

Development of Hypertension and Effects of Benazepril Hydrochloride in a Canine Remnant Kidney Model of Chronic Renal Failure

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(Received 26 July 2007/Accepted 17 January 2008)

ABSTRACT. In order to determine whether hypertension would develop in dogs with chronic renal failure, we performed 7/8 renal ablation in 6 healthy dogs and compared pre- and post-ablation blood pressures determined by telemetry. One month after the renal ablation, blood urea nitrogen and creatinine were significantly increased ($p < 0.05$), creatinine clearance was decreased ($p < 0.05$), and blood pressure was increased significantly ($p < 0.05$). Simultaneously, plasma renin activity, angiotensin I and II, and aldosterone were elevated significantly ($p < 0.05$) compared with the values obtained from 11 healthy dogs with intact renal function. The dogs with induced renal failure and hypertension were administered an angiotensin-converting enzyme inhibitor, benazepril hydrochloride, once daily for 2 weeks at 2 mg/kg body weight, and changes in blood pressure and the renin-angiotensin-aldosterone (RAA) system were determined. During the administration of benazepril hydrochloride, blood pressure, angiotensin II and aldosterone decreased significantly ($p < 0.05$) and, upon discontinuation of administration, increased to the pre-administration levels ($p < 0.05$). Plasma renin activity and angiotensin I showed no significant changes throughout the administration study. These results provide experimental evidence that hypertension develops in dogs with chronic renal failure through mechanisms involving the RAA system and demonstrate that benazepril hydrochloride improves renal hypertension in dogs.

KEY WORDS: angiotensin-converting enzyme inhibitor, benazepril, canine, renal ablation, renal hypertension.

J. Vet. Med. Sci. 70(5): 455–460, 2008

Hypertension is classified into essential and secondary hypertension and, in humans, essential hypertension accounts for 80 to 90% of hypertension patients [24]. In contrast, essential hypertension is relatively rare in veterinary practice [7, 33]. Underlying reasons are that hypertension *per se* has no characteristic symptoms and blood pressure is not routinely determined in veterinary practice. Therefore, it is important to diagnose diseases that would lead to secondary hypertension and to identify the risk of developing secondary hypertension. Causes of secondary hypertension include renoparenchymal diseases, renovascular diseases, diabetes, Cushing syndrome, primary hyperaldosteronism, pheochromocytoma and hypothyroidism and, of those, renoparenchymal disease-associated hypertension is most common in humans [24]. The mechanism of renal hypertension is thought to involve renal insufficiency-associated body fluid retention, increases in cardiac output and peripheral vessel resistance, activation of the renin-angiotensin-aldosterone (RAA) system and suppression of the kallikrein-kinin-prostaglandin system [2, 3, 17].

A link between chronic renal failure and hypertension has been suggested in dogs and cats [1, 6, 12, 13, 22, 26, 27, 29, 30, 34, 36–38]. Activation of the RAA system and development of hypertension in association with renal failure have been reported in cats [20, 30, 41]. In dogs, development of hypertension following partial renal ablation has been described [10, 14]; however, involvement of the RAA sys-

tem has not been verified by measuring the RAA system.

In the present study, we examined whether hypertension would develop in dogs with experimentally induced chronic renal failure and evaluated the potential causal role of the RAA system. Renal ablation was used to prepare a canine model of chronic renal failure, and blood pressure was determined by telemetry, which causes minimum stress and allows continuous around-the-clock measurements. In addition, we administered benazepril hydrochloride, a biliary-excreted angiotensin-converting enzyme (ACE) inhibitor, and evaluated its effects on renal hypertension and the RAA system.

MATERIALS AND METHODS

Animals: The study involved adult mongrel dogs ($n=6$; 3 males and 3 females; body weight 7.0 to 14.5 kg) that showed no abnormalities in general clinical examination, blood biochemistry or urinalysis. The dogs were kept under the previously described conditions [31] with free access to water and meals given at 8:00 to 9:00 and 19:00 to 20:00.

