consent of the cat's owner. Blood samples were obtained by jugular venipuncture at the time of diagnosis of hypertension, before initiating antihypertensive medication. Owners routinely were asked to withhold food for 8 hours before the visit to the practice. The Ethics and Welfare Committee of the Royal Veterinary College approved the study protocol. Blood samples were taken into lithium heparin tubes and were centrifuged to produce heparinized plasma for full biochemical analysis. The total thyroxine concentration was measured in all nonazotemic cats at entry to the study and also in all cats where the history (polyphagia, weight loss), clinical examination findings (palpable goiter, tachycardia, low body condition score), or results of biochemical analysis (increases in alanine aminotransferase or alkaline phosphatase activity) were consistent with hyperthyroidism.

In all cases in which the urinary bladder was palpable, a urine sample was collected by cystocentesis. Samples were chilled between collection and analysis. Urinalysis was performed within a few hours of sample collection and included measurement of specific gravity by refractometry, measurement of pH, semi-quantitative biochemical analysis by using chemical reagent strips,[e] and urine sediment examination. Urine culture was performed when there was microscopic evidence of pyuria or bacturia or where clinical signs were consistent with a urinary tract infection (hematuria, stranguria, or both). After urinalysis urine samples were centrifuged at 1000 $\times g$ at 4°C for 10 minutes and urine supernatant was then separated and stored at −80°C. UP : C ratios were evaluated retrospectively (February 2005) by using stored samples from cats at diagnosis of hypertension (pre UP : C), before starting amlodipine besylate treatment. A UP : C (post UP : C) after treatment was also evaluated retrospectively by using stored samples from the first time point after stabilization of blood pressure, at which a urine sample was obtained (Table 1). In most cases, this coincided with the first visit analyzed as part of the evaluation of time-averaged systolic blood pressure (SBPOT). Cats were excluded from UP : C evaluation if an active sediment was found on urine microscopy or where there the collected sample was grossly hematuric.

Table 1. Survival data for cats with systemic hypertension.

	N	Median	[25th, 75th Percentile] or (Range)
SBP at diagnosis of hypertension	141	195	[184, 214]
Total no. visits/cat	141	7	(3–42)
Survival (days)[a]	89	259	(18–1584)
Follow-up of cats censored from study (days)[b]	52	255	(28–1232)

SBP, systolic blood pressure.

[a] Represents those cats that died or were euthanized during the study.

[b] Represents time in study of those cats that were alive at the end of the study.

Hypertension was treated in all cases with amlodipine besylate[f] at an initial dose of 0.625 mg/cat once daily. Cats were reexamined after 7–21 days to ensure efficacy of treatment. If SBP measurements remained higher than 160 mm Hg, then the dose of amlodipine besylate was increased to 1.25 mg/cat once daily (Table 1). All cats with evidence of azotemia (plasma creatinine concentration) >1.9 mg/dL (>177 μmol/L) and clinical signs consistent with chronic renal disease (polydipsia, polyuria, palpably small kidneys) were offered a phosphate-restricted diet,[g] although compliance was variable. The diet was provided to the clients free of charge. Cats with uncontrolled hyperphosphatemia despite renal dietary therapy were prescribed aluminium hydroxide.[h] Cats that showed persistent hypokalemia were treated with potassium gluconate.[i] Hyperthyroidism was treated either with carbimazole[j] alone or in combination with surgical thyroidectomy. Other medications used during this study were prescribed on an individual basis in accordance with underlying disease conditions.

