Renal Baroreceptor Control of Acute Renin Release in Normotensive, Nephrogenic and Neurogenic Hypertensive Dogs

By Sandford L. Skinner, M.D., James W. McCubbin, M.D., and Irvine H. Page, M.D.

Normal kidneys have recently been shown to possess a pressure sensing mechanism that responds to small reductions in mean renal arterial perfusion pressure by increasing the rate of renin secretion.1,2 This baroreceptor function of the kidney is operative within physiological ranges of pressure and thus may be a homeostatic mechanism participating in control of normal arterial pressure. The term “renal baroreceptor” is used in its broadest sense to indicate a system within the kidney that responds to change in perfusion pressure by altering the rate of renin secretion.

We have suggested that dysfunction of the renal baroreceptor may be concerned in the genesis and maintenance of renal hypertension.1 Since renin secretion is suppressed in normal animals when perfusion pressure is raised,2 if renin release occurs in renal hypertension, the working range of the baroreceptor must be changed. Absence of a change would be strong evidence against participation of the renin-angiotensin system in hypertension. To determine whether an altered range of responsiveness might be unique to nephrogenic hypertension, the range of the renal baroreceptor response has also been determined in dogs with chronic neurogenic hypertension.

Methods

Adult, mongrel dogs weighing 10 to 20 kg were selected on the basis of a mean arterial pressure of less than 135 mm Hg as measured by direct puncture of a femoral artery with the untrained dog lying on its back while being gently restrained. Renal hypertension was produced by placement of a Goldblatt clamp and contralateral nephrectomy or by the perinephritis method of Page; chronic neurogenic hypertension was produced by section of the carotid sinus and aortic depressor nerves. Animals were used only when mean femoral arterial pressure, measured weekly, had been 170 mm Hg or more for at least four weeks.

After an overnight fast, a final blood pressure measurement was taken without anesthesia the morning of the experiment. Sodium pentobarbital (30 mg/kg iv) was selected as the anesthetic agent because its vagoparalytic action increases heart rate and, in normal dogs, causes a higher arterial pressure than present before anesthesia. Our previous experiments indicated that such an increase in renal perfusion pressure would reduce renin secretion. Under these circumstances, it should be possible to lower perfusion pressure in a stepwise fashion and so detect at what level an increased rate of renin release occurs.

Following anesthesia the left renal pedicle was exposed retroperitoneally through a flank incision and the probe of a noncannulating square-wave electromagnetic flowmeter* applied to the left renal artery. The validity of this method for measuring renal blood flow has been discussed previously.2 A tape was passed around the aorta above the renal arteries and made into a sliding noose by passing both ends through a short length of polyethylene tubing. Using this tape the aorta could be constricted to produce graded reductions of pressure in the renal arteries. At the end of each experiment the position of the tape was examined and found to be at least one-half inch above both renal arteries. Renal venous blood was collected as required through a polyethylene catheter (outside diameter 1.5 mm), threaded into the left renal vein via the

* Carolina Medical Electronics.
left testicular or ovarian vein and passed peripherally into the hilum. Pressure in the aorta at the level of the renal arteries was recorded continuously by means of a strain gauge manometer and a polyethylene catheter passed through a femoral artery. Intermittent positive pressure respiration was delivered by a piston-type respirator. Five per cent dextrose in physiological saline was given by slow intravenous drip.

**PLASMA PRESSOR ASSAY**

The details of this method have been discussed previously. Briefly, 5 ml samples of arterial and renal venous blood were collected simultaneously and mixed with disodium ethylenediamine tetraacetic acid, (EDTA, 5 × 10⁻³ M) which acted both as an anticoagulant and an inhibitor of angiotensinase A. The blood was immediately cooled to 8°C and centrifuged while cold. The plasma was separated, divided into three portions, and then frozen within ten minutes of collection. At a later time two portions of each plasma sample were incubated for one hour and four hours respectively. The pH of plasma remained at 7.4 ± 0.05 throughout as measured by pH meter.

The pressor activity generated in plasma as a result of incubation was assayed using anesthetized rats treated with pentolinium in the manner previously described. The volume of plasma injected was 0.1 ml in all instances.

