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Effects of Benazepril Hydrochloride in Cats with Experimentally Induced or Spontaneously Occurring Chronic Renal Failure

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ABSTRACT. We examined effects of an angiotensin converting-enzyme inhibitor, benazepril hydrochloride (BH), on renal hypertension and chronic renal failure (CRF) in cats. For experimental CRF, healthy cats (n=5) underwent 7/8 renal ablation. After renal insufficiency and hypertension were confirmed by blood urea nitrogen (BUN), serum creatinine, creatinine clearance and telemetric recording of systemic blood pressure, BH was administered orally once daily at 0.9 to 2.0 mg/kg/day for 2 to 3 weeks. Within 2 months after renal ablation, renal failure and hypertension developed as evidenced by significant increases in BUN, serum creatinine and systemic blood pressure ($p<0.01$ or 0.05) and significantly decreased creatinine clearance accompanied by elevated plasma renin activity, angiotensin I and II, and aldosterone ($p<0.01$ or 0.05). BH administration corrected systemic hypertension ($p<0.05$) and significantly reduced angiotensin II and aldosterone ($p<0.05$). Upon discontinuation of BH, these values returned to the pre-administration levels. Studies on spontaneous CRF enrolled 11 cats with spontaneously occurring CRF. BH was administered orally to 6 cats once daily for 24 weeks at a final dose of 1.0 mg/kg/day, while 5 cats served as control. BH administration reduced serum creatinine and urinary protein concentration in every cat. Results demonstrate that in cats, loss of renal mass leads to activation of the renin-angiotensin-aldosterone system and associated renal hypertension, and indicate that BH is effective in correcting renal hypertension and may provide renal benefits to cats with CRF.

KEY WORDS: benazepril hydrochloride, chronic renal failure, feline, hypertension.

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Hypertension can be classified into essential hypertension and secondary hypertension. While the cause of essential hypertension is unknown, the most frequent form of secondary hypertension is renal hypertension [22]. Development of renal hypertension involves retention of body fluid occurring with renal dysfunction, increases in cardiac output and peripheral blood vessel resistance, increased activities of pressor factors, such as the renin-angiotensin-aldosterone (RAA) system, and suppression of depressor factors, including the kallikrein-kinin-prostaglandin system [13, 37]. Similar to human practice, the incidence of chronic renal failure (CRF) and associated hypertension has been increasing recently in small animal practice [20, 29, 38], necessitating its diagnostic criteria and therapies.

In small animal practice, radical therapies such as kidney transplantation are not practical for the treatment of CRF and, in general, symptomatic and conservative treatments are used in an attempt to improve uremic symptoms and to prevent the progression of renal insufficiency. It has been demonstrated in both experimental animals and humans that hyperactivation of the RAA system and resultant hypertension play a pivotal role in the progression of renal failure [35, 43]. In deed, antagonism of the RAA system by either angiotensin converting-enzyme (ACE) inhibitors or blockers of angiotensin (ANG) receptors has been shown to correct hypertension and decelerate the progression of CRF in humans [5, 27]. Of the available ACE inhibitors, benazepril hydrochloride (BH) is different in that BH is excreted in both bile and urine [44]. Because of this property, BH does not accumulate in the body of animals with renal dysfunction [19], indicating its potential as a safe therapeutic means for CRF of small animals.

In the present study, we examined therapeutic effects of BH on CRF and renal hypertension in cats. To this end, we experimentally induced CRF in cats by renal ablation, and examined the effects of BH on blood pressure and the activity of the RAA system. We also examined clinical effects of BH in cats with spontaneously occurring CRF.

MATERIALS AND METHODS

Experimental CRF model

Animals: Five mixed-breed cats (body weight ranging from 2.0 to 3.2 kg; 2 males and 3 females) with no abnormalities on general clinical examinations, blood and serum biochemical examinations and urinalysis were used. Cats were kept under the conditions we have described previously [28], given water *ad libitum* and fed with Waltham Feline Veterinary Diet Renal Support Low Phosphorus Low Protein Diet® (Master Foods Ltd., Tokyo, Japan).

Experimental induction of CRF: After monitoring baseline blood pressure for approximately 3 months, 7/8 renal ablation was performed. Briefly, the right kidney was nephrectomized and, a few weeks later, part of the ventral and dorsal branches of the renal artery of the left kidney were ligated to reduce the blood supply to 1/4 of the origi-

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nal. Since individual cats differed in the branching pattern of the renal artery, we monitored grossly for ischemic areas of the left kidney after the ligation. Cats were diagnosed with renal failure and hypertension when they showed increases in blood urea nitrogen (BUN) and serum creatinine (Cr), a decrease in Cr clearance (CCr), and a consistent increase in systemic blood pressure.