Survival Data

After initial stabilization, repeat examinations at 6-week intervals were available for all cats, based on their clinical status. Survival in days was calculated from the date of initiating antihypertensive medication until either death or euthanasia or the study end point (January 3, 2005). Where available, the date of death was recorded from the medical records. However, if the cat died at home and the owner knew only the month of death, then it was assumed that the cat died on the 15th day of that month. No attempt was made to classify the cause of death. Euthanasia was performed in accordance with the wishes of the owner and with guidance from the clinician, based on the cat's health status and quality of life. Because the majority of these animals were being treated without charge (although owners were encouraged to make an anonymous donation to the charity clinic), there were no financial implications affecting treatment considerations in these

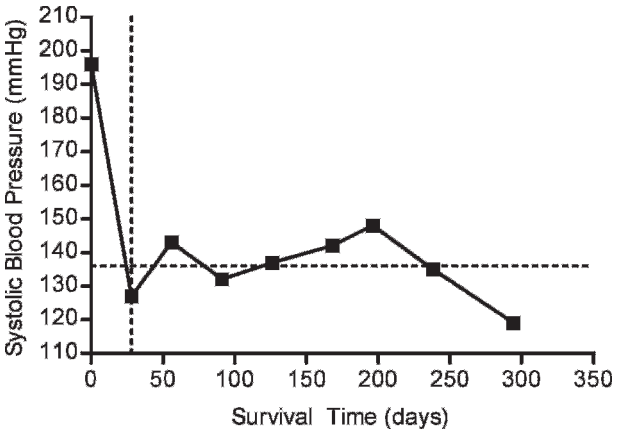

Fig 1. Example of calculated time-averaged systolic blood pressure (SBPOT) by using the area under the curve (AUC) for 1 cat. The AUC was calculated by using the area to the right of the vertical dashed line, excluding the first hypertensive measurement. This was performed by using computer software[k] and was repeated for each of the hypertensive cats. The AUC was used to calculate the SBPOT (SBPOT = [AUC/days survival]) as represented by the horizontal dashed line.

cats or influencing the decision regarding euthanasia. Cats were censored from the study if they were still alive at the study end point.

SBPOT

SBP was evaluated at every visit over the survival period for each cat. A SBPOT was calculated based on the area under the curve (AUC) by using the equation [AUC/survival] (days) (Fig 1). This was calculated by including only SBP measurements recorded once each cat was stabilized on treatment. For inclusion in the study, each cat had to have at least 1 mean SBP measurement recorded while on treatment. Cats were allocated into quartiles based on their SBPOT, representing incremental categories of blood pressure control.

Statistical Analysis

Computerized statistical software[k,l] was used for all analyses. Probabilities ≤ .05 were considered significant. Data are reported as median (25th percentile, 75th percentile) unless otherwise stated. UP:C data was log transformed to normalize the data before parametric analysis and was compared pre- and post-treatment of hypertension by using a paired *t*-test. Pretreatment UP:C was evaluated in urine samples obtained at the diagnosis of hypertension before initiating any antihypertensive medication. Post-treatment UP:C measurements were made by using the first urine sample available after stabilization of blood pressure (Table 2). Clinical variables were compared between SBPOT quartiles by using the nonparametric Kruskal-Wallis test for continuous data or the chi-square test for categorical data test as appropriate. Where significant differences were present a Mann-Whitney *U* test with Bonferroni correction was used for post hoc analysis. A one-way analysis of variance was used to evaluate the difference in survival and change in proteinuria among cats stratified in accordance with their International Renal Interest Society (IRIS)[m] staging of UP:C at diagnosis of hypertension. A Bonferroni post test was used for post hoc analysis. Survival analysis was performed by using the Cox proportional hazards model. Univariate analysis was performed to identify potential predictive variables at the diagnosis of hypertension. Variables that were significant ($P < .05$) in the univariate

Table 2. Measures of stabilization of blood pressure and proteinuria in 141 cats with hypertension.

