Autoregulation of Glomerular Filtration in Renin-Depleted Dogs[1] (37354)

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Autoregulation of glomerular filtration has been attributed to activity of the renin–angiotensin system (1, 2). On the basis of micropuncture studies in normal and renin-depleted rats, Thurau *et al.* suggested that sodium concentration in the macula densa area of the distal tubule was a major determinant of afferent glomerular arteriolar tone (1). More specifically, it was proposed that high sodium concentrations in the distal tubule induced the release of renin from the macula densa which converted an α-2-globulin to angiotensin I which in turn was converted to angiotensin II, a vasoactive polypeptide, resulting in shutdown of the glomerulus associated with that nephron. In rats depleted of renin, autoregulation was said to be diminished or abolished (2). However, subsequent studies by Belleau and Earley indicated that renin-depleted dogs were capable of autoregulation of renal blood flow (3). No information is available as to whether or not autoregulation of glomerular filtration rate and filtration fraction occurs in the renin-depleted kidney. The present study was undertaken in an attempt to obtain such information and, in addition, to examine the effects of alterations of renal perfusion pressure on renal plasma flow and water, sodium, and potassium excretion in renin-depleted dogs.

Materials and Methods. Five adult mongrel dogs (1 male, 4 females) weighing 13.6–22.7 kg were used for the renin-depletion experiments. Each was treated daily with 6 g sodium chloride given orally and 12.5 mg desoxycorticosterone acetate (DOCA) in oil given intramuscularly for 6–8 days. The dogs were not fed for 18 hr prior to study, but had free access to water. They were anesthetized with pentobarbital sodium (approx 25 mg/kg body wt) administered intravenously and were then intubated endotracheally. Surgical anesthesia was maintained thereafter by supplemental doses of anesthetic. The left kidney was approached through the paralumbar fossa with the dog lying in right lateral recumbency. The left ureter was cannulated for urine collection and a silk snare was placed around the renal artery at the point of its origin from the aorta. A small polyethylene catheter was passed retrograde via a femoral artery and manipulated into the renal artery so that its tip lay about 1 cm proximal to the renal arterial bifurcation. One dog (Expt 3) had two small left renal arteries originating directly from the aorta. In this instance, the catheter was positioned in the aorta between the points of renal arterial origins and the snare was placed around the aorta proximal to the cranial renal artery. Renal arterial blood pressure was measured via the renal arterial cannula and systemic blood pressure was recorded from the opposite femoral artery using a Statham pressure transducer and a Sanborn multichannel recorder. In Expt 3, systemic blood pressure was recorded from a cannulated radial artery.

Two and one-half percent dextrose in water was infused into a jugular vein at the rate of 40–60 ml/kg over a period of 20–40 min to establish diuresis. Thereafter the rate of infusion was adjusted to correspond to the

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rate of urine flow. Infusion rates were not altered after sampling was begun. Creatinine and para-aminohippuric acid (PAH), after initial priming doses, were infused at a constant rate via a cephalic vein. Urine and plasma were analyzed for creatinine and PAH using a Technicon Autoanalyzer. The hematocrit of femoral arterial blood was determined by the microhematocrit method. Osmolality of urine and plasma was measured by depression of the freezing point and sodium and potassium by flame photometry.

When urine output reached a steady state, blood and urine samples were collected. The renal artery was then constricted using the snare so as to reduce renal perfusion pressure by approximately 10–20 mm Hg. Urine flow and renal arterial blood pressure usually stabilized within 30 min at which time the above collection and pressure-reducing procedures were repeated. In some instances, sampling was performed after increasing the renal arterial pressure by reducing the amount of arterial constriction. In this manner, two to seven determinations were obtained from each dog at different renal perfusion pressures. Urine was generally collected for 5-min periods; in those instances where the rate of flow was low, 10-min samples were collected.

Exogenous creatinine clearance was used as a measure of glomerular filtration rate (GFR). Filtration fraction (FF), osmolal clearance (C_{osm}), free water clearance (C_{H_2O}) and sodium and potassium excretion rates (UNa^+V and UK^+V) were calculated by standard methods. Renal plasma flow (RPF) was calculated as $C_{PAH}/0.8$. Renal blood flow (RBF) was then determined as RPF/(1.00 — Hct). Standard analyses were performed to determine best fitting regression lines between renal arterial blood pressure and GFR, RPF, FF, UV, UNa^+V and UK^+V (4).

Procedures identical to those described above were performed using two normal dogs, 1 male (14.1 kg) and 1 female (9.1 kg).