BH administration: BH was administered orally at a daily dose of 2.5 or 5 mg (0.92–2.0 mg/kg/day) for 2 or 3 weeks.

Blood pressure: Blood pressure was measured by a telemetric system as we have previously described [28]. A transmitter (Data Sciences International, Minnesota, U.S.A.) was implanted in the femoral artery, and systolic, diastolic and mean blood pressures were monitored continuously for 24 hr without anesthesia or restraint. The average blood pressure was calculated every 24 hr and presented as 24-hr blood pressure.

Blood biochemistry and urinalysis: Blood and urine samples were collected before and 7 days after the initiation of BH administration and 7 days after the completion of the administration to determine BUN, serum Cr, CCr and the levels of RAA components, including plasma renin activity (PRA) and the concentrations of circulating ANG I, ANG II and aldosterone (ALD). BUN and Cr were determined by enzyme UV method and Jaffe method, respectively, on COBAS MIRA S chemical analyzer (Japan Roche, Tokyo, Japan). CCr was determined by 30-min endogenous creatinine clearance method. The bladder was flushed with saline solution and, urine was collected for 30 min *via* a catheter immediately before meals to avoid the influence of food intake. CCr was calculated in m*l*/min/kg by the following formula:

CCr (m*l*/min/kg) = urinary Cr concentration (mg/m*l*) × urine volume (m*l*/min) / (serum Cr concentration (mg/m*l*) × body weight (kg))

For measurement of PRA, ANG I and II, and ALD levels, blood was sampled between 16:00 and 17:00 to avoid the influence of the time-dependent variations [28]. After anticoagulation with EDTA, samples were immediately cooled, centrifuged at 3000 rpm for 5 min at 4°C and subjected to sandwich radioimmunoassay for PRA, dextran-coated charcoal radioimmunoassay assay for ANG I and II, and solid-phase radioimmunoassay for ALD at Sumitomo Metal Bioscience Ltd. (Tokyo, Japan).

Spontaneously occurring CRF

Animals: Experiments on spontaneously occurring CRF included 11 outpatient cats that were diagnosed with CRF at Azabu University Teaching Animal Hospital (Table 1). CRF was diagnosed by physical examination, palpation, and over 2 weeks of azotemia as evidenced by elevated levels of BUN and serum Cr. To confirm the diagnosis, blood and urine samples were collected from these cats at least twice before the study (Table 1). No specific restriction was imposed upon diet.

BH administration: Cats with spontaneously occurring CRF were allocated to BH Group (n=6) or Control Group (n=5) according to the owner's consent on the use of BH, and BH was administered orally to the BH Group for 24 weeks at 0.25 mg/kg/day in the initial week, 0.5 mg/kg/day

Table 1. Cats with spontaneously occurring chronic renal failure[a)]

Animal	Age (years)	Body weight (kg)	Serum blood urea nitrogen (mg/d*l*)		Serum creatinine (mg/d*l*)		Urinary protein[b)]		Major Clinical symptoms
			1st	2nd	1st	2nd	1st	2nd	
Control Group									
Cont 1	approx. 6	2.2	40.0	41.0	2.8	2.9	3+	2+	
Cont 2	approx. 5	2.3	51.0	52.0	3.1	3.3	2+	2+	Polydipsia,
Cont 3	4	2.8	41.0	42.0	2.1	2.2	2+	2+	Polyuria and
Cont 4	2	3.7	39.0	40.0	2.9	2.8	1+	2+	sporadic
Cont 5	2	3.7	42.0	41.0	3.1	2.9	2+	2+	vomiting
Mean	3.8	2.9	42.6	43.2	2.8	2.8	N.A.	N.A.	
BH Group									
ACE 1	15	3.8	67.1	33.8	5.7	3.7	2+	2+	
ACE 2	6	4.2	35.8	48.3	3	3.9	2+	2+	Polydipsia,
ACE 3	4	3.7	38.7	38.3	2.7	2.6	3+	3+	Polyuria and
ACE 4	6	5.0	N.D.	62.5	N.D.	3.9	2+	2+	sporadic
ACE 5	13	3.4	39.4	46.5	2	2.9	2+	2+	vomiting
ACE 6	6	6.6	39.6	53.7	2.8	3.4	3+	3+	
Mean	8.3	4.5	44.1	47.2	3.2	3.4	N.A.	N.A.	

a) Blood urea nitrogen, serum creatinine and urinary protein concentration were determined twice before the study to establish the diagnosis of renal failure.

b) Urinary protein concentration was determined by stick test using the following grading; +/– for borderline, 1+ for 30 mg/d*l* and greater, 2+ for 100 mg/d*l* and greater, and 3+ for 300 mg/d*l* and greater. Because of the nature of the grading, means are not available for urinary protein.

Abbreviations are: approx. = approximately; N.A. = not available; N.D. = not determined.

in the second week and 1.0 mg/kg/day in the third week and thereafter. No other treatment was given during the study period.

Blood chemistry and urinalysis: Clinical symptoms, BUN, serum Cr and phosphate, and urinary protein were examined once a week. Urine samples were collected *via* a catheter, and urinary protein concentration was assessed by a stick test (N-Multistick; Bayer Medical, Tokyo, Japan) according to the manufacturer's instruction using the following grading: +/– for borderline, 1+ for 30 mg/d*l* and greater, 2+ for 100 mg/d*l* and greater, and 3+ for 300 mg/d*l* and greater.

The protocol of the present study was in accordance with the National Institute of Health Guide for Care and Use of Laboratory Animals and approved by the Institutional Review Board of Azabu University School of Veterinary Medicine.

Statistical analysis: The values are presented as means ± SD. Data obtained in experimental CRF were analyzed by the Mann-Whitney test. For spontaneously occurring CRF, data were analyzed by the Wilcoxon test. Differences were considered significant at $p<0.05$.

RESULTS

Induction of experimental CRF: Approximately 2 months after renal ablation, cats developed azotemia, as evidenced by significant increases in BUN and serum Cr from the pre-ablation values of 24.3 ± 5.0 mg/d*l* and 1.3 ± 0.2 mg/d*l* to 44.6 ± 19.8 mg/d*l* and 2.3 ± 0.6 mg/d*l*, respectively ($p<0.01$) (Fig. 1). In parallel, CCr was decreased from 1.9 ± 0.3 m*l*/min/kg to 1.2 ± 0.3 m*l*/min/kg ($p<0.01$) (Fig. 1).

Concurrent with reduction in renal function, systolic, mean and diastolic blood pressures were increased significantly from the pre-ablation values of 125.5 ± 4.4, 100.9 ± 5.2 and 84.0 ± 6.2 mmHg to 161.1 ± 39.6, 133.1 ± 32.3 and 112.8 ± 29.0 mmHg, respectively ($p<0.01$) (Fig. 2).

All 4 components of the RAA system were significantly elevated in nephrectomized cats (Fig. 3), with PRA at 28.5 ± 35.9 *n*g/m*l*/hr ($p<0.05$ vs. 2.9 ± 1.9 *n*g/m*l*/hr before renal ablation), ANG I at 33,047 ± 35,679 *p*g/m*l* ($p<0.05$ vs. 1,115 ± 967 *p*g/m*l* before renal ablation), ANG II at 10,488 ± 5,204 *p*g/m*l* ($p<0.05$ vs. 327 ± 236 *p*g/m*l* before renal ablation) and ALD at 320 ± 599 *n*g/d*l* ($p<0.05$ vs. 9.8 ± 9.0 *n*g/d*l* before renal ablation) (Fig. 3).

These results indicated that CRF and renal hypertension were successfully induced in these cats.

Effects of BH on experimentally induced CRF: BH administration markedly improved the hypertensive state of cats with experimentally induced CRF (Fig. 4). After 7 days of BH administration, systolic, mean and diastolic blood pressures were all decreased significantly from the pre-administration values of 143.5 ± 8.8, 118.6 ± 8.1 and 99.3 ± 6.4 mmHg to 124.9 ± 4.4, 101.1 ± 2.5 and 83.7 ± 2.2 mmHg, respectively ($p<0.05$). Within 7 days after the discontinuation of BH administration, systolic, mean and diastolic blood pressures were increased significantly to 144.0 ± 14.6, 121.0 ± 12.6 and 102.0 ± 9.4 mmHg ($p<0.05$), respectively. These values were statistically undistinguishable from the pre-BH values.

The components of the RRA system were by and large showed a tendency of decreasing upon BH administration (Fig. 5). PRA and ANG I were reduced from their respective pre-BH values of 31.3 ± 40.7 *n*g/m*l*/hr and 37,277 ± 39,771 *p*g/m*l* to 13.6 ± 5.1 *n*g/m*l*/hr and 16,941 ± 9,738 *p*g/m*l*; however, the differences did not attain statistical significance. ANG II and ALD were decreased significantly from 11,884 ± 8,627 *p*g/m*l* and 457 ± 630 *n*g/d*l* to 414 ± 242 *p*g/

