

# Efficacy of Monotherapy with Benazepril, an Angiotensin Converting Enzyme Inhibitor, in Dogs with Naturally Acquired Chronic Mitral Insufficiency

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**ABSTRACT.** Benazepril (BP), an angiotensin convertive enzyme inhibitor, was administered orally once daily for 4 weeks to 31 dogs with mild to moderate (NYHA functional classes II and III) congestive heart failure caused from mitral insufficiency (MI). There were no significant changes in clinical signs, electrocardiogram findings, radiographical observations and plasma biochemical results in 11 dogs treated with placebo for 4 weeks. In 31 dogs treated with BP, appetite increased, and mean scores of heart failure signs, such as activity, exercise tolerance, cough and respiratory effort, were significantly improved. No dog displays signs suggesting systemic hypotension. One dog died suddenly on the 26th day of treatment with BP. This dog had good vigor and appetite till the evening before the death, and cough and exercise tolerance had been gradually improving. The heart rate and ECG parameters of BP treated dogs did not change significantly, but length of long axis of the heart decreased. In plasma biochemical tests, plasma urea nitrogen (UN) levels did not change significantly, and plasma creatinine (CRE) levels increased slightly within the normal ranges during BP trial. Two dogs had higher plasma UN levels with slightly higher plasma CRE levels, but had normal general condition and other biochemical results. Plasma ACE activity decreased to 57.3% of pre-treatment level at 4 weeks after BP treatment. It is concluded that BP monotherapy was efficacious at least in dogs with relatively low grade congestive heart failure caused by MI. — **KEY WORDS:** ACE inhibitor, benazepril, canine, congestive heart failure, mitral insufficiency.

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Angiotensin converting enzyme (ACE) inhibitors are potent vasodilator [6]. In humans and dogs, the effectiveness of ACE inhibitor treatment for hypertension and congestive heart failure has been well established [4, 6, 7, 10], and trials indicate that the drugs improve the quality and duration of life [1–3, 14]. Many ACE inhibitors have been developed, and some are now in use in veterinary medicine. Benazepril (BP) is a new orally active and long acting ACE inhibitor without a sulfhydryl group [11, 12, 18]. The biological action of benazepril is considered to be exerted through benazeprilat, its active metabolite. Benazeprilat is excreted equally via liver and kidney [16]; therefore BP can be used safely also in cases with renal dysfunction.

It is usually recommended that an ACE inhibitor is prescribed together with appropriate doses of digoxin and furosemide in dogs with congestive heart failure caused by dilated cardiomyopathy or mitral insufficiency (MI) [6, 10]. Because the use of an ACE inhibitor is usually recognized as a supportive therapy, there have been no clinical studies on monotherapy with an ACE inhibitor in canine congestive heart failure. The objective of the present study was to evaluate the clinical efficacy and safety of BP monotherapy in dogs with naturally acquired, relatively mild to moderate, congestive heart failure caused by MI.

## MATERIALS AND METHODS

**Dogs:** Experimental dogs are listed in Table 1. All 31 dogs were outpatients of the Veterinary Hospital of Gifu University, and had naturally acquired MI. One dog was

classified into the modified New York Heart Association (NYHA) functional class I, and other 30 dogs were in class II or III [5]. When it was arbitrarily graded on a scale of I to VI [17], the intensity of a heart murmur was in class II/VI to IV/VI. Twenty-one dogs received BP-containing tablets for 4 weeks (BP trial). Ten dogs received placebo tablets for the first 4 weeks (placebo trial), and they were then enrolled into the group administered BP-containing tablets for the next 4 weeks. As the normal control of plasma ACE activity, clinically healthy 12 dogs were used.

**Drug:** BP (Fortecor, Ciba-Geigy Japan Ltd., Tokyo) was administered as tablets containing 5 mg of BP chloride. For placebo, an identical tablet without containing BP was used. Dogs received BP orally at a mean dose of  $0.52 \pm 0.22$  mg/kg (range 0.27 to 1.19 mg/kg) once daily for 4 weeks without concomitant administration of other heart and vascular drugs, such as digitalis, diuretics and other vasodilators. Some additional drugs were used according to other diseases or signs, and these concomitant drugs used with BP are listed in Table 1.

