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Renal Vasodilatation Caused by Captopril in Conscious Normotensive and Goldblatt Hypertensive Dogs (40896)

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Abstract. Blood pressure and renal blood flow were monitored in conscious normotensive and two-kidney one-clip Goldblatt hypertensive dogs. Captopril administered IV in a single dose of 0.1 mg/kg to normotensives increased renal blood flow by 26.8 ± 7.6% and decreased renal vascular resistance, but did not significantly change blood pressure. Cumulative doses of 0.1 and 0.2 mg/kg increased renal blood flow by 29.9 ± 6.5%, and decreased renal vascular resistance and blood pressure significantly. Qualitatively similar changes in blood flow and vascular resistance of the contralateral kidney were obtained in the hypertensives. Blood pressure was reduced by a mean of 11.8 ± 4.5 mm Hg, renal blood flow increased by 36.2 ± 7.9% by the low dose, blood pressure decreased by 18.4 ± 2.7 mm Hg, and renal blood flow increased by 42.3 ± 11.4% by cumulative doses of the inhibitor. Plasma renin activity was increased by captopril in the normotensives and a greater increase in plasma renin activity was obtained in the hypertensives. The hypotensive and renal vasodilator effects of captopril appear to be related to blockade of the influence of the renin–angiotensin system, but another action, potentiation of kinin-induced vasodilatation, may also be involved.

Through the use of angiotensin antagonists and angiotensin converting enzyme inhibitors, much knowledge has been gained concerning the influence of the renin–angiotensin system on renal hemodynamics under physiological and pathophysiological conditions (1, 2). Endogenous angiotensin II appears to be involved in the autoregulation of glomerular filtration rate (3), and also in the regulation of overall renal vascular tone. Evidence for the latter derives from the findings that agents which block the function of the renin–angiotensin system produce an increase in renal blood flow (RBF) in various pathophysiological states. Renal vasodilatation produced by angiotensin antagonists and converting enzyme inhibitors has been demonstrated in animals in low salt states (4–7), after hemorrhage (8), and in renovascular hypertensives (9, 10). No evidence of an effect of these agents on renal vascular tone in normal sodium replete animals or humans has been presented, with the exception of renal vasodilatation seen in anesthetized animals (10–13). Because of increased renin levels due to operative trauma and anesthesia, results obtained with angiotensin antagonists and converting enzyme inhibitors in anesthetized animals are not directly applicable to the intact conscious animal or human.

Because there is little or no information available concerning the effect of converting enzyme inhibitors on total renal blood flow in unanesthetized normal and hypertensive animals, we considered it important to examine the effects of the converting enzyme inhibitor, captopril, in a conscious instrumented canine preparation. We selected a low dose of captopril to give IV to dogs, based on previous data which established a maximal blockade of the pressor response to angiotensin I in the rat (14). The effect of the converting enzyme inhibitor was determined on blood pressure (BP), RBF, renal vascular resistance (RVR), and plasma renin activity (PRA) in normotensive and two-kidney one-clip hypertensive dogs.

Methods. Twenty dogs of both sexes, weighing 18.3–28 kg and quarantined before use, were employed in various aspects of this investigation. Nine animals were studied before making them hypertensive and after they were made hypertensive. The other eleven dogs were utilized in either the normotensive or hypertensive state. All dogs were fed a standard canine chow (0.11 meq sodium/g and 0.17 meq

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potassium/g), supplemented with canned meat or scraps. Our dogs routinely eat 300–600 g/day or 33–66 meq/day sodium and 41–102 meq/day potassium. The experimental preparation has been described in detail previously (15) and will only be summarized here. Systemic arterial blood pressure was recorded from a tygon tubing catheter positioned in the aorta proximal to the origin of the left renal artery, and drugs were administered IV into a catheter implanted in the jugular or femoral vein.

Renal blood flow (RBF) was monitored with either a Carolina (King, N.C.) or Zepeda (Seattle, Wash.) electromagnetic flowmeter which was coupled to a precalibrated Zepeda flow probe (4 or 5 mm) implanted on the left renal artery. Zero blood flow was obtained by injection of a bolus of 5 to 10 μg of angiotensin II, which caused a rapid fall in RBF to zero, and in 14 of the 20 dogs by electrically zeroing the flowmeter. Two kidney one-clip Goldblatt hypertension was produced in anesthetized dogs by constricting the right renal artery until blood flow was reduced by approximately 60% as measured electromagnetically, and the clamp was tightened subsequently if hypertension didn't develop within a week. In four of the hypertensive dogs the contralateral renal artery was also clamped later in the course of the studies on these animals.

Arterial PRA was determined by radioimmunoassay as routinely performed in this laboratory (16) utilizing angiotensin-I-specific antiserum. Two- to three-milliliter blood samples were collected in chilled plastic syringes containing 1 mg/ml disodium EDTA, and centrifuged at 4°C. One milliliter of plasma was added to 2 ml maleate buffer (pH 6), 1 ml of the mixture containing 8.3 μg/ml phenylmethylsulfonyl fluoride was incubated for 1 hr at 37°C, and 1 ml was kept on ice. Radioimmunoassay was carried out on aliquots of the incubated and unincubated plasma–maleate samples.

Two series of experiments with captopril were carried out on normotensive dogs. In one group of eight dogs (Group 1N), the drug was administered in a single dose of 0.1 mg/kg. Values of BP, RBF, and PRA and of the response to angiotensin I administered IV were obtained before and at the time of the peak effect of captopril on RBF. Twenty minutes after the maximal change caused by captopril, a final series of measurements of BP and RBF were made. The second group of normotensives (Group 2N) consisted of seven animals that were studied in a similar fashion as the above, except that two consecutive doses of captopril were administered (0.1 and 0.2 mg/kg); the second dose was given immediately after the peak response to the first was obtained. The recovery period was taken 20 min after the peak response to 0.2 mg/kg of captopril.

Similarly designed experiments were conducted on two groups of 7 hypertensive dogs each (Groups 1H and 2H) in which similar dose schedules were adhered to as in the normotensives. The experiments on the hypertensive dogs were carried out during the period of 2 to 28 (mean of 8) days following the initial Goldblatt clamping or after tightening the clamp. In 9 of the 14 dogs, the effect of captopril on these parameters was reassessed at a later time (18 to 67, mean of 40 days) after the clamping procedure. Four of these 9 dogs underwent constriction of the contralateral artery as described above in order to sustain the hypertension.

The mean increase in BP and PRA caused by renal artery clamping was 32.8 ± 5.3 mm Hg and 4.4 ± 1.4 ng angiotensin I/ml/hr, respectively, in the 14 hypertensives at the time of the initial captopril experiments. After completion of the studies on these dogs their kidneys were examined at autopsy. In all but 1 of the hypertensives, both kidneys were normal in appearance.

Statistical evaluation was by analysis of variance (when performing multiple comparisons), linear regression analysis and t test for unpaired data. Changes in PRA were compared by Wilcoxon's signed-rank test (17) because of heterogeneity of variance. Data are presented as mean ± SEM, and $P < 0.05$ was considered statistically significant.

Results. Blood pressure and renal vascular responses to captopril in normotensive and hypertensive dogs. In normotensive dogs (Group 1N) a single dose of 0.1 mg/kg

of captopril exerted a small hypotensive effect, and caused a significant increase in RBF (Fig. 1a). Changes in RBF and BP occurred gradually, and the peak effect was attained at varying times, but usually within 10 min. BP and RBF are shown for the peak effect of the drug, and at 20 min after the maximal response to captopril. RBF was augmented by 26.8 ± 7.6% in these eight experiments. Renal vascular resistance (RVR) decreased from 0.61 ± 0.09 to 0.48 ± 0.08 mm Hg ml/min^{-1} ($P < 0.01$). As seen in the recovery period, BP and RBF returned toward control; however, RBF tended to remain elevated. Plasma renin activity (PRA) was 0.61 ± 0.09 in the control period and increased to 1.7 ± 0.38 ng/ml/hr angiotensin I ($P < 0.02$) after captopril.

