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Relation of Renal Arterial Pressure to Activity of Renin-Angiotensin System in Renal Hypertension.* (32023)

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Previous studies in both the rat(1,2) and the dog(3) demonstrate clearly that experimental renal hypertension can be divided into two distinct phases. There is an acute phase characterized by the presence in both the renal vein blood and the general circulation of a potent vasopressor agent with properties similar to angiotensin. After approximately 2 weeks a chronic phase ensues in which, despite the persistence of the hypertensive state, blood from the renal vein and from the general circulation ceases to show vasopressor activity. This is in accord with reports that the levels of plasma renin(4,5) or angiotensin (6), are elevated in dogs with early renal hypertension and are normal in the chronic stage.

Since renal arterial pressure(7,8,9,10,11) is probably the factor which governs the release of renin by the juxtaglomerular apparatus of the kidney, the present study was undertaken to determine whether the change in activity of the renin-angiotensin system during the course of renal hypertension could be correlated with the levels of renal arterial pressure.

Method. Production of unilateral hypertension. One hundred ninety-five white male rats weighing about 200 g were used. Under nembutal anesthesia the abdominal aorta just above the ostium of the left renal artery was reduced to a diameter of 0.25 mm by ligating the vessel around a stylet of this diameter and then removing the stylet. This led to rapid ischemic atrophy of the left kidney while the right kidney remained intact.

Determination of systemic blood pressure and the left renal arterial blood pressure. Mean systemic blood pressure was obtained under anesthesia by inserting a polyethylene catheter into the brachial artery and connecting it to a Hg manometer. Control readings were made prior to the operative procedure. The mean pressure in the left main renal artery was determined in a similar manner by inserting a catheter into this vessel and directing it toward the aorta. Since the artery had to be ligated on withdrawing the catheter, only one reading could be obtained for each animal and the rat was then discarded. Determinations of both the systemic and the left renal arterial pressure were made at intervals of stat to 6 months after constriction of the aorta.

From past experience in our laboratory it was known that following constriction of the aorta the pressures in both the femoral and the left renal artery are quite similar or even identical. This observation was useful since the renal arterial pressure could be taken only once, while arterial pressure could be obtained several times in the same femoral vessel. By following the femoral arterial pressure serially in all rats, especially during the first 2 weeks after operation, the animals could be divided into groups with either a rapid, or average, or slow return to normal of the arterial pressure distal to the aortic constriction. With these

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results serving as a guide, the renal arterial pressure was then taken at an appropriate time as the final step in the experiment.

Assay for vasopressor material. Samples of blood (0.5 ml each) were obtained from the left renal vein (ischemic kidney) by venipuncture and assayed immediately for the presence of vasoconstrictor activity(1). The samples were injected through a polyethylene catheter into the femoral vein of recipient rats which had received pentolinium tartrate subcutaneously (4 mg/100 g body weight) for ganglionic blockade. The response of the recipient was measured by the rise in mean blood pressure in mm Hg as read directly from a Hg manometer connected by a polyethylene catheter to the femoral artery, or as recorded by a Statham gauge manometer on a Grass polygraph. Each assay on a hypertensive rat was controlled by injecting the same recipient with 0.5 ml left renal vein blood from a sham operated or intact normotensive animal.

A total of 192 assays for pressor material was performed at intervals from 1 day to 6 months after contriction of the aorta on hypertensive rats whose renal arterial pressure ranged from 38 to 150 mm Hg. An assay was considered positive when it produced a rise in blood pressure in the recipient rat which exceeded by at least 8 mm Hg the rise produced by normotensive control blood. In the great majority of positive assays the elevation of pressure obtained with hypertensive blood exceeded that from normotensive blood by 10-44 mm Hg. The type of response was similar to that observed with synthetic angiotensin. The blood pressure of the recipient began to rise within several seconds, reached a peak at about 1 minute, and then returned to the initial base line in about 3-5 minutes. Renal vein blood from the normotensive control rats uniformly elicited either a minimal response (2-8 mm Hg) or none at all.

Levels of plasma renin in renal vein blood. Plasma renin was determined according to a method recently described by Gould and others(12). Two ml of blood was withdrawn from the renal vein for each analysis and was collected in a syringe containing 1 or 2 drops of heparin. The plasma was treated so as to be free of angiotensinase activity, dialyzed, and then incubated with an excess of hog renin substrate. This provided a zero order reaction velocity of angiotensin formation. The concentration of angiotensin was measured by means of a direct rat pressor assay and the results were expressed as nanograms of angiotensin II formed per ml of plasma.

TABLE I. Systemic and Renal Arterial Blood Pressure.

	Brachial arterial pressure		Renal arterial pressure	
Time*	Mean	Range	Mean	Range
Stat			36	22- 40
1 day	150	136-174	48	32- 60
3 days	164	140-190	60	40- 78
1 wk	180	162-212	72	48-116
2 "	200	170-220	100	62-136
1 mo	206	170-230	110	70-138
6 wk	196	180-240	110	80-156
2 mo	216	180-300	116	86-154
3 "	210	176-300	126	90-150
6 "	206	174-290	130	100-170

* From 12 to 18 renal arterial pressures and from 18 to 22 brachial arterial pressures were taken at each time interval after constricting the aorta.

