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Effect of Angiotensin Converting Enzyme Inhibition on Renal Autoregulation (38117)

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(Introduced by Robert J. T. Joy)

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The mechanisms responsible for renal autoregulation continue to arouse considerable interest, and much of the present controversy is centered upon the role of the renin-angiotensin system in modulating the renal hemodynamic response to alterations in renal arterial pressure. Britton proposed a renin-renal autoregulation hypothesis which postulated that plasma angiotensinogen (renin substrate) and converting enzyme interact with cytoplasmic renin at the luminal surfact of the wall of the afferent arteriole to affect the arterial tone (1). In an earlier study, Waugh and Shanks observed that perfusion of isolated kidneys with an artificial colloidal perfusate resulted in loss of autoregulation, while the addition of fresh plasma to the perfusate restored the autoregulatory phenomenon (2). If the renin-angiotensin system is responsible for renal autoregulation and the presence of angiotensin converting enzyme is an essential participant in the autoregulatory process, then the infusion of an angiotensin converting enzyme inhibitor into the renal circulation should modify renal autoregulation. The current study was designed to evaluate the effects on renal autoregulation of limiting the conversion of angiotensin I to angiotensin II during a reduction in renal perfusion pressure.

Methods. Experiments were performed on 15 female dogs (wt: 19.2 ± 1.2 kg) anesthetized with intravenous pentobarbitol (30 mg/kg) and placed on a positive pressure respirator.[1] During surgical preparation an infusion of Ringers solution was started and approximately 400 ml administered over 2 hr to replace fluid losses. Catheters were introduced into both ureters via a suprapubic incision and a femoral artery was cannulated to withdraw blood samples as well as to monitor blood pressure. The left kidney was exposed through a retroperitoneal flank incision and with a minimum of dissection the aorta, left renal artery and ovarian vein were exposed. A modified Blalock clamp (3) was applied loosely across the aorta cephalad to the right renal artery. The ovarian vein was cannulated with a length of Teflon tubing and the tip advanced to the orifice of the renal vein. The curved shaft of a #25 gauge needle, attached to two lengths of tubing by a "Y" connection, was inserted into the left renal artery for infusion of 0.9% saline solution, angiotensin I, and angiotensin converting enzyme inhibitor (SQ20881)[2] at a rate of 0.5 ml/min.

A minimum of 2 hr was allowed to elapse for recovery following the surgical procedures. During this interval appropriate priming and maintenance infusions of p-aminohippurate (PAH) and ^{125}I-iothalamate (Abbott Laboratories, No. Chicago, Ill.) were administered and 30–45 min were allowed for equilibration of these substances before urine collection periods of 20 min duration were started. Blood samples from the femoral artery and renal vein were withdrawn 3 min before the mid point of each period.

To determine the effectiveness of the intra-

[1] In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animals Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences—National Research Council.

[2] Kindly supplied by Dr. Z. Horovitz, Squibb Institute for Medical Research, Princeton, New Jersey.

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renal infusion of the converting enzyme inhibitor (CEI) in inhibiting the conversion of angiotensin I to angiotensin II, 4 dogs (Group I) were studied by the following protocol: (a) 3 control periods; (b) 3 periods during the intrarenal infusion of angiotensin I at a rate of 10 ng/kg/min; and, (c) 3 periods during the simultaneous infusion of angiotensin I and CEI at a rate of 50 μg/kg/min. In a second group (Group II) of 9 dogs the effect of CEI on renal autoregulation was evaluated using the following protocol: (a) 3 control periods; (b) 3 periods during the intrarenal infusion of CEI (15 or 50 μg/kg/min); and (c) 3 periods during continued CEI infusion in which renal perfusion pressure was reduced by supraaortic constriction. In 6 of the dogs in Group II a catheter was introduced into the jugular vein, advanced to the right heart, and angiotensin I (1 μg) or angiotensin II (0.63 μg) was injected before and after the administration of CEI. This was done in order to assess the effectiveness of systemic converting enzyme inhibition by monitoring the altered pressor response to angiotensin.

Analytic procedures were as previously described for this laboratory (3, 4). The clearance of ^{125}I-iothalamate was used as an index of glomerular filtration rate (GFR) and the clearance of PAH (C_{PAH}) as a measure of effective renal plasma flow (ERPF). Filtration fraction (FF) was calculated as the ratio of GFR to C_{PAH}. Effective renal blood flow (ERBF) was calculated as ERPF/1-Hct and renal vascular resistance (RVR) in mmHg/ml/min was estimated from the ratio of blood pressure to ERBF. Renin secretory rate (RSR) was calculated from the ERPF, corrected for PAH extraction, and the renal venous-arterial renin difference, and was expressed in ng of angiotensin I per min. Statistical analyses using the paired t test were performed according to Snedecor and Cochran (5), and all results are presented as mean plus or minus standard error ($\pm$ SE).