		N	Median	[25th, 75th Percentile] or (Range)
Days until stabilization of SBP[a]		141	20	[14, 28]
Visits until stabilization of SBP		141	1 visit	n = 101
			2 visits	n = 33
			3 visits	n = 3
			4 visits	n = 3
SBP at stabilization of blood pressure		141	152	[142, 161]
Weight of cats at stabilization of blood pressure		141	3.60	[3.08, 4.50]
Amlodipine besylate (mg/kg)[b]		141	0.20	[0.16, 0.26]
Days until increase in amlodipine besylate dose[c]		68	21	[14, 49]
Visits until increase in amlodipine besylate dose[c]		68	2	(2–19)
Days until UP:C measurement after treatment[d]		105	35	[20, 63]
No. visits until UP:C measurement after treatment[d]		105	3	(2–8)
UP:C at diagnosis of hypertension		118	0.31	[0.19, 0.59]
UP:C after treatment of hypertension		108	0.21	[0.12, 0.42]
Change in UP:C with treatment of hypertension[e]	UP:C < 0.2	33	−0.01	[−0.05, 0.06]
	UP:C 0.2–0.4	31	−0.07	[−0.12, 0.005]
	UP:C 0.4	41	−0.28	[−0.51, −0.04]

SBP, systolic blood pressure; SBPOT, time-averaged SBP; AUC, area under curve; UP:C, urine protein to creatinine ratio; IRIS, International Renal Interest Society.

[a] Represents number of days from starting amlodipine besylate treatment until cat was considered to have adequate control of SBP; at this point the cat was entered into the SBPOT AUC analysis.

[b] Calculated by using the weight and amlodipine besylate dose at the first (n = 130) or second visit (n = 11), after stabilization of blood pressure.

[c] Represents days/visits from diagnosis of hypertension until dose was increased from 0.625–1.25 mg/cat/day.

[d] Represents the number of days/visits from diagnosis of hypertension, starting amlodipine besylate treatment and before treatment UP:C until UP:C measured after treatment.

[e] Divided into IRIS classification based on UP:C measurement at diagnosis of hypertension.

Table 3. Comparison of clinical variables between quartiles based on time averaged systolic blood pressure (median; [25th percentile, 75th percentile]).

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
N	35	35	35	36
SBPOT (mm Hg)	137 [132, 141]	148 [145, 151]	157 [155, 158]	170 [164, 174]
SBP at diagnosis (mm Hg)	192 [184, 209]	186[a] [181, 205]	196 [184, 214]	209[a] [190, 227]
Age (years)	15.0 [13.1, 16.2]	14.8 [13.6, 16.6]	14.0 [13, 15]	15.0 [13, 16]
Creatinine (mg/dL)	2.1 [1.7, 2.7]	2.4 [1.8, 3.0]	2.1 [1.5, 2.5]	2.1 [1.7, 2.7]
UP : C at diagnosis	0.23[a] [0.19, 0.32]	0.30 [0.17, 0.59]	0.36 [0.11, 0.55]	0.46[a] [0.29, 0.94]
UP : C after treatment	0.17 [0.11, 0.22]	0.27 [0.11, 0.74]	0.22 [0.11, 0.43]	0.26 [0.17, 0.54]
Phosphorus (mg/dL)	4.09 [3.44, 5.17]	4.77 [3.87, 5.64]	4.40 [3.94, 5.46]	4.77 [4.12, 6.73]
PCV (%)	36 [32, 38]	35 [31, 39]	37 [34, 41]	35 [30, 39]
No. cats with retinal lesions	13	14	17	14
Total visits/cat	8 [5, 12]	6[a] [3/11]	9[a] [5, 21]	6.5 [3.25, 13]
Survival (days)	293 [201, 493]	202 [88, 346]	307 [167, 792]	162 [83, 522]

SBP, systolic blood pressure; SBPOT, time-averaged SBP; UP : C, urine protein to creatinine ratio.
[a] Represents statistically significant difference between quartiles ($p < .05$).