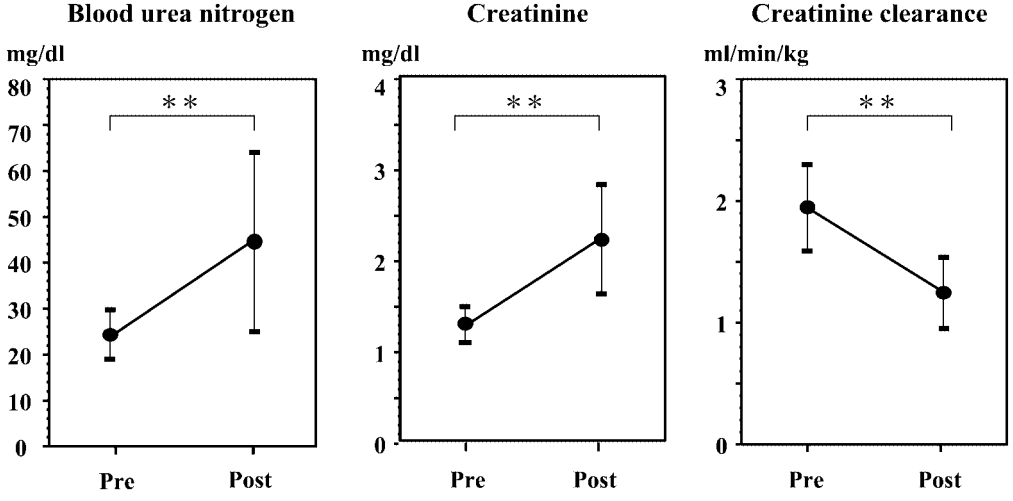

Fig. 1. Changes in renal function prior to and after preparation of feline experimental chronic renal failure model. Chronic renal failure model was prepared by subjecting healthy cats (n=5) to 7/8 renal ablation *via* nephrectomy of the right kidney and ligation of part of the left renal artery. Blood urea nitrogen, serum creatinine and creatinine clearance were determined both prior to and approximately 2 months after renal ablation. Pre-ablation (Pre) and post-ablation (Post) values are shown as means ± SD. **, $p<0.01$ vs. pre-ablation values.

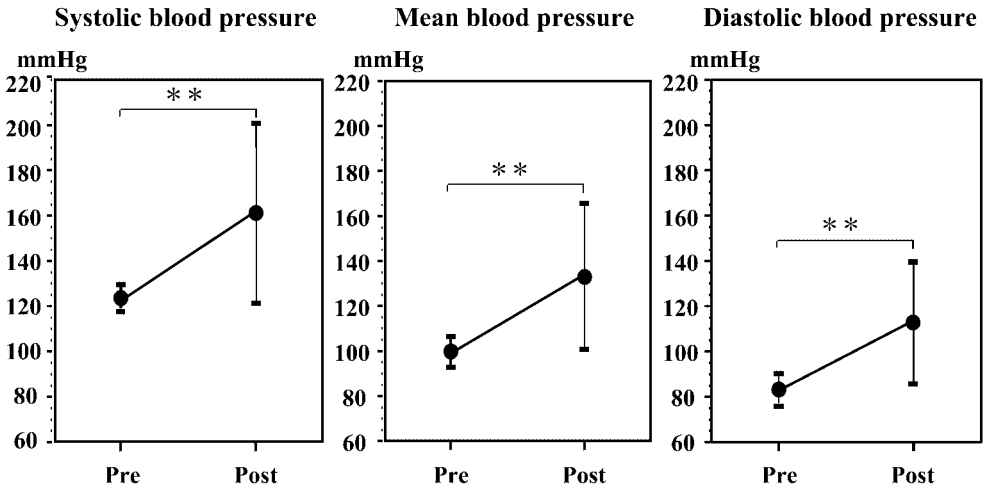

Fig. 2. Changes in systolic, mean and diastolic blood pressures prior to and after preparation of feline experimental chronic renal failure model. Both prior to and after 7/8 renal ablation, systolic, mean and diastolic blood pressures were continuously recorded by telemetry (n=5). Pre-ablation (Pre) and post-ablation (Post) values are shown as means ± SD. **, $p<0.01$ vs. pre-ablation values.