Telemetric blood pressure measurements: Blood pressure was determined by telemetric system as described previously [31]. The catheter of the transmitter for blood pressure measurement (TA11PA-C40; DATA SCIENCE INTERNATIONAL Inc., Tokyo, Japan) was indwelled within the femoral artery, and blood pressure was determined without anesthesia or constraint. Systolic, mean and diastolic blood pressures were determined every 5 min and averaged every 24 hr, and these “24-hr blood pressures” were used for analysis.

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Preparation of chronic renal failure model: Following premedication with atropine sulfate, anesthesia was induced with thiopental sodium and, after tracheal intubation, maintained with isoflurane. Celiotomy was performed *via* abdominal midline incision, and the right kidney was excised. Two to 4 weeks later, the dorsal branches of the renal artery were ligated, followed by ligation of some of the ventral branches to reduce the blood supply to the left kidney by 75% (7/8 renal ablation). Since branching of the renal artery varies from individual to individual, we visually verified infarct areas of the left kidney.

At least 1 month after 7/8 renal ablation, blood urea nitrogen (BUN), serum creatinine (Cr) and creatinine clearance (CCr) were determined to judge the presence or absence of renal failure. BUN and Cr were determined by the enzyme UV method and Jaffe method, respectively, on COBAS MIRA S (Japan Roche, Inc., Tokyo). CCr was determined by 30-min endogenous creatinine clearance method [41]. Dogs were diagnosed with renal failure when BUN and Cr were significantly increased and CCr was significantly decreased from the pre-ablation values.

To evaluate blood pressure, 24-hr blood pressures obtained during the 5-day periods prior to and following 7/8 renal ablation were averaged for systolic, mean and diastolic blood pressures and used for analysis. Hypertension was diagnosed when significant increases were observed in blood pressure.

For the evaluation of the RAA system, plasma renin activity (PRA), circulating angiotensin I concentration (ANG I), angiotensin II concentration (ANG II) and aldosterone concentration (ALD) were determined. In order to avoid the influence of time-dependent changes in the RAA system, blood was sampled between 16:00 and 18:00 as previously described [31]. Following anticoagulation with ethylenediaminetetraacetic acid, blood samples were quickly cooled and centrifuged at 3,000 rpm for 5 min at 4°C. Plasma was stored frozen and subjected to radioimmunoassay (Sumitomo Metal Bioscience Ltd., Tokyo, Japan). PRA was determined by assessing the activity of plasma to produce ANG I by hydrolyzing angiotensinogen and expressed as ng of ANG I produced per ml of plasma per hr (ng/ml/hr). ANG I and II were determined by dextran-charcoal radioimmunoassay, and ALD was measured by solid-phase radioimmunoassay. As a control, the RAA system was also determined in adult mongrel dogs (n=11; 6 males and 5 females) with no abnormalities in general clinical examination, blood biochemistry or urinalysis.

Effects of benazepril hydrochloride in chronic renal failure model: An ACE inhibitor, benazepril hydrochloride (Fortekor TM; Novartis Agro Inc. [presently, Novartis Animal Health Inc.], Tokyo, Japan), was administered orally to the chronic renal failure model dogs with hypertension once daily for 2 weeks at a daily dose of 2 mg/kg body weight.

During the study period, 24-hr blood pressures were obtained for systolic, mean and diastolic blood pressures, and their averages for the 5-day periods prior to and during the administration and following the discontinuation were

compared. The period following the discontinuation was the 5-day period beginning 1 week after the discontinuation. PRA, ANG I and II, ALD, BUN, Cr and CCr were determined on the final day of each period.

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: Values are expressed as means \pm standard deviation (S.D.). Data were subjected to analysis of variance, and values of blood pressure were analyzed by the Student's *t*-test. Other parameters were analyzed by the Mann-Whitney test. Differences were considered significant at $p < 0.05$.

