Relationship of Sodium Retention Produced by Catapres to Changes in Renal Hemodynamics[1] (36024)

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Clinically, catapres [St-155, Clonidine, 2-(2,6-dichlorophenyl-1-amino-2-imidazoline · HCl] has been shown to be a potent oral antihypertensive agent (1, 2). One of the few side effects that has been experienced with this compound is a decrease in sodium excretion ($U_{Na}V$) (2, 3). Onesti *et al.* (3) found that although $U_{Na}V$ was depressed, renal plasma flow (RPF) and glomerular filtration rate (GFR), which were estimated by the clearance of para-aminohippurate (C_{PAH}) and inulin, respectively, were not altered. Thus, in the absence of changes in renal hemodynamics, they suggested that catapres could be acting via a direct tubular mechanism to enhance the reabsorption of sodium. Laubie and Schmitt (4) noted a decrease in RPF and renal blood flow (RBF), estimated from PAH extraction, and $U_{Na}V$ but no change in GFR or renal vascular resistance (RVR) during the hypotension caused by systemic catapres (10–20 μg/kg).

The present study was undertaken to further investigate the possibility that alterations in renal hemodynamics might be involved in the sodium retention. Total renal blood flow as well as the C_{PAH} were determined. Catapres was infused into a renal artery in order to minimize systemic actions of the drug. In addition, an attempt was made to antagonize the responses with an alpha adrenergic blocking agent.

Methods. Mongrel dogs of either sex, weighing between 17 and 22 kg, were anesthetized with pentobarbital sodium (30 mg/kg, iv). The trachea was intubated and blood pressure (MAP) was monitered with a pressure transducer (Statham P23AA) via a carotid artery catheter. The femoral artery and vein were catheterized for the collection of blood and the administration of solutions, respectively. A sustaining infusion of 0.4% inulin, 0.08% PAH in 0.9% NaCl, was administered at a rate of 0.25 ml/kg per min. A kidney was approached via a retroperitoneal flank incision. If more than one renal artery was encountered the contralateral kidney was used. If both kidneys had more than one renal artery the animal was not used. A catheter was passed into the exposed ureter for the unilateral collection of urine. A flow probe was placed around the renal artery and connected to a square wave electromagnetic flowmeter (Carolina Medical Electronics). This provided a direct measurement of total RBF. The MAP and RBF were recorded continuously on a Beckman Type R Dynograph. A 23 gauge scalp needle was passed retrograde into the renal artery for the direct administration of drug into the kidney. A 0.9% solution of NaCl was continuously infused at a rate of 1.0 ml/min.

When urine flow (V) had stabilized, three 10 min control urine collections were taken. Catapres was then infused, during the next three 10 min collection periods, directly into the renal artery. The catapres concentration was varied to provide different doses at the same infusion rate. Five animals were used at each dose. Blood was collected at the midpoint of each 30 min collection period.

RVR is expressed as resistance units (RU) and was calculated by dividing MAP (mm Hg) by RBF (ml/min). The GFR (ml/min) was estimated from the clearance of inulin. Inulin was determined by the method of Schreiner (5) and PAH was determined by the method of Smith *et al.* (6). Sodium

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TABLE I. Effects of Catapres on Renal Hemodynamics and Excretion (mean difference from control ± standard error).[a]

	Catapres (ng/kg·min, ia)		
	250	500	1000
RBF (ml/min)	−45 ± 8.0[b]	−60 ± 18[b]	−95 ± 5.4[b]
BP (mm Hg)	0.0 ± 4.4	0.0 ± 0.29	12 ± 6.2
RVR (RU)	0.07 ± 0.02	0.24 ± 0.13	0.35 ± 0.02[b]
GFR (ml/min)	3.0 ± 3.4	−5.0 ± 0.89[b]	−5.0 ± 4.2
C_{PAH} (ml/min)	−6.0 ± 1.8[b]	−18 ± 6.4[b]	−31 ± 12
$U_{Na}V$ (μEq/min)	10 ± 20	−55 ± 18[b]	−59 ± 11[b]
U_KV (μEq/min)	3.0 ± 8.3	−6.0 ± 1.7[b]	−14 ± 4.9
V (ml/min)	0.3 ± 0.08[b]	−0.3 ± 0.09[b]	−0.2 ± 0.09

[a] $N = 5$.
[b] Significant difference from control ($p < .05$).

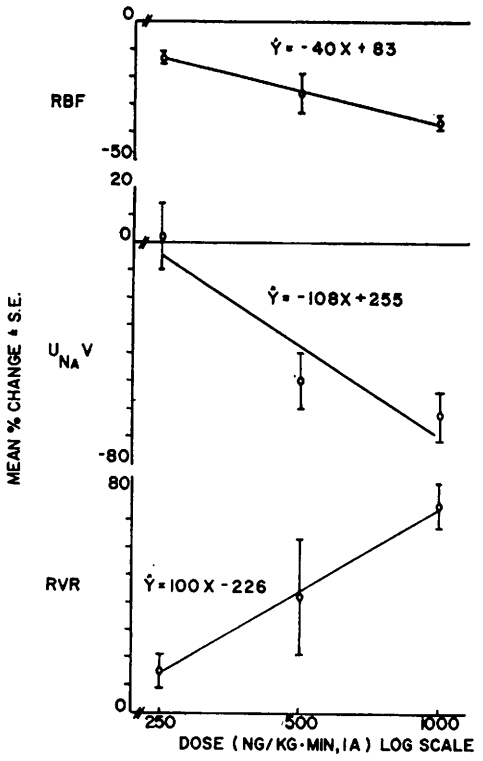

FIG. 1. Dose response of renal blood flow (RBF), sodium excretion ($U_{Na}V$) and renal vascular resistance (RVR) following intra-arterial catapres: Each point represents 5 animals.

and potassium concentrations were determined using a Coleman flame photometer.