**Procedures:** The MI was diagnosed by a systolic cardiac murmur with auscultation, and abnormal valve action and blood regurgitation findings with 2 dimension and color-doppler echocardiography (EUB-165, Hitachi Medical Corp., Tokyo). Clinical check-up, radiography, electrocardiography (ECG, ECG 8820, Nihon Kohden Co., Ltd., Tokyo) and plasma biochemical tests (Dry-Chem 5,500V and 800V, Fuji Photo-Film Co., Ltd., Tokyo) were performed before and 1, 2, and 4 weeks after treatment. Plasma ACE activity was measured by Kasahara method [15].

Table 1. Outline of experimental dogs at the start of trial

Dog No.	Trial	Breed	Age	Sex	Body weight (kg)	NYHA class	Heart murmur (/VI)	Other diseases or signs	Concomitant drug
3618	BP	Mongrel	11	Female	11.4	II	IV	Gingivitis	None
3619	BP	Dachshund	9	Male	7.4	II	III	No signs	None
3657	BP	Mongrel	9	Male	4.4	II	III	Gingivitis	None
3667	BP	Pomeranian	7	Male	3.1	II	III	Hypothyroidism	Vitamin E, liothyronine
3671	BP	Mongrel	15	Male	11.0	III	IV	Vomit	None
3669	BP	Toy poodle	11	Male	4.5	II	III	No signs	None
3668	BP	Shetland sheepdog	11	Female	8.5	II	II	Gastritis	Famotidine
3690	BP	Chin	12	Male	5.0	II	IV	Otitis externa, urolithiasis, gingivitis	None
3698	BP	Mongrel	9	Female	17.7	III	IV	Gingivitis	None
3714	BP	Mongrel	11	Female	6.9	III	IV	Gingivitis	None
3670	BP	Mongrel	12	Male	4.5	II	III	Gingivitis	None
3724	BP	Pomeranian	10	Male	3.1	II	III	Collapsed trachea	None
3725	BP	Maltese	15	Male	4.7	II	IV	Gingivitis	None
3726	BP	Yorkshire terrier	9	Male	3.0	II	II	No signs	None
3627	BP	Shih Tzu	5	Male	7.5	II	III	Collapsed trachea	None
3728	BP	Maltese	12	Male	4.2	II	III	No signs	None
3739	BP	Mongrel	11	Male	7.8	II	III	Heartworm disease	None
3749	BP	Dachshund	12	Male	10.8	III	IV	Pyrexia, herniated intervertebral discs	Cefalexin, lysozyme
3767	BP	Mongrel	11	Female	10.0	II	III	No signs	None
3768	BP	Toy poodle	9	Female	3.5	II	III	Anal sac disease	BM-GM (topical)
3769	BP	Mongrel	14	Male	7.8	III	III	Cataract, gingivitis	None
3782	PL-BP	Toy poodle	12	Male	2.8	III	IV	Glaucoma, gingivitis	Ampicillin
3827	PL-BP	Toy poodle	13	Male	4.7	III	IV	Cataract, gingivitis	Norfloxacin
3841	PL-BP	Maltese	13	Female	2.7	III	IV	Gingivitis	Enrofloxacin
3846	PL-BP	Maltese	12	Female	2.8	II	III	No signs	None
3847	PL-BP	Mongrel	13	Female	5.3	III	III	Gingivitis, Anal sac disease	Enrofloxacin
3855	PL-BP	Pomeranian	14	Male	2.1	III	III	No signs	None
3877	PL-BP	Mongrel	9	Female	8.7	II	II	Gingivitis	None
3998	PL-BP	Toy poodle	12	Female	4.6	II	II	Anal sac disease, gingivitis	Ampicillin
4006	PL-BP	Shiba dog	12	Male	7.0	I	III	No signs	None
4017	PL-BP	Mongrel	14	Male	10.4	II	IV	No signs	None

BP: Benazepril, PL-BP: placebo then enrolled into benazepril trial. BM-GM: betamethasone and gentamicin.

**Data analysis:** Clinical signs were evaluated with the score schemes (Table 2). Statistical assessment of the mean scores before and after treatment was made with Wilcoxon-Signed ranks test. The data of laboratory tests and ECG were represented as mean  $\pm$  standard deviation (SD), and the paired-Student's *t*-test was employed for the comparison of the data before and after treatment. Differences were considered as significant at a probability value of less than 0.05.