RESULTS

Between pre-7/8 ablation and 1 month after 7/8 renal ablation, BUN and Cr increased significantly from 9.9 ± 2.4 mg/dl to 22.6 ± 5.9 mg/dl and from 0.9 ± 0.2 mg/dl to 2.8 ± 0.5 mg/dl, respectively ($p < 0.05$), and CCr decreased significantly from 2.4 ± 0.5 ml/min/kg to 1.0 ± 0.2 ml/min/kg ($p < 0.05$). Systolic, mean and diastolic blood pressures were significantly increased from 120.4 ± 10.3 mmHg to 152.5 ± 18.9 mmHg, from 87.8 ± 5.1 mmHg to 114.4 ± 14.6 mmHg, and from 71.3 ± 2.7 mmHg to 93.6 ± 11.7 mmHg, respectively ($p < 0.05$) (Fig. 1A). PRA, ANG I and II, and ALD 1 month after 7/8 renal ablation were 6.0 ± 1.4 ng/ml/hr, 7312.8 ± 552.9 pg/ml, 3612.4 ± 1067.3 pg/ml and 230.2 ± 84.5 ng/dl, respectively, and were all significantly higher than the respective values of 1.2 ± 0.9 ng/ml/hr, 474.4 ± 276.4 pg/ml, 184.0 ± 143.2 pg/ml and 5.2 ± 6.5 ng/dl found in healthy dogs (Fig. 1B).

Figure 2A illustrates the changes in blood pressure that occurred during the benazepril administration study. Systolic, mean and diastolic blood pressures were significantly decreased from the pre-administration values of 153.7 ± 12.0 mmHg, 115.9 ± 7.8 mmHg and 95.3 ± 5.6 mmHg to 137.8 ± 12.4 mmHg, 102.0 ± 7.0 mmHg and 82.9 ± 3.6 mmHg, respectively ($p < 0.05$). After benazepril was discontinued, systolic and mean blood pressures were 146.5 ± 11.2 mmHg and 108.7 ± 8.2 mmHg, respectively, and were significantly higher than those during the administration ($p < 0.05$). Diastolic blood pressure increased to 88.5 ± 7.1 mmHg, with no significant difference (Fig. 2A).

Changes in the RAA system occurring between the pre- and post-benazepril administration periods are illustrated in Fig. 2B. PRA and ANG I were 6.3 ± 1.9 ng/ml/hr and 7189.4 ± 611.7 pg/ml, respectively, prior to the administration and 8.1 ± 1.3 ng/ml/hr and 7980.8 ± 2521.6 pg/ml, respectively, during the administration, demonstrating no significant differences. They did not change significantly following the discontinuation at 8.5 ± 3.0 ng/ml/hr and 7291.0 ± 4053.5 pg/ml. In contrast, ANG II and ALD were significantly decreased between the pre- and during administration periods from 4005.0 ± 1559.3 pg/ml to $111.2 \pm$

