Effects of the calcium channel antagonist amlodipine in cats with surgically induced hypertensive renal insufficiency

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Objective—To determine whether amlodipine besylate decreases systemic arterial blood pressure (BP) and reduces the prevalence of complications in cats with induced hypertensive renal insufficiency.

Animals—20 cats with partial nephrectomy.

Procedure—Following reduction in renal mass, 10 cats were administered 0.25 mg of amlodipine/kg, PO, q 24 h (group A). Ten cats served as a control group (group C). Systolic BP (SBP), diastolic BP (DBP), and mean BP (MBP), physical activity, and pulse rate were measured continuously for 36 days by use of radiotelemetric devices.

Results—Compared with values for clinically normal cats, SBP, DBP, and MBP were significantly increased in cats of group C. Cats in group A had significant reductions in SBP, DBP, and MBP, compared with values for cats in group C. Albuminuria but not urine protein-to-creatinine ratio was significantly correlated (R^2 = 0.317) with SBP in hypertensive cats. Prevalence of ocular lesions attributable to systemic hypertension in group C (7 cats) was greater than that observed in group A (2). Two cats in group C were euthanized on day 16 because of nuerologic complications attributed to systemic hypertension. One normotensive cat in group A was euthanized because of purulent enteritis of unknown cause on day 27.

Conclusions and Clinical Relevance—Amlodipine had an antihypertensive effect in cats with coexistent systemic hypertension and renal insufficiency. Its use may improve the prognosis for cats with systemic hypertension by decreasing the risk of ocular injury or neurologic complications induced by high BP. (*Am J Vet Res* 2002;63:833–839)

Renal insufficiency has been associated with systemic hypertension in cats.[1] Mild to moderate systemic hypertension was reported in 17 of 28 cats that had naturally occurring chronic renal failure.[2] Sustained hypertension produces ocular injury [3-8] and is hypothesized to damage other organs including the kidneys, brain, heart, and blood vessels.[9] Clinical observations in cats with untreated systemic hypertension include lethargy,[10] blindness,[5,11] retinal hemorrhage and detachment,[6,8,9] cerebral hemorrhage,[7] seizures,[6,8,12] stupor,[12] and ventricular hypertrophy,[13] and it can lead to death.[12] Renal microvasculature may be particularly susceptible to hypertensive injury, particularly in cats with renal insufficiency in which preglomerular vasodilation[14] could allow high **blood pressure (BP)** to be transmitted directly to the glomerular capillary bed.

In a retrospective study,[12] 21 of 34 cats receiving renal allografts had severe neurologic complications as a consequence of systemic hypertension. In those cats, antihypertensive therapy with SC administration of hydralazine reduced the prevalence of postoperative seizures. Similarly, orally administered vasodilators are often used as antihypertensive treatments in people with naturally developing renal disease and coexisting systemic hypertension, largely because these agents may have beneficial intrarenal hemodynamic effects.[15,16] Excellent antihypertensive efficacy has been reported for long-term use of the orally administered vasodilator amlodipine in cats with various long-standing naturally developing renal diseases.[1,17] We hypothesized that treatment with amlodipine would reduce the magnitude of systemic hypertension in cats with hypertensive renal insufficiency, thereby reducing the number of adverse effects attributable to high BP.

Materials and Methods

Animals—Twenty domestic shorthair cats of either sex that were 6 to 12 months old were included in the study. For identification of each cat, a microchip[a] was aseptically placed in the subcutaneous tissues over the wing of the left ileum. All cats were treated for endoparasites and vaccinated against common viral diseases, and all had negative results for immunologic tests for feline immunodeficiency virus and FeLV. Each cat was housed separately in an isolated room maintained at 21 to 23 C and 12 hours of light (7 AM to 7 PM) and 12 hours of darkness (7 PM to 7 AM) daily throughout the study. All animal experiments were conducted in accordance with published guidelines[18] and were approved by an institutional animal care committee.

Reduction in renal mass—Each cat was anesthetized, and selected branches of the left interlobar artery were ligated to induce partial renal infarction. A biopsy specimen was obtained from the infarcted section of the left kidney. Day of surgery on the left kidney was designated day 0. On day 15, nephrectomy of the right kidney was performed. The overall effect produced a reduction of 11/12 of the renal mass, as described elsewhere.[19]

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Radiotelemetry system—Measurement of **systolic BP (SBP)**, **diastolic BP (DBP)**, **mean BP (MBP)**, pulse rate, and motor activity was accomplished with the aid of a radiotelemetry system[b] that used an implant[c] aseptically inserted in the femoral artery and positioned in the descending aorta, as described elsewhere.[20] Briefly, the implant consisted of a transducer that sensed, processed, and transmitted the magnitude of intra-arterial pressure to a receiver.[d] This receiver converted the radio-frequency signal from the implant to a digital pulse that was readable by a data collection system.[e] The data collection system determined and analyzed SBP, DBP, MBP, pulse rate, and physical activity from modulations in the radio-frequency signal. All implants and the telemetry BP system were tested in vitro by use of a mercury manometer to assure accuracy between 0 and 200 mm Hg prior to implantation and after removal. Physical activity measurements were obtained by sensing changes in signal strength that resulted when a cat moved about its cage. The data collection system counted the number of movements over a specified sample interval and calculated the physical activity in arbitrary units. All radiotelemetry measurements were recorded as a mean value for 10 seconds every 5 minutes for 24 hours daily from days 3 to 36.

Study protocol—Starting on day –5, each cat was provided ad libitum access to the study diet.[f] Each cat was offered a measured amount of the diet (generally 100 g) that was intended to exceed its daily food intake. Daily food intake was determined by weighing any remaining food each morning beginning on day –3.

Daily clinical observation was initiated on day –4. Each cat was observed daily by a veterinarian. The observation included assessment of behavior, neurologic function, and fecal characteristics as well as notation of any observable physical abnormalities such as vomiting or ocular abnormalities. An ophthalmic examination consisting of applanation tonometry, biomicroscopy, and indirect ophthalmoscopy was performed on day –3. We did not detect abnormal ophthalmic findings at the time of the initial ophthalmic examination, with the exception of a focal pigmented inactive chorioretinitis lesion in the dorsolateral tapetal fundus of 1 cat. That lesion remained unchanged throughout the study. A second ophthalmic examination was performed in all cats (at the completion of the study on day 36 for 17 cats and immediately before they were euthanized for 3 cats that did not complete the entire study).

On the morning of day 3, the cats were allocated into 10 blocks (2 cats/block) on the basis of the rank order of a mean 8-hour value for SBP measured during the preceding 8-hour interval (midnight to 8 AM). Within each pair of cats, 1 was randomly assigned to a treatment group (group A), and the other was assigned to a control group (group C); thus, there were 10 cats in each group.

Beginning after assignment on day 3 and continuing until completion of the study on day 36, cats in group A received amlodipine besylate,[g] and cats in group C received dextrose-cellulose tablets. Amlodipine was prepared with the aid of a pill cutter.[h] Tablets were cut into increments of 0.625 mg and placed in a No. 3 gelatin capsule.[i] Target dosage was 0.25 mg of amlodipine/kg, PO, q 24 h. Control cats were given approximately 30 mg of dextrose-cellulose,[j] PO, q 24 h; the dextrose-cellulose tables were also placed in a No. 3 gelatin capsule for oral administration.

Food was withheld overnight, and body weight then was determined on days 0, 22, and 36. Samples of blood and urine were collected by venipuncture and cystocentesis, respectively. Serum concentrations of creatinine, electrolytes, and urea nitrogen, and the urine protein-to-creatinine ratio were determined by use of a semi-automated analyzer.[k] Urinary albumin concentration was measured with the aid of an ELISA,[l] and this value was indexed to the urine creatinine concentration. Intra- and interassay coefficient of variation for the albumin assay was 3.1 and 14.0%, respectively. The lower limit of detection for this assay was 8.6 ng of albumin/ml.

Urine specific gravity was measured by use of a refractometer.[m] Urinalysis and aerobic bacterial culture of urine samples was performed in accordance with standard methods.

Necropsy—At the completion of the study (day 36), cats were euthanized by administration of an overdose of sodium pentobarbital. Immediately after each cat was euthnatized, the left kidney was removed and preserved in neutral-buffered 10% formalin. Postmortem examination was performed on each cat. A section of each left kidney was stained with hematoxylin and periodic acid-Schiff stains prior to histologic examination. For each section, 25 cortical glomeruli were examined, and the degree of glomerular change was recorded as mesangial matrix expansion, which was evaluated by use of a semi-quantitative scale (0, normal [no change]; 1, mild change; 2, moderate change; 3, severe change) that has been described elsewhere.[20] Using the same histologic sections, a similar scale was used to evaluate the degree of interstitial infiltrate, tubular change, and interstitial fibrosis.