Analyses were performed on blood withdrawn from a group of 14 rats between 1 and 7 days after constriction of the aorta and at a time when the left renal arterial pressure ranged from 38 to 72 mm Hg. Determinations on a second group of 14 rats were made on samples taken between 1 and 6 months after constriction of the aorta at a time when the left renal arterial pressure ranged from 96 to 150 mm Hg. Control values were obtained on 18 animals which were either normal or sham operated.

Results. Systemic and renal arterial blood pressures. Table I shows the mean systemic blood pressure at intervals from 1 day to 6 months after constriction of the aorta. Hypertensive levels were reached almost uniformly within a few days and at 2 weeks the mean pressure was 200 mm Hg. The pressure then remained in the hypertensive range over the 6 month period of the study.

The pressures in the left main renal artery are shown in Table I. Starting from a mean of 36 mm Hg immediately after the aorta was constricted, the renal arterial pressure of all rats showed a gradual and progressive rise

TABLE II. Pressor Activity of Renal Vein Blood in Relation to Renal Arterial Pressure.

BP (mm Hg)	No. assays	No. pos.	No. neg.
≤80	65	60 (92%)	5 (8%)
>80	102	6 (5%)	96 (95%)

TABLE III. Assays of Renal Vein Blood for Vasopressor Material.

Time performed	No. performed	No. positive	% Positive
1-7 days	50	42	84
2 wk	34	9	26
1 mo	40	6	15
6 wk	28	3	11
2 mo	18	2	11
3-6 mo	22	0	0

with time. The mean value was 60 and 72 mm Hg at 3 days and 1 week respectively. The pressure in most animals reached at least 80 mm Hg between 1 and 2 weeks and at 2 weeks and 1 month was 100 and 110 mm Hg respectively, *i.e.,* in the range of normal renal arterial pressure. There was a further slight rise over the next few months and at 6 months the mean level was 130 mm Hg. While in most instances the pressures obtained at 3 and 6 months were either within the normal range or slightly to moderately higher than normal, several animals reached hypertensive levels of 150-170 mm Hg. The renal arterial pressures at all time intervals after constriction of the aorta were 50-110 mm Hg lower than the systemic pressure as measured simultaneously in the brachial artery. In other words the pressure gradients across the constriction in the aorta were similar in the acute and chronic stages of hypertension.

While the renal arterial pressure generally returned to at least 80 mm Hg within 1-2 weeks after constriction of the aorta, some rats attained this level within 3 days to 1 week. On the other hand in a small number of animals the elevation of pressure occurred at a slower rate and 2-4 weeks elapsed before a level of 80 mm Hg was reached. Two rats required 8-10 weeks to reach this level. However in no instance was there a renal arterial pressure below 90 mm Hg at 3 months or one below 100 mm Hg at 6 months.

Assays for vasopressor material. The vasopressor activity of samples of blood taken from the left renal vein of hypertensive rats correlated closely with the level of the left renal arterial pressure (Table II). Of 65 rats whose blood was assayed when the pressure was 80 mm Hg or less, *i.e.,* from 1 day-8-weeks after constricting the aorta, 92% yielded positive tests. In contrast when renal arterial pressure was above 80 mm Hg, as in the case of 102 rats which were assayed from 3 days-6-months after constricting the aorta, 95% of the tests were negative.

As shown in Table III the incidence of positive assays could also be correlated with the duration of the hypertensive state. The great majority of tests made on blood withdrawn from the left renal vein during the first week after constricting the aorta were positive. The incidence of positive tests declined substantially between the first and second weeks and only 15% of the assays performed at one month were positive. Rats which yielded a positive assay at 2 weeks were retested serially at intervals of a few days to 1 week until they became negative. Only 2 hypertensive animals still remained positive at 6 weeks and these became negative at 2 months and 10 weeks respectively. All assays performed on rats which had been hypertensive for 3-6 months were negative for vasopressor material.

Levels of renin in renal vein blood. Table IV shows the levels of renin in left renal vein blood from hypertensive rats and from normotensive control rats. The samples from hypertensive rats were withdrawn from 1-7 days after constricting the aorta, at a time when the renal arterial pressure was uniformly below 80 mm Hg. The levels of renin in these animals, expressed as nanograms of

TABLE IV. Renin Levels in Renal Vein Plasma.*

Rats	Time obtained	No. levels obtained	Ng angiotensin Mean	Ng angiotensin Range
Normal		18	75	60-100
Acute renal hypertension	1-7 days	14	160	120-200
Chronic renal hypertension	1-6 mo	14	42	24- 55

* Expressed as nanograms angiotensin II formed per ml of plasma.

angiotensin II formed per ml of plasma, were uniformly higher than the levels present in renal vein blood obtained from the sham operated control rats, *i.e.*, a mean of 160 ng as against 76 ng. On the other hand determinations of renin made on blood withdrawn from the left renal vein of hypertensive rats at intervals of 1-6 months after constricting the aorta and when the renal arterial pressure was uniformly above 80 mm Hg (92-150 mm Hg), yielded a mean level of 42 ng which was approximately half the mean value obtained for the normotensive controls.