## RESULTS

As shown in Table 2, there were no significant changes in clinical signs during placebo treatment. Appetite increased significantly during the BP trial, and mean scores of clinical signs of heart failure, such as activity, exercise tolerance, cough and respiratory effort, were significantly improved. Activity was improved in 5 dogs, but not changed in the other 26 dogs, those had almost normal activity before and throughout the trial. Exercise tolerance was normal throughout the trial in 14 dogs, was improved in 9 dogs, and did not change in 1 dog, but became transiently worse only in 1 dogs (No. 3657). The other 6

dogs did not take exercise. Cough was not observed in 10 dogs. It decreased in 14 dogs, increased in 2 dogs (Nos. 3668 and 4017), and did not change in 5 dogs. Respiratory effort was improved in 18 dogs, but became transiently worse in 2 dogs (Nos. 3698 and 3767). One or more signs of activity, exercise tolerance, cough and respiratory effort were improved in 24 of 31 dogs (77.4%), became to transiently worse in 4 dogs (12.9%), and did not change in 3 dogs (9.7%). One dog (No. 3668) vomited sometimes before and throughout the trial. Syncope, which had been observed in 2 dogs before the trial, disappeared in 1 dog (No. 3877), but not in another dog (No. 3841). Ascites was not observed in any dog. No dogs displayed signs suggesting systemic hypotension, such as depression, weakness, anorexia and unsteady gait. Body weight tended to decrease in the placebo trial, and increased in the BP trial. During the BP trial, one dog (No. 3728) died suddenly on the 26th treatment day. This dog had good vigor and appetite till the evening before the death, and cough and exercise tolerance had been gradually improving.

As shown in Table 3, heart rate and other ECG parameters did not change significantly both in the placebo and BP trials. There were no obvious changes in heart ventricular

Table 2. Clinical signs

Sign	Trial		Before		1 week		2 weeks		4 weeks
Appetite	Placebo	10	2.20 ± 0.63	10	2.00 ± 0.67	10	1.90 ± 0.57	10	2.00 ± 0.67
	BP	31	1.90 ± 0.47	31	2.23* ± 0.43	31	2.29** ± 0.46	30	2.20* ± 0.41
Thirsty	Placebo	10	2.20 ± 0.63	10	1.80 ± 0.42	10	2.10 ± 0.32	10	1.90 ± 0.30
	BP	31	2.00 ± 0.45	31	2.10 ± 0.40	31	2.10 ± 0.30	31	2.10 ± 0.30
Activity	Placebo	10	2.00 ± 0.67	10	2.00 ± 0.67	10	2.00 ± 0.67	10	2.00 ± 0.67
	BP	31	1.32 ± 0.65	31	1.19 ± 0.48	31	1.16* ± 0.37	30	1.17* ± 0.38
Exercise tolerance	Placebo	10	2.18 ± 0.90	10	2.18 ± 1.08	10	2.00 ± 1.10	10	1.91 ± 1.04
	BP	25	1.68 ± 0.95	25	1.32 ± 0.75	25	1.24* ± 0.66	24	1.17** ± 0.56
Cough	Placebo	10	2.00 ± 1.15	10	2.10 ± 1.20	10	1.90 ± 1.00	10	2.00 ± 1.15
	BP	31	2.03 ± 1.02	31	1.94 ± 1.00	31	1.80 ± 1.00	30	1.63* ± 1.00
Respiratory effort	Placebo	10	2.10 ± 1.20	10	2.10 ± 1.20	10	2.00 ± 1.10	10	2.20 ± 1.14
	BP	31	1.87 ± 0.88	31	1.68 ± 0.75	31	1.40** ± 0.70	30	1.10** ± 0.31
Cardiac murmur	Placebo	10	3.05 ± 0.96	10	3.10 ± 1.00	10	3.10 ± 1.00	10	3.15 ± 0.75
	BP	31	3.18 ± 0.65	31	3.10 ± 0.70	25	3.10 ± 0.70	30	2.97 ± 1.09

Data are expressed as No. of dogs and mean score ± SD, BP: benazepril.

\*, \*\*: Significantly different from the value before treatment. Asterisk indicates with  $P < 0.05$  and  $P < 0.01$ , respectively. Score = Appetite (1: decrease, 2: no change, 3: increase); thirst (1: decrease, 2: no change, 3: increase); activity (1: normal, 2: responsive but relatively low activity, 3: low activity and weak response, 4: without response and action); exercise tolerance (1: normal, 2: tachypnoea or cough with hard exercise, 3: tachypnoea or stop moving with light exercise, 4: refusal to move); cough (1: not observed, 2: moderately with hard exercise, 3: moderately with light exercise or rest, 4: frequent with light exercise or rest); respiratory effort (1: not observed, 2: moderate with hard exercise, 3: moderate with light exercise or rest, 4: frequent with light exercise or rest); cardiac murmur: grading according to Levine's classification [17].

sizes on radiograms. However, as shown in Fig. 1, mainstem bronchial compression was improved in 23 of 30 dogs (76.7%) from 1 or 2 weeks after start of BP treatment. On heart sizes (Table 4), length of long axis decreased significantly, but that of short axis did not change.