**DETECTION OF AN INCREASED RATE OF RENIN SECRETION**

The premise for concluding that under the conditions of these experiments increased pressor material in incubated renal venous plasma indicated increased renin secretion has been fully discussed elsewhere. In the present investigation two additions have been made to the original criteria: (1) A difference in pressor activity between plasma samples was considered significant only if it amounted to 25% or more of the standard response to 2 mg (nanogram = 10⁻⁹ grams) of angiotensin in that rat. (2) Using the electrophoretic method of angiotensin separation developed by Smeby et al., further confirmation has been obtained that the pressor material in incubated plasma is angiotensin. Smeby applied his method to selected incubated plasma samples, some of which from the rat assay, were considered to contain angiotensin and others were thought to contain little or none. The two techniques, his and the one used in these experiments, gave parallel results, each detecting approximately the same amounts of angiotensin.

**Results**

In seven normal dogs the aorta was constricted above the kidneys so as to cause progressive 20 mm Hg reductions of pressure in the aorta and the renal arteries for periods of 15 minutes. Figure 1 shows one such experiment and demonstrates the technique that has been used in all subsequent experiments to determine the range of renal perfusion pressures over which release of renin occurs. Renal perfusion pressure was reduced from 110 to 50 mm Hg in 3 steps of 20 mm Hg. Left renal blood flow decreased with each reduction of perfusion pressure. At the times indicated (1 to 5) samples of arterial and renal venous blood were collected and the plasma samples were prepared for assay. The four lower tracings in figure 1 show the results of corresponding plasma assays and illustrate in detail the manner in which the timing and degree of increased renin secretion were detected. In all assays, 2 ng of angiotensin (A) were injected at regular intervals to determine the sensitivity of the rat.

The level at which an increase in pressor activity was considered significant has been discussed in Methods. After one hour of incubation at 37°C, it is apparent that samples 3 and 4 of renal venous plasma display significant increase in pressor activity over the control samples, whereas the response to sample 2, although larger than the control, is not considered to be changed significantly. After prolonging the incubation time to four hours, the response to sample 2 is clearly larger than those to samples 1 and 5. Increased pressor material therefore appeared in renal venous blood incubated four hours when perfusion pressure was reduced to 90 mm Hg from the resting level of 110 mm Hg. Tracings of the relevant responses to these samples incubated for four hours have been placed in the upper record at the respective times of sampling in order that the time of appearance of increased pressor material can be seen more readily. That the pressor material is angiotensin was confirmed by using the criteria previously described.

During more prolonged and severe reductions of renal perfusion pressure, renin is released in even larger amounts, and angiotensin can be detected in unincubated renal ve-
Detection of increased renin secretion during reduction of renal arterial perfusion pressure produced by graded aortic constriction. Normal dog, no. 4, table 1. Above: mean blood flow in left renal artery and mean pressure in aorta. Numbers refer to the times of sampling of arterial and renal venous blood. Pressor responses to four hour incubated plasma are traced across the record. Middle: assays of pressor activity in one and four hour incubated renal venous plasma using the rat blood pressure method. Bottom: (left) arteriovenous difference in one hour incubated plasma; (right) unincubated renal venous plasma. A: angiotensin 2 ng (0.1 ml), a: arterial plasma (0.1 ml), v: renal venous plasma (0.1 ml).
RENNIN RELEASE IN HYPERTENSIVE DOGS

In unincubated samples, kept cold from the time of collection to prevent further formation of angiotensin by renin, significant pressor activity appeared during the most severe reduction in perfusion pressure. Sample 4 showed considerable activity, and it is probable that sample 3 also had more activity than samples 1 and 5.

The moderate and prolonged rise of systemic pressure following release of aortic constriction probably depends in the main on previous release of these large amounts of renin into the peripheral circulation. This is also illustrated at the bottom of figure 1 by the arteriovenous difference between plasma pressor activities across the kidney before and during aortic constriction. Control samples show little activity in either arterial or venous blood after one hour of incubation, but the samples designated 3, taken when perfusion pressure was 75 mm Hg, show considerable activity in both arterial and venous blood. The greater activity of renal venous plasma, compared with arterial plasma, indicates that the kidney is secreting renin. During a 20- to 30-minute period following release of aortic constriction, pressor activity largely disappears.

Table 1 summarizes the findings in the normal dogs. In most experiments, pentobarbital anesthesia itself caused a rise in mean arterial pressure. This higher than normal renal perfusion pressure had the advantage of providing a resting pressure level well above the expected range for renin release, thus permitting detection when perfusion pressure was lowered in steps as near 20 mm Hg as possible. An increased rate of renin secretion could be detected in the range 120 to 70 mm Hg when the renal venous samples were incubated for one hour. With the more sensitive index of renin secretion provided by 4-hour incubation, renin release could be detected at a slightly higher range of pressure, 120 to 90 mm Hg. Removal of the right kidney from dog no. 7 two weeks previously did not cause the level at which renin was released to differ from normal dogs.

Renal blood flows before aortic constriction and at the end of the first 15-minute period during which an increased rate of renin secretion was first detected are also included in table 1. There were small decreases in most experiments which contrast with our previous experiments. This is accounted for in large part by the arbitrarily selected 20 mm Hg reductions of perfusion pressure employed. The previous experiments involved carefully graded constrictions of the aorta with the purpose of avoiding change of flow. Since those experiments established that renin release occurs in the absence of change in blood flow, it was not considered important to avoid flow changes in the present experiments, especially in view of the more prolonged, stepwise reduction of perfusion pressure. As renin is released and angiotensin accumulates in cir-

**TABLE 1**

<table>
<thead>
<tr>
<th>No.</th>
<th>Wt (kg)</th>
<th>Mean arterial pressure Unanesthetized</th>
<th>Anesthetized</th>
<th>Perfusion pressure at which renin increased</th>
<th>Left renal blood flow Control</th>
<th>During renin release</th>
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<tr>
<td></td>
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<td>155</td>
<td>110</td>
<td>110</td>
<td>115</td>
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</table>

* Two renal arteries (flow not measurable).
† Right nephrectomy two weeks previously.
culating blood, it probably causes renal vasocostriction and thus tends to reduce flow. This would explain why renal blood flow remains reduced for long periods in some experiments after release of aortic constriction, as illustrated in figure 1. Since renin release ceases when mean pressure rises, despite persistent lowered flow, the effect is probably of no consequence in the present experiments.

**RENAL HYPERTENSIVE DOGS: PERINEPHRITIS HYPERTENSION**

Six dogs were made hypertensive by the perinephritis method of Page and, when hypertension of not less than 170 mm Hg had been present for a minimum of four weeks, were subjected to altered renal perfusion pressures in the same manner as in the normal dogs. Figure 2 illustrates one of these experiments on a dog hypertensive for five weeks. From a resting pressure level of 185 mm Hg, renal perfusion pressure was reduced in steps of approximately 20 mm Hg; renin secretion was increased in sample 2 taken at 165 mm Hg. Only the relevant assays have been included in this diagram but, as in normal dogs, all the necessary criteria that this pressor material reflected increased renin secretion were fulfilled. Sample 3 of renal venous plasma, taken at a pressure of 140 mm Hg, demonstrated an even more striking increase in pressor activity, while the unincubated samples did not vary significantly from the control. Movement of the dog at a perfusion pressure of 140 mm Hg caused transient decreases of pressure, but these would not be expected to influence the amount of renin in samples taken ten minutes later. Previous experiments show that release of renin due to transient reduction of perfusion pressure stops within a minute or two after reinstating normal perfusion.

The data for all perinephritis hypertensive dogs are included in table 2. In contrast with normal dogs, mean arterial pressure was usually lowered slightly by pentobarbital anesthesia. In four of the six dogs, aortic constriction caused renin secretion at much higher levels of perfusion pressure than in normal dogs and, again, in the absence of major reduction in blood flow. This is especially evident in the 4-hour incubated plasma.

Two of the dogs did not conform to this pattern. The control plasma of no. 5 displayed a remarkable amount of pressor activity (more than 40 ng/ml after 1 hr of incubation), and reduction of renal perfusion pressure did not cause more to appear. On the day previous to the experiment, this dog became obviously ill and arterial pressure had risen over a few days to 225 mm Hg from previously recorded levels of 190 mm Hg. The findings suggest that the rate of renin secretion was already maximal at the resting pressure level. Dog no. 6, in contrast with the

**Table 2**

<table>
<thead>
<tr>
<th>No.</th>
<th>Wt (kg)</th>
<th>Mean arterial pressure</th>
<th>Perfusion pressure at which renin increased</th>
<th>Left renal blood flow</th>
<th>Duration of hypertension and comments</th>
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<tr>
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<td></td>
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<td>14.8</td>
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<td>190</td>
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</tr>
<tr>
<td>6</td>
<td>10.8</td>
<td>190</td>
<td>190</td>
<td>Not †</td>
<td>Not †</td>
</tr>
</tbody>
</table>

* Flow from the larger of two renal arteries.
† High renin levels in control plasma before a drop in pressure.
‡ Not released at 120 mm Hg, the lowest pressure at which measured.

This may explain, perhaps, the failure of renin secretion.

RENAL HYPERTENSION: GOLDBLATT CLAMP

Table 3 summarizes the data from experiments on four dogