Evaluation of a technique of inducing hypertensive renal insufficiency in cats

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Objective—To compare 2 techniques of inducing combined renal insufficiency and systemic hypertension in cats.

Animals—22 cats 6 to 12 months of age.

Procedures—Cats were randomly assigned to 1 of 3 groups. Control (C) group cats had 2 intact kidneys, remnant kidney (RK) group cats underwent unilateral partial renal infarction and contralateral nephrectomy, and remnant-wrap (W) group cats underwent unilateral partial renal infarction and partial abtation and wrapping of the contralateral kidney. Systemic arterial blood pressure (BP) was measured continuously by use of implanted radiotelemetric devices. Renal function was assessed via determination of glomerular filtration rate, measurement of serum creatinine and BUN concentrations, and determination of urine protein-to-creatinine ratio (UP/C). Serum aldosterone concentration and plasma renin activity were measured on day 75.

Results—Systolic BP was significantly higher in groups RK and W than in group C, and systolic BP was significantly higher in group W than in group RK. Serum aldosterone concentration and plasma renin activity were significantly higher in group W, compared with groups C and RK. Glomerular filtration rate was significantly lower in groups RK and W, compared with group C. Histologic indices of renal injury and UP/C were significantly higher in group W, compared with groups C and RK.

Conclusions and Clinical Relevance—Hypertensive renal insufficiency in group W was characterized by marked sustained systemic hypertension, decreased renal function, proteinuria, activation of the renin-angiotensin-aldosterone axis, and renal structural injury. Results support the hypothesis that marked systemic hypertension, activation of the renin-angiotensin-aldosterone axis, and proteinuria may damage the kidney of cats with preexisting renal insufficiency. (*Am J Vet Res* 2004;65:1006–1013)

A link between systemic hypertension and **chronic kidney disease (CKD)** has been recognized in cats.[1-5] Chronic kidney disease may lead to hypertension as a result of disordered renal neurohumoral output and changes in body electrolyte and fluid balance.[6] In humans[7] and rats,[8] it is well-known that chronically high systemic arterial **blood pressure (BP)** can damage the kidney. Although CKD is common in cats[9] and those cats frequently have concurrent hypertension,[2] it is not clear whether high BP leads to or exacerbates renal injury in cats.

The best characterized technique for inducing coexisting renal insufficiency and systemic hypertension in cats is the remnant kidney technique in which uninephrectomy is combined with contralateral partial renal infarction[10-14]; this is associated with moderate hypertension, and BP in cats decreases gradually after 30 days.[13] In contrast, cats with naturally occurring CKD often develop severe hypertension.[1,3,15] An experimental technique that causes changes that more closely resemble those in cats with naturally occurring hypertension and CKD would be valuable. The objective of the study reported here was to develop a technique of inducing combined systemic hypertension and renal insufficiency that was associated with sustained systemic hypertension in cats.

Materials and Methods

Cats—Twenty-two domestic shorthair cats of either sex and 6 to 12 months of age were included in the study. A microchip[a] used to identify each cat was implanted SC at the base of the tail. All cats were treated for endoparasites and vaccinated against common viral diseases. Test results for FIV and FeLV infection were negative. All cats had **serum creatinine (SCr)** and BUN concentrations and **urine protein-to-creatinine ratios (UP/C)** within the reference range for cats at the University of Georgia Veterinary Medical Teaching Hospital. The cats were housed individually in isolated rooms maintained at 21° to 23°C with 12 hours of light (7 AM to 7 PM) and dark (7 PM to 7 AM) throughout the study. All animal experimentation was conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care Committee of the University of Georgia.

Renal mass reduction—Each cat was randomly assigned to 1 of 3 groups: 2-**kidney control (C)**, **remnant kidney technique (RK)**, or **remnant-wrap technique (W)**. All surgical procedures were performed under general anesthesia. On the day of the first surgery (day 0 of the study), a radiotelemetric BP implant[b] was placed SC in the flank of each cat with the implant catheter positioned in the right femoral artery, as described.[16] A biopsy specimen was obtained from the area of the kidney to undergo infarction in group RK and ablation in group W. Biopsy specimens were immediately placed into neutral-buffered 10% formalin. Cats in group RK underwent partial left renal infarction via ligation of selected interlobar arteries that supplied approxi-

Received June 25, 2003.
Accepted August 25, 2003.
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Supported in part by the Veterinary Medical Experiment Station of the College of Veterinary Medicine of the University of Georgia.
Presented in abstract form at the 20th Annual American College of Veterinary Internal Medicine Forum, Dallas, May 2002.
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mately five sixths of the kidney. Cats in group W underwent partial right renal ablation via sharp resection of the cranial and caudal poles of the kidney; the kidney remnant was wrapped in sterile silk[c] followed by sterile cellophane.[d] The resection resulted in reduction in right renal mass of approximately two thirds. The second surgery was performed on day 14 of the study. At this time, cats in the RK group underwent right nephrectomy and cats in group W underwent partial left renal infarction as described for group RK. Total reduction in renal mass was approximately eleven twelfths in group RK and nine twelfths in group W. Cats in group C did not undergo any surgical procedure on day 14.

