DIFFERENT EFFECTS OF CAPTOPRIL ON BLOOD PRESSURE IN THE ACUTE AND CHRONIC TWO-KIDNEY GOLDBLATT HYPERTENSIVE DOGS

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Captopril was administered to acute (8 to 14 days after unilateral renal artery constriction) and chronic (71 to 127 days after the constriction) two-kidney Goldblatt hypertensive dogs, and to normotensive ones for 21 days (oral administration of 10, 20 and 40 mg/kg/day, consecutively each 7-day period). The decrease of arterial blood pressure was remarkable in hypertensive animals with high plasma renin activity, but not in the normotensive animals. In the acute stage of hypertension, the antihypertensive effect of captopril was dose-dependent and persistent even after its cessation. In the chronic stage of hypertension, blood pressure also decreased, but the response was not dose-dependent and did not continue after cessation. Plasma renin activity rose in both hypertensive and normotensive animals during the treatment with captopril. There were no significant changes in heart rate, daily urinary volume, sodium balance, and renal clearances of sodium (C_{Na}), potassium (C_K), chloride (C_{Cl}) and creatinine (C_{Cr}). Circulating blood volume was also not altered. These results indicate that the main mechanism of antihypertensive effect of captopril in two-kidney Goldblatt hypertensive dogs is an inhibition of the angiotensin converting enzyme. In addition, the different effects in the acute and chronic hypertensive dogs suggest that some differences exist in the mechanism(s) of maintaining blood pressure between the two stages of two-kidney Goldblatt hypertension in dogs.

THE effects of captopril have been studied extensively not only in animals^{1,2} but also in normal volunteers^{3,4} and in patients with various types of hypertension⁵⁻⁸. Investigations have also been made in genetically hypertensive rats⁹⁻¹¹ and in experimentally developed hypertensive animals: one-kidney, one clip renal hypertensive rats and dogs,^{12,13} two-kidney, one clip renal hypertensive rats^{11,14,15} and two-kidney

perinephritic hypertensive dogs.¹⁶ It has been reported that the hypotensive effect of captopril is closely related to the level of plasma renin activity^{6,17}. In other reports, however, no correlation has been found between plasma renin activity and the hypotensive effect of this agent^{5,7,8}. Captopril was reported to cause no reduction of blood pressure in normotensive man,³ but it induced a marked decrease of blood pressure in normotensive animals.² An augmented level of endogenous kinins by an inhibition of kininase II, which is identical with the angiotensin converting enzyme, was also con-

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sidered to have a role in the hypotensive mechanisms of captopril^{18,19}

Captopril is a useful pharmacological tool for the analysis of the role of the renin-angiotensin system in many biological processes. Thus, the role and participation of the renin-angiotensin system in the maintenance of blood pressure have been extensively investigated with captopril using experimental hypertensive animals.^{12,17,20}

We studied the antihypertensive effect of captopril in two-kidney Goldblatt hypertensive dogs (one renal artery constricted, contralateral kidney left intact), comparing its effects in the acute and chronic stages.

METHODS

Two-kidney Goldblatt Hypertension in Dogs

Twelve female beagles weighing 10 to 13 kg were fed commercial dog meal at 16:00 every day, with a daily intake of 32 mEq of sodium and 20 mEq of potassium, and were given tap water freely. They were trained to sit quietly on the experimental stand during observation. The animals were anesthetized with 30 mg/kg of intravenous pentobarbital sodium and then a polyethylene tube (Intramedic, PE 100) was implanted in the right femoral artery for the measurement of arterial blood pressure, the other end being exposed at the back in the interscapular area. The tube was filled with sterile heparin solution (100 U/ml) to prevent blood coagulation. Aminobenzyl penicillin sodium (250 mg/day i.m.) was administered for 5 days.

After the animals recovered from the operation, arterial blood pressure and heart rate were measured at 10:00 every morning. The blood pressure was measured by a pressure transducer (Statham, P23Db) and heart rate by a tachometer (San-ei, 2140), and were recorded using a pen-writing oscillograph (San-ei, Recti Horiz 8S). After waiting several days for confirming the stabilization of these parameters, about 3 ml of arterial blood sample was taken at 10:30 for the determination of plasma renin activity and plasma levels of electrolytes (sodium, potassium and chloride) and of creatinine. Daily urinary volume was measured at 16:00 and urinary concentrations of the electrolytes and creatinine were also determined. Thus, the control daily sodium balance was confirmed (fecal sodium excretion was ignored) and renal clearance of sodium (C_{Na}), potassium (C_K), chloride (C_{Cl}) and creatinine (C_{Cr}) were calculated.

The animals were anesthetized again with pentobarbital sodium, and the left renal artery was exposed *via* retroperitoneal approach and constricted with silk thread to decrease renal blood flow by 75% while measuring the blood flow by an electromagnetic flow meter (Narco, RT-500). Arterial pressure, heart rate and urinary volume were measured every day and daily sodium balance was determined. Plasma renin activity and renal clearances were measured on the day before the operation and 1, 3, 7 and 10 days after the operation. Blood pressure, heart rate, urinary volume and sodium balance after the constriction of the renal artery were compared with preoperative control values expressed as the mean values of these parameters during the 5 days preceding the operation. When a high level of mean blood pressure above 120 mmHg was sustained over a 7-day period, hypertension was regarded as established.

Circulating blood volume was measured 4 days before and 4 to 7 days after the operation by the Evans blue diluting method.

Administration of Captopril to Dogs with Acute Hypertension

Eight acute hypertensive dogs were used. During the 5 days of control observation, arterial pressure, heart rate, urinary volume and sodium balance were measured every day and the mean value of each parameter was used as the control value. The control observation of plasma renin activity and renal clearances was performed on the day just before the beginning of captopril treatment. Then captopril was administered orally at 10:30 every day after the measurements of arterial pressure and heart rate for 21 days: 10 mg/kg/ day for the first 7 days and 20 and 40 mg/kg/ day for each of the following 7 days. Daily urinary volume and sodium balance were measured. The clearances of the electrolytes and creatinine and plasma renin activity were estimated. The observation was continued for 7 days following the cessation of captopril. Circulating blood volume was measured on the 7th day of the captopril treatment of 40 mg/kg/day and was compared with that in the control period.

Administration of Captopril to Dogs with Chronic Hypertension

After study in the acute stage, the animals with unilateral constriction of the renal artery were maintained in an ordinary condition with-

TABLE I CHANGES IN BLOOD PRESSURE (BP), PLASMA RENIN ACTIVITY (PRA) AND CIRCULATING BLOOD VOLUME (BV) BEFORE AND AFTER CONstriction OF THE LEFT RENAL ARTERY IN DOGS

	Before	After constriction of the left renal artery (days)						Normotensive dogs	
		1	3	7	10	8-14	71-127		
B P (mmHg)	systolic	163 ± 3	185 ± 5**	194 ± 8**	181 ± 11*	183 ± 8*	182 ± 6*	176 ± 10*	159 ± 4
	diastolic	93 ± 4	102 ± 4**	105 ± 4**	92 ± 4	98 ± 5	98 ± 4*	97 ± 3	84 ± 3
	mean	103 ± 5	128 ± 4**	134 ± 2***	125 ± 4**	123 ± 5*	127 ± 2**	127 ± 3**	108 ± 2
		(8)	(8)	(8)	(8)	(5)	(8)	(5)	(4)
P R A (ng Ag I/ml/hr)	0.72 ± 0.35 (8)	4.01 ± 1.00* (8)	3.06 ± 0.33** (8)	1.67 ± 0.28* (8)	1.18 ± 0.32* (5)	1.28 ± 0.32* (8)	0.68 ± 0.31 (5)	0.75 ± 0.17 (4)	
B V (ml/kg)	86.4 ± 3.6 (4)		88.9 ± 6.5 (4)	(4-7 days after the operation)		85.3 ± 7.5 (4)	106.9 ± 8.2 (4)	77.4 ± 4.8 (4)	

Values are presented as means ± standard errors. Numbers in parentheses indicate numbers of observations.
*: $p < 0.05$, **: $p < 0.01$ and ***: $p < 0.001$ in comparison with values obtained before the operation.

out any drug. Seventy-one to 127 days after the operation, 5 hypertensive animals were used for the study in the chronic stage of two-kidney Goldblatt hypertension. They were given the same drug protocol as that in the acute stage. Blood pressure, heart rate, daily urinary volume, plasma renin activity, daily sodium balance, C_{Na} , C_K , C_{Cl} , C_{Cr} and circulating blood volume were measured.

Control Study in Normotensive Dogs

Four normotensive dogs with an indwelling catheter were used. Sham-operation was not performed. They were administered captopril according to the same protocol as that in the hypertensive animals and the effects of captopril on the above-mentioned parameters were observed.

Biochemical Analyses and Determination of Circulating Blood Volume

Plasma renin activity was measured by the radioimmunoassay method of Haber et al.²¹ using a commercial assay kit (Renin RIA kit, Dinabot, Tokyo) and expressed as ng angiotensin I formation per ml of plasma per hour. The concentration of sodium and potassium in plasma and urine was measured by a flame photometer (Hitachi, 205D) and that of chloride was determined by coulometric titration using a chloride counter (Hiranuma, CL-3). The measurement of creatinine level was performed by Folin-Wu method using a commercial test kit (Wako, Creatinine-Test).

Circulating blood volume was measured using the Evans blue diluting method as detailed previously by Nakanishi.²² The first sample of 2 ml of heparinized venous blood was collected from the cephalic vein for the blank test. Then 0.4 mg/kg of Evans blue was injected intravenously. Ten and 30 min after the injection of the dye, the 2nd and the 3rd samples of 2 ml of venous blood were taken from the other cephalic vein. These samples were centrifuged ($1,700 \times g$ for 10 min) and each one ml of the supernatant was diluted with 4 ml of saline. The concentration of the dye was measured by means of a spectrophotometer (Shimazu, DM-3A, wave length = 620 nm). The plasma concentration of the dye was determined as the mean value of the 2nd and the 3rd samples. Thus, the circulating blood volume was calculated as follows:

Fig. 1. A: Blood pressure (BP: systolic, diastolic and mean arterial blood pressure), heart rate (HR), plasma renin activity (PRA), B: daily urinary volume (UV), daily sodium balance (Na Bal.), renal clearances of sodium (CNa), potassium (CK), chloride (CCl) and of creatinine (Ccr) before and after constriction of the left renal artery in 8 dogs. The mean values of BP, HR and UV obtained during 5 days before the operation and the values of PRA and renal clearances on the day before the operation are presented as the control values.

*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, significantly different from the value before the operation.

circulating blood volume (ml/kg)

$$= \frac{\text{amount of injected Evans blue (mg)}}{\text{plasma concentration of Evans blue (mg/ml)}} \times \frac{100}{(100 - \text{hematocrit (\%)})} \times \frac{1}{\text{body weight (kg)}}$$

Statistical Analysis

All values are presented as means $\pm$ standard errors. Statistical significance of differences between the values obtained were determined according to Student's *t*-test and values of *p* less than 0.05 were considered significant.

RESULTS

Establishment of Hypertension by Unilateral Constriction of the Renal Artery

By constriction of the left renal artery, hypertension was established in 8 of 12 dogs used. In these 8 animals, blood pressure significantly increased after constriction of the renal artery and a high level of blood pressure was maintained (Table I and Fig. 1). Plasma renin activity also

increased immediately after the operation and a higher level than that found before the constriction persisted over 10 days, though it tended to revert to the control level. Heart rate showed no significant change. Urinary volume tended to increase. Urinary excretion and renal clearance of electrolytes did not increase but rather decreased. Sodium balance was not significantly changed. Creatinine clearance decreased to about 60% of the pre-operative control level for one to 3 days after the operation and then gradually returned to the subcontrol level (Fig. 1). Circulating blood volume tended to increase 4 to 7 days after the operation (Table I).

The Effects of Orally Administered Captopril in Acute Hypertensive Dogs

The administration of captopril was started 8 to 14 days after the operation. A marked decrease in blood pressure was observed immediately after the commencement of administration in all animals with acute hypertension (Fig. 2). Further decrease of blood pressure to the control level

Fig. 2. A: Changes in blood pressure (BP), heart rate (HR), plasma renin activity (PRA), B: daily urinary volume (UV), daily sodium balance (Na Bal.) and renal clearances of sodium (C_{Na}), potassium (C_K), chloride (C_{Cl}) and creatinine (C_{Cr}) by captopril in 8 acute two-kidney Goldblatt hypertensive dogs. The values of BP, HR and UV on -5~-1, 30~34 and 40~44 days, are their means during 5 days before the treatment and after the cessation of captopril.

*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, significantly different from the value before the treatment with captopril.

Fig. 3. Circulating blood volume before and during the treatment with captopril in normotensive, acute hypertensive and chronic hypertensive dogs. The number of observations is shown in parentheses.

was achieved with higher doses of 20 and 40 mg/kg/day. The blood pressure remained reduced after the cessation of the drug and did not fully return to the control level even 40 days after its cessation. Plasma renin activity increased in a dose-dependent manner and immediately returned to the control level after stopping of the treatment. Heart rate showed only a slight increase during the treatment with captopril (Fig. 2). Urinary volume decreased but sodium excretion increased, resulting in a negative sodium balance, though these changes were not statistically significant (Fig. 2). Renal clearances were not altered (Fig. 2) and the effect of captopril on circulating blood volume was indefinite (Fig. 3).

The Effects of Orally Administered Captopril in Chronic Hypertensive Dogs

Although blood pressure was decreased by treatment with captopril in chronic hypertensive dogs, this reduction was not so obvious as that observed in acute hypertensive animals (Fig. 4). The dose-dependent decrease of blood pressure was not confirmed and the hypertensive state

Fig.4. A: Changes in blood pressure (BP), heart rate (HR), plasma renin activity (PRA), B: daily urinary volume (UV), daily sodium balance (Na Bal.) and renal clearances of sodium (C_{Na}), potassium (C_K), chloride (C_{Cl}) and of creatinine (C_{Cr}) by captopril in 5 chronic two-kidney Golblatt hypertensive dogs. Simboles are the same as in Fig. 2.

Fig.5. A: Changes in blood pressure (BP), heart rate (HR), plasma renin activity (PRA), B: daily urinary volume (UV), daily sodium balance (Na Bal.) and renal clearances of sodium (C_{Na}), potassium (C_K), chloride (C_{Cl}) and of creatinine (C_{Cr}) by captopril in 4 normotensive dogs.

relapsed without delay when the treatment was interrupted. Plasma renin activity increased in the same manner as that in acute hypertensive animals. Heart rate, urinary volume, sodium balance and renal clearances were not influenced (Fig. 4) and circulating blood volume tended to decrease by captopril (Fig. 3).

The Effects of Orally Administered Captopril in Normotensive Dogs

In normotensive dogs, no changes were observed in any of the parameters including blood pressure, heart rate, urinary volume, sodium balance, C_{Na} , C_K , C_{Cl} , C_{Cr} and circulating blood volume, but plasma renin activity increased in a dose-dependent manner during the captopril administration by the same procedure as that used in the hypertensive animals (Figs. 3 and 5).

DISCUSSION

Hypertension with high plasma renin activity was successfully developed by unilateral constriction of the renal artery in beagle dogs. This increase of blood pressure is thought to be due to the activation of the renin-angiotensin system.²³ Though plasma renin activity was lowered by the 10th day after the operation, relatively high activity was still maintained as compared with the control value before the operation. Sodium retention was not observed and the circulating blood volume did not tend to increase. Thus, this hypertension was probably produced mainly by the rise of the endogenous angiotensin II level which increases the peripheral vascular tone.

The effect of captopril in reducing blood pressure has been principally accounted for by the inhibition of angiotensin converting enzyme.^{12,24-26} In the acute stage of two-kidney Goldblatt hypertensive dogs, blood pressure is likely to be sustained at a high level by the activation of the renin-angiotensin system. In the present study, captopril markedly decreased the blood pressure of acute hypertensive dogs in a dose-dependent manner and almost normalized the blood pressure. Thus, it may be concluded that captopril-induced reduction of blood pressure in the acute stage of hypertension was produced mainly by the inhibition of angiotensin converting enzyme.

On the other hand, captopril produced only partial and non-dose-dependent reduction of blood pressure in the chronic stage of hypertensive dogs. Therefore, some difference was sug-

gested in the mechanism of maintaining blood pressure in chronic hypertension from that operating in the acute stage of hypertension. Actually, Watkins et al.²⁷ observed in chronic two-kidney hypertensive dogs that an infusion of an angiotensin II antagonist, Sar¹-Ala⁸ angiotensin II, failed to change the blood pressure, and they concluded that the renin-angiotensin system is not critically involved in the maintenance of chronic renovascular hypertension. In the chronic hypertension, blood pressure regulation may also be accomplished by baroreceptor mechanism²⁸ and the renin-angiotensin system has only a partial role in the maintenance of blood pressure; renin may be prone to be released from kidney with constricted artery, though the "resting" level of plasma renin is normal.

Captopril exerted no effect in normotensive dogs except for a dose-dependent rise of plasma renin activity, which was induced by an inhibition of angiotensin converting enzyme. The case was the same in hypertensive dogs of both the acute and chronic stages. In normotensive dogs, the regulation of blood pressure is achieved chiefly by autonomic nervous control, especially through baroreceptor control and some other mechanism(s). The renin-angiotensin system may have little relation with the regulation of blood pressure in normotensive dogs.

Hypervolemia is suggested as one of the pathogeneses in two-kidney Goldblatt hypertension. Although circulating blood volume was analyzed in only 3 or 4 animals in the present study, it does not statistically increase after renal artery constriction and its decrease by captopril was slight. These insignificant changes of circulating blood volume indicated that the alteration of blood volume may have no relation with the cause of high blood pressure in the two-kidney Goldblatt hypertensive dogs and with the hypotensive effect of captopril at least in the present study. The antihypertensive effect of captopril independent of converting enzyme inhibition has been presented^{5,7,8} and the evidence for other depressor mechanisms have been shown: contribution of kinins;²⁹ interaction of prostaglandins;^{8,30-32} alteration in the responsiveness of the vasculature to vasoactive substances;³³ non-specific vasodilating action;³⁴ and diuretic or natriuretic effect of this agent.^{8,14,25,35} We have also reported the participation of kinins and prostaglandins in the hypotensive effect of captopril from an observation on the treatment with aprotinin, Sar¹-Ile⁸ angiotensin II and

indomethacin using anesthetized mongrel dogs.³⁶ Thus, the hypotensive effect of captopril in the chronic stage of hypertension was possibly brought about through some mechanisms other than the inhibition of the angiotensin converting enzyme.

The mechanism of sustained reduction of blood pressure by captopril after cessation of the treatment in the acute hypertensive animals remains to be elucidated.

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