PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 167, 242–247 (1981)

Renal Vasodilator Responses to Captopril in Dogs Pretreated with Indomethacin[1] (41157)

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Abstract. Renal vasodilator responses to captopril administered intravenously were evaluated in pentobarbital anesthetized dogs pretreated with indomethacin to determine whether synthesis and release of vasodilator prostaglandins are involved in the response. Renal artery blood flow was measured using electromagnetic flowmetry and renal vascular resistance was calculated from the ratio of mean arterial blood pressure/renal artery blood flow. In control dogs, captopril caused significant dose-related increases (ranging from 9 ± 2 to 37 ± 6 ml/min) in renal artery blood flow and decreases in renal vascular resistance. The drug also decreased mean arterial blood pressure by 22 ± 3 mm Hg, whereas, heart rate was not significantly altered from precaptopril control values. In indomethacin pretreated dogs, the renal vasodilator and systemic hypotensive responses of captopril were not attenuated. The data suggest that captopril causes renal vasodilation by a mechanism independent of prostaglandins.

Captopril (D-3-mercapto-2-methylpropanoyl-L-proline) effectively inhibits angiotensin-converting enzyme (1), thereby, blocking the pharmacological effects of angiotensin I (2). Since kininase II is the same enzyme (dipeptidyl carboxy-peptidase) as the converting enzyme (3) and is responsible for the inactivation of bradykinin, the pharmacological actions of bradykinin are enhanced after captopril administration (4). Recent reports indicate that captopril increases renal blood flow in conscious (5) or anesthetized dogs (6). The purpose of the present investigation was to determine whether the renal vasodilator effect of captopril is mediated by a prostaglandin mechanism. Toward this end, the renal vascular effects of captopril were evaluated in dogs pretreated with indomethacin in order to inhibit synthesis of prostaglandins.

Materials and Methods. Eighteen mongrel dogs (either sex) weighing 8–20 kg were used in this study. The dogs were fed a standard laboratory canine diet (Ralston Purina Company, No. 5006) once daily and allowed free access to water. The dogs were anesthetized with pentobarbital sodium (45 mg/kg, ip), intubated with an endotracheal tube, and allowed to breathe spontaneously. A femoral vein and artery were cannulated to administer drugs and to monitor blood pressure, respectively. Heart rate was detected with a cardiotachometer triggered by the arterial pressure pulse. The left renal artery was exposed by a retroperitoneal incision and a calibrated electromagnetic flow probe (8 to 10-mm circumference, Carolina Medical Electronics) was placed around the renal artery to continuously monitor renal artery blood flow. Renal vascular resistance was calculated as the ratio of mean arterial blood pressure/renal artery blood flow. All recordings were made on a Beckman polygraph (R 612).

Two experimental groups (nine in each) of dogs were studied. One group received captopril infused intravenously at progressively increasing infusion rates of 2.5, 25, and 250 μg/kg/min (total volume administered equals 22 ml), each infusion for 5 min. Peak responses (absolute units of change from precaptopril control values) were determined during each infusion rate for mean arterial blood pressure, renal artery blood flow, renal vascular resistance, and cardiac rate. In a second group of dogs, the identi-

[1] A preliminary report on this subject was presented at the Federation Meetings, Anaheim, California, 1980, and published in abstract form in Fed. Proc. 39, 1180, 1980.

0037-9727/81/060242-06$01.00/0

cal dosing protocol was followed with the exception that the dogs were pretreated with indomethacin meglumine. The dose calculated as free base (2.5 mg/kg, dissolved in 0.9% NaCl) was infused intravenously over 10 min.

Twenty minutes after completion of indomethacin infusion, captopril was administered at the three infusion rates. This dose of indomethacin was sufficient to block (50–75%) the renal vasodilator effect of arachidonic acid (0.5 mg/kg, intrarenal artery). Inhibition of arachidonic acid to increase renal artery blood flow was used as an index of blockade of prostaglandin synthesis as reported previously (7, 8).