Radiotelemetry system—Systemic arterial BP, heart rate, and physical activity were measured and recorded continuously by use of a radiotelemetry system[e] that used the radiotelemetric implant[b] placed in the femoral artery. The implant transducer senses, processes, and transmits a radio frequency representation of the intra-arterial pressure in the descending aorta to a receiver.[f] The receiver converts the radio frequency input from the implant to a digital signal that is translated and recorded by a data collection system.[e] Motor activity is detected as a change in the strength of the signal, which is the result of movement of the cat relative to the recording antenna. Motor activity was recorded in arbitrary units, as described.[16] All implants were calibrated by use of a mercury manometer prior to implantation. All radiotelemetry measurements were recorded as a mean value for 10 seconds every 5 minutes for 24 hours daily from days 3 to 140 of the study. For the purposes of this study, systemic hypertension in groups W and RK was defined as a 24-hour mean systolic BP significantly greater than the corresponding value for group C.

General health observations—Each cat was observed at least once daily during the study. Behavior, neurologic function, and fecal character were assessed, and any abnormalities (eg, vomiting) were recorded. An ophthalmologic examination was performed by an ophthalmologist without knowledge of group origin in all surviving cats on day 90 of the study. The examination included slit lamp biomicroscopy, applanation tonometry, and indirect ophthalmoscopy.

Diet—Each cat was daily offered a premeasured amount of the study diet[g] (generally 100 g) that exceeded its daily metabolic energy requirement for maintenance. Food remaining from the previous day was weighed each morning beginning on day –4 until the end of the study, and daily food intake was recorded.

Phase I (days 1 to 90)—Cats were weighed on days 0, 38, 75, and 90. Blood samples were collected via jugular venipuncture, and urine samples were collected via cystocentesis or voiding on days 0, 38, 75, and 90. Serum creatinine and BUN concentrations and UP/C were measured by use of a semiautomated biochemistry analyzer.[h] A complete urinalysis and aerobic bacteriologic culture of urine were performed. **Glomerular filtration rate (GFR)** and **renal plasma flow (RPF)** were estimated on day 75 via measurement of urinary clearance of exogenously administered inulin and *p*-aminohippuric acid, respectively, as described.[13] On day 75 of the study, blood samples for measurement of serum aldosterone concentrations and plasma renin activities of conscious cats were collected and measured by use of radioimmunoassay techniques in a commercial laboratory.[i]

Antihypertensive drug treatment during phase I—To decrease the anticipated prevalence of hypertensive encephalopathy in the postoperative period, cats in groups RK and W were treated with 0.25 mg of amlodipine besylate[j]/kg, PO, once daily from days 3 to 25, as described.[14] Cats in group C were treated similarly.

Phase II antihypertensive drug trials (days 91 to 140)—To assess the response of BP of group W cats to treatment with antagonists of the renin-angiotensin-aldosterone axis and calcium channels, cats in each group (C, RK, and W) were paired on the basis of rank order of systolic BP. One cat in each pair was randomly assigned to 1 of 2 treatment orders on day 91. Cats assigned to the first treatment order (treatment A) were treated with amlodipine besylate (0.25 mg/kg, PO, q 24 h; n = 9; 3 from group C, 4 from group RK, and 2 from group W) for 7 days, not treated for 5 days, and then treated with sustained-release diltiazem HCl[k] (10 mg/kg, PO, q 24 h) for 7 days. Cats assigned to treatment B were treated with sustained-release diltiazem HCl during the first 7-day period (n = 10; 4 from group C, 4 from group RK, and 2 from group W) and with amlodipine besylate during the second 7-day period.

After 7 days of no treatment, all cats were assigned to treatment C and treated with 0.5 mg of enalapril maleate[l]/kg, PO, once daily for 8 days. For the next 6 days, the cats were treated with 4 mg of losartan K[m]/kg, PO, once daily in addition to enalapril.

During phase II, all drugs were administered to cats at 8 AM. Blood and urine samples were collected on the last day of each drug treatment period after withholding food for 12 to 16 hours for measurement of SCr and BUN concentrations and determination of UP/C.

Postmortem examination—Cats in groups RK and W were euthanatized via overdose of sodium pentobarbital if they developed clinical signs compatible with hypertensive encephalopathy (ie, ataxia, depression, and seizures coincident with a systolic BP > 170 mm Hg). Otherwise, cats in groups RK and W were euthanatized between days 140 and 150. Immediately after euthanasia, the left kidney was removed and fixed in neutral-buffered 10% formalin and a complete postmortem examination was performed. A histologic section from the noninfarcted portion of the left kidney was stained with hematoxylin and periodic acid Schiff stains. Twenty-five cortical glomeruli in each histologic section were examined, and the degree of glomerulosclerosis was evaluated by use of a semiquantitative scale (0 = no change [normal]; 1 = mild change; 2 = moderate change, and 3 = severe change), as described.[13] A similar scale was used to evaluate the degree of interstitial fibrosis and tubular atrophy in the same histologic section. A lesion index for glomerulosclerosis, tubular atrophy, and interstitial fibrosis was derived from the arithmetic mean value for each parameter. Kidneys of group C cats were not examined histologically.