analysis and those thought to be of biological significance, were entered into a multivariate analysis. Because of a lack of independence among the 3 measures of proteinuria (UP : C before treatment, UP : C after treatment, and change in UP : C), these variables were analyzed in separate models. A backward elimination stepwise likelihood ratio method was used for multivariate analysis, and the outcome variable was the time until death from any cause (Table 3). The following variables were entered into all multivariate models: SBPOT and plasma phosphorus concentration categorized into quartiles, plasma creatinine concentration stratified in accordance with the IRIS[b] staging system, age entered as a continuous variable, and previous history or diagnosis of hyperthyroidism entered as a dichotomous variable. Plasma creatinine concentration was stratified in accordance with the IRIS staging scheme as follows: stage I (creatinine <140 μmol/L [<1.6 mg/dL]), stage II (creatinine 140–249 μmol/L [1.6–2.8 mg/dL]), stage III (creatinine 250–440 μmol/L [2.8–5.0 mg/dL]), and stage IV (creatinine >440 μmol/L [>5.0 mg/dL]). Because only 2 cats were included in the IRIS stage IV group, these were combined with IRIS stage III for all statistical analysis. In addition, stage II was further subdivided into stage II nonazotemic (creatinine 140–177 μmol/L [1.6–1.8 mg/dL]) and stage II azotemic (creatinine 177–250 μmol/L [1.9–2.8 mg/dL]) to reflect cats that had plasma creatinine concentrations below or above the laboratory reference range, respectively.

In model 1, UP : C before treatment was entered, stratified into 3 groups, in accordance with the IRIS staging scheme[m]: nonproteinuric (<0.2), mild proteinuria (0.2–0.4), proteinuric (>0.4). In model 2 UP : C after treatment was entered stratified in accordance with the IRIS staging scheme. In model 3, change in UP : C was entered divided into quartiles. The assumptions of the proportionality of the hazard model were assessed graphically by examining the log cumulative hazard plot. Model fit was assessed graphically by plotting Cox Snell residuals against survival.

Results

One hundred and forty-one hypertensive cats were included in the study; 933 cats were evaluated for the first time at the geriatric cat clinics between January 1998 and February 2005. Data of 42 of the cats in this study were reported.[14]

Age at diagnosis of hypertension was 15.0 (13.0, 16.0) years. On physical examination the most common findings were palpable goiter in 33.3% (47/141), a systolic heart murmur in 31.2% (44/141), and dental disease in 17% (24/141) of cats. Ocular lesions were found at diagnosis of hypertension in 41.4% (58/141) of cats and included patchy hyper-reflective areas, small bullae, tortuous narrowed vessels, bullous retinal detachment, retinal hemorrhage, and gross hyphema.

During the study period, the protocol for antihypertensive medication was not followed for 5 cats that were started on amlodipine at a dose of 1.25 mg once daily. In these cats, the median at diagnosis was 189 mm Hg (range, 180–277 mm Hg) and their body weight was 5.17 kg (range, 3.7–6.2 kg) (Table 2). The cat with the lowest body weight, therefore, was receiving 0.34 mg/kg amlodipine besylate, which is in the upper quartile for the dose of amlodipine besylate used in this study.

Plasma biochemistry results were available before treatment of hypertension for 135 of 141 cats, and urine samples were obtained from 124 cats. Azotemia, defined as a creatinine concentration of >1.9 mg/dL (177 μmol/L) (IRIS class IIb, III, or IV) was present in 58% of cats (78/135) at diagnosis of hypertension. Eighteen cats were classified as nonazotemic (IRIS class I and IIa) and euthyroid. Of these nonazotemic, euthyroid cats 22% (4/18) had a urine specific gravity > 1.040, with UP : C measurements of 0.2, 0.36, 0.43, and 0.63.

Fifty-two cats were diagnosed with hyperthyroidism (total T4 > 55 nmol/L), either before development of hypertension (n = 33) or at diagnosis of hypertension (n = 19). Between entry into the study and death or euthanasia or the study end point, a further 12 cats were diagnosed with hyperthyroidism.