Data are expressed as mean values ± standard errors. The Student *t* test was used for paired data (differences) or for between group comparisons (group means). *P* values less than 0.05 are considered statistically significant.

Results. Captopril increases renal artery blood flow in a dose-related manner ranging from 9 ± 2 to 37 ± 6 ml/min (Table I). The increase in renal blood flow was due to renal vasodilation since calculated renal vascular resistance was significantly decreased at all doses. The drug also decreased mean arterial blood pressure (6 ± 1 to 22 ± 3 mm Hg), whereas, heart rate was not significantly changed from precaptopril control values.

In order to determine whether endogenous prostaglandins are involved in the renal vasodilator response, captopril was examined in nine dogs pretreated with indomethacin (2.5 mg/kg, iv). Indomethacin (Fig. 1) significantly decreased renal artery blood flow (192 ± 14 to 143 ± 15 ml/min) and increased renal vascular resistance (0.645 ± 0.05 to 0.972 ± 0.12 mm Hg · min/ml). This dose of indomethacin was considered sufficient to block enzymatic synthesis of vasodilator prostaglandins since renal vasodilation by the prostaglandin precursor, arachidonic acid, was blocked (50–75%). Results in Fig. 2 compare the renal vasodilator effect of captopril in control and in indomethacin-pretreated dogs.

The data indicate that indomethacin pretreatment did not attenuate the renal vasodilator response of captopril. Captopril significantly increased renal artery blood flow (ranging from 26 ± 6 to 64 ± 10 ml/min) and decreased renal vascular resistance at all doses studied. Additionally, the vasodepressor response of captopril was not reduced in dogs pretreated with indomethacin.

Discussion. In previous studies, Murthy *et al.* (6) using electromagnetic flowmetry reported that captopril administered intravenously increases renal artery blood flow in pentobarbital anesthetized dogs. McCaa *et al.* (5) have demonstrated that captopril given orally increases effective renal plasma flow (estimated from clearance of [^{131}I]iodohippurate) in conscious sodium-deficient dogs.

Our data confirm these findings that captopril causes renal vasodilation in dogs and extend observations on its renal vascular mechanism. In this regard, our study evaluated the proposal that vasodilator prostaglandins may be involved as mediators of captopril-induced renal vasodilation. Data derived in this research indicate that the renal dilator effect of captopril is not dependent upon a prostaglandin vasodilatory mechanism since the renal dilator effect was not attenuated in dogs pretreated with indomethacin. Several reports indicate that indomethacin inhibits renal prostaglandin synthesis (9–14). For example, Wong and Zimmerman (13) showed that indomethacin (2 mg/kg) significantly decreased the renal secretion rate of PGE (determined by radioimmunoassay) by at least 80% in pentobarbital-anesthetized dogs. A similar degree of inhibition was observed at a dose of indomethacin of 5 mg/kg. Kaloyanides *et al.* (14) demonstrated that indomethacin (2 mg/kg) suppressed renal prostaglandin E_2 secretion, as measured by radioimmunoassay, to zero within 20 min after administration in the isolated perfused dog kidney. Zambraski and Dunn (11) using radioimmunoassay to detect PGE_2 have reported that indomethacin (2 mg/kg) significantly depressed prostaglandin synthesis as measured by reductions in both renal venous (60%) and

TABLE I. RENAL VASODILATOR RESPONSE TO CAPTOPRIL IN NINE PENTOBARBITAL ANESTHETIZED DOGS

	Control (precaptopril)	Captopril infusion rate[a] (μg/kg/min, iv)					
		2.5	Difference	25	Difference	250	Difference
Mean arterial blood pressure (mm Hg)	122 ± 5[b]	116 ± 5	−6 ± 1[c]	107 ± 6	−15 ± 2[c]	99 ± 6	−22 ± 3[c]
Renal blood flow (ml/min)	123 ± 15	132 ± 15	+9 ± 2[c]	148 ± 18	+26 ± 5[c]	160 ± 18	+37 ± 6[c]
Renal vascular resistance (mm Hg·min/ml)	1.121 ± 0.153	0.976 ± 0.122	−0.145 ± 0.37[c]	0.818 ± 0.120	−0.303 ± 0.05[c]	0.699 ± 0.100	−0.422 ± 0.078[c]
Cardiac rate beats/min	142 ± 7	141 ± 7	−1 ± 1	151 ± 9	+9 ± 7	149 ± 7	+7 ± 4

[a] Each infusion for 5 min.
[b] Mean values ± SE.
[c] Values are significantly different ($P < 0.05$) based on paired analysis; values of cardiac rate are not statistically significant ($P > 0.05$).