Data and statistical analyses—Data were expressed as mean ± SEM. The BP and physical activity data are reported as 24-hour mean values unless otherwise specified. A commercial software package[n] was used to perform statistical analyses. Intergroup comparisons were made by use of an ANOVA, and repeated measures ANOVA were used when parameters were assessed serially. When a significant global effect among the 3 groups was identified, the Fisher protected least-significant difference test was used to compare individual group means. Correlations between variables were determined by use of linear regression analysis. For the histologic lesion scores in which a significant global effect among the 3 groups was identified by use of the nonparametric Kruskal-Wallis test, individual group means were compared by use of the Mann-Whitney *U* test. Values of $P < 0.05$ were considered significant.

Results

Systemic blood pressure—Compared with values in group C, systolic BP was significantly higher in

group RK and further increased in group W (**Table 1**). The systolic BP significantly ($P < 0.05$) increased and remained high in group RK after cessation of treatment with amlodipine besylate on day 25 (**Figure 1**); the systolic BP significantly ($P < 0.05$) decreased in group RK between days 50 to 90. In contrast, systolic BP was significantly higher in group W than in groups C and RK from days 12 to 90. Systolic BP increased and remained stable from days 45 to 90. During phase II of the study (**Table 2**), the mean BP in group W significantly ($P < 0.05$) decreased as a result of euthanasia of the most severely hypertensive cats. Other BP parameters (mean and diastolic BP) were also significantly different among groups RK, W, and C.

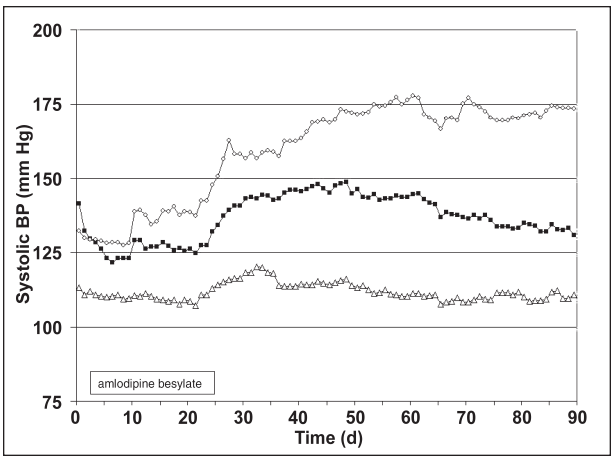

Figure 1—The 24-hour mean systolic arterial blood pressure (BP [mm Hg]) in cats in a remnant-wrap group (W, open circles), remnant kidney group (RK, solid squares), and 2-kidney control group (C, open triangles) from days 1 to 90 of a study of induced hypertensive renal insufficiency in cats. Cats were treated with amlodipine besylate from day 3 to 25. The 24-hour mean systolic BP was significantly ($P < 0.05$) higher in groups RK and W, compared with group C, and the 24-hour mean systolic BP in group W was significantly higher than that of group RK.

Table 1—Data obtained from cats in a 2-kidney control (C) group, remnant kidney (RK) group, and remnant-wrap (W) group during phase I (days 1 to 90) of a study of induced hypertensive renal insufficiency in cats.

	Group		
Parameter	**C**	**RK**	**W**
No. and sex	7 F	6 F and 2 M	5 F and 2 M
Body weight (kg)	2.73 ± 0.39	3.14 ± 0.45	3.09 ± 0.48
Food intake (kcal/kg/d)	100 ± 3[a]	86 ± 4[b]	72 ± 4[c]
Systolic BP (mm Hg)*	113 ± 3[a]	141 ± 7[b]	168 ± 6[c]
Diastolic BP (mm Hg)*	82 ± 3[a]	102 ± 5[b]	120 ± 5[c]
Mean BP (mm Hg)*	95 ± 3[a]	116 ± 6[b]	133 ± 5[c]
Heart rate (beats/min)*	190 ± 8[a]	191 ± 9[a]	186 ± 9[a]
Physical activity (units)	6.9 ± 1.2[a]	7.7 ± 1.3[a]	3.0 ± 0.5[b]
RPF (mL/min/kg)	9.76 ± 0.71[a]	4.50 ± 0.68[b]	4.01 ± 0.48[b]
GFR (mL/min/kg)	3.55 ± 0.35[a]	1.51 ± 0.25[b]	1.34 ± 0.15[b]
Filtration fraction	0.37 ± 0.04[a]	0.34 ± 0.01[a]	0.34 ± 0.02[a]
Serum creatinine concentration (mg/dL)	1.40 ± 0.04[a]	2.35 ± 0.14[b]	2.33 ± 0.15[b]
BUN (mg/dL)	24.3 ± 0.7[a]	45.3 ± 2.7[b]	43.3 ± 3.3[b]
Urine protein-to-creatinine ratio	0.11 ± 0.01[a]	0.25 ± 0.06[a]	1.16 ± 0.30[b]
Serum aldosterone concentration (ng/dL)	1.5 ± 0.4[a]	5.0 ± 1.2[a]	53.6 ± 12.1[b]
Plasma renin activity (ng/mL/h)	1.4 ± 0.3[a]	1.4 ± 0.3[a]	5.7 ± 1.4[b]

[a-c]Values in each row with different superscripts are significantly ($P < 0.05$) different.
*Only values obtained after discontinuation of amlodipine besylate treatment (day 25) were included.
F = Female. M = Male. BP = Systemic arterial blood pressure. RPF = Renal plasma flow. GFR = Glomerular filtration rate.
Values are expressed as mean ± SEM.

Clinical observations—The overall mean value for physical activity was significantly lower in group W, compared with groups C and RK, during phase I of the study (Table 1) and remained significantly lower throughout the study. Four cats in group W that developed ataxia and signs of depression on days 33, 69, 89, and 115 were euthanatized. One cat in group RK developed similar clinical signs on day 116 and was euthanatized. All 5 cats had marked systemic hypertension 24 to 48 hours prior to the development of neurologic signs; peak 24-hour mean systolic BPs were 235, 205, 189, 183, and 181 mm Hg.

Ophthalmologic examinations on day 90 revealed a focal area of tapetal hazing that was interpreted as a variant of normal in 1 cat in group C. In contrast, 1 or more ophthalmologic abnormalities were detected in 7 of 12 cats with decreased renal function (2/4 surviving cats in group W and 5/8 cats in group RK). Three cats in group W were euthanatized prior to the ophthalmologic examinations, and it was not known whether these cats had ocular lesions. In 1 cat in group RK, bilateral tortuous retinal vessels were observed; this cat developed hypertensive encephalopathy on day 116. A second cat in group RK had a mottled tapetum with bilateral multifocal hyporeflective areas of intraretinal edema and narrowing and straightening of retinal arterioles. A third cat in group RK had generalized tapetal hazing and multiple focal opacities interpreted as areas of intraretinal fluid accumulation. Generalized tapetal hazing was the only abnormal finding in 2 other cats of group RK. Bilateral multifocal shallow bullous retinal detachments measuring up to 1 optic disc in diameter were detected in 1 cat in group W. The other cat in group W that developed hypertensive encephalopathy at 115 days had generalized tapetal hazing, bilateral peripapillary multifocal vermiform lesions that suggested retinal reattachment, and narrowing and straightening of retinal arterioles. The peak 24-hour mean systolic BP of the 5 cats with ocular lesions in group RK during phase I were 148, 161, 165, 165, and 182 mm Hg; the peak 24-hour mean systolic BP of cats with ocular lesions in group W were 175 and 205 mm Hg. Anterior segment lesions were not observed in any cats.

Renal function—Glomerular filtration rate and RPF were significantly lower in groups RK and W, compared with group C (Table 1). The lower GFR was associated with mild azotemia in groups RK and W. Mean UP/C was significantly higher in group W, compared with group C; however, there was no significant difference in mean UP/C between groups C and RK.

Renin-angiotensin-aldosterone axis—There were no significant differences in mean serum aldosterone concentration and plasma renin activity between groups RK and C (Table 1). In contrast, serum aldos-

Table 2—The 24-hour mean systolic arterial BP (mm Hg; mean ± SEM) in group-C, RK, W cats treated with calcium channel antagonists (amlodipine besylate and sustained-release diltiazem HCl) and inhibitors of the renin-angiotensin-aldosterone axis (enalapril maleate and losartan K) during days 91 to 140 of a study of induced hypertensive renal insufficiency in cats.

	91–110				Days 110–140			
Group	Pretreatment	Amlodipine	Diltiazem	Posttreatment	Pretreatment	Enalapril	Enalapril and Losartan	Posttreatment
C	110 ± 1[a]	99 ± 3[b]	109 ± 1[a]	110 ± 2[a]	109 ± 4[a]	104 ± 3[a]	102 ± 3[a]	106 ± 3[a]
RK	133 ± 9[a]	118 ± 7[b]	125 ± 8[a,b]	139 ± 10[a]	133 ± 11[a]	129 ± 10[a]	127 ± 10[a]	128 ± 8[a]
W	174 ± 11[a]	139 ± 10[b]	155 ± 8[a,b]	181 ± 13[a]	153 ± 11[a]	145 ± 9[a]	140 ± 9[a]	149 ± 11[a]

[a-c]For each treatment period, values in each row with different superscripts are significantly ($P < 0.05$) different.
During the first treatment period (days 91 to 110) there were 7 cats in group C, 7 cats in group RK, and 4 cats in group W. During the second treatment period (days 110 to 140) there were 7 cats in group C, 7 cats in group RK, and 3 cats in group W.

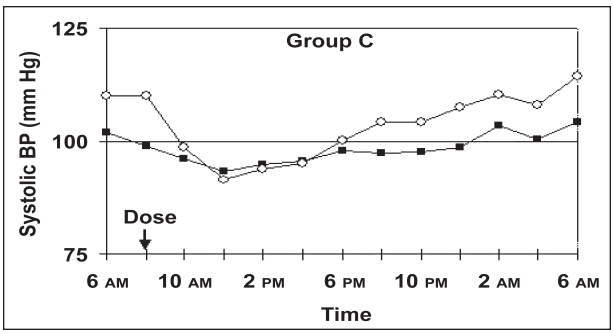

Figure 2—Mean systolic arterial BP (mm Hg) in cats in group C after treatment at 8 AM with diltiazem HCl (open circles) or amlodipine besylate (solid squares) on day 2 of the drug treatment period in phase II (days 91 to 110) of the study.

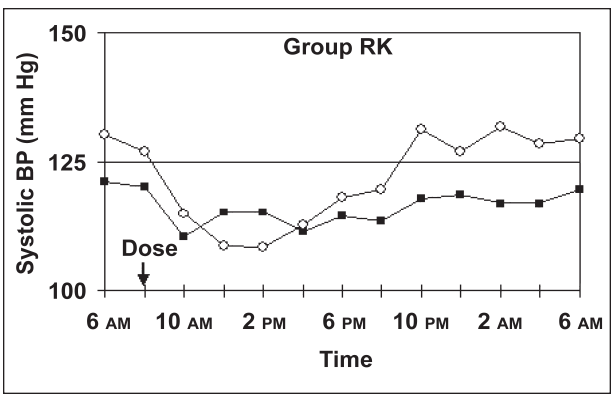

Figure 3—Mean systolic arterial BP (mm Hg) in cats in group RK after treatment at 8 AM with diltiazem HCl (open circles) or amlodipine besylate (solid squares) on day 2 of the drug treatment period in phase II (days 91 to 110) of the study.

terone concentration and plasma renin activity were significantly higher in group W, compared with groups C and RK (Table 1). In group W, significant positive correlations between systolic BP and serum aldosterone concentration (r^2 = 0.52) and systolic BP and plasma renin activity (r^2 = 0.59) were found. Plasma renin activity and serum aldosterone concentration had no significant correlations with systolic BP in groups C and RK.

Antihypertensive drug trials—There were no significant differences in BP measurements between treatment order A and B for each medication, so results were combined. The 24-hour mean systolic BP during 7 days of treatment with the calcium channel antagonist

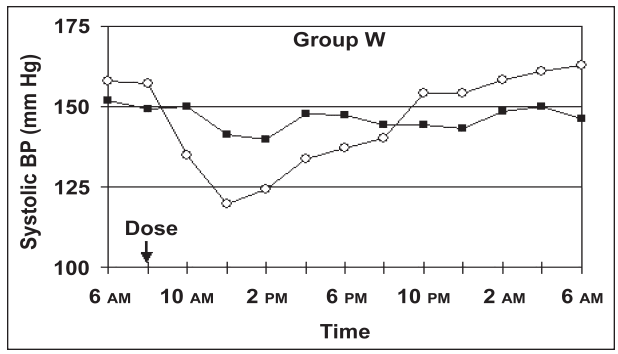

Figure 4—Mean systolic arterial BP (mm Hg) in cats in group W after treatment at 8 AM with diltiazem HCl (open circles) or amlodipine besylate (solid squares) on day 2 of the drug treatment period in phase II (days 91 to 110) of the study.

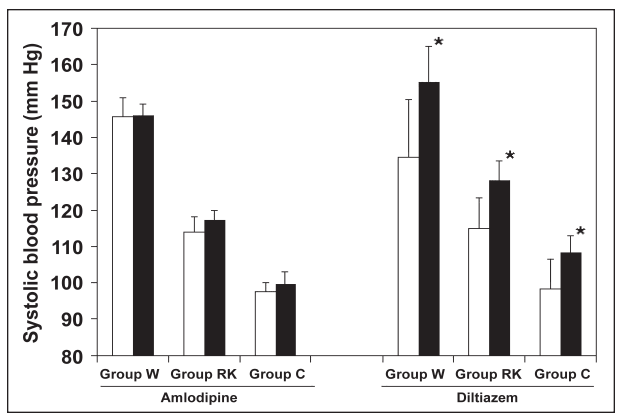

Figure 5—Mean ± SEM systolic arterial BP (mm Hg) in the 12-hour period (8 AM to 8 PM; open bar) after treatment with amlodipine besylate or diltiazem HCl and the subsequent 12-hour period (8 PM to 8 AM; solid bar) in cats in groups W, RK, and C on the second day of drug treatment during phase II (days 91 to 110) of the study. No significant differences in mean systolic arterial BP between the two 12-hour periods in groups W, RK, and C that were treated with amlodipine besylate were found. *Mean systolic arterial BP was significantly ($P < 0.05$) higher in the 8 PM to 8 AM time period compared with the 8 AM to 8 PM time period in groups W, RK, and C that were treated with diltiazem.

amlodipine besylate was significantly lower than those in the pretreatment and posttreatment periods in groups C, RK, and W (Table 2). The 24-hour mean systolic BP during the 7 days of treatment with sustained-release diltiazem HCl was not significantly different from those in the pretreatment and posttreatment periods in groups C, RK, and W. The daily pattern of change in systolic BP

in the 3 groups of cats during antihypertensive drug treatment revealed a persistent response to amlodipine besylate throughout a 24-hour period (**Figures 2–4**). However, with diltiazem HCl treatment, a biphasic pattern was revealed; an antihypertensive effect ($P < 0.05$) at 4 to 6 hours after treatment and a subsequent loss of antihypertensive efficacy by 12 hours after treatment in all 3 groups was detected (**Figure 5**). The 24-hour mean systolic BPs during treatment with enalapril maleate or enalapril maleate and losartan K were not significantly different from those in the pretreatment and posttreatment periods in groups C, RK, and W. There were no significant effects of antihypertensive treatments on SCr and BUN concentrations or UP/C.

Postmortem examinations—Five cats that were euthanatized when they developed neurologic signs had gross evidence of cerebral edema. In all of these cats, herniation of the middle vermis of the cerebellum through the foramen magnum and flattening of the cerebral gyri were evident. No other nonrenal lesions were observed on gross postmortem examination of cats in groups RK and W. Cats in group C were not euthanatized.

Initial (day 0) mean lesion indices in groups RK and W for glomerulosclerosis (0.17 ± 0.04 and 0.10 ± 0.02, respectively), tubular atrophy (0.06 ± 0.06 and 0.00 ± 0.00, respectively), and interstitial fibrosis (0.06 ± 0.06 and 0.00 ± 0.00, respectively) were not significantly different between groups. Compared with initial lesion indices, lesion indices for all 3 lesions were significantly higher in the postmortem samples in group W; however, only the lesion index for glomerulosclerosis was significantly higher in group RK. The lesion indices (groups W and RK, respectively) for glomerulosclerosis (1.22 ± 0.27 and 0.60 ± 0.11), tubular atrophy (1.06 ± 0.24 and 0.00 ± 0.00), and interstitial fibrosis (0.86 ± 0.37 and 0.00 ± 0.00) were significantly ($P < 0.05$) higher in group W than in group RK.

Discussion

Cats in group W had systemic hypertension and renal insufficiency with proteinuria and histologic evidence of renal structural damage. Increases in systolic, diastolic, and mean BP were dramatic, sustained, and associated with activation of the renin-angiotensin-aldosterone axis. End-organ damage (ie, eyes and brain) was frequently observed.

Historically, RK groups have been used to study CKD in cats.[10-14] In rodents,[17] RK groups have provided information regarding the pathophysiology of CKD and the effects of systemic hypertension on the kidney.[8] An advantage of the use of remnant kidneys is that the remnant renal tissue is initially normal; subsequent functional and structural changes are likely the result of decreased GFR. In cats, the remnant kidney technique results in mild systemic hypertension that decreases in severity over time.[13] These mild increases in BP do not appear to be associated with progressive renal injury; GFR remains stable, and renal structural changes are mild.[11,12]

Perinephric wrapping has been used to induce systemic hypertension in several species, including dogs[18,19] in which unilateral nephrectomy was combined with contralateral renal wrapping. Renal wrapping induces perinephric inflammation and fibrosis with subsequent compression of the renal parenchyma and vasculature, which likely interferes with the transmission of high BP to the underlying renal parenchyma and its pressure-sensitive microvasculature. Therefore, the effect of high BP on the wrapped kidney cannot be studied. A recently described technique that uses perinephric wrapping and contralateral partial renal infarction resolved this problem in dogs[o]; the remnant-wrap technique used in our study was a modified version of that technique.

Determinants of renal function, including RPF, GFR, BUN, and SCr concentrations, were similar in groups W and RK. In both groups, GFR was 60% lower than in the control group and resulted in the development of mild azotemia. Although BP in both groups was higher than in group c, BP in group W was significantly higher than in group RK. The dramatic hypertension in group W persisted throughout the 90-day study and was similar in magnitude to the systemic hypertension frequently observed in cats with naturally occurring CKD.[1-5] The remnant-wrap technique, therefore, provides an opportunity to investigate the relationship between systemic hypertension and the progression of feline CKD.

The high plasma renin activity and serum aldosterone concentration in group W indicated that this technique, in contrast to the RK technique, induced activation of the renin-angiotensin-aldosterone axis. All cats in our study were fed the same sodium-restricted diet; therefore, it is unlikely that diet played a role in causing differences in plasma renin activity and serum aldosterone concentration between techniques. Because both techniques include partial infarction of a kidney, it is likely that the wrapped renal tissue was the source of renin in cats of group W. Plasma renin activity and serum aldosterone concentration were measured only once (day 75) during the study. At this time point, cats in group RK had mild hypertension, whereas cats in group W had marked and stable hypertension. The positive correlations between BP and plasma renin activity and BP and serum aldosterone concentration support the contention that the renin-angiotensin-aldosterone axis played a central role in the development and maintenance of systemic hypertension at this time point in the cats of group W. In previous studies[4,20-22] of cats with naturally occurring renal disease, some but not all hypertensive cats had high serum aldosterone concentration, high plasma renin activity, or both, which was similar in magnitude to those in our group W cats. The causes of hypertension in cats with spontaneous renal diseases are likely varied, multifactorial, or both; the pathogeneses may be similar to those in the cats in our study or may differ substantially.

Treatment with inhibitors of the renin-angiotensin-aldosterone axis (ie, enalapril maleate and losartan K) did not lower BP in any of the 3 groups of cats. This is not a surprising finding for cats in group c because maintenance of BP in clinically normal cats is not uniquely dependent on the renin-angiotensin-aldosterone axis. Similarly, cats in the RK group had minimal activation of the renin-angiotensin-aldosterone axis; therefore, no apparent response to treat-