Results. Group I studies were designed to evaluate the ability of infused CEI to reverse the effects of exogenously administered angiotensin I. A dose of intrarenal angiotensin I was chosen, based on preliminary observations, which resulted in renal function alterations without alteration in systemic blood

TABLE I. Group I: Effect of a Renal Artery Infusion of Angiotensin I, or Angiotensin I Plus Converting Enzyme Inhibitor (CEI) on Renal Function in Both Infused and Contralateral Kidneys.[a, b]

	BP (mmHg)	V (ml/min)	GFR (ml/min)	ERBF (ml/min)	FF (GFR/C_{PAH})	RVR (mmHg/ml/min)	$U_{Na}V$ (μEq/min)	EFF_{Na} (%)
a) CONTROL	139 $\pm$ 4							
Infused		0.50 $\pm$ 0.18	38 $\pm$ 4	181 $\pm$ 31	0.37 $\pm$ 0.01	0.83 $\pm$ 0.12	105.8 $\pm$ 40.3	1.66 $\pm$ 0.66
Contralateral		0.36 $\pm$ 0.10	40 $\pm$ 4	187 $\pm$ 34	0.38 $\pm$ 0.01	0.81 $\pm$ 0.11	71.9 $\pm$ 22.9	1.06 $\pm$ 0.37
b) ANGIOTENSIN I	140 $\pm$ 3							
Infused		0.26 $\pm$ 0.07	32 $\pm$ 4*	124 $\pm$ 23*	0.45 $\pm$ 0.02*	1.27 $\pm$ 0.23*	37.4 $\pm$ 15.6	0.66 $\pm$ 0.28
Contralateral		0.32 $\pm$ 0.07	40 $\pm$ 4	171 $\pm$ 22	0.41 $\pm$ 0.02	0.86 $\pm$ 0.88	57.1 $\pm$ 13.5	0.75 $\pm$ 0.26
c) ANGIOTENSIN I + CEI	129 $\pm$ 2							
Infused		0.35 $\pm$ 0.07	35 $\pm$ 4	172 $\pm$ 38	0.37 $\pm$ 0.02	0.84 $\pm$ 0.14	71.2 $\pm$ 19.4	1.10 $\pm$ 0.39
Contralateral		0.41 $\pm$ 0.06	41 $\pm$ 4	210 $\pm$ 41	0.35 $\pm$ 0.02	0.68 $\pm$ 0.11	89.6 $\pm$ 21.8	1.22 $\pm$ 0.43

[a] Values are means $\pm$ SE for 4 dogs. BP: mean aortic blood pressure; V: urine volume; GFR: glomerular filtration rate; ERBF: effective renal blood flow; FF: filtration fraction; RVR: renal vascular resistance.

[b] * Significantly different from control at the 5% confidence limits or below, using a paired t test.

TABLE II. Group II: Effect of Intrarenal Infusion of Angiotensin Converting Enzyme Inhibitor (CEI) on Renal Autoregulation in Both Infused and Contralateral Kidneys During a Decrease in Perfusion Pressure.[a]

	BP (mmHg)	V (ml/min)	GFR (ml/min)	ERBF (ml/min)	FF (GFR/C_{PAH})	RVR (mmHg/ml/min)	$U_{Na}V$ (μEq/min)	EFF_{Na} (%)
a) CONTROL	129 ± 4							
Infused		0.43 ± 0.08	37 ± 3	198 ± 22	0.34 ± 0.02	0.73 ± 0.10	94.9 ± 18.1	1.83 ± 0.31
Contralateral		0.40 ± 0.09	38 ± 3	203 ± 21	0.35 ± 0.02	0.70 ± 0.08	81.7 ± 20.6	1.56 ± 0.39
b) CEI	117 ± 4*							
Infused		0.62 ± 0.08*	39 ± 4*	217 ± 29	0.34 ± 0.02	0.64 ± 0.10	141.7 ± 16.1*	2.68 ± 0.38*
Contralateral		0.51 ± 0.10*	41 ± 4	235 ± 33	0.33 ± 0.02	0.62 ± 0.11*	105.4 ± 22.9	2.06 ± 0.54
c) CEI + AORTIC CONSTRICTION	79 ± 2*							
Infused		0.24 ± 0.05*	35 ± 3	247 ± 38*	0.28 ± 0.03*	0.40 ± 0.07*	32.9 ± 10.3*	0.72 ± 0.23*
Contralateral		0.18 ± 0.05*	31 ± 3	225 ± 31	0.26 ± 0.03*	0.43 ± 0.07*	20.9 ± 7.4*	0.46 ± 0.16*