Paired UP : C data before and after treatment with amlodipine besylate are available for 105 cats. By using a paired *t*-test, a significant decline in log UP : C measurement was seen with treatment of hypertension in these 105 cats ($P < .001$). A decline in UP : C measurement with amlodipine besylate treatment was detected in 69.5% cats (73/105), with a median decline of 0.12 (0.32, 0.05). Therefore, in 30.5% of cats (32/105), UP : C increased with treatment. The increase in UP : C in these 32 cats was 0.075 (0.03, 0.19), and 12.4% of cats (13/105) demonstrated an increase in

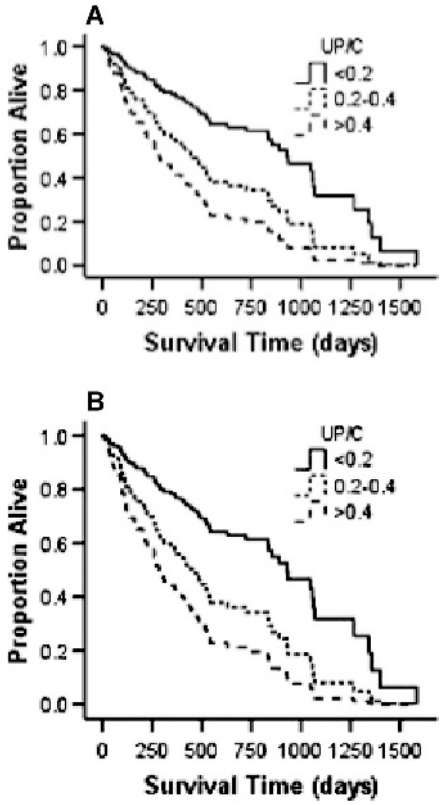

Fig 2. Survival curves constructed by using Cox's proportional hazards regression analysis with stratification according for UP : C before (**A**) and UP : C after treatment (**B**). The curves are constructed by using data from 141 hypertensive cats of which 89 died.

UP : C of >0.1. A significant difference was found in the change in UP : C with amlodipine besylate treatment between cats that were classified as nonproteinuric (<0.2) and proteinuric (>0.4) ($P = .001$) and also between mildly proteinuric (0.2–0.4) and proteinuric cats ($P = .014$) at diagnosis of hypertension (Table 2).

At the study end point (January 3, 2005), 52 of 141 cats remained alive and were censored from the survival analysis. Death occurred in 89 cats that were included in the survival analysis (Table 2). In multivariate model 1 and model 2, proteinuria pre- and post-treatment were the only variables to remain significantly associated with survival (Fig 2; Table 4). In model 3, a change in proteinuria and creatinine concentration, stratified in accordance with the IRIS staging were the only factors remaining in the model and were significantly associated with survival. The assumptions of the proportionality of the hazard model in these models were met. Log cumulative hazard curves were approximately parallel for each model, and no pattern was apparent when evaluating Cox Snell Residuals graphically.

When evaluating only those cats that died or were euthanized during the study period, a significant difference in survival ($P < .001$) was identified among cats stratified by IRIS staging of proteinuria at diagnosis of hypertension: nonproteinuric (n = 21), 490 days (217–1169 days); mild proteinuria (n = 24), 313 days (124–607 days); proteinuric (n = 33), 162 days (73–406 days). By using the Bonferroni post-test, the significant difference was identified between nonproteinuric and proteinuric cats ($P < .001$) and also between nonproteinuric and mildly proteinuric cats ($P = .04$).

Discussion

The aim of this study was to determine the survival time of cats presenting to first-opinion clinics with systolic hypertension and whether the degree of blood pressure control over time influences survival in these cats. The median survival time of the cats that died during this study was 260 days (range, 18–1584 days) and appears to be shorter than in both previous studies of hypertension in cats.[3,7] It is likely that this discrepancy in survival time for hypertensive cats simply reflects the larger sample size and the greater degree of variation in proteinuria present in cats in this study (Table 2). It is important to appreciate that, aside from SBPOT, the variables included within the survival models were evaluated only at diagnosis of hypertension. It is possible that the status of these and other covariates might have changed from baseline over time and that this may have influenced the survival and ultimate cause of death of hypertensive cats included in this study.

In the current study, 86.7% of cats were diagnosed with azotemia, hyperthyroidism, or a combination of both conditions coincident with the diagnosis of hypertension. Of the cats, 13.3% (18/135) were defined as nonazotemic and euthyroid; however, the presence of renal insufficiency cannot be excluded in these cats, because urine concentrating ability was variable and direct measurements of GFR were not available. Plasma thyroxine concentrations were not evaluated in all azotemic cats at diagnosis of hypertension. Renal disease can lead to the suppression of plasma thyroxine concentrations, therefore, substantially complicating the diagnosis of hyperthyroidism.[20,21] It, therefore, is possible that, in a small number of cats, the diagnosis of hyperthyroidism could have been missed at diagnosis of hypertension. However, any cat throughout the duration of the study with clinical signs consistent with hyperthyroidism would have had a thyroxine concentration evaluated at that stage and would have been treated appropriately. The presence or the absence of hyperthyroidism was considered a risk factor within the univariate and multivariate analysis and was not found to be associated with survival in hypertensive cats.

Adequate control of SBP in systemic hypertension is poorly defined. Our primary aim as clinicians is the prevention of end organ damage and, in particular, hypertensive retinopathy/choroidopathy, retinal detachment, and subsequent irreversible blindness. Overall, the prevalence of hypertensive retinopathy/choroidopathy in this study was lower (41.4% [58/141]) than has previously been reported by our group (70% [14/20]).[1] This is likely to reflect both the larger sample size and the use of regular monitoring of SBP in geriatric cats, such that systolic hypertension was diagnosed in many cats before the development of ocular disease.

Table 4: Univariate models of survival in cats with systolic hypertension.

							95% CI for Exp (B)	
		N	B	SE	Sig	Exp (B)	Lower	Upper
Model 1	<0.2	36			0.004			
IRIS stage UP:C	0.2–0.4	34	0.779	0.329	0.018	2.18	1.14	4.16
before treatment	>0.4	48	1.058	0.317	0.001	2.89	1.55	5.38
Model 2	<0.2	49			0.002			
IRIS stage UP:C after	0.2–0.4	30	0.738	0.297	0.013	2.09	1.17	3.75
treatment	>0.4	29	1.019	0.305	0.001	2.77	1.53	5.03
Model 3	<(−0.19)	27			0.007			
Change in UP:C	(−0.19)–(−0.059)	26	−0.546	0.323	0.091	0.58	0.31	1.09
	(−0.06)–(0.02)	26	−1.451	0.418	0.001	0.23	0.10	0.53
	> (0.02)	26	−0.424	0.336	0.206	0.65	0.34	1.26
Model 4	<143	35			0.076			
SBPOT (mm Hg)	143–153	35	0.226	0.315	0.472	1.25	0.68	2.33
	154–161	35	−0.422	0.318	0.184	0.66	0.35	1.22
	>161	36	0.335	0.287	0.243	1.40	0.80	2.46
Model 5	≤184	40			0.573			
SBP at diagnosis of	185–195	31	0.056	0.301	0.852	1.06	0.59	1.91
hypertension (mm Hg)	196–214	36	−0.218	0.306	0.477	0.80	0.44	1.47
	>215	34	0.220	0.288	0.446	1.25	0.71	2.19
Model 6	≤3.7	34			0.049			
Phosphorus (mg/dL)	3.8–4.6	34	0.175	0.323	0.588	1.19	0.63	2.25
	4.7–5.9	34	0.220	0.304	0.469	1.25	0.69	2.26
	≥6	33	0.803	0.307	0.009	2.23	1.22	4.07
Model 7	I	26			0.263			
IRIS Stage Creatinine	IIa	31	−0.185	0.331	0.576	0.83	0.44	1.59
	IIb	49	−0.392	0.313	0.209	0.68	0.37	1.25
	III and IV	29	0.196	0.355	0.582	1.22	0.61	2.44
Model 8	Never	77						
Thyroid status	diagnosed							
	Diagnosed	64	0.251	0.218	0.249	1.29	0.84	1.97
Model 9	Continuous	130	0.057	0.046	0.221	1.06	0.97	1.16
Age (years)	variable							

UP:C, urine protein to creatinine ratio; B, estimated coefficient; Sig, significance; Exp (B), hazard ratio; SE, standard error; CI, confidence interval; IRIS, International Renal Interest Society.

Previous clinical studies documented retinal lesions in cats with SBP > 168 mm Hg, although a variety of different techniques were used for the measurement of blood pressure.[1,4,6,22,23] When a nephrectomy model of renal disease and hypertension was used, cats developed retinal lesions with SBP > 160 mm Hg.[24] Although our definition of systemic hypertension was SBP > 170 mm Hg, we used a target blood pressure of <160 mm Hg after initiation of treatment for blood pressure control, leaving an undefined region between 160 and 170 mm Hg. From clinical experience and when taking into consideration the studies documented above, our target for blood pressure control (<160 mm Hg) is the level at which we feel there is a reduced risk of the development of hypertensive retinopathy, choroidopathy, or both. This can be substantiated by the fact that hypertensive retinal lesions/hemorrhages were only documented to worsen or progress to retinal detachment in 6 of 141 cats after initiation of antihypertensive medication.

Feline hypertension is also complicated by the occurrence of white-coat hypertension.[19] In this study, concern may be raised over the prevalence of white-coat hypertension, because relatively few cats presented with hypertensive retinal lesions. This study represented a population of both azotemic and nonazotemic hypertensive cats. Previous studies evaluated the prevalence of systemic hypertension only in azotemic cats.[1] In the human literature, it has been suggested that the presence of chronic renal disease is an additional risk factor for the development of hypertensive retinopathy.[25] However, it is possible that a proportion of cats, particularly within the nonazotemic, euthyroid group, represent false-positive cases with white-coat hypertension.

Cats were started on an initial dose of 0.625 mg/cat of amlodipine besylate. In 50% of cats, it was necessary to increase the dose of amlodipine to 1.25 mg/cat either during the stabilization period or during the follow-up period (Table 1). The stabilization period, which also represents the time from diagnosis of hypertension until inclusion in the SBPOT AUC analysis, was relatively short for all cats (median, 20 days), with 95.7% of cats (135/141) requiring only 1–2 visits for stabilization of

blood pressure (Table 1). Therefore, the stabilization period had limited effect on the time available for evaluation of SBPOT during the period of survival or follow-up. All clients were offered regular examinations for their cats at 7- to 21-day intervals until blood pressure was considered stabilized. However, client availability to return to the clinic, to some extent, influenced the time until stabilization.

A significant decline in UP : C was found with treatment of hypertension when using amlodipine besylate. This change in UP : C was most marked in cats defined as proteinuric at diagnosis of hypertension. This finding is of clinical importance in feline medicine, because there have been concerns regarding the use of calcium channel blockers as sole antihypertensive agents in the human literature. Calcium channel blockers such as amlodipine besylate cause preferential vasodilation of the afferent arteriole. Therefore, failure to adequately control blood pressure may result in defective autoregulation and transmission of high pressures to the glomerulus, exacerbating glomerular damage and potential protein leakage.

When cats were divided into quartiles based on their SBPOT, there was found to be no significant difference in survival between quartiles suggesting, that the level of blood pressure control achieved did not influence survival times. Similarly, in each of the Cox's proportional hazards models, where a measure of proteinuria was also included, neither SBP at diagnosis of hypertension nor the level of blood pressure control evaluated by SBPOT were significantly associated with survival. This complements a recently published paper from our group that found that the presence of hypertension was not independently associated with survival in cats with naturally occurring renal disease.[14] In that study, it was suggested that the lack of association between hypertension and survival could be attributed to the adequate control of blood pressure with antihypertensive medication. The current study suggests that adequate blood pressure control may not be a primary determinant of survival in hypertensive cats with concurrent renal disease.