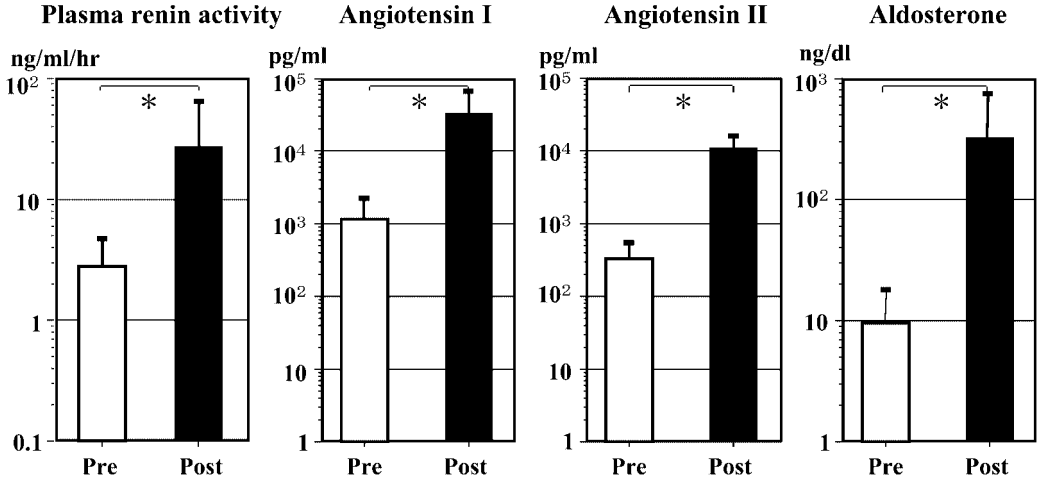

Fig. 3. Changes in the renin-angiotensin-aldosterone system prior to and after preparation of feline experimental chronic renal failure model. Both prior to and after 7/8 renal ablation, plasma renin activity, angiotensin I, angiotensin II and aldosterone were determined by radioimmunoassay (n=5). Pre-ablation (Pre) and post-ablation (Post) values are shown as means ± SD. *, $p<0.05$ vs. pre-ablation values.

m*l* and 10 ± 10 *n*g/d*l*, respectively ($p<0.05$). Upon discontinuation of BH administration, PRA and ANG I remained reduced at 12.1 ± 3.5 *n*g/ml/hr and 13,789 ± 6,477 *p*g/m*l*, respectively. In contrast, ANG II and ALD increased significantly to 9,552 ± 8,921 *p*g/m*l* and 138 ± 110 *n*g/d*l*, respectively, both of which were indistinguishable from the pre-BH values ($p<0.05$ vs. the values during BH administration; N.S. vs. pre-BH values).

Meanwhile, the values of clinical parameters for the pre- and during BH administration and after BH discontinuation were 57.7 ± 42.1, 57.8 ± 29.2 and 56.0 ± 20.2 mg/d*l* for BUN, 2.5 ± 1.6, 2.7 ± 1.2 and 2.5 ± 0.9 mg/d*l* for serum Cr, and 1.2 ± 0.5, 1.2 ± 0.4 and 1.2 ± 0.5 ml/min/kg for CCr, respectively, indicating no significant differences.

Effects of BH on spontaneously occurring CRF: Through the 24 weeks of the study period, the untreated Control Group showed a tendency to increase in the levels of BUN, serum Cr and phosphate from the respective pre-administration values (Table 2). In contrast, the BH Group showed a significant decrease in serum Cr from the 12th week of BH administration until the completion of the study ($p<0.05$). Decreases were also seen in BUN and serum phosphate, although the differences did not attain statistical significance (Table 2).

Prior to BH administration, the grade of urinary protein was 2+ or higher in both the Control and BH Group, with

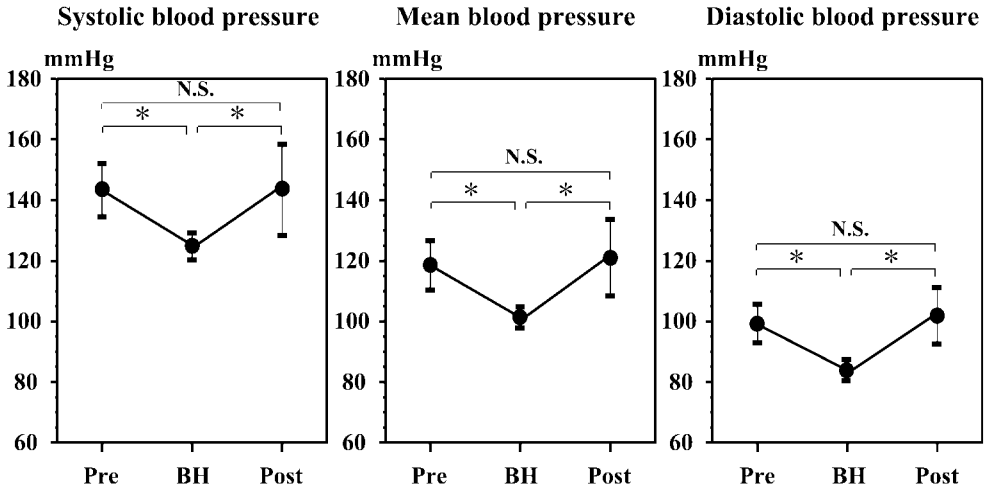

Fig. 4. Effects of benazepril hydrochloride on systemic blood pressure in feline experimental chronic renal failure model. Benazepril hydrochloride (BH) was orally administered to cats with 7/8 renal ablation (n=5) daily at 0.9 to 2.0 mg/kg/day for 2 to 3 weeks, and systolic, mean and diastolic blood pressures were recorded continuously by telemetry. Pre-administration (Pre), during administration (BH) and post-administration (Post) values are shown as means ± SD. *, $p<0.05$; N.S. = not significant.