Table 5 shows changes in plasma biochemical test results. There were no significant changes in laboratory test results during the placebo trial. Throughout the placebo trial, one

dog (No. 3855) had a high plasma urea nitrogen (UN) level (78 mg/dl to 100 mg/dl) with slightly higher plasma creatinine (CRE, 1.4 to 1.7 mg/dl) and potassium (K, 4.5 mEq/l to 5.2 mEq/l) levels, but vigor, appetite and activity were almost normal. On the BP trial, plasma UN levels did not change significantly, but plasma CRE levels increased slightly. One dog (No. 3668) had a slightly higher plasma UN level (37 mg/dl) before BP treatment. In this dog, the

Table 3. Heart rate and ECG parameters

Variable	Trial	Before		1 week		2 weeks		4 weeks	
Heart rate (beat/min)	Placebo	10	152	10	144	10	141	10	148
			$\pm 27$		$\pm 19$		$\pm 23$		$\pm 22$
			116 to 200		120 to 185		103 to 177		116 to 185
BP	BP	31	157	31	160	24	159	30	157
			$\pm 37$		$\pm 33$		$\pm 33$		$\pm 37$
			107 to 267		108 to 242		122 to 283		100 to 283
p time (msec)	Placebo	10	57	10	57	10	56	10	57
			$\pm 13$		$\pm 10$		$\pm 9$		$\pm 4$
			40 to 80		46 to 74		40 to 66		54 to 60
BP	BP	25	51	25	53	25	53	22	53
			$\pm 8$		$\pm 14$		$\pm 12$		$\pm 10$
			36 to 68		36 to 96		36 to 86		36 to 66
p-Q time (msec)	Placebo	10	64	10	85	10	82	10	90
			$\pm 12$		$\pm 11$		$\pm 12$		$\pm 9$
			74 to 106		66 to 100		60 to 100		80 to 100
BP	BP	25	64	25	62	25	60	25	62
			$\pm 24$		$\pm 23$		$\pm 22$		$\pm 25$
			22 to 100		32 to 100		32 to 100		26 to 120
QRS time (msec)	Placebo	10	73	10	75	10	76	10	66
			$\pm 14$		$\pm 13$		$\pm 13$		$\pm 9$
			60 to 100		60 to 100		60 to 100		60 to 80
BP	BP	22	64	22	64	22	63	22	66
			$\pm 9$		$\pm 11$		$\pm 12$		$\pm 12$
			44 to 82		44 to 86		38 to 88		44 to 100
p altitude (mV)	Placebo	10	0.39	10	0.35	10	0.39	10	0.37
			$\pm 0.14$		$\pm 0.09$		$\pm 0.11$		$\pm 0.10$
			0.10 to 0.57		0.27 to 0.50		0.23 to 0.53		0.20 to 0.57
BP	BP	25	0.32	25	0.32	25	0.32	25	0.31
			$\pm 0.10$		$\pm 0.09$		$\pm 0.09$		$\pm 0.10$
			0.16 to 0.57		0.18 to 0.57		0.15 to 0.53		0.15 to 0.57
R altitude (mV)	Placebo	10	2.03	10	1.66	10	2.04	10	2.03
			$\pm 0.72$		$\pm 0.35$		$\pm 0.50$		$\pm 0.52$
			1.37 to 3.53		1.23 to 2.37		1.23 to 2.63		1.53 to 3.20
BP	BP	25	1.80	25	1.68	25	1.68	25	1.72
			$\pm 0.66$		$\pm 0.54$		$\pm 0.60$		$\pm 0.62$
			0.55 to 3.20		0.50 to 2.50		0.54 to 2.70		0.42 to 2.73
Mean axis (degree)	Placebo	10	76.9	10	70.4	10	57.7	10	61.4
			$\pm 26.0$		$\pm 31.2$		$\pm 18.1$		$\pm 13.7$
			56 to 133		30 to 124		35 to 84		39 to 80
BP	BP	25	48.2	25	58.9	25	54.0	25	47.4
			$\pm 51.8$		$\pm 26.9$		$\pm 46.3$		$\pm 32.2$
			-169 to 117		3 to 127		-120 to 164		-50 to 106