[a] Values are means ± SE for 9 dogs, *Significantly different from control at the 5% confidence limits or below using a paired t test. For abbreviations, see Table I.

pressure. As shown in Table I, the infusion of 10 μg/kg/min angiotensin I did not result in any significant alteration in mean aortic blood pressure. As compared to control values a 32 ± 2% decrease in ERBF ($P < 0.01$) and a 17 ± 1% decrease in GFR ($P < 0.001$) were observed in the infused kidney during angiotensin I administration. Consequently, FF increased from 0.37 ± 0.01 to 0.45 ± 0.02 ($P < 0.005$) and calculated RVR rose from 0.83 ± 0.12 mm Hg/ml/min to 1.27 ± 0.23 mm Hg/ml/min ($P < 0.05$) during angiotensin I administration. In contrast, save for a small but significant rise in RVR, there were no significant alterations in these variables observed in the contralateral kidney during angiotensin infusion. When CEI and angiotensin I were simultaneously infused mean aortic blood pressure decreased from 140 ± 3 to 129 ± 2 mm Hg. As noted in Table I the concomitant infusion of CEI reversed the alterations in RVR, GFR, ERBF and FF observed on the infused side during the administration of angiotensin I alone. During the combined infusion of CEI and angiotensin I the observed values for ERBF, GFR, and RVR in the contralateral kidney were not different from control ($P > 0.05$). Thus, the dose of CEI infused reversed the renal hemodynamic and functional effects of the administered exogenous angiotensin I.

The results of the Group II studies are presented in Table II. Preceding the control periods, a 1 μg bolus of angiotensin I given into the right heart of 6 of the 9 Group II dogs resulted in a 28 ± 4 mm Hg rise in mean aortic pressure. In contrast, this same dose resulted in a 3 ± 1 mm Hg rise when given 158 ± 11 min after the onset of intrarenal arterial CEI infusion, consistent with a marked inhibition of angiotensin converting enzyme. In 2 of these dogs, 0.63 μg of angiotensin II given during CEI infusion resulted in pressor responses of 17 and 27 mm Hg. When compared to control values (Table II) the administration of CEI resulted in a 12 ± 3 mm Hg decrease ($P < 0.01$) in mean aortic blood pressure, similar in magnitude to that observed after CEI administration in Group I studies. RVR decreased in both infused and contralateral kidneys by 14 ± 6% and 15 ± 6%, respectively, during CEI infusion because

of the significant drop in blood pressure and the tendency for ERBF to increase. This decrease, however, was significant only in the noninfused kidney. While CEI increased urine flow in both infused ($P < 0.02$) and noninfused ($P < 0.05$) kidneys, significant alterations in GFR and sodium excretion were only observed on the infused side.

Supra-renal aortic clamping resulted in a fall in mean aortic blood pressure, as measured below the clamp, to 79 ± 2 mm Hg ($P < 0.001$). The calculated RVR declined to values significantly lower than control in both the infused and noninfused kidneys (Table II) as mean ERBF in the infused kidney increased ($P < 0.05$) compared to control values, while ERBF of the noninfused kidney was not different from control ($P > 0.05$). Therefore, renal autoregulation of blood flow was not impaired during the administration of CEI. Similarly, GFR on the infused side was not significantly different from control ($P > 0.05$) at the lower perfusion pressure while the GFR of 31 ± 3 ml/min in the noninfused side was lower than control ($P < 0.05$). Urine flow and sodium excretion, which increased in both kidneys during CEI infusion alone, declined to values significantly lower than control in both infused and noninfused kidneys following aortic constriction.

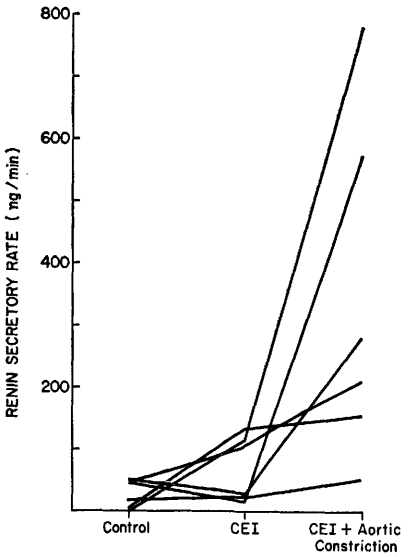

FIG. 1. Alterations in renin secretory rate of the infused kidney during the 3 phases of Group II studies in 6 dogs.