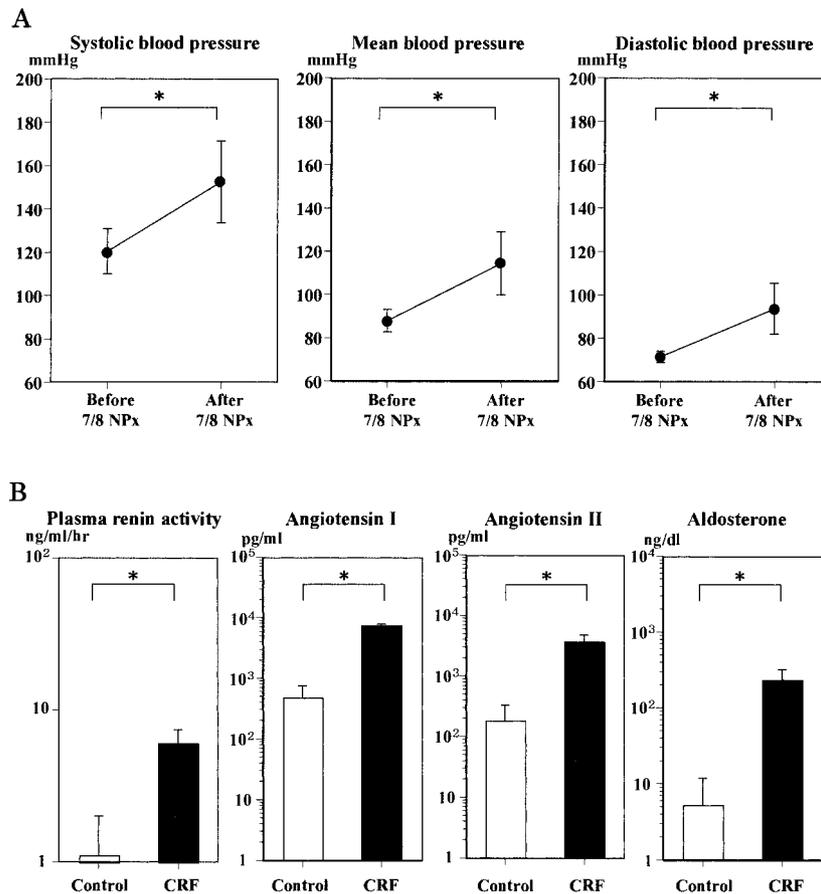


Fig. 1. Systemic blood pressure before and after 7/8 renal ablation and the renin-angiotensin-aldosterone system in dogs with no abnormalities in renal function and dogs with 7/8 renal ablation. A, Systolic, mean and diastolic blood pressures were determined by telemetry before and after 7/8 renal ablation (n=6). Values before (Before 7/8 NPx) and after (After 7/8 NPx) renal ablation are expressed in means \pm S.D. B, Plasma renin activity, angiotensin I and II, and aldosterone were determined by radioimmunoassay in dogs with no abnormalities in renal function (Control; n=11) and those with 7/8 renal ablation (CRF; n=6). Values for both animal groups are expressed in means \pm S.D. Plasma renin activity, angiotensin I and II, and aldosterone are shown in a logarithmic scale. * $p < 0.05$ vs. pre-ablation values or dogs with normal renal function.

106.2 $\mu\text{g/ml}$ and from $212.6 \pm 108.6 \text{ ng/dl}$ to $13.4 \pm 10.8 \text{ ng/dl}$, respectively. Following discontinuation of benazepril, ANG II and ALD were increased significantly to $2304.6 \pm 1657.7 \text{ pg/ml}$ and $337.6 \pm 279.3 \text{ ng/dl}$, respectively ($p < 0.05$) (Fig. 2B). No significant changes were observed in BUN (27.6 ± 4.1 , 30.0 ± 6.3 and $31.6 \pm 10.3 \text{ mg/dl}$ in the pre-, during and post-administration, respectively), Cr (2.4 ± 0.9 , 2.5 ± 1.1 and $2.4 \pm 1.2 \text{ mg/dl}$) or CCr (1.46 ± 0.14 , 1.46 ± 0.14 and $1.48 \pm 0.15 \text{ ml/min/kg}$).

DISCUSSION

Complication of renal diseases with hypertension has been recognized in dogs and cats [1, 12, 22, 26, 27, 34, 37, 38], and 50 to 93% incidence of hypertension have been

reported in dogs with renal diseases [13, 36]. We have also found hypertension in dogs and cats with chronic renal failure [29, 30]. Renal hypertension occurs as a result of renal arterial occlusion, i.e. renovascular hypertension, or secondarily to loss of functioning nephrons. Occurrence of renovascular hypertension in dogs has been verified by the Goldblatt model in which hypertension is induced by constricting the renal arteries [3, 4, 19, 23, 32]. However, in order to consider renal hypertension in small animal practice, more common nephron loss-associated hypertension is important.