ment with these inhibitors was observed. Unexpectedly, cats in group W that had clear evidence of renin-angiotensin-aldosterone axis activation on day 75 failed to respond to treatment with enalapril maleate and losartan K. By this time in the study (days 110 to 140), 4 of 7 cats in group W had developed hypertensive encephalopathy and had been euthanatized. The 3 surviving cats in group W that were treated with enalapril maleate and losartan K between days 110 and 140 were, not unexpectedly, the members of this group with the lowest systolic BP, plasma renin activity, and serum aldosterone concentration. Because plasma renin activity and serum aldosterone concentration were measured only on day 75, it is not known whether renin-angiotensin-aldosterone axis activation persisted to the end of our study. In dogs studied by use of the original technique, the later stages of hypertension were associated with low plasma renin activity.[18] The absence of BP decreases in response to treatment with enalapril maleate, and losartan K may also be the result of drug-related factors that limit the efficacy of these agents in cats. The rationale for the use of losartan K and the dosage chosen was extrapolated from studies in rodents[23,24] and humans,[25,26] although little is known about the potential efficacy or appropriate dosage of losartan K in cats. A preliminary study[p] revealed that losartan K was ineffective as an antihypertensive agent in cats. In the same study, the commonly recommended dosage of enalapril maleate (0.5 mg/kg, q 24 h) induced an incomplete blockade of the pressor response to angiotensin I in cats,[p] suggesting that alternative pathways (other than via angiotensin converting enzyme) for conversion of angiotensin I to angiotensin II may exist in cats, as has been proposed in other species, including humans.[27] Enalapril maleate and losartan K both require hepatic bioactivation that could be limited in cats.

Despite the failure to have an effect on systemic hypertension in groups RK and W, angiotensin converting enzyme inhibition may still be useful for treatment of CKD. The angiotensin converting enzyme inhibitor benazepril lowers glomerular capillary blood pressure more dramatically than systemic BP in cats with remnant kidneys.[13] Glomerular capillary blood pressure is likely a more important determinant of hypertensive renal damage than is systemic BP.[28]

Treatment with the calcium channel antagonists amlodipine besylate and diltiazem HCl lowered BP (at least transiently) in all 3 groups of cats. The BP response of cats in groups W and RK to treatment with amlodipine was consistent with those responses reported in cats with naturally occurring systemic hypertension[29,30] and cats with remnant kidneys.[14] Although treatment with the sustained-release form of diltiazem HCl resulted in a marked BP lowering effect, this effect was not maintained for a full 24-hour period, suggesting that twice-daily treatment at a reduced dose may prove to be efficacious, although this has not been investigated. Some cats in group c that were treated with calcium channel antagonists had a 24-hour mean systolic BP < 100 mm Hg. Clinical signs of systemic hypotension were not detected in our study; however, these signs would be difficult to detect in cats. Normotensive and hypotensive cats with CKD and concurrent body fluid volume disorders may develop clinically evident hypotension when treated with antihypertensive drugs; this hypotension could lead to renal ischemia or renal dysfunction. Therefore, although calcium channel antagonists are effective antihypertensive agents in cats, BP should be measured prior to administration because treatment may induce adverse effects in normotensive or hypotensive cats.

A critical determinant of the quality and longevity of life in animals and humans with CKD is the rate at which CKD progresses to end-stage renal failure. Progression is an inherent property of CKD[31]; however, factors contributing to progression of renal disease in cats are not well-understood.[28] Cats in the RK and W groups developed glomerular and tubulointerstitial lesions. However, cats in group W had more severe lesions in the glomerular and tubulointerstitial compartments than did cats in group RK. Interestingly, the mean GFR in group W was similar to that in group RK, despite the less extensive reduction of renal mass in group W (75% vs 92% in group RK). The more severe glomerular and tubulointerstitial lesions in group W may be related to the activation of the renin-angiotensin-aldosterone axis, degree of increase in BP, or degree of proteinuria, all of which are known or suspected risk factors for progression of renal disease in humans,[7,32] rats,[8,33] and possibly dogs.[34,35,q] In kidneys of cats with decreased GFR, an adaptive dilation of the afferent arteriole occurs and results in an increase in glomerular capillary BP,[36] an effect known to cause glomerular injury in rats.[17] A study[13] of the effects of angiotensin converting enzyme inhibition in cats with decreased GFR by use of micropuncture techniques suggests that angiotensin II preferentially constricts the efferent arteriole, thus increasing glomerular capillary blood pressure further. The ability of the afferent arteriole to protect the glomerular capillary from increases in BP (via vasoconstriction of the afferent arteriole) is disrupted in dogs[37,38] and rats[8] with decreased GFR. In our cats with high BP, constriction of the efferent arteriole coupled with dilation of the afferent arteriole that was unresponsive to changes in BP could have acted in concert to enhance the susceptibility of the renal microvasculature to hypertensive injury. Cats in group W had a significantly higher degree of proteinuria than did cats in the RK and control groups; proteinuria may activate local factors that contribute to tubulointerstitial and glomerular injury and may itself be exacerbated by glomerular hypertension.[39,40]

Other differences between groups RK and W do not likely explain the differences in severity of renal lesions between the 2 groups. Cats in group RK ingested more food than those of group W; therefore, the hypothetical beneficial effects of restriction of phosphate,[10] calorie,[41] or protein[41] intake did not play a role in determining the differences in severity of renal lesions. Ingestion of greater amounts of n-3 polyunsaturated fatty acids, which were components of the study diet, may have had a renoprotective effect in the RK group; data in dogs support this hypothesis.[42] Similar data do not exist for cats, and the dietary lipid intakes in each group differed only in absolute, not relative,

amounts of n-3 and n-6 polyunsaturated fatty acids. Therefore, it is less likely that these fatty acids played a role in determining the differences in renal structure. Although antihypertensive drugs were administered prior to histologic studies, cats were treated for only a brief period and all cats were treated with the same drugs. Because only 3 of 7 cats in group W but 7 of 8 cats in group RK completed the entire 140 days of the study, the possibility that a protective drug effect played a role in determining the lesser severity of lesions in cats of group RK cannot be fully eliminated. However, long-term administration of similar or identical drugs failed to induce a difference in renal morphologic features in cats with remnant kidneys.[13,14] The more severe lesions in group W are therefore most likely attributable to the specific effects on BP, renin-angiotensin-aldosterone axis, and degree of proteinuria.