Data are expressed as No. of dogs, mean  $\pm$  SD and minimum to maximum values, BP: benazepril

UN level decreased to 23 mg/dl at 1 week, but increased to 60 mg/dl and 74 mg/dl at 2 weeks and 4 weeks after, respectively. However, this dogs showed good vigor and appetite, and had normal other biochemical test results with slightly higher plasma CRE levels (1.2 mg/dl to 1.6 mg/dl). In another dog (No. 3855) with higher plasma UN level (from 78 mg/dl to 100 mg/dl) during the placebo trial, the level decreased from 91 mg/dl at the beginning of BP trial to 40 mg/dl after 1 week, but increased to 109 mg/dl and 99 mg/dl at 2 weeks and 4 weeks, respectively. Plasma CRE levels were 1.4 mg/dl, 1.6 mg/dl, 1.7 mg/dl, and 1.2 mg/dl before and at 1, 2 and 4 weeks, respectively. Plasma sodium and chloride concentrations decreased slightly, but potassium level did not change significantly. As shown in Table 6, mean plasma ACE activity was  $5.3 \pm 1.2$  IU/L in

12 control dogs. Plasma ACE activities at the start of trial were significantly ( $P < 0.01$ ) higher in the placebo and BP groups than in the control dogs. The activities did not change during placebo trial, and decreased significantly ( $P < 0.01$ ) at 1, 2 and 4 weeks of BP trial. Mean activity at 4 weeks was 57.3 % of pre-treatment level.

## DISCUSSION

Inhibition of ACE decreases arterial and ventricular filling pressures, and peripheral vascular resistance, and increases cardiac output [4, 13]. The rationale for using ACE inhibitors in congestive heart failure is the facilitation of ventricular emptying by reducing the peripheral vascular resistance [6]. The beneficial effect of BP on myocardial

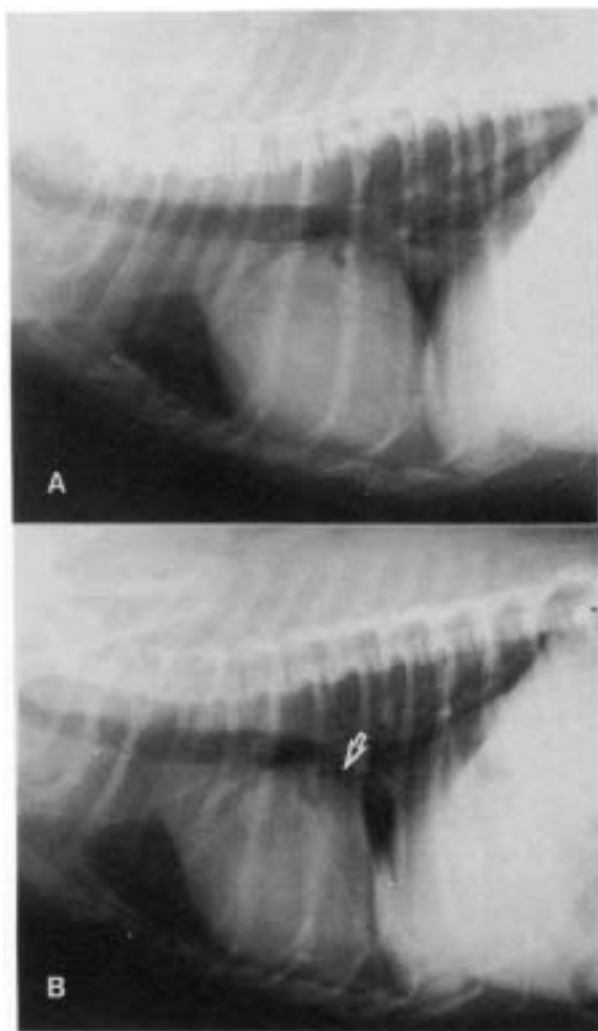


Fig. 1. Radiographs of No. 3657 dog before (A) and at 2 weeks after (B) BP trial. Compared with A, the mainstem bronchial compression is improved as allows in B.

performance may be due to reduction of total peripheral resistance, which causes a decrease in the wall tension of the left ventricle and myocardial oxygen consumption [13, 15]. Most dogs used in the present study belonged to mild to moderate classes of NYHA heart failure classification (classes II and III). During BP treatment, clinical signs of heart failure were improved in 24 of 31 dogs (77.4%). Therefore, it is considered that BP monotherapy was efficacious at least in dogs with congestive heart failure of relatively low grade from MI. No significant changes were found in ECG data. However, decreases in mainstem bronchial compression and length of long axis of the heart in radiography, suggesting reduction of left atrial expanding, were observed. The treatment might induce vascular dilatation and decrease in venous blood return to the heart [8].