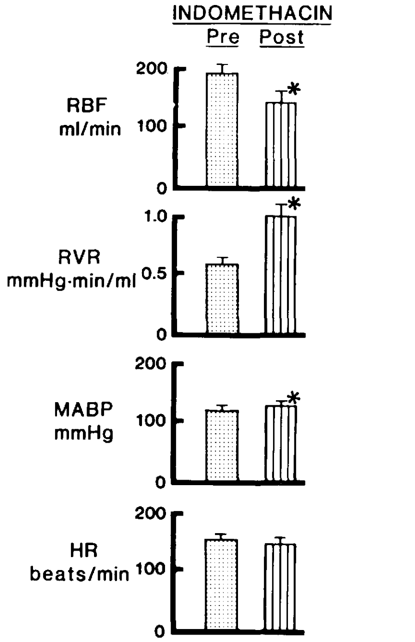

FIG. 1. Effect of intravenously administered indomethacin (2.5 mg/kg over 10 min) in nine pentobarbital-anesthetized dogs. Data are summarized from values taken immediately prior to indomethacin infusion (Pre) and 20 min after completion (Post) of infusion. Asterisk indicates significantly different ($P < 0.05$) from predrug control.

urine PGE_2 (77%) concentrations in conscious dogs. Lonigro and co-workers (16) indicated that a direct correlation exists between the reduction in renal artery blood flow and the decrease in efflux of PGE in renal venous blood after indomethacin administration. In the present study, indomethacin (2.5 mg/kg, iv) decreased renal artery blood flow, and increased renal vascular resistance as reported by others (8, 15–17). Despite using a slightly greater dose of indomethacin than has been reported by others to decrease renal artery blood flow and to substantially inhibit renal prostaglandin synthesis, captopril was still capable of causing renal vasodilation. These findings suggest that the renal dilator effect of captopril results from an action of the drug independent of vasodilator prostaglandins.

Our data suggesting a lack of involvement of prostaglandins are in agreement with those of Wong and Zimmerman (13), who reported that captopril increased renal artery blood flow in anesthetized nonhypotensive hemorrhaged dogs without causing an increase in renal venous PGE concentration and PGE secretion rate. Additionally, under the experimental conditions of nonhypotensive hemorrhage, indomethacin did not attenuate captopril-induced renal dilation (13). Further evidence for lack of involvement of vasodilatory prostaglandins in the renal dilator effect of captopril is the finding of Olsen and Arrigoni-Martelli (18), who found no increase in urinary PGE after captopril administration to conscious dogs. These data showing a lack of inhibition by indomethacin on captopril-induced renal vasodilation or vasodepression in the dog are in agreement with the data of Antonaccio *et al.* (19) showing that indomethacin had no significant effect on the antihypertensive activity of captopril in the spontaneously hypertensive rat. The increase in plasma renin activity caused by captopril also was not altered by indomethacin in normotensive or spontaneously hypertensive rats (19). These results coupled with these present findings suggest that the cardiovascular pharmacology of captopril is not dependent on synthesis and release of prostaglandins. A recent report by Wong and Zimmerman (20) indicates that renal vasodilation observed after intravenous administration of captopril results from inhibition of angiotensin converting enzyme at an extrarenal site (e.g., lung). These findings implicate circulating peptides in the renal dilator action of captopril rather than those locally formed within the kidney.

The increases (ml/min) in renal artery blood flow in response to captopril was greater at each dose in indomethacin-pretreated dogs relative to those receiving captopril alone (Fig. 2), a finding which is similar to that reported by Lonigro *et al.* (9) that indomethacin pretreatment augments (rather than blocks) the renal dilator response of bradykinin. Similarly, Flamenbaum *et al.* (21) showed that prostaglandin synthetase inhibition with meclofenamate does not attenuate the renal vasodilator effect of bradykinin. Recently, Matthews and Johnston (22) indicate that whole blood immunoreactive bradykinin levels are in-

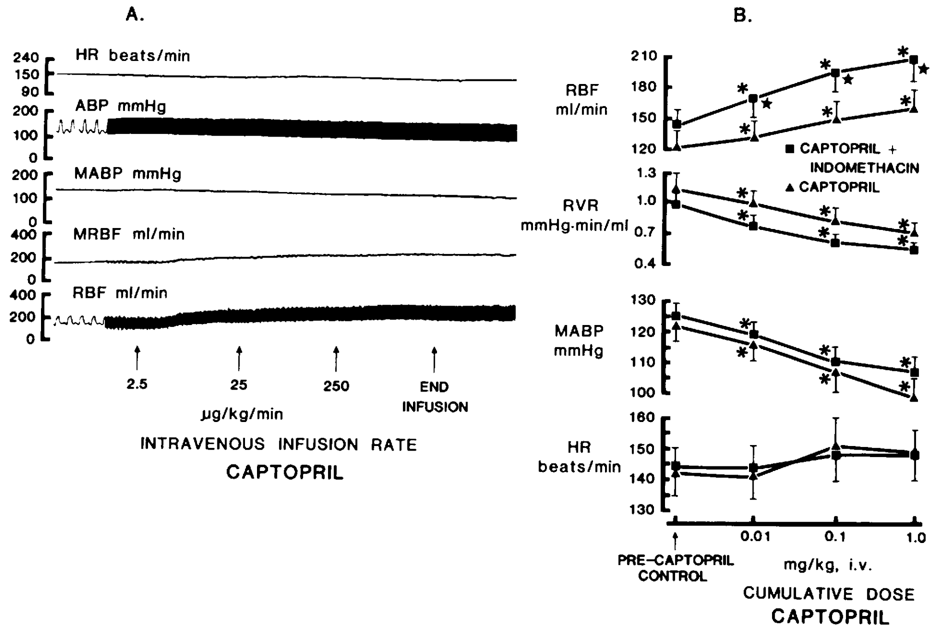

FIG. 2. (A) Experimental record of renal vasodilator effect of captopril after intravenous infusion in a pentobarbital-anesthetized dog pretreated with indomethacin (2.5 mg/kg, iv). (B) Comparison of renal vasodilator responses of captopril in control dogs (captopril alone) and in dogs pretreated with indomethacin. Asterisk indicates significant increases (paired analysis) in renal artery blood flow at all doses within each experimental group relative to precaptopril control. Group mean analysis (stars, $P < 0.05$) in renal artery blood flow are significantly greater in the indomethacin-pretreated group. Data are summarized for nine dogs per experimental group.

creased in rats following captopril. These findings taken together with the present results leave open the possibility that captopril may increase renal blood flow, at least in part, by a bradykinin mechanism. Alternatively, the renal dilator mechanism may be attributed to its blocking effect of the renin angiotensin system. Recently McCaa (23) has provided data showing that the continuous infusion of angiotensin II in sodium-deficient dogs during treatment with captopril restores arterial blood pressure, urinary sodium excretion, and plasma aldosterone concentration to control levels observed in untreated sodium-deficient dogs. Those findings raise the possibility that the hypotensive and natriuretic effects of captopril are due to inhibition of angiotensin II formation.

In summary, captopril caused a dose-related increase in renal artery blood flow after intravenous administration to pentobarbital-anesthetized dogs. Pretreatment of dogs with indomethacin to block prostaglandin synthesis did not attenuate the renal vasodilator effect of captopril, suggesting that its mechanism of renal vasodilation is not dependent upon the synthesis and release of vasodilator prostaglandins.

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Received September 16, 1980. P.S.E.B.M. 1981, Vol. 167.