Results. Stepwise reductions in renal arterial blood pressure over the range of 175–85 mm Hg in renin-depleted and from 130–61 mm Hg in normal dogs was associated with little or no change in glomerular filtration rate or filtration fraction (Fig. 1). The

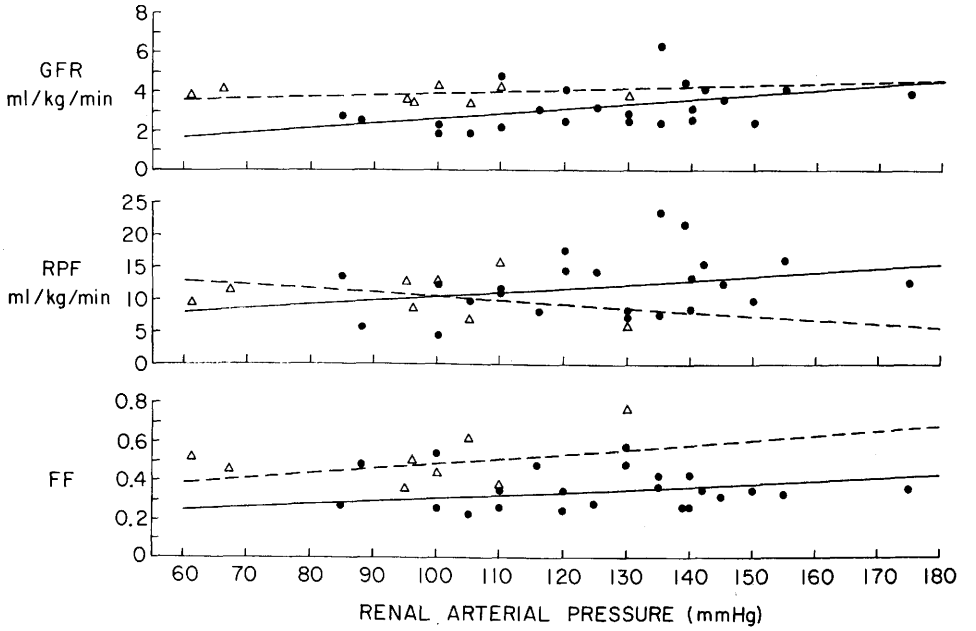

FIG. 1. The effects of decreasing renal arterial pressure on glomerular filtration rate (GFR), renal plasma flow (RPF) and filtration fraction (FF) in renin-depleted (closed circles and solid lines) and normal (open triangles and dotted lines) dogs.

TABLE I.

Experiment No.	RAP mmHg	RPF ml/kg/min	RBF ml/kg/min	C_{cr} ml/kg/min	C_{PAH} ml/kg/min
1	144	8.45	12.99	3.11	6.75
	130	7.62	11.36	2.99	6.09
	116	8.12	12.12	3.05	6.49
	88	6.90	10.13	2.59	5.49
2	150	9.94	17.74	2.45	7.27
	140	13.56	23.70	2.65	10.73
	125	14.54	25.90	3.13	11.62
	110	11.17	19.02	2.13	8.10
	100	12.25	21.10	2.36	9.37
	85	13.65	24.92	2.83	11.10
3	145	14.63	29.86	3.70	11.71
	120	12.50	23.59	2.49	10.01
4	175	12.41	--	3.59	9.94
	155	16.11	--	4.17	13.16
	142	15.45	--	4.14	11.36
	139	21.92	--	4.53	17.52
	135	23.47	--	6.61	18.66
	120	17.75	--	4.02	11.36
	110	11.36	--	4.95	14.26
5	135	7.95	13.23	2.50	5.93
	130	8.33	15.42	2.54	6.67
	105	9.89	19.57	1.92	7.92
	100	4.49	8.16	1.96	3.61
6 (Normal)	130	6.07	10.94	3.78	4.86
	105	7.00	13.34	3.43	5.59
	96	8.81	16.18	3.51	7.04
7 (Normal)	110	15.96	30.96	4.66	12.70
	100	12.78	22.84	4.34	10.20
	95	12.62	22.13	3.66	10.00
	67	11.56	20.11	4.11	9.20
	61	9.94	18.16	3.99	7.90

RAP = Renal arterial blood pressure;
RPF = Renal plasma flow;
RBF = Renal blood flow;
C_{cr} = Creatinine clearance;
C_{PAH} = para-aminohippuric acid clearance,
FF = filtration fraction;
C_{osm} = Osmolal clearance;

TABLE I. (cont.)

FF	C_{osm} ml/kg/min	UV ml/kg/min	$UNa^{+}V$ μEq/kg/min	$UK^{+}V$ μEq/kg/min	C_{H_2O} ml/kg/min
0.43	0.12	0.12	7.91	1.80	0.00
0.49	0.12	0.13	7.37	1.43	+0.01
0.48	0.12	0.12	7.32	1.54	0.00
0.48	0.08	0.06	6.73	0.99	-0.02
0.34	--	0.22	0.55	1.80	--
0.26	0.04	0.15	0.43	1.08	+0.11
0.29	--	0.22	1.09	2.48	--
0.26	--	0.07	0.14	0.73	--
0.26	--	0.07	0.13	1.14	--
0.27	--	0.08	0.22	1.14	--
0.31	0.07	0.25	0.06	0.85	+0.18
0.25	0.08	0.19	0.03	0.77	+0.11
0.35	0.20	0.36	12.86	3.62	+0.16
0.32	0.22	0.12	11.46	2.35	-0.10
0.34	0.16	0.10	9.71	2.35	-0.06
0.26	0.18	0.13	12.24	2.96	-0.05
0.36	0.14	0.08	8.56	2.40	-0.06
0.35	0.07	0.16	1.02	1.57	+0.09
0.35	0.21	0.09	2.96	2.94	-0.12
0.42	0.18	0.47	1.58	1.42	+0.29
0.57	0.22	0.57	1.98	1.02	+0.35
0.24	0.12	0.07	0.18	0.45	-0.05
0.54	0.10	0.19	0.41	0.17	+0.09
0.77	0.42	0.19	30.94	4.33	+0.17
0.61	0.21	0.17	8.06	3.34	-0.04
0.50	0.17	0.16	5.96	3.21	-0.01
0.37	--	0.39	1.77	2.24	--
0.43	--	0.25	1.40	0.65	--
0.36	--	0.16	0.61	0.61	--
0.44	--	0.14	0.09	0.40	--
0.51	--	0.01	0.12	0.28	--