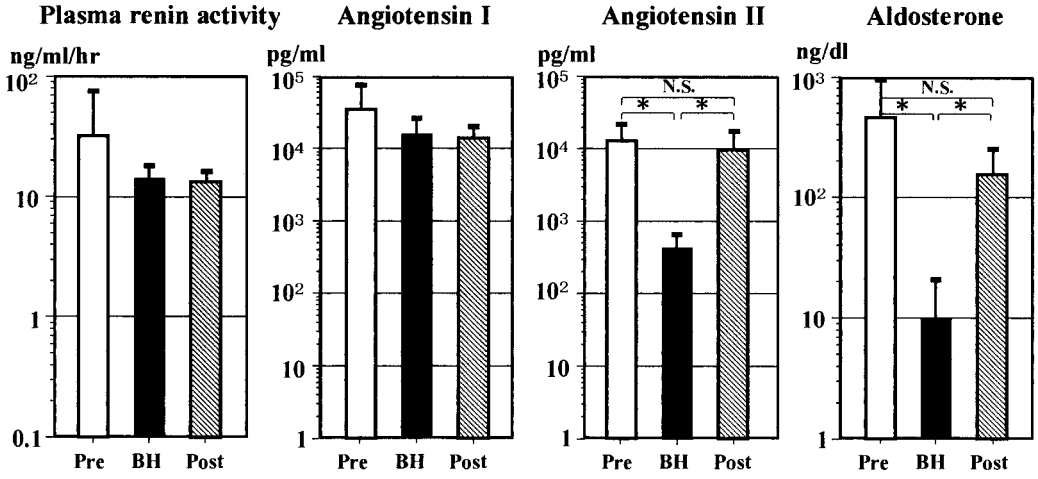

Fig. 5. Effects of benazepril hydrochloride on the renin-angiotensin-aldosterone system in feline experimental chronic renal failure model. Benazepril hydrochloride (BH) was orally administered to cats with 7/8 renal ablation (n=5) daily at 0.9 to 2.0 mg/kg/day for 2 to 3 weeks, and plasma renin activity, angiotensin I, angiotensin II and aldosterone were determined by radioimmunoassay (n=5). Pre-administration (Pre), during administration (BH) and post-administration (Post) values are shown as means ± SD. *, $p<0.05$; N.S. = not significant.

two cats of the BH Group being 3+ (Table 1). Throughout the administration period, urinary protein remained at similar levels in the Control Group and, at the end of the study period, four cats were 2+ and one was 1+. In contrast, the number of cats with 1+ or a greater grade of urinary protein decreased in the BH Group (Table 3). By the 1st week of BH administration, 2 of the 6 cats were 2+ and the other four were 1+ and, by the end of BH administration, every cat of the BH Group was negative for urinary protein (Table 3). Of those, 5 cats became either borderline or negative for urinary protein by the 2nd week of BH administration, and the remaining cat became negative by the 24th week of the administration.

DISCUSSION

In the present study, we examined effects of an ACE inhibitor, BH, in cats with CRF. In approximately 2 months after 7/8 renal ablation, BUN and serum Cr were both elevated, with a decrease in CCr, and systemic blood pressure was elevated in parallel with increases in PRA, ANG I, ANG II and ALD. Administration of BH for 2 to 3 weeks corrected systemic blood pressure and decreased ANG II and ALD, while no significant changes were seen in BUN,

Table 2. Changes in clinical parameters for renal function prior to and during benazepril hydrochloride (BH) administration in cats with spontaneously occurring chronic renal failure[a)]