Adverse effects of ACE inhibitors include systemic hypotension, renal dysfunction, gastro-intestinal upsets

(vomiting, diarrhea, and anorexia), and hyperkalemia. Azotemia may result from functional renal insufficiency in conjunction with ACE-inhibitor therapy [6]. In the present study, signs suggesting hypotension were not observed in any dog through trial. One dog (No. 3668) showed cough, vomit, and azotemia. In this dog, however, signs of cough and vomiting and slightly higher plasma UN and CRE levels had been observed already before treatment. Plasma UN levels decreased 1 week after, then increased from 2 weeks after BP treatment, but plasma CRE and K levels increased slightly, and activity and appetite of the dog were very good. Another azotemic dog (No. 3855) had a higher plasma UN level with slightly higher plasma CRE and K levels during the placebo trial, and these variables did not increase during the BP trial. These observations suggested pre-renal azotemia, and it was not clear that the azotemia was due to an adverse reaction of BP treatment. Plasma CRE level increased slightly during the BP trial. However, the levels were within the normal ranges, and those were not significant clinically. One dog (No. 3728) died suddenly on the 26th day of treatment with BP. In humans treated with ACE inhibitors, a relationship between decreased ventricular ectopy and sudden death, and reduced norepinephrine release has been suggested [6]. This dog had showed good vigor and appetite till the evening of the death. Cough, exercise tolerance and activity improved. The cause of the death was unknown, because the episode was during trip with his owner. From references [3] and our clinical experiences, sudden death might happen in dogs with MI.

The beneficial results presented in this study suggest that BP monotherapy is one of the first-choices for management of dogs with mild to moderate congestive heart failure caused from MI. Besides, in dogs with signs of more severe heart failure like as NYHA class IV, concomitant use of ACE inhibitor, diuretic, digoxin and other vascular dilators must be considered, because it has been considered that an ACE inhibitor showed higher efficacy combined with these drugs in human patients with hypertension and heart failure [1, 14]. However, combined use of an ACE inhibitor and a diuretic have potential adverse reactions [6, 7]. A trial of BP in combination with diuretics and/or cardionics is needed in dogs with more severe heart failure.

## REFERENCES

1. Captopril Multicenter Research Group 1983. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *J. Am. Coll. Cardiol.* 2: 755-763.
2. The CONSENSUS Trial Study Group 1987. Effects of enalapril on mortality in severe congestive heart failure: Results of the cooperative North Scandinavian enalapril survival study (CONSENSUS). *New Engl. J. Med.* 316: 1429-1435.
3. The COVE Study Group 1995. Controlled clinical evaluation of enalapril in dogs with heart failure: Results of the cooperative veterinary enalapril study group. *J. Vet. Int. Med.* 9: 243-252.
4. Cody, R. J. 1984. Haemodynamic responses to specific renin-

Table 4. Heart size

Variable	Trial	Before		1 week		2 weeks		4 weeks	
Long axis (mm)	Placebo	10	67.5 ± 15.1 50 to 102	10	68.5 ± 15.7 51 to 104	10	68.8 ± 15.2 5 to 104	10	69.2 ± 16.1 50 to 106
		25	73.2 ± 16.2 50 to 107	25	70.9** ± 16.4 48 to 108	25	71.7** ± 15.9 49 to 105	25	72.2* ± 16.9 47 to 107
	BP	25	66.1 ± 14.3 45 to 101	25	66.2 ± 16.1 41 to 107	25	66.5 ± 15.3 44 to 105	25	66.0 ± 16.1 42 to 108
		25	66.1 ± 14.3 45 to 101	25	66.2 ± 16.1 41 to 107	25	66.5 ± 15.3 44 to 105	25	66.0 ± 16.1 42 to 108
Short axis (mm)	Placebo	10	62.4 ± 13.1 46 to 94	10	61.9 ± 12.9 46 to 94	10	62.9 ± 13.8 44 to 96	10	62.8 ± 13.3 45 to 94
		25	66.1 ± 14.3 45 to 101	25	66.2 ± 16.1 41 to 107	25	66.5 ± 15.3 44 to 105	25	66.0 ± 16.1 42 to 108
	BP	25	66.1 ± 14.3 45 to 101	25	66.2 ± 16.1 41 to 107	25	66.5 ± 15.3 44 to 105	25	66.0 ± 16.1 42 to 108
		25	66.1 ± 14.3 45 to 101	25	66.2 ± 16.1 41 to 107	25	66.5 ± 15.3 44 to 105	25	66.0 ± 16.1 42 to 108

Data are expressed as No. of dogs, mean ± SD and minimum to maximum values. BP: benazepril.

\*, \*\*: Significantly different from the value before treatment. Each asterisk indicates  $P < 0.05$  and  $P < 0.01$ , respectively.

- angiotensin inhibitors in hypertension and congestive heart failure. *Drug* 28: 144–169.
- Ettinger, S. J. 1989. Valvular heart disease. pp. 1031–1050. *In: Textbook of Veterinary Internal Medicine. Diseases of the Dog and Cat*, 3rd ed. (Ettinger, S. J. and Feldman, E. C. eds.), W. B. Saunders, Philadelphia.
- Fox, P. R. and Sisson, D. D. 1995. Angiotensin-converting enzyme inhibitors. pp. 786–791. *In: Kirk's Current Veterinary Therapy. XII. Small Animal Practice* (Bonagura, J. D. ed.), W. B. Saunders, Philadelphia.
- Gavras, H. and Gavras, I. 1988. Angiotensin converting enzyme inhibitors. Properties and side effects. *Hypertension* 11: II-37-II-41.
- Ishibashi, T., Tatebe, S., Mitomi, A., Tanaka, M., and Imai, S. 1991. Hemodynamic effects of benazepril, an angiotensin-converting enzyme inhibitor, as studied in conscious normotensive dogs. *Cardiovasc. Drug Therapy* 5: 635–642.
- Kasahara, Y. and Ashihara, Y. 1981. Colorimetry of angiotensin-I converting enzyme activity in serum. *Clin.Chem.* 27: 1922–1925.
- Keene, B. W. and Bonagura, J. D. 1995. Therapy of heart failure. pp. 780–786. *In: Kirk's Current Veterinary Therapy. XII. Small Animal Practice* (Bonagura, J. D. ed.), W. B. Saunders, Philadelphia.
- King, J. N., Mauron, C., and Kaiser, G. 1995. Pharmacokinetics of the active metabolite of benazepril, benazeprilat, and inhibition of plasma angiotensin-converting enzyme activity after single and repeated administrations to dogs. *Am. J. Vet. Res.* 56: 1620–1628.
- Kuroda, K., Fukuda, Y., Nakao, K., and Inukai, T. 1990. Antihypertensive mechanism of action of the novel angiotensin converting enzyme inhibitor benazepril. *Arzneim. Forsch/Drug Res.* 40: 968–973.
- Nakazawa, M., Suwanobori, T., Iwasaki, K., and Imai, S. 1991. Hemodynamic effects of benazeprilat in the anesthetized dog with acute ventricular failure. *Jpn. J. Pharmacol.* 56: 369–375.
- SOLVED Investigators 1992. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. *Circulation.* 86: 431–438.
- Sonnenblick, E. H. and LeJemtel, T. H. 1989. Pathophysiology of congestive heart failure. *Am. J. Med.* 87: 88S–91S.
- Waldmeier, F. and Schmid, K. 1989. Disposition of [ $^{14}$ C]-benazepril hydrochloride in rat, dog and baboon. Absorption, distribution, kinetics, biotransformation and excretion. *Arzneim.-Forsch/Drug Res.* 39: 62–67.
- Ware, W. A. 1995. Abnormal heart sounds and heart murmurs. pp. 86–89. *In: Textbook of Veterinary Internal Medicine. Diseases of the Dog and Cat*, 4th ed. (Ettinger, S. J. and Feldman, E. C. eds.), W. B. Saunders, Philadelphia.
- Webb, R. L., Miller, D., Traina, V., and Gomez, H. J. 1990. *Benazepril. Cardiovasc. Drug Rev.* 8: 89–104.