UV = Urine volume;
$UNa^{+}V$ = Sodium excretion;
$UK^{+}V$ = Potassium excretion; and
C_{H_2O} = free water clearance.

results obtained in the individual experiments are shown in Table I. Fluctuations in renal blood flow and renal plasma flow were observed in each experiment. However, the changes were not always related to alterations in perfusion pressure. Urine flow, sodium and potassium excretion and osmolal clearance were consistently diminished as renal perfusion pressure was reduced. Below a perfusion pressure of 60 mm Hg, no urine was formed. Arterial hematocrit values were constant during each experiment.

Systemic arterial blood pressure did not change or was decreased in association with renal arterial constriction in renin-depleted dogs. Systemic pressure rose progressively in one normal dog and was unchanged in the other as renal perfusion pressure was reduced.

Discussion. The above results indicate that the glomerular filtration rate in kidneys from both normal and renin-depleted dogs autoregulates over a wide range of renal perfusion pressures. The findings are not in agreement with the autoregulation hypothesis proposed by Thurau *et al.* (2) which requires activation of angiotensin II through renin in order to effect glomerular arterial constriction, since the dogs in the present study were renin-depleted. Hence, it would seem unlikely that the control of filtration at an individual glomerulus is affected by changes in renin release that are related to alterations in the sodium concentration present in the distal tubule associated with that glomerulus. In addition, Gottschalk and Leyssac have performed micropuncture studies and found that retrograde injections of hypertonic sodium chloride into the distal tubule was not accompanied by the tubular collapse that would be indicative of glomerular shutdown (5). It has been suggested that the discrepancy between this study and that of Thurau, in which tubular collapse was noted, may be explained by the observation that the former studies were performed on intact kidneys, whereas the latter were done using decapsulated kidneys (5).

The experiments of Belleau and Earley demonstrated autoregulation of renal blood flow subsequent to reductions in renal arterial blood pressure before, during and after infusions of angiotensin (3). In the present study, calculated renal plasma and blood flows were relatively stable. However, failure to demonstrate autoregulation of renal plasma and blood flow under the experimental conditions may have been related to changes in the extraction ratio of PAH following renal arterial constriction.

Measurements of plasma renin activity or renin content of the kidneys were not made in these experiments. However, in a previous study we reported that pretreatment of dogs with DOCA and salt has been shown to be associated with very low levels of renal venous renin. Furthermore, no significant elevation in renin levels was observed following reduction of renal arterial pressure to one-half of the systemic arterial pressure for 40 min in depleted dogs, whereas a fourfold increase in renin activity occurred in the control (6).

The data obtained in the present experiments, using renin-depleted dogs, indicate that urine flow and the excretion of sodium, potassium, and water are diminished in proportion to reductions in renal perfusion pressure while GFR is not changed. These findings are similar to those described by Selkurt (7) and Blake *et al.* (8) who used normal dogs. Tobian, in his consideration of those studies, suggested that renin may have been responsible for the phenomenon (9). He proposed that renin might influence the tubular epithelium so as to effect an increase in sodium reabsorption under conditions of reduced renal perfusion. Conversely, in association with high perfusion pressures, renin release would be shut off with a subsequent increase in sodium excretion. However, the fact that the studies reported here utilized renin-depleted dogs would appear to preclude the possibility of a role for renin. In the interpretation of the results obtained in his study, Selkurt considered that interstitial pressure might vary in proportion to perfusion pressure and thus influence diffusion in such a manner that high interstitial pressure would impede and low pressure enhance sodium and water reabsorption (7). Subsequent studies have shown, however, that interstitial pressure is not affected by changes in perfusion pressure

(10). It has been suggested that medullary blood flow does not autoregulate. If so, it is possible that the influence of perfusion pressure on water and electrolyte excretion is related to medullary blood flow (10).

Summary. Reduction of renal arterial pressure in normal and renin-depleted dogs was associated with little or no change in glomerular filtration rate or filtration fraction. Urine flow, sodium and potassium excretion and osmolal clearance were consistently diminished. The results indicated that activation of angiotensin II through renin was not necessary for autoregulation of glomerular filtration and filtration fraction.

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