	Prior to BH	During BH administration (Weeks after the initiation of administration)							
		1	2	4	8	12	16	20	24
Blood urea nitrogen (mg/d*l*)									
Control	43.2 ± 4.4	44.7 ± 5.7	43.0 ± 5.6	41.4 ± 4.9	43.1 ± 6.8	44.3 ± 7.4	44.5 ± 7.1	44.6 ± 7.6	43.8 ± 6.9
BH	47.2 ± 9.5	40.8 ± 7.7	37.0 ± 6.9	39.7 ± 10.0	35.3 ± 3.2	39.7 ± 11.0	38.6 ± 13.0	36.0 ± 14.0	37.7 ± 14.0
Serum creatinine (mg/d*l*)									
Control	2.8 ± 0.4	2.8 ± 0.4	2.9 ± 0.4	2.9 ± 0.4	2.9 ± 0.4	2.9 ± 0.3	2.9 ± 0.3	3.0 ± 0.4	3.0 ± 0.4
BH	3.4 ± 0.5	3.0 ± 0.4	2.7 ± 0.2	2.7 ± 0.2	2.6 ± 0.4	2.5 ± 0.3*	2.3 ± 0.3*	2.5 ± 0.3*	2.6 ± 0.4*
Serum phosphate (mg/d*l*)									
Control	5.8 ± 0.1	5.9 ± 0.2	5.9 ± 0.3	6.0 ± 0.1	6.0 ± 0.2	6.0 ± 0.1	6.1 ± 0.3	6.0 ± 0.3	6.1 ± 0.2
BH	5.2 ± 0.9	5.0 ± 0.2	4.6 ± 0.4	4.5 ± 0.4	4.2 ± 0.5	4.7 ± 0.8	4.8 ± 1.0	4.2 ± 0.7	4.3 ± 0.4

a) Blood urea nitrogen, serum creatinine and phosphate, and urinary protein concentration were determined in the Control group (n=5) and the BH group (n=6) both prior to and during BH administration. Values are means ± SD.
*, $p<0.05$ vs. prior to BH.
Abbreviations are: BH = benazepril hydrochloride.

Table 3. Changes in urinary protein concentration prior to and during benazepril hydrochloride (BH) administration in cats with spontaneously occurring chronic renal failure[a)]

Animal group	Prior to BH	During BH administration (Weeks after the initiation of administration)							
		1	2	4	8	12	16	20	24
Control	5/5[b)]	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5
BH	6/6	6/6	1/6	1/6	1/6	1/6	1/6	1/6	0/6

a) Urinary protein concentration was determined in the Control group (n=5) and the BH group (BH; n=6) by stick test using the following grading; +/– for borderline, 1+ for 30 mg/d*l* and greater, 2+ for 100 mg/d*l* and greater, and 3+ for 300 mg/d*l* and greater.
b) Values are the number of cats with 1+ or a greater grade of urinary protein/the number of cats examined.
Abbreviations are: BH = benazepril hydrochloride.

serum Cr or CCr. Upon discontinuation of BH, systemic blood pressure as well as ANG II and ALD returned to the pre-administration levels. In cats with spontaneously occurring CRF, 24 weeks of BH administration improved serum Cr and urinary protein, with no further increase in BUN or serum phosphate.

CRF is an irreversible, progressive disease that advances to glomerulosclerosis and interstitial fibrosis and, eventually, to end-stage renal failure [35, 43]. It has been recognized that various endocrine systems and cytokines are involved in the development of renal hypertension and the progression of CRF [16]. In particular, hyperactivation of the RAA system plays a pivotal role in accelerating renal dysfunction and structural deterioration [16, 35, 43]. Renal ablation has been utilized to induce experimental CRF in rats and other experimental animals [12]. In order to gain insight into the pathogenesis of renal hypertension in cats, we developed a feline model of CRF. Following 7/8 renal ablation, BUN, serum Cr and systemic blood pressure were all increased in association with a reduction in CCr. Concurrently, a marked increase was observed in the level of circulating ANG II. Thus, the present feline model of CRF successfully duplicated the conditions found in humans and rodent models of CRF [16, 35, 43].

In our feline model of CRF, hypertension was associated with increases in the components of the RAA system. In general, the RAA system becomes activated to compensate for a decrease in renal function caused by primary renal disease or experimental renal ablation. Renin secreted by juxtaglomerular cells of the kidney converts angiotensinogen to ANG I. ANG I is hydrolyzed by ACE to produce ANG II. ANG II acts upon renal efferent arterioles to induce contraction, thereby increasing glomerular capillary pressure and filtration, and raises systemic blood pressure by contracting peripheral blood vessels and by facilitating sodium and water reabsorption at proximal tubules. In addition, ANG II stimulates the adrenal cortex to secrete ALD. ALD decreases the loss of sodium and fluid at distal tubules, further contributing to increased blood pressure. The fact that BH administration effectively decreased both systemic blood pressure and circulating ANG II provides strong evidence that renal hypertension seen in our feline CRF model is secondary to the activation of the RAA system. This notion is further supported by the finding that upon discontinuation of BH, blood pressures, ANG II and ALD returned to pre-BH levels.