Table 5. Biochemical test results

Variable	Trial	Before		1 week		2 weeks		4 weeks	
Urea nitrogen (mg/dl)	Placebo	10	24.8	10	24.6	10	24.7	10	25.7
			$\pm 21.2$		$\pm 22.7$		$\pm 27.5$		$\pm 24.2$
			7.6 to 77.5		9.0 to 86.4		7.5 to 99.8		10.9 to 90.6
	BP	31	21.9	31	22.2	25	23.0	30	23.0
			$\pm 15.3$		$\pm 14.7$		$\pm 20.8$		$\pm 19.1$
			9.8 to 90.6		5.9 to 44.1		6.8 to 109		86 to 99.2
Creatinine (mg/dl)	Placebo	10	0.83	10	0.88	10	0.85	10	0.80
			$\pm 0.53$		$\pm 0.44$		$\pm 0.46$		$\pm 0.35$
			0.4 to 1.7		0.4 to 1.7		0.3 to 1.7		0.3 to 1.4
	BP	31	0.77	31	0.85*	25	0.86*	30	0.83*
			$\pm 0.30$		$\pm 0.30$		$\pm 0.40$		$\pm 0.30$
			0.3 to 1.4		0.5 to 1.6		0.4 to 1.7		0.4 to 1.5
ALT (IU/l)	Placebo	10	44	10	69	10	52	10	53
			$\pm 24$		$\pm 73$		$\pm 46$		$\pm 32$
			14 to 83		18 to 273		12 to 175		15 to 102
	BP	31	57	31	59	25	45	30	63
			$\pm 47$		$\pm 46$		$\pm 27$		$\pm 53$
			4 to 222		2 to 231		5 to 108		5 to 231
ALP (IU/l) (msec)	Placebo	10	268	10	236	10	234	10	207
			$\pm 401$		$\pm 295$		$\pm 257$		$\pm 163$
			68 to 1397		59 to 1057		87 to 951		52 to 609
	BP	28	162	28	189	25	180	28	180
			$\pm 118$		$\pm 153$		$\pm 104$		$\pm 128$
			11 to 609		20 to 555		41 to 419		39 to 528
Sodium (mEq/l)	Placebo	10	144	10	147	10	147	10	147
			$\pm 9$		$\pm 3$		$\pm 2$		$\pm 2$
			120 to 150		143 to 152		143 to 150		144 to 151
	BP	31	148	31	145**	25	146**	30	146*
			$\pm 3$		$\pm 4$		$\pm 3$		$\pm 4$
			140 to 154		131 to 151		139 to 151		133 to 152
Potassium (mEq/l)	Placebo	10	3.8	10	4.2	10	4.0	10	4.1
			$\pm 0.7$		$\pm 0.5$		$\pm 0.4$		$\pm 0.2$
			2.5 to 5.2		3.4 to 4.9		3.7 to 4.7		3.7 to 4.5
	BP	26	3.9	26	4.1	25	4.0	26	3.9
			$\pm 0.4$		$\pm 0.3$		$\pm 0.4$		$\pm 0.3$
			3.0 to 4.6		3.3 to 4.6		3.2 to 4.8		3.2 to 4.5
Chloride (mEq/l)	Placebo	10	108	10	111	10	112	10	111
			$\pm 9$		$\pm 3$		$\pm 2$		$\pm 4$
			85 to 116		108 to 115		109 to 116		104 to 115
	BP	31	112	31	110*	25	110*	30	111
			$\pm 4$		$\pm 4$		$\pm 3$		$\pm 5$
			103 to 121		102 to 118		104 to 115		100 to 119

Data are expressed as No. of dogs, mean  $\pm$  SD and minimum to maximum values, BP: benazepril.

\*, \*\*: Significantly different from the value before treatment. Asterisk indicates  $P < 0.05$  and  $P < 0.01$ , respectively.

Table 6. Plasma ACE activity

Variable	Trial	Before		1 week		2 weeks		4 weeks	
ACE (IU/l)	Control	12	5.3 ± 1.2 3.6 to 7.4						
	Palaebro	10	6.9 ± 2.3 4.1 to 10.6	10	7.8 ± 2.4 4.1 to 11.2	10	8.1 ± 2.8 4.5 to 12.9	10	8.1 ± 2.3 5.5 to 12.1
	BP	25	7.5 ± 2.4 4.2 to 13.7	25	5.0** ± 2.3 0.5 to 9.3	25	5.4** ± 2.8 0.5 to 9.9	25	4.3** ± 2.6 1.0 to 9.2

Data are expressed as No. of dogs, mean ± SD and minimum to maximum values.  
Control: Clinically healthy 12 dogs, BP: benazepril.

\*, \*\*: Significantly different from the value before treatment. Asterisk indicates  $P<0.05$  and  $P<0.01$ , respectively.