Discussion. Our findings agree fairly well with those of Bounous and Shumacher(13) who studied dogs rendered hypertensive by means of a unilateral renal artery clamp. Renal arterial pressure distal to the stenosis was reduced at 10 minutes and 1 hour after applying the clamp but returned to normal levels 3 months later. Stahl(14) reported that renal arterial pressure in dogs subjected to coarctation of the aorta was initially lower and then later returned to normal levels.

In this study 2 parameters of renal humoral pressor activity correlated closely with the level of renal arterial pressure. When the latter was below 80 mm Hg, as during approximately the first week or two after constricting the aorta, blood taken from the renal vein contained a potent vasopressor agent and also an elevated content of renin. By 2 weeks renal arterial pressure had usually reverted to normal or near normal levels and this was associated with, and probably responsible for, a decline in juxtaglomerular activity as reflected in disappearance of the vasopressor agent from renal vein blood as well as a marked reduction in the output of renin. The rise in renal arterial pressure from its initial low level was probably due to the increase in pressure proximal to the constriction, *i.e.*, systemic hypertension, and to the development of collateral circulation to the injured kidney.

Although a few animals required some 8-10 weeks before renal arterial pressure was restored to normal levels there was not a single rat in which a pressure of 80 mm Hg or less persisted indefinitely or in which either vasopressor material or an elevated content of renin continued to be demonstrable in renal vein blood. These findings suggest that the etiologic participation of the renin-angiotensin system is limited to the acute stage of renal hypertension. The chronic stage is apparently sustained by some mechanism other than a renal humoral one.

Renal arterial pressure and hence presumably the intraluminal pressure in the vasa afferentia governs the vasomotor tone of these vessels(15,16,17) and thus appears to be an important factor in regulating the discharge of renin from the kidney. A significant reduction in pressure results in loss of tonus and dilatation of the arteriole which, in turn, through a mechanism not clearly defined or perhaps a stretch reflex(18), causes increased release of renin from the juxtaglomerular apparatus. Just the opposite occurs with increased afferent arteriolar pressure since vascular tonus is enhanced, the arteriole contracts, and the release of renin is diminished.

Both the tonus of the renal arterioles and the autoregulation of renal blood flow are homeostatically related to renal arterial pressure. Following constriction of the renal artery Schmid and Spencer(19) found that renal blood flow was autoregulated until the renal arterial pressure was reduced to 70 mm Hg. Shipley and Study(20) reported that renal blood flow was autoregulated at pressures above 80 mm Hg where efferent arteriolar tone begins while glomerular filtration rate is autoregulated at pressures of 100-110 mm Hg where afferent arteriolar tone begins. In our study excess activity of the renin-angiotensin system was demonstrable only at renal arterial pressures below 80 mm Hg, *i.e.*, presumably when autoregulation of renal blood flow was absent.

While reduced renal arterial pressure was primarily responsible for the enhanced release of renin in our animals, possibly this operated at least in part through a sodium mechanism rather than solely by way of its hemodynamic effect. No doubt the effect of reduced renal arterial pressure on the renin-angiotensin system can be modified by a salt load or by restriction of salt or by the use of diuretics (5,21). However none of these is applicable to this study. On the other hand, the low

renal arterial pressure in our rats would be expected to reduce the amount of filtered sodium in the kidney(22,23,24) and perhaps increase tubular reabsorption of sodium(21) and these, in turn, would reduce the concentration of sodium at the macula densa and diminish its excretion by the kidney. The association of low renal arterial pressure with increased release of renin is compatible with the proposal by Vander(21) that renin release is inversely proportional to sodium excretion. However, our results are difficult to reconcile with other studies which present evidence that a low sodium concentration at the macula densa(25) or decreased osmolarity of the distal tubular fluid(26) results in constriction of the afferent arterioles and hence diminishes the output of renin.

Summary. Unilateral renal hypertension was produced in rats by constricting the aorta just above the ostium of the left renal artery. This caused a sharp reduction in renal arterial pressure which usually remained below 80 mm Hg for 1 to 2 weeks. During this interval the renal vein blood contained a potent vasopressor agent and an elevated content of renin. By 2 weeks the left renal arterial pressure had returned to normal levels in most animals and this was associated with disappearance of the vasopressor agent from renal vein blood as well as a marked reduction in the output of renin. Not a single rat was encountered in which a low renal arterial pressure persisted indefinitely or in which the kidney continued to produce excess vasopressor material or to discharge an increased amount of renin. These findings indicate that(1) in unilateral renal hypertension the renal arterial pressure probably governs the release of renin by the kidney and that(2) low renal arterial pressure and hence increased activity of the renin-angiotensin system are limited to the early or acute stage of renal hypertension.

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