Statistical analysis—A commercial software package[n] was used to perform statistical analyses. Data were reported as mean ± SEM. Values of $P < 0.05$ were considered significant. Data obtained via telemetry for BP and physical activity were reported as 24-hour mean values unless otherwise specified. Survival analysis was conducted by use of the Kaplan-Meier method. Prevalence of ocular lesions was assessed by use of χ^2 analysis. Data for food intake and physical activity were pooled in multiple-day intervals (days 3 to 5, 6 to 10, 11 to 16, 17 to 20, 21 to 25, 26 to 30, and 31 to 35) for analysis. Comparisons between groups were performed by use of independent Student *t*-tests, which were paired when appropriate. A repeated-measures ANOVA was conducted when appropriate. When a significant overall effect was identified, the Fisher protected least-significant difference test was used to compare individual means.

Results

Clinical observations—Mean ± SEM rate of amlodipine administration was 0.23 ± 0.06 mg/kg daily (range, 0.18 to 0.31 mg/kg daily) to cats in group A from days 3 to 36. Two cats in the control group were euthanatized after they developed severe ataxia that rapidly progressed to profound lethargy on day 16 of the study. Those 2 cats had severe systemic hypertension (SBP, 234.4 and 198.2 mm Hg, respectively) 12 to 18 hours before onset of abnormal neurologic signs. One cat in group A became lethargic and developed bloody diarrhea on day 24; it was euthanatized on day 27. This abnormality was apparently unrelated to increases in BP, because that cat had a mean overall SBP of 130.2 mm Hg during the study, and the SBP gradually decreased during the diarrheic episode to a value of 101.2 mm Hg on day 27; thus, the episode of diarrhea was not attributed to hypertension. There was not a significant ($P = 0.17$) difference between groups in the number of fatalities attributable to hypertension. Data for BP, physical activity, and daily food intake for these 3 cats were excluded from subsequent statistical analysis.

Nine cats had abnormal ophthalmic findings. In group A, 1 cat that completed the study had tortuous

retinal vessels with narrowing and straightening of the arterioles, and another cat had a focal area of intra-retinal edema. In group C, 7 cats had 1 or more abnormal ophthalmic findings: 1 cat had fibrin formation in the anterior chamber; 1 cat had a focal area of intraretinal edema as well as narrowing and straightening of the arterioles; 1 cat had generalized tapetal hazing and narrowing and straightening of the arterioles; 1 cat had generalized tapetal hazing, narrowing and straightening of the arterioles, and tortuous retinal vessels; 1 cat had tortuous retinal vessels only; and 2 cats had generalized tapetal hazing without other ophthalmic abnormalities. The prevalence of ocular lesions in cats of group C was significantly greater than that of cats in group A. Other clinical abnormalities were not observed during the study.

Food intake was similar between groups before day 15 and after day 20, and data for those intervals were pooled (**Fig 1**). However, food intake was significantly reduced in group A for several days (days 16 to 20) after surgery to remove the right kidney. Physical activity, although nearly identical in both groups at the time cats were assigned to the groups (**Table 1**), was significantly greater in control cats for several days (days 16 to 20) after surgery to remove the right kidney, compared with values for treated cats (Fig 1). A similar pattern in which physical activity was greater in cats of group C was observed before day 15 and after day 20; because those values did not differ significantly, data for those intervals were pooled. Body weight was not significantly different between groups at any point during the study. Mean ± SEM body weight for cats in group C was 3.02 ± 0.18, 3.02 ± 0.22, and 3.27 ± 0.23 kg on days 3, 21, and 36, respectively, whereas mean body weight for cats in group A was 2.96 ± 0.15, 2.88 ± 0.15, and 3.13 ± 0.18 kg on days 3, 21, and 36, respectively.