Partial renal ablation is used in rats to prepare a model of chronic renal failure, and its procedures include surgical partial removal of the kidneys and artificial renal infarction by ligating branches of the renal arteries [5, 16, 28]. A dog

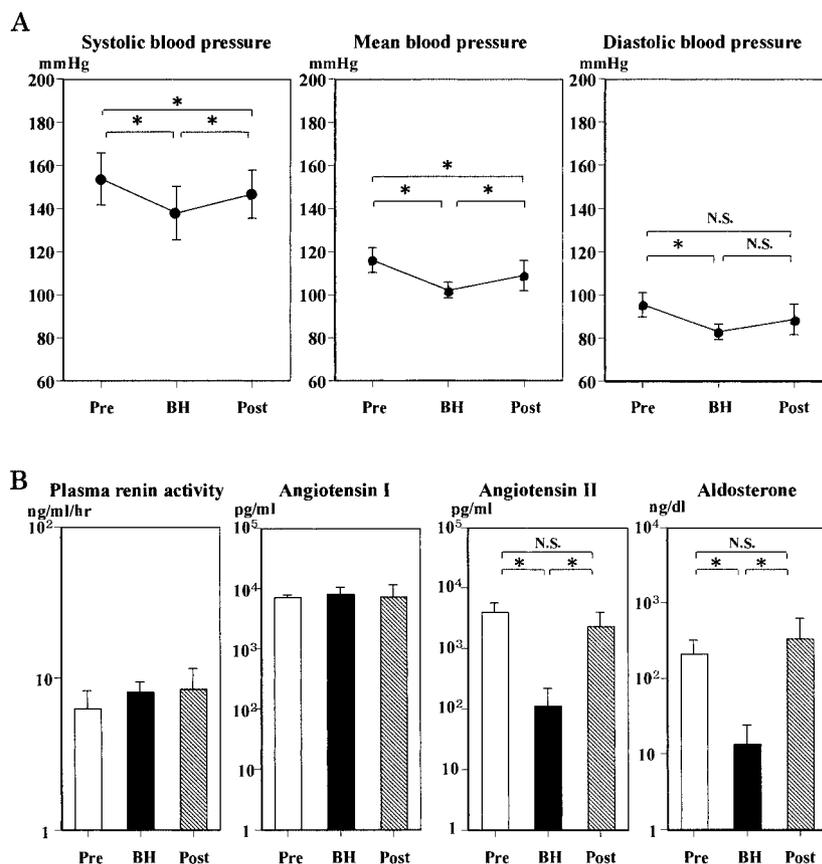


Fig. 2. Effects of benazepril hydrochloride on blood pressure and the renin-angiotensin-aldosterone system in dog models of chronic renal failure. Benazepril hydrochloride (2 mg/kg/day) was orally administered daily for 2 weeks to hypertensive dogs with 7/8 renal ablation (n=6). A, Systolic, mean and diastolic blood pressures were determined continuously by telemetry. B, Plasma renin activity, angiotensin I and II, and aldosterone were determined by radioimmunoassay. Average values are expressed in means \pm S.D. for the 5-day periods before (Pre) and during (BH) administration, and after discontinuation of administration (Post). Plasma renin activity, angiotensin I and II, and aldosterone are shown in a logarithmic scale. * $p < 0.05$. N.S., not significant.

model of renal hypertension has been described using unilateral nephrectomy and 5/6 ablation of the mass of the remaining kidney [14]. In the present study, we created chronic renal failure model by nephrectomizing one kidney and ligating some of the renal arterial branches of the remaining kidney to reduce its blood supply to 1/4 of the original. Furthermore, we employed telemetry, which allows accurate determination of blood pressure in the absence of anesthesia or constraint. We have previously demonstrated that telemetrically acquired 24-hr blood pressure is suitable for evaluating or comparing individual blood pressure in dogs [31].

In the present chronic renal failure model, apparent increases were observed in blood pressure in association with increases in BUN and Cr and a decrease in CCr. In addition, the RAA system was significantly activated compared to that in healthy dogs with no renal problems. These

findings indicate that systemic hypertension was experimentally induced by reducing the functioning nephrons, and suggest that the RAA system was involved in the development of nephron loss associated- hypertension in dogs. Kitagawa *et al.* [21] performed 3/4 renal ablation in healthy dogs and, approximately 1 month later, found increases in BUN and Cr and decreases in renal plasma flow and glomerular filtration rate, while they found no significant changes in oscillometrically determined mean blood pressure. Brown *et al.* [11] found increases in glomerular pressure 1 month after 3/4 renal ablation, but blood pressure was not increased. However, these authors found increases in systolic and diastolic blood pressures 3 months after 11/12 renal ablation [10]. Thus, the development of hypertension may depend on what fraction of functioning nephrons is ablated. Considering these previous findings, we employed 7/8 renal ablation in the present study. We previously

described the occurrence of renal failure and systemic hypertension in cats following 7/8 renal ablation [41].

In order to investigate the effects of inhibiting the RAA system on nephron loss-associated systemic hypertension, we administered benazepril hydrochloride to our canine chronic renal failure model with hypertension. During the administration, PRA and ANG I remained at high levels, whereas ANG II and ALD decreased markedly. These results verify that ACE-catalyzed hydrolysis of ANG I to ANG II was inhibited. In addition, blood pressure decreased significantly without aggravating BUN, Cr or CCr. ACE inhibitors are associated with the risk of acute hypotension and a rapid drop in glomerular filtration rate [25]. Although we used benazepril at 2 mg/kg/day, twice the upper limit of the commonly-used dose, to ensure the drug's pharmacological effects, neither marked decrease in systemic blood pressure nor aggravation of renal function were observed. Kitagawa *et al.* [21] administered benazepril to dogs with renal ablation for 15 days at 10 mg/kg/day, 20-fold the upper limit of the commonly-used dose; however, blood pressure remained at the pre-ablation levels and no improvement was seen in BUN or Cr. Together with the fact that they found no increase in blood pressure in dogs with 3/4 renal ablation, their findings suggest that the RAA system was not activated. In the present study, blood pressure, ANG II and ALD returned to the pre-administration levels after discontinuation of benazepril, indicating that benazepril caused no irreversible changes in the RAA system. Overall, our findings show that benazepril corrected renal injury-associated systemic hypertension by suppressing ANG II production, demonstrating that activation of the RAA system plays a central role in the development of nephron loss associated- hypertension in dogs.

Excessive activation of the RAA system and resulting hypertension play critical roles in the progression of renal failure [35, 42]. Antagonism of the RAA system using ACE inhibitors or ANG receptor blockers corrects hypertension and suppresses the progression of chronic renal failure [5, 8]. Since the advent of ACE inhibitors, various types of ACE inhibitor have been developed and, along with ANG receptor blockers, have become mainstay conservative treatments for chronic renal failure in humans [8, 18, 35, 42]. Effects of such ACE inhibitors as enalapril and benazepril on renal failure are also being recognized in dogs and cats [9, 10, 15]. Benazepril hydrochloride has the merit of being excreted in bile and urine, a characteristic not found in other ACE inhibitors [40]. The clearance of benazeprilat, the effective metabolite of benazepril, increased in dogs with experimentally induced renal failure, whereas clearance was decreased to 40 to 55% for the effective metabolite of enalapril [39]. Studies by Kitagawa *et al.* [21] have shown that benazepril hydrochloride does not accumulate in animals with renal insufficiency, suggesting that benazepril is a safe medication for chronic renal failure in small animals. Our present study also shows that benazepril was associated with neither acute reduction of renal function nor hypotension, and blood pressure recovered to the pre-administration lev-

els after discontinuation of benazepril, further underlining short-lived and reversible actions of benazepril.

The present study verifies that loss of functioning nephrons causes hypertension in dogs in association with activation of the RAA system. Since benazepril hydrochloride manifested depressor effects without affecting renal function, benazepril hydrochloride is an effective medication for hypertension in small animal practice.

ACKNOWLEDGMENT. We are grateful to Novartis Animal Health Inc. for providing us with benazepril hydrochloride.

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