In cats with experimental CRF, BH caused no significant changes in BUN, serum Cr or CCr. A large loss of function-

ing nephrons, such as one seen with 7/8 renal ablation, results in a large reduction of renal function that cannot be fully compensated by physiological increases in glomerular filtration. Hyperfiltration hypothesis dictates that increased glomerular filtration causes physical damages to the glomerulus, leading to progressive renal injury [6]. Excessive ANG II plays its major pathogenic role in increasing glomerular perfusion pressure and tubulointerstitial insults, thereby damages remnant nephrons and aggravates renal structural deterioration and dysfunction [16, 35, 43]. Thus, the observed correction of systemic blood pressure and the lack of further aggravation of the renal functional parameters suggest that BH suppressed the adverse influence of ANG II on the remnant nephrons.

Previously, we have performed non-invasive blood pressure measurements in cats with spontaneously occurring CRF and reported that the cats developed hypertension in association with increases in the RAA system [29], suggesting activation of the RAA system in spontaneously occurring CRF in cats. Because ACE inhibitors carry the risk of hypotension and acute reduction in glomerular filtration [23], we chose to increase the dose of BH gradually to the final dose of 1 mg/kg/day, the dose found sufficient to inhibit ACE activity in cats [17, 18].

In cats with spontaneously occurring CRF, we found that BH administration improved serum Cr and urinary protein. BUN and serum phosphate were also decreased, although the differences did not reach statistical significance. In contrast, no sign of improvement was seen in untreated Control Group; rather, the parameters showed a tendency to increase. Studies in humans as well as experimental animals have highlighted proteinuria as a strong progression factor and indicated that its reduction is a critical effect of ACE inhibition [27, 33, 35]. The possibility of renal structural regeneration has been raised for ACE inhibition in a rat model of spontaneous renal disease [34]. Renal ablation is comparable to physical removal of nephrons whereas nephrons in spontaneously occurring CRF are damaged but not eliminated. Thus, in the light of the above mentioned recent studies, our findings may provide support for the potential benefits of BH to damaged nephrons in the clinical setting.

In humans, essential hypertension accounts for 80 to 90% of hypertensive patients, and the remaining patients have secondary hypertension arising from renovascular or renoparenchymatous diseases, diabetes, Cushing's syndrome, primary hyperaldosteronism, pheochromocytosis, or hypothyroidism [22]. Of those, hypertension associated with renopharenchymatous diseases is most frequent in humans [22]. Contrary to humans, essential hypertension is thought uncommon in dogs [4, 31, 41]. Incidence of hypertension in dogs with renal diseases has been reported to range from 50 to 93% [11, 38], and a link between renal diseases and hypertension has been suggested in dogs and cats [1, 10, 20, 25, 26, 29, 32, 39, 40]. However, a causal role of renal diseases in hypertension has not been established in small animals. In this regard, Goldblatt hypertension, induced by constricting the renal artery, has been developed in dogs as an animal model of renovascular hypertension [2, 3, 15, 21, 30], providing evidence that renovascular hypertension can develop in dogs through activation of the RAA system. Yet, spontaneous occurrence of renovascular hypertension has not been described in small animals. Therefore, to consider renal hypertension of small animals, we gave first priority to renal hypertension arising from renoparenchymatous diseases and, to reproduce the conditions, we chose renal ablation by unilateral nephrectomy and ligation of the renal artery, as has been used in rats [12]. A similar approach has been applied to dogs [8, 9, 24, 36].

Since the advent of ACE inhibitors, a variety of ACE inhibitors have been developed and, along with blockers of ANG receptors, become a mainstay of conservative therapies for CRF in humans [5, 14, 35, 43]. Of the available ACE inhibitors, BH is different in that it is excreted in urine and bile [45]. Pharmacokinetic studies showed that in cats, up to 85% of benazeprilat, the active metabolite of BH, is eliminated via biliary excretion [18], and repeated oral administrations of BH result in a little accumulation of benazeprilat [17]. Similarly, clearance of plasma benazeprilat was found to increase in dogs with experimentally induced renal insufficiency, while that of enalapril, another ACE inhibitor, was decreased to 40 to 55% [42]. Moreover, BH was equally effective to improve systemic blood pressure and glomerular filtration at 0.25 to 2 mg/kg/day in cats with experimentally induced renal insufficiency [7, 18]. A recent randomized controlled clinical study demonstrated that benazepril conferred substantial renal benefits to humans with advanced renal insufficiency [14]. Together with these studies, our present observations demonstrate that BH is effective for renal hypertension and offers renal benefits to cats with CRF.

In conclusion, our findings demonstrate that renal ablation in cats is followed by development of renal failure and hypertension via activation of the RAA system, and BH is effective in correcting renal hypertension. Results also suggest that BH may bring benefits to renal function in CRF beyond the suppression of renal hypertension. We conclude that BH is an effective conservative treatment for CRF in cats.

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