The same dose of the inhibitor followed by double the dose (0.2 mg/kg) was administered to another group of dogs (Group 2N). A similar hypotensive and renal vasodilator effect was obtained with the initial dose as was produced in the Group 1N animals, and the higher dose decreased BP but did not further affect RBF (Fig. 1a). RBF was increased by 22.6 ± 5.2% with the 0.1 mg/kg dose, and by 29.9 ± 6.5% by the 0.2 mg/kg dose given sequentially in Group 2N. RVR decreased from the control value of 0.43 ± 0.06 to 0.31 ± 0.04 mm Hg ml/min^{-1} ($P < 0.05$) and to 0.27 ± 0.04 mm Hg ml/min^{-1} ($P < 0.01$) after the 0.1 and 0.2 mg/kg doses, respectively. PRA was 1.37 ± 0.40 ng/ml/hr angiotensin I in the control period and was variably increased after the two doses of captopril to 10.1 ± 6.2 ng/ml/hr angiotensin I (NS). In the recovery period, BP had returned to control, but RBF remained elevated.

Qualitatively similar, but quantitatively greater effects of captopril on BP and RBF were seen in the two-kidney one-clip hypertensive dogs (Fig. 1b). The BP decrement and RBF increment brought about by captopril, 0.1 mg/kg, tended to be greater in the Group 1H animals than in the

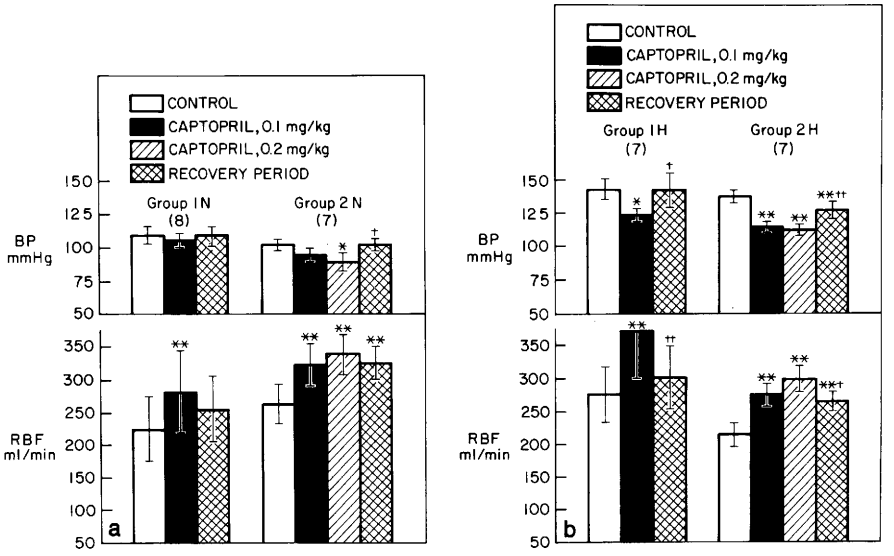

FIG. 1. (a) Blood pressure (BP) and renal blood flow (RBF) in control period, maximal effect after captopril, and in recovery period 20 min later in normotensive dogs. Group 1N was given a single dose of 0.1 mg/kg of captopril and Group 2N was given a single dose followed by a second dose of 0.2 mg/kg. *$P < 0.05$ and **$P < 0.01$ compared to control value. †$P < 0.05$ compared to value obtained after captopril, 0.2 mg/kg. (b) Blood pressure (BP) and renal blood flow (RBF) in control period, effect after captopril when RBF had stabilized, and in recovery period, in hypertensive dogs. *$P < 0.05$, **$P < 0.01$ compared to control. †$P < 0.05$, ††$P < 0.01$ compared to value obtained after captopril 0.2 mg/kg.

normotensive animals. Values of BP and RBF obtained after captopril in the hypertensives were statistically different from control (Fig. 1b). The percentage increase in RBF above control was 36.2 ± 7.9 in these seven experiments. RVR was decreased from 0.67 ± 0.16 to 0.40 ± 0.04 mm Hg ml/min^{-1} ($P < 0.01$) after captopril. As in the normotensive dogs, the BP and RBF changed gradually and the peak effect occurred within the same time interval. In some hypertensive dogs, however, the peak effect subsided, and the RBF stabilized at a level somewhat lower than the maximum, and it was the latter rather than the former value which is included in the data. Twenty minutes were allowed to pass before recovery values were obtained and as shown in Fig. 1b, recovery was nearly complete in Group 1H as evidenced by the return of BP and RBF to approximately the control level. PRA was 3.9 ± 1.0 ng/ml/hr angiotensin I in the control period and was increased to 14.8 ± 4.6 ng/ml/hr angiotensin I after captopril ($P < 0.02$).

In the second group of hypertensives (Group 2H) given cumulative doses of 0.1 and 0.2 mg/kg of captopril, the first dose appeared to cause a near maximal response because the second dose caused slightly but not significantly greater effects on BP and RBF. In the recovery period BP and RBF began to return toward the control values (Fig. 1b), but recovery was less complete than after the single dose of 0.1 mg/kg of captopril. RBF was increased 30.3 ± 12% by 0.1 mg/kg and 42.3 ± 11.4% by 0.2 mg/kg of the inhibitor. RVR was decreased from 0.67 ± 0.43 to 0.43 ± 0.03 mm Hg ml/min^{-1} ($P < 0.05$) and 0.36 ± 0.04 mm Hg ml/min^{-1} ($P < 0.01$), respectively, by these consecutive doses of captopril. PRA was 6.7 ± 2.7 ng/ml/hr angiotensin I in the control period, and was increased to 36.5 ± 11.1 ($P < 0.02$) after both doses of captopril.

We compared the changes in BP, RBF, RVR, and PRA caused by the two doses of captopril in the seven hypertensives making up Group 2H to the changes caused by these doses of the drug in the seven normotensives comprising Group 2N. The decrease in BP and increase in PRA were statistically greater in the hypertensive than in the normotensive animals ($P < 0.05$), but the changes in RBF and RVR were not different.

The effect of captopril on the response to angiotensin I administered IV in the normotensive and hypertensive animals is presented in Figs. 2a and b, respectively. Both the BP increase (mm Hg) and the percentage change in RBF caused by angiotensin I were markedly reduced by the lower dose in the normotensives and hypertensives, and were nearly abolished by cumulative doses of the inhibitor. There tended to be some restoration of the responses after the single dose in the recovery period, but little or no change in the recovery period after cumulative doses of captopril.

Blood pressure and renal vascular responses to captopril in later stage of two-kidney one-clip hypertension. Identical experiments with captopril were conducted on nine of the hypertensive animals from Groups 1H and 2H at a later stage of the hypertension. In order to sustain the hypertension in four dogs, the contralateral renal artery was constricted in addition to the renal artery which was originally clamped. Flow in the contralateral renal artery was maintained in three of these four dogs despite the constriction. In the animal whose flow recording ceased, only BP could be studied in the later stage. For comparative purposes, results of the first experiment with captopril are summarized on the left of Fig. 3, and the results of the second experiment are on the right. The interval after Goldblatt clamping was a mean of 6.4 days for the experiments during the early stage of the hypertension and 40 days after the original clamping for the experiments during the later stage. Control BP did not change over this interval, but control PRA decreased from 4.5 ± 0.91 in experiment 1 to 2.8 ± 1.0 ng/ml/hr angiotensin (NS) in experiment 2. Captopril 0.1 mg/kg caused a 13.4 ± 5.3 mm Hg ($P < 0.05$) or 9.4 ± 2.9% greater decrease in BP in the first compared to the second experiment, but the drug caused approximately the same change in RBF and RVR in the two experiments. The effect of captopril on PRA was obtained in four of the nine dogs

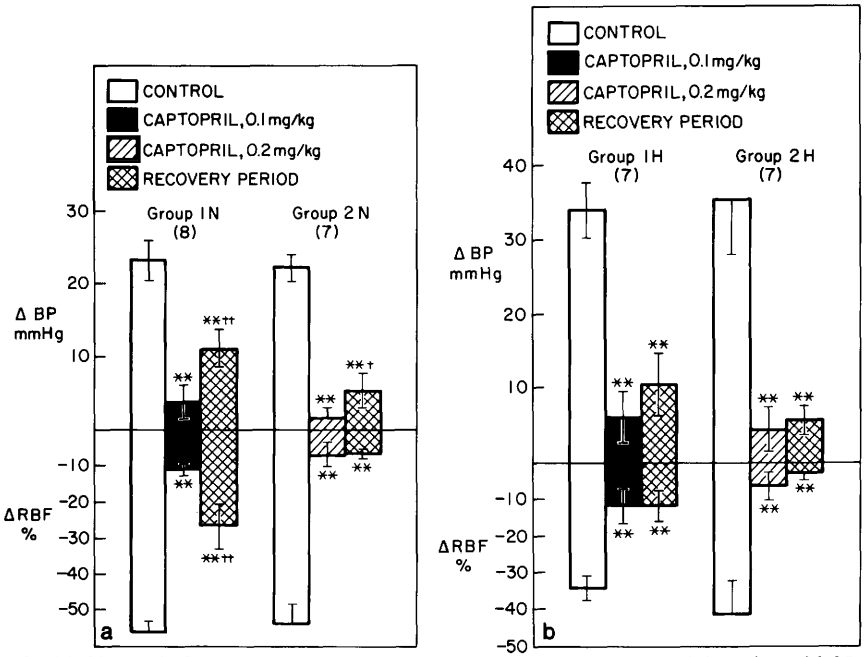

FIG. 2. (a) Change in BP and percentage change in RBF caused by IV administration of 0.05 μg/kg of angiotensin I in normotensive dogs in control period, after captopril, and in recovery period. $^{**}P < 0.01$ compared to control. $^{\dagger}P < 0.05$ and $^{\dagger\dagger}P < 0.01$ compared to value after captopril 0.1 or 0.2 mg/kg. (b) Change in BP and percentage change in RBF caused by IV administration of 0.05 μg/kg of angiotensin I in hypertensive dogs in control period after captopril and in recovery period. $^{**}P < 0.01$ compared to control.

at the later stage, and PRA was increased in three of the four dogs.

Discussion. The finding of an increase in RBF in the contralateral kidney of the two-kidney one-clip Goldblatt hypertensive dog produced by converting enzyme inhibition has several important implications. First, it suggests the presence of renal vascular tone mediated by endogenous angiotensin in the normal kidney of the Goldblatt hypertensive dog under basal conditions. Since captopril also potentiates bradykinin, it is conceivable that kinins may also influence renal vascular tone in these animals. Because the contralateral kidney is depleted of renin (18), it is probable that circulating rather than intrarenal angiotensin is responsible for this tonic influence. The present results also suggest a potentially beneficial action of captopril on the kidney of hypertensive patients who might receive the drug. A 30–40% increase in RBF in the face of a 20–30 mm Hg fall in mean BP elicited by the drug represents a

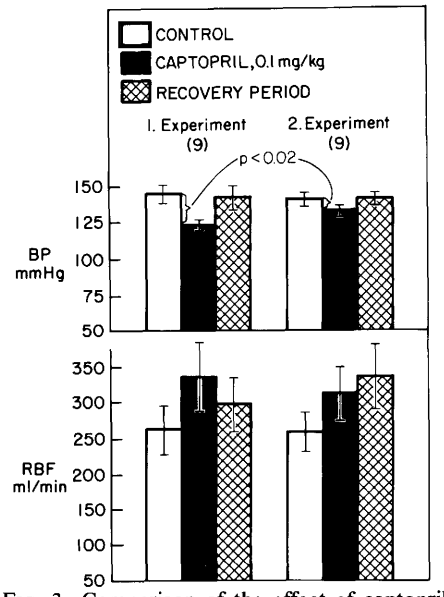

FIG. 3. Comparison of the effect of captopril, 0.1 mg/kg, on BP and RBF in hypertensive dogs in experiment 1, carried out on the average 6 days post-Goldblatt clamping, and in experiment 2 carried out on the average 40 days after initial Goldblatt clamping.

large vasodilator effect. In general, other antihypertensive drugs decrease renal vascular resistance, but do not always increase RBF.

There was a qualitatively similar vasodilator response to captopril in the normotensive dogs. This was a consistent finding and occurred regardless of the fact that the normotensive dogs were fed a diet with normal salt content, and had lower PRA (0.61–1.37 ng/ml/hr angiotensin I) levels than the hypertensives (3.9–6.7 ng/ml/hr angiotensin I). PRA of our normotensive dogs agrees well with that reported for normotensive dogs studied in other laboratories (19, 20). Previous findings of an increase in RBF caused by captopril and teprotide have been made in anesthetized surgically traumatized dogs and those on low salt diet (4–7, 10–13), conditions in which the renin–angiotensin system is stimulated. No renal vasodilatation has been found in salt-replete animals and humans having a low PRA (5–7, 21). In the sodium replete dog, RBF measured by the microsphere method was unchanged in three dogs and increased in one dog 20 min after teprotide, 0.5 mg/kg IV. This difference in results with teprotide may relate to a dissimilarity in action between the two converting enzyme inhibitors, or to the fact that RBF may not have been altered in the majority of the dogs at the time of measurement with the microspheres. As reported in the present study, the time of the maximal renal vasodilator response to captopril varies.

Captopril caused a greater hypotensive effect and increase in PRA in hypertensive than in normotensive animals, whereas the effect on RBF was similar. These results suggest a tonic influence of the renin–angiotensin system not only on normal BP, as has recently been reported in humans (22), but also on the renal vascular bed. In previous studies saralasin, an angiotensin antagonist, did not increase RBF in the conscious Goldblatt hypertensive dog, but did lower BP (15, 16). The agonistic action of saralasin which is more apparent in the unanesthetized animal may mask its renal vasodilator effect, since an increase in RBF has been observed during intrarenal infusion of saralasin in anesthetized Goldblatt hypertensive dogs (10).

At the present time we are unable to say what the exact mechanism of the hypotension and renal vasodilatation is in this study. The fact that an increase in RBF occurred in both normotensive and hypertensive dogs in which PRA levels differed would suggest that other factors besides the degree of activation of the renin–angiotensin system determine the renal vascular response to captopril. Nevertheless, the possibility cannot be dismissed at present that normal circulating or intrarenal levels of renin do influence renal vascular tone, and that this influence is equivalent in normotensive and two-kidney one-clip hypertensive dogs.

The hypotensive and renal vasodilator potency of captopril in the conscious dog resembles that previously found in the anesthetized animal (11). The 0.1 mg/kg dose of captopril would appear to have exerted a maximum effect on BP and RBF because the higher dose of 0.2 mg/kg following the lower dose had no additional effects. Duration of blockade was greater after the cumulative doses of the blocker. There tended to be a return of RBF and BP to control before there was a comparable recovery of the response to exogenous angiotensin I with the lower dose of captopril. With the higher dose regimen, however, the duration of action of the drug on BP and RBF and on the response to angiotensin was longer, since the effects on these parameters persisted through the recovery period. Much larger doses of captopril may decrease BP by another mechanism in addition to converting enzyme inhibition (23).

Hypotension produced by captopril can be maintained for months when the drug is administered orally on a chronic basis (24). The drug is also effective in essential hypertensive humans with long-standing elevation in BP (25). It was expected, therefore, that captopril would have been effective in lowering BP in the later stage of the hypertension in our animals. The hypotensive response to the drug was small in the later stage of the hypertension (experiment 2) and significantly less than that seen in the early stage (experiment 1). The

renal vasodilator response, however, did not differ in the two stages of the hypertension. A fall in PRA noted in the majority of the dogs in the later stage of the hypertension may have accounted for the lesser hypotensive response to captopril. In renal hypertensive rats refractory to acute administration of captopril, a long-term infusion of the inhibitor caused a sustained decrease in BP (26). Conceivably, persistence of the renal vasodilator response to captopril, as seen in the present study, could contribute to the ability of this agent to lower BP by a long-term effect, namely, by affecting sodium and water balance in the chronic phase of hypertension.

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