Proteinuria by measurement of UP : C both before and after treatment of hypertension, and change in proteinuria with amlodipine besylate treatment were found to be the variables significantly and independently associated with shorter survival times in this population of hypertensive cats. Cats in the current study with time-averaged blood pressure in the upper quartile had significantly greater proteinuria (0.46, [0.29, 0.94]) at diagnosis of hypertension than those in the lowest quartile (0.23, [0.19, 0.32]). These results suggest that, in cats, which are more proteinuric, long-term adequate control of blood pressure may be more problematic. Every attempt was made to achieve adequate control of blood pressure (<160 mm Hg) throughout the duration of the study. Amlodipine besylate is an effective antihypertensive medication in cats and the majority of cats, even within the upper quartile of SBPOT, showed a significant reduction in SBP after initiating treatment. However, ultimately, the study was reliant on the compliance of owners to attend appointments, medicate their cat, and to ensure continuity of treatment. It is interesting to note that, when no measure of proteinuria was included in models 1 and 2, SBPOT was the variable most significantly associated with survival.

In human patients, hypertension and proteinuria are 2 of the major risk factors for the development and progression of kidney disease. As such, there are recommendations that the target for blood pressure control should be based not only on SBP measurements but also on the degree of proteinuria.[11] In human patients, it is often not a single antihypertensive medication but a multimodal drug protocol that is followed to allow optimal renal protection in hypertensive patients, including the use of ACE inhibitors and angiotensin receptor blockers.[26] This is interesting when we consider the cat in which chronic renal disease is commonly associated with hypertension[2,4,22] and that this survival analysis demonstrated that proteinuria was the variable most significantly associated with survival in hypertensive cats. Limited information is currently available in the feline literature regarding the use of ACE inhibitors and whether they have a beneficial effect on slowing progression of renal disease or reducing the degree of proteinuria.[27] Further study is warranted to determine whether proteinuria is a marker of renal disease that is likely to be more rapidly progressive or whether proteinuria itself may be acting as a causative agent in renal injury or other target-organ damage. If the latter is true, then interventions that reduce the severity of proteinuria are likely to improve survival. However, if proteinuria is acting purely as a marker then interventions to reduce proteinuria may have no additional benefit. Ultimately, further study is warranted to define the role of proteinuria and to establish guidelines for adequate blood pressure and potentially proteinuria control in cats.

Footnotes

[a] Elliott J, Fletcher M, Syme HM. Idiopathic feline hypertension: Epidemiological study. J Vet Intern Med 2003;17:754 (abstract).

[b] Elliott, J. for the ACVIM Hypertension Consensus Statement Group. Hypertension consensus report; an update. Proceedings of ACVIM Forum 2006, Louisville, KY, 654–655.

[c] Parks Electronic Doppler flow probe- Model 811B; Perimed UK, Bury St Edmunds, UK

[d] Mydriacyl, Alcon, UK

[e] BM multistix, BVL, Lewis, UK

[f] Amlodipine 0.625–1.25 mg/cat/d, Istin, Pfizer, Sandwich, Kent, UK

[g] Feline Low Phosphorus, Low Protein Diet, WALTHAM Pet Nutrition, Melton Mowbray, Leicestershire, UK

[h] Aluminium hydroxide 10–30 mg/kg q8–12h, Alucaps, Loughborough, Leicestershire, UK

[i] Tumil-K 2 mmol q12h, Arnold's Veterinary Products, Shrewsbury, UK

[j] Neomercazole 5 mg q8–12h, Roche, Welwyn Garden City, Hertfordshire, UK

[k] SPSS 13.0 for Windows, SPSS Inc, San Diego, CA

[l] GraphPad Prism version 3.02 for Windows, GraphPad Software, San Diego, CA

[m] IRIS staging as accepted by the European Society for Veterinary Nephrology and Urology (ESVNU)

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