Figure 1 depicts the alterations observed in RSR on the infused side during the phases of the protocol used to study Group II dogs. CEI alone did not result in a significant increase in RSR. When renal perfusion pressure was decreased by cross clamping to a mean value 50 ± 4 mm Hg below control a significant rise in RSR was observed.

Discussion. Alterations in renin-angiotensin system activity may be viewed either as the initiator of or the consequence of renal autoregulation. The autoregulation of renal blood flow and glomerular filtration rate may be considered the effects of mechanisms initiated by the renin-angiotensin system which adjust tubular sodium load to tubular reabsorptive capacity. According to this thesis, a diminution in renal perfusion pressure results in decreased tubular fluid flow rate, increased sodium absorption and decreased distal tubular sodium load. This results in an inhibition of renin release, decreased angiotensin generation and a diminution in renal vascular resistance such that renal blood flow and glomerular filtration rate return towards normal (i.e., "autoregulated") and the stimulation for renin-angiotensin system activity is appropriately modulated (6). Direct evidence for this hypothesis is lacking. Although loss of renal autoregulatory ability after renal renin depletion by sodium loading has been cited in support of this theory (6), recent studies have demonstrated maintenance of renal autoregulatory efficiency in the face of renin depletion (3, 7, 8). Autoregulation has also been demonstrated to persist when sodium homeostasis is normalized by saline or mannitol infusion during diminished renal perfusion pressure (9). Furthermore, renal autoregulation has been demonstrated to persist during infusion of angiotensin, a maneuver which should limit autoregulation were it mediated by decreases in the generation of angiotensin (3, 7, 10).

Alternatively, the hemodynamic alterations associated with renal autoregulation may, in turn, increase renin-angiotensin system activity. In this regard, a proportional increase in renin-angiotensin system activity with decreased perfusion pressure has been demonstrated in intact unanesthetized dogs (11), anesthetized intact dogs (9, 12, 13), as well

as in anesthetized dogs in which the cardiovascular control loops of the central nervous system were eliminated (14, 15). Cowley and Guyton demonstrated maximal renin release coincident with the lower limits of renal autoregulation, suggesting that renin release was independent of further decrements in glomerular filtration rate or renal blood flow (14). Additional evidence that renal hemodynamic alterations induce alterations in the renin-angiotensin system has been provided by the study of renal blood flow distribution in relation to renin secretion and renal autoregulation. Abe and coworkers (16) were able to demonstrate a redistribution of cortical blood flow, characterized by diminished outer cortical blood flow, only at the lower limits of renal autoregulation, suggesting that released renin did not cause the redistribution of blood flow but rather that the decrease in outer cortical flow beyond the autoregulatory range stimulated renin secretion. If the generation of angiotensin was an essential phenomenon in the efficiency of renal autoregulation then preventing conversion from the inactive decapeptide, angiotensin I, to the vaso-active octapeptide, angiotensin II, should have precluded maintenance of renal blood flow with a reduction in renal perfusion pressure.

The evolutionary utility of increased renin-angiotensin system activity in response to diminished renal perfusion pressure is apparent from studies (10, 14, 15), which suggest that the gain of the basic renin-angiotensin constrictor loop may be capable of at least a 50% return towards normal of the diminished blood pressure sensed by the kidney. The observed responses in the renin-angiotensin system to decreased renal perfusion and subsequent alterations in systemic blood pressure may further substantiate a role for the renin-angiotensin system in the moment to moment regulation of blood pressure.

It is apparent that the efficiency of renal autoregulation is not disturbed by either renal renin depletion (3, 8), or the effective elimination of the generation of the vasoactive octapeptide angiotensin II. The current study does not provide any evidence for a primary role of the renin-angiotensin system in renal autoregulation. It suggests, since renal autoregulation was not impaired under the conditions of this study, that even when renin-angiotensin system activity is increased as a consequence of renal autoregulation that it does not play a significant role in modifying the renal autoregulatory process. The demonstration that GFR was more efficiently autoregulated in the infused kidney, as well as the significant increase in effective renal blood flow in the infused kidney, indeed may suggest that the renin-angiotensin system may play a role in limiting the extent of renal autoregulation.

Summary. The role of the renin-angiotensin system in the autoregulation of renal blood flow and glomerular filtration rate was examined in the dog. The angiotensin converting enzyme inhibitor, SQ20881, was continuously infused into one renal artery during a reduction in renal perfusion pressure to both kidneys. Renal autoregulation was maintained in the infused kidney despite the continuous infusion of a dose of SQ20881 which was shown to completely reverse the renal hemodynamic effects of exogenously administered angiotensin I in a second group of experiments.

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