The differences in the histologic lesions between groups W and RK observed at the end of the study suggest a differential rate of progression of renal injury. Serum creatinine concentration, however, was not significantly different between these groups, and GFR was not measured at the end of the study; therefore, functional differences may or may not have been present. No firm conclusions may be drawn; however, our results support the hypothesis that marked systemic hypertension in association with activation of the renin-angiotensin-aldosterone axis and proteinuria damages the kidneys of cats with preexisting renal insufficiency.

The RK and W techniques of inducing renal insufficiency are useful for the study of the effects of moderate to severe systemic hypertension on the kidneys and other end organs. Ocular manifestations of systemic hypertension have been identified in cats with naturally occurring disease[1,3,15,29,43-46] and in cats with experimentally induced systemic hypertension.[14] The most commonly observed ocular lesions in cats include diffuse retinal edema; small intraretinal hemorrhages; focal bullous retinal detachment[43]; serous retinal detachment; extensive subretinal, intraretinal, and vitreal hemorrhages; hyphema[1,15,44-46]; and secondary glaucoma as a result of recurrent intraocular hemorrhage.[45] These lesions were detected mainly in cats that had been chronically ill for several weeks or months, with blindness as 1 of the major clinical complaints.[46] The pathogenesis of hypertensive retinopathy, in which BP exceeds the autoregulatory mechanism of retinal arterioles, is similar to that of other susceptible tissues. The ophthalmologic lesions detected in the cats of our study were considered early signs of systemic hypertension and likely originated in choroidal blood vessels.[45] The choriocapillaris apparently lacks autoregulatory mechanisms and is therefore more susceptible to damage caused by systemic hypertension. Hazing of the tapetum and focal intraretinal edema are attributable to leakage of plasma and fibrinogen from the choriocapillaris.[45] Persistent hypertension may cause more damage, and intraretinal hemorrhages may eventually be detected.[43] Lesions developed in 1 cat whose 24-hour mean systolic BP never exceeded 150 mm Hg and in 3 other cats with peak 24-hour mean systolic BP of ≤ 165 mm Hg. Only 2 cats with ocular lesions had a 24-hour mean systolic BP > 180 mm Hg prior to observation of lesions. Although transient bouts of higher systolic BP may have occurred in affected cats, our data clearly indicate that hypertensive retinopathy may occur in a cat with only moderate hypertension.

In our study, 4 of 7 cats in group W developed hypertensive encephalopathy, a recognized complication of high BP in cats.[3,47] Clinical changes in neurologic status were associated with systolic BP > 180 mm Hg and, in all but 1 cat, with an increase in systolic BP ≥ 15 mm Hg in the 48 hours preceding the onset of neurologic signs. Cerebral edema and cerebellar herniation were observed on postmortem examination; these findings are consistent with the hypothesis that BP exceeded the upper limit of cerebral arteriolar autoregulatory capability, inducing cerebral capillary hypertension and resultant interstitial edema. The subsequent increase in intracranial pressure likely led to cerebellar herniation and neurologic signs, as reported in humans.[48] Cats in group W also had low physical activity throughout the study that could not be attributed to differences in renal function. This inactivity could represent an effect of high BP, possibly a neurologic effect, in this group of cats.

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[a]IMI-1000 Implantable Micro Identification, BMDS, Seaford, Del.
[b]Model TA11PA-C40, Data Sciences International, St Paul, Minn.
[c]100% handwoven silk fabric, Kabadi Fabrics, Kabadi, India.
[d]Cellophane, DowBrands, Indianapolis, Ind.
[e]Dataquest Advanced Research Technology Version 2.2, Data Sciences International, St Paul, Minn.
[f]Model RLA-2000, Data Sciences International, St Paul, Minn.
[g]Hill's Prescription Diet Feline K/D Dry, Hill's Petfoods, Topeka, Kan.
[h]Hitachi 912, Boehringer Mannheim Corp, Indianapolis, Ind.
[i]LabCorp, Laboratory Corporation of America, Burlington, NC.
[j]Norvasc, Pfizer Inc, New York, NY.
[k]Dilacor XR, Watson Laboratories, Corona, Calif.
[l]Enacard, Merck, Sharp & Dohme Research Laboratories, Rahway, NJ.
[m]Cozaar, DuPont Pharma, Wilmington, Del.
[n]Statview 4.5, Abacus, Berkeley, Calif.
[o]Finco DR, Cooper TA. A new model of hypertensive renal failure in dogs (abstr). *J Vet Intern Med* 2000;14:353A.
[p]Reynolds V, Mathur S, Sheldon S, et al. Losartan fails to block angiotensin pressor response in cats (abstr). *J Vet Intern Med* 2002;16:341A.
[q]Brown SA, Brown CA, Hendi R. Does systemic hypertension damage the canine kidney? (abstr). *J Vet Intern Med* 2000;14:351A.

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