Cardiovascular variables—Reported mean ± SD values[20] obtained by use of telemetry from clinically normal cats in our laboratory was 125.1 ± 10.5, 89.3 ± 9.3, and 105.3 ± 10.0 mm Hg for SBP, DBP, and MBP, respectively. In comparison, cats in group C had significantly increased BP values throughout the study (**Table 2**). Administration of amlodipine on days 3 to 36 produced a significant antihypertensive effect detected beginning on day 5 and continuing until the end of the study (**Fig 2**).

Results of serum and urine biochemical analyses—Mean serum concentrations of BUN, creatinine, and electrolytes were not significantly different between groups during the study. Mean BUN and creatinine concentrations in cats of group C were 22 ± 1 and 1.1 ± 0.04, 76 ± 12 and 3.5 ± 0.7, and 56 ± 7 and 2.9 ± 0.5 mg/dl on days 0, 21, and 36, respectively. In group A, mean BUN and creatinine concentrations were 21 ± 1 and 1.1 ± 0.1, 71 ± 7 and 3.6 ± 0.5, and 55 ± 5 and 2.8 ± 0.4 mg/dl on days 0, 21, and 36, respectively. Mean urine protein-to-creatinine ratio and mean urine albumin-to-creatinine ratio did not differ significantly between groups during the study. Initial values for albuminuria were not significantly different between groups, and the overall mean value at day 3 was 10.6 ± 2.0 mg of albumin/g of creatinine (8.1 ± 1.5 mg of albumin/g of creatinine in group A and 12.9 ± 3.6 mg of albumin/g of creatinine in group C). Although albuminuria was not significantly different between groups, urinary albumin excretion increased toward the end of the study in cats of group C (mean final value, 47.2 ± 26.2 mg of albumin/g of creatinine), compared with cats of group A (mean final value, 22.5 ± 6.3 mg of albumin/g of creatinine). When data from all cats were analyzed, SBP and albuminuria on day 36 were not significantly correlated (R^2 = 0.222; P = 0.056). Furthermore, in 7 cats with SBP that was

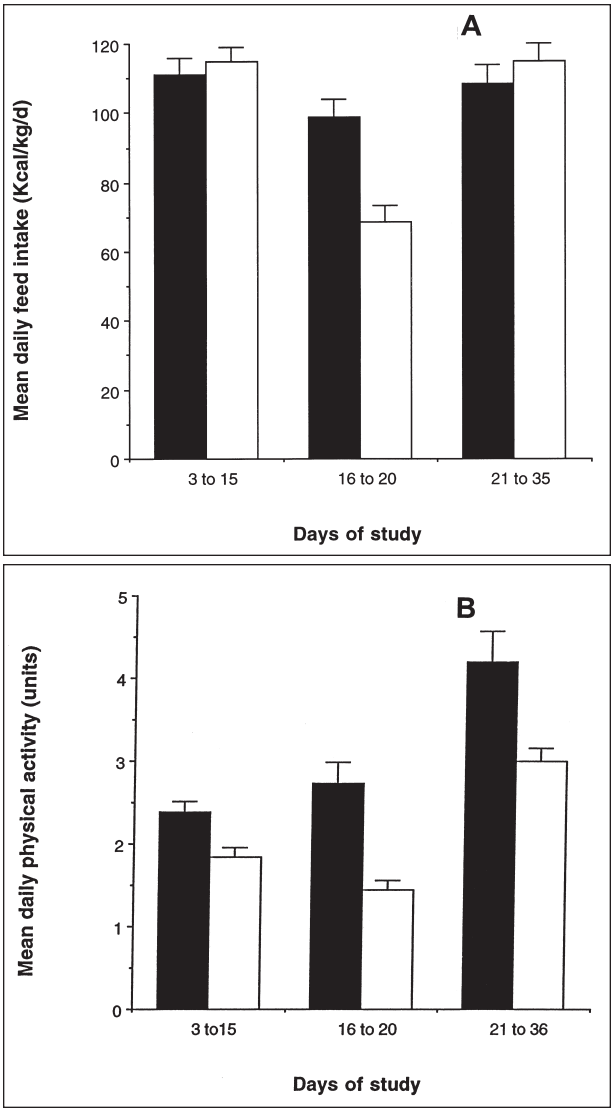

Figure 1—Mean ± SEM values for feed intake (A) and amount of physical activity (B) in cats with surgically induced renal insufficiency. The left kidney was partially ligated to cause renal infarction (day 0). Nephrectomy of the right kidney was performed on day 15. On the basis of an 8-hour mean blood pressure value, cats were assigned to groups on day 3. Cats received dextrose-cellulose (control group; solid bars) or 0.25 mg of amlodipine besylate/kg/d (open bars) from days 3 to 36. There was significantly ($P < 0.05$) lower feed intake during days 16 to 20 in cats that received amlodipine, compared with cats in the control group. However, there was significantly ($P < 0.05$) more physical activity during days 16 to 20 in cats in the control group, compared with cats that received amlodipine.

less than the mean value previously obtained in clinical normal cats in our laboratory[20] (ie, 125.1 mm Hg), there was not an apparent correlation between SBP and urinary albumin excretion. However, in 10 cats with SBP that exceeded the previously reported mean value, we did detect a significant correlation (R^2 = 0.317; $P < 0.05$) between albuminuria and SBP.

Table 1—Values for several variables at the time cats with surgically induced renal insufficiency were assigned into 2 groups (10 cats/group) to receive orally administered dextrose-cellulose (control group) or 25 mg of amlodipine besylate/kg/d

Variable	Control group	Amlodipine group
Sex	6 females, 4 males	5 females, 5 males
Body weight (kg)	3.02 ± 0.18	2.96 ± 0.15
Systolic blood pressure (mm Hg)	148.2 ± 6.8	145.2 ± 5.1
Diastolic blood pressure (mm Hg)	117.3 ± 9.4	111.3 ± 4.5
Mean blood pressure (mm Hg)	128.1 ± 5.7	126.9 ± 4.9
Pulse rate (Number of pulses/min)	194.0 ± 3.9	183.7 ± 6.7
Physical activity (arbitrary units)	0.8 ± 0.1	0.7 ± 0.2

For all variables except sex, values reported are mean ± SEM.

Table 2—Mean ± SEM values for several variables in 2 groups of cats (10 cats/group) during oral administration of dextrose-cellulose (control group) or amlodipine (25 mg/kg/d)

Variable	Control group	Amlodipine group
Amlodipine besylate (mg/kg/d)	0	0.23 ± 0.06
Serum creatinine concentration (mg/dl)	2.48 ± 0.34	2.48 ± 0.30
BUN concentration (mg/dl)	51.4 ± 6.5	49.1 ± 5.0
Urine albumin-to-creatinine ratio (mg:g)	37.5 ± 13.8	24.6 ± 6.0
Urine protein-to-creatinine ratio	0.36 ± 0.04	0.31 ± 0.02
Urine specific gravity	1.039 ± 0.003	1.037 ± 0.003
Systolic blood pressure (mm Hg)	151.4 ± 6.6	122.2 ± 3.6*
Diastolic blood pressure (mm Hg)	111.4 ± 5.6	88.5 ± 3.3*
Mean blood pressure (mm Hg)	129.2 ± 6.1	102.9 ± 3.4*
Pulse rate (Number of pulses/min)	188.2 ± 4.6	187.5 ± 4.2
Physical activity (arbitrary units)	3.06 ± 0.56	2.24 ± 0.34

*Value differs significantly ($P < 0.05$) from value for control group.

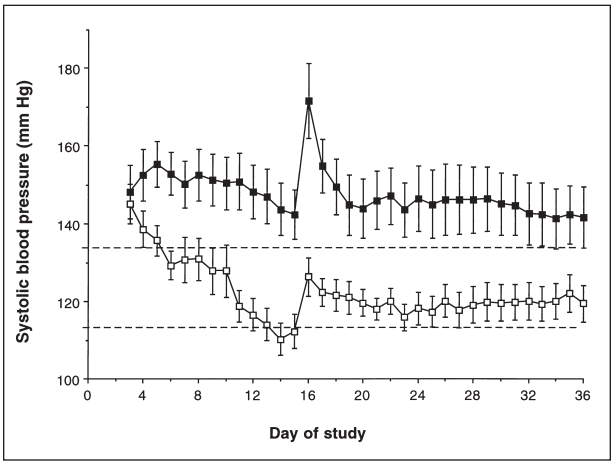

Figure 2—Mean ± SEM values for systolic blood pressure obtained by use of radiotelemetry from 20 cats with surgically induced renal insufficiency. Cats received dextrose-cellulose (control group; solid squares) or 0.25 mg of amlodipine/kg/d (open squares) from days 3 to 36. There was a significant ($P < 0.05$) antihypertensive effect of amlodipine beginning on day 5 and continuing until the end of the study. Dashed lines represent mean ± SD values for similarly obtained data from 6 clinically normal cats.[1]

Necropsy—The middle cerebellar vermis herniated through the foramen magnum in both cats of group C that developed progressive stupor and were euthanized on day 16. In these cats, the meninges were congested with mild flattening of the cerebral gyri. The cat of group A that had bloody diarrhea and was euthanized on day 27 had purulent enteritis of unknown cause.

Histologic examination of renal specimens—Mean morphologic scores at baseline for glomerular lesions (group A, 0.035 ± 0.017; group C, 0.022 ± 0.011), interstitial lesions (group A, 0.060 ± 0.051; group C, 0.010 ± 0.004), and tubular lesions (group A, 0.060 ± 0.051; group C, 0.010 ± 0.004) were not significantly different between groups. Mean morphologic scores at the end of the study for glomerular lesions (group A, 0.325 ± 0.065; group C, 0.225 ± 0.047), interstitial lesions (group A, 0.214 ± 0.115; group C, 0.166 ± 0.077), and tubular lesions (group A, 0.158 ± 0.076; group C, 0.170 ± 0.107) were significantly worse than baseline values but were uniformly mild and not different between groups.

Discussion

In cats with combined renal insufficiency and systemic hypertension, oral administration of amlodipine at a rate of 0.25 mg/kg/d produced a significant antihypertensive effect. The SBP, DBP, and MBP were reduced by approximately 30 mm Hg in cats receiving amlodipine. The BP in cats receiving amlodipine was similar to that previously reported[20] by our laboratory group for clinically normal cats.

Systemic hypertension reportedly is common in cats with naturally occurring renal insufficiency. In 1 study,[2] mild to moderate systemic hypertension was reported in 17 of 28 cats that had various chronic renal diseases. The pathogenesis of hypertension in cats with renal diseases has not been extensively studied, although analysis of evidence indicates that the renin-angiotensin system plays a role in the maintenance of high BP in a minority of affected cats.[21] This is controversial, however.[22] The mechanisms contributing to systemic hypertension in cats for the model used in the study reported here are incompletely understood. It is tempting to speculate that infarcted renal tissue and marginally ischemic tissue may activate the renin-angiotensin system, and there is support for this proposed mechanism in rodents.[23] However, similar to cats with naturally occurring renal disease, results of other studies[24,o] do not support a prominent role for the renin-angiotensin system in sustaining hypertension in cats with experimentally induced hypertension. In particular, inhibition of converting enzymes produces only a modest decrease in BP in cats by use of this model.[24] In contrast, the study reported here documented a dramatic effect of the calcium channel antagonist amlodipine. Cats with concurrent naturally occurring renal disease and systemic hypertension appear to have a similar pattern of response to antihypertensive therapy.[1,17,21] Amlodipine reportedly is an effective antihypertensive agent in cats with chronic renal failure,[1,17] but **angiotensin converting enzyme (ACE)** inhibitors

reportedly are less effective in this setting.[21] It is interesting that hydralazine, a direct-acting vasodilator, was apparently effective when used to treat acute onset hypertension in cats receiving renal allografts.[12] Taken together, these data indicate that direct vasodilation with a calcium channel antagonist or hydralazine may be an effective approach for decreasing BP in cats with coexisting systemic hypertension and renal disease. Furthermore, results are similar in cats with induced hypertension as a result of the model described here and cats with naturally occurring renal disease.

Ophthalmic findings identified with systemic hypertension include changes in the retinal vasculature (tortuosity of retinal vessels, narrowing and straightening of arterioles, variation in caliber of retinal vessels), changes in the choroidal vasculature (tapetal haziness related to choriocapillaris leakage), sub- and intraretinal hemorrhage, sub- and intraretinal edema, retinal detachments, hyphema, and secondary glaucoma.[3-5,7,8,25-29] Nine cats in our study had 1 or more of these ophthalmic changes including fibrin formation in the anterior chamber, narrowing and straightening of arterioles, tortuosity of retinal vessels, intraretinal edema, or a hazy tapetal fundus. The study reported here provides evidence that treatment with amlodipine provided substantial protection of ocular tissues. It is interesting to speculate that this beneficial effect was prophylactic in nature, but the limited number of observations precludes firm conclusions regarding time and course for development of ocular lesions.

A hazy opacity of the tapetal fundus attributable to leakage of plasma and fibrinogen from the choriocapillaris is reported to be an early ophthalmic sign of systemic hypertension.[29] Signs of hypertensive choroidopathy are the result of anatomic arrangement of the choriocapillaris and a lack of autoregulation of blood flow.[4,29] Autoregulation of the retinal vasculature in the face of hypertension results in reactive vasoconstriction predisposing to the hypertensive retinopathy signs of narrowing and straightening of arterioles and tortuosity of vessels.[3,8,25-27,30] Breakthroughs in autoregulation result in vasodilation, endothelial cell loss, breaks in the blood-retinal barrier, and secondary retinal exudative changes. Choroidal ischemia, ischemia of pigmented retinal epithelium, and fibrinoid necrosis of arteriole walls develop with persistent hypertension and predispose to subretinal exudation, retinal detachment, and retinal hemorrhage.[3,7,8,25-27,29,30]

The degree of systemic hypertension required to produce signs of hypertensive retinopathy or choroidopathy is not known. In the study reported here, cats with abnormal ophthalmic findings had, at some point, a mean daily SBP ≥ 160 mm Hg. This observation may explain why 2 cats in group A that had transient hypertension developed retinal lesions.

Hypertensive encephalopathy may be defined as cerebral dysfunction following an acute increase in BP with a lack of brain infarction or hemorrhage.[6,12,31] Two of 10 cats in the control group in the study reported here developed hypertensive encephalopathy associated with cerebellar herniation. The most likely mechanism for the development of this lesion is hyperperfusion and cerebral edema secondary to failure of autoregulation of cerebral arterioles.[31] This hypothesis is consistent with the finding of cerebellar herniation in the affected cats.

One cat in group A was euthanatized because of dehydration caused by bloody diarrhea associated with purulent enteritis of an unknown cause. Although we cannot exclude the possibility that this lesion was linked to administration of amlodipine, that cat was normotensive at the onset of this complication.

Renal morphometric changes were not observed in the 2 groups of cats. Chronic increases in BP contribute to renal damage in humans,[32] rodents,[33] and dogs.[p,q] In cats with renal insufficiency, afferent arterioles are dilated in an adaptive attempt to sustain **glomerular filtration rate (GFR)**.[14] Thus, high BP may be transmitted through these dilated vessels to the renal microvasculature and may cause glomerular damage and progressive decline in renal function.[34] Although amlodipine had an antihypertensive effect in the study reported here, its effect on the magnitude of proteinuria was not significant, perhaps because of the small number of cats in each group. However, albuminuria was related to the degree of increase in BP in hypertensive cats. Albuminuria may represent a more sensitive measure of renal damage in cats, compared to total proteinuria, which is assessed as the urine protein-to-creatinine ratio by use of a nonspecific assay for total urinary protein content. However, additional studies will be required to completely characterize the value of albuminuria as a prognostic tool. Analysis of results for the study reported here suggests that there can be substantial increases in BP in cats for up to 1 month without dramatic effects on renal structure or function. Whether longer periods of systemic hypertension or greater increases in BP would induce additional evidence of renal damage in cats remains unclear.

Changes in systemic arterial BP may alter GFR via hemodynamic mechanisms. In clinically normal dogs, renal autoregulation of GFR ensures that renal function is stable despite variations in BP.[35] However, renal autoregulation is abnormal in dogs with chronic renal disease.[35] Although renal autoregulation has not been studied in cats, antihypertensive treatments could decrease BP and, thus, GFR. In a multiple-center study conducted on dogs with congestive heart failure,[36-38] treatment with an ACE inhibitor decreased GFR in only a few dogs. Because calcium channel antagonists preferentially dilate afferent arterioles,[39] they may preserve GFR despite inducing decreases in systemic BP. The study reported here documented that administration of amlodipine could induce a substantial reduction in BP in mildly azotemic cats without apparent adverse effects on GFR, at least as reflected in crude indices of GFR such as serum creatinine and BUN concentrations. In people with naturally occurring renal diseases and coexisting systemic hypertension, vasodilators are often used as antihypertensive treatments largely because these agents may have beneficial intrarenal hemodynamic effects.[15,16] The ACE inhibitors have been used with variable antihypertensive efficacy to treat cats and dogs with systemic hypertension after naturally developing[21,40] and experimentally induced[24,39]

renal diseases. Use of ACE inhibitors is advocated on the basis of the effects these agents have in decreasing intraglomerular pressure by preferentially dilating efferent arterioles.[24,39] Calcium channel antagonists preferentially dilate afferent arterioles in dogs[39]; thus, they may not be similarly effective for causing a decrease in intraglomerular pressure. However, given their dramatic effects in decreasing systemic BP and their currently uncharacterized effects in the renal microvasculature of cats, it is not possible to predict the net effect of calcium channel antagonists on glomerular capillary pressure in cats. Direct renal micropuncture studies will be required to address this issue.

Cats that received amlodipine were hypotensive on days 14 and 15 (mean SBP, 111.7 and 113.5 mm Hg, respectively). However, immediately after ligation of selected branches of the right interlobar artery, SBP increased to 127 mm Hg. During the 5 days after surgical removal of the right kidney, cats receiving dextrose-cellulose tablets had improved appetites and increased amounts of activity, compared with the normotensive cats that received amlodipine. Because these cats were markedly hypertensive at that time, these results seem contrary to expectations and could be evidence of an adverse effect of amlodipine treatment. However, cats that received amlodipine were not hypotensive during this time and had adequate caloric intake throughout the remainder of the study, allowing them to maintain or slightly increase their body weight during the 36-day study. Furthermore, a reduction in appetite and amount of activity would be expected after surgery, and such a reduction was observed in cats of group A but not in cats of group C. It is interesting to speculate that acute effects of systemic hypertension observed in cats in group C may have altered physical activity and appetite. In our experience, we have observed that cats with severe hypertension may have exceptional appetites immediately prior to the development of abnormal neurologic signs. It was not possible for us to determine the source of differences in behavior in the immediate postoperative period in the cats of this study. This deserves further investigation.

It has been suggested in other studies[1,13,17] that amlodipine has an antihypertensive effect in cats with naturally developing chronic renal failure. However, the BP measurements in those studies were conducted in conscious cats and were obtained by use of indirect techniques. When measured in conscious animals by use of indirect techniques, BP may be increased by anxiety, a phenomenon termed the white-coat effect.[41] The white-coat effect is attributed to excitement, anxiety, or both that is associated with the measurement of BP. It would be expected that a vasodilatory agent, such as amlodipine, would reduce the magnitude of this effect. This could lead to an overestimation of true antihypertensive efficacy, because antihypertensive effects attributed to therapeutic agents could be caused, wholly or in part, by an effect to reduce this white-coat effect. This is true even with placebo-controlled studies. Several studies[42-50] have provided evidence that continuous or frequent intermittent measurement of true BP is a better predictor of BP than conventional single-sample measurement of BP. Therefore, mean 24-hour ambulatory BP measurement is widely accepted as the criterion-referenced standard for assessment of efficacy of antihypertensive agents. A radiotelemetric system was used in the study reported here, because it allowed continuous measurement of BP in undisturbed and unrestrained cats and, thus, avoided the complication of the white-coat effect. Our results document that the substantial antihypertensive effects of amlodipine in cats are attributable to an effect on BP separate from the white-coat effect.

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[a]IMI-1000 Implantable Micro Identification, BMDS, Seaford, Del.
[b]Dataquest ART (for Windows), Data Sciences Int, St Paul, Minn.
[c]Model TA11PA-C40, Data Sciences Int, St Paul, Minn.
[d]Model RLA-2000, Data Sciences Int, St Paul, Minn.
[e]Dataquest ART 2.0 data collection system, Data Sciences Int, St Paul, Minn.
[f]Hill's Prescription Diet Feline K/D dry, Hills Petfoods, Topeka, Kan.
[g]Norvasc, 2.5 mg, Pfizer Laboratories, Division of Pfizer Inc, New York, NY.
[h]MPLS, Quanterron Inc, Burnsville, Minn.
[i]NDC0002-2410-02, Eli Lilly & Co, Indianapolis, Ind.
[j]Glucose tablets, The Kroger Co, Cincinnati, Ohio.
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