In five experiments, dogs were pretreated with phenoxybenzamine (10 mg/kg, iv) 1 hr before the control collection. The completeness of alpha blockade was tested by injection of norepinephrine (1–2 μg) into a renal artery before and after the administration of phenoxybenzamine.

Catapres and norepinephrine were dissolved in 0.9% NaCl. Phenoxybenzamine was dissolved in propylene glycol with sonication.

Results. Table I shows the effects of infusing catapres into the renal circulation. The low dose of catapres (250 ng/kg·min, ia) produced a significant reduction RBF and C_{PAH}; V was significantly elevated. The middle dose of catapres (500 ng/kg·min, ia) produced significant reduction in RBF, GFR, C_{PAH}, $U_{Na}V$, U_KV, and V. The high dose of catapres (1000 ng/kg·min, ia) produced a significant reduction in RBF and $U_{Na}V$, while RVR was significantly elevated.

In Fig. 1, the regression lines were calcu-

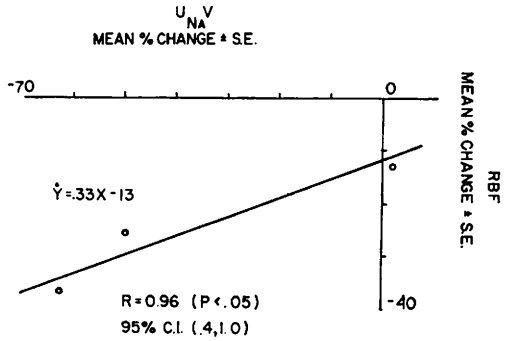

FIG. 2. Linear correlation between mean percentage change in renal blood flow (RBF) and sodium excretion ($U_{Na}V$) following intra-arterial catapres: Each point represents 5 animals at a particular dose.

TABLE II. Effect of Phenoxybenzamine on Changes in Renal Blood Flow Produced by Norepinephrine and Catapres (mean difference from control ± standard error).[a]

Treatment	Renal blood flow (ml/min)	
	Control animals	Phenoxybenzamine-treated animals
Norepinephrine, 1-2 μg, ia	−130 ± 24[b]	−5.0 ± 3.0
Catapres, 250 ng/kg min, ia	−45 ± 8.0[b]	−40 ± 9.3[b]

[a] $N = 5$.
[b] Significant difference from control ($p < .05$).

lated by the method of least squares. An analysis of variance test for linear regression and deviation from linearity was determined for each parameter. This analysis indicated that RBF, $U_{Na}V$, and RVR had significant regressions from zero but no significant deviation from linearity.

The linear correlation coefficient ($r = 0.96$) and its 95% confidence interval (+ 0.4, + 1.0) were calculated for the regression of the mean percentage change in RBF and the mean percentage change in $U_{Na}V$ (Fig. 2) and found to be significant. The line was calculated by the method of least squares. It was noted that $U_{Na}V$ was not depressed until RBF had declined by a mean of 13%.

Table II shows the mean difference ± standard error for norepinephrine and catapres from control values in control animals and animals treated with phenoxybenzamine. Significance was determined by Student's t test (paired comparison). When the decrease in RBF produced by catapres in the absence and presence of phenoxybenzamine was compared by means of Student's t test (group comparison), no significant difference was found. The response to norepinephrine, however, was significantly reduced in phenoxybenzamine-treated animals.

Discussion. Onesti and co-workers' (3) observation of a decrease in $U_{Na}V$ in the absence of any change in RPF gave rise to their suggestion of a direct tubular action of catapres. In their study, RPF was estimated by C_{PAH}, a method that does not give total RBF. In contrast, our studies demonstrated a dose-dependent reduction in total RBF and increase in RVR. Furthermore, a high degree of correlation was noted between RBF and $U_{Na}V$, and, in fact, $U_{Na}V$ did not begin to change until RBF had decreased by a mean of 13% (Fig. 2). Earley and Friedler (7) have demonstrated that manipulation of renal blood flow during saline-induced natriuresis produced changes in the net reabsorption of sodium. When RBF was increased, sodium reabsorption was depressed; and when RBF was decreased, sodium reabsorption was enhanced. Also, in a review by Earley and Daugharty (8), they suggest that RVR and postglomerular hydrostatic pressure are important inputs to an intrarenal mechanism mediating the net reabsorption of sodium. Since our study included the observation that RVR increased without concomitant change in GFR, which is suggestive of a vasconstriction distal to the glomerulus, it is possible that we were seeing a reduction in postglomerular hydrostatic pressure. Thus, catapres appears to alter some of the important physical factors regulating sodium reabsorption in such a way that increased sodium reabsorption and, therefore, decreased $U_{Na}V$ result. Although the possibility of some direct tubular action of catapres cannot be ruled out, the evidence indicates that the sodium retention produced by catapres can be attributed entirely to altered renal hemodynamics.

The decrease in RBF and increase in RVR are consistent with the alpha adrenergic stimulant properties of this compound (9–11). Thus, it is difficult to interpret the observation that phenoxybenzamine did not alter the decrease in RBF induced by catapres but abolished the norepinephrine-induced decrease in RBF. Several investigators have shown that doses of phenoxybenzamine up to 15 mg/kg do not antagonize the initial pressor action of catapres (12–15).

Summary. Catapres infused directly into a renal artery produces a dose related decrease in RBF and $U_{Na}V$, along with a dose-related increase in RVR. A high degree of correlation existed between RBF and $U_{Na}V$. These data indicate that the sodium retention caused by

catapres is dependent upon the renal hemodynamic changes induced by this agent. Pretreatment with phenoxybenzamine did not alter any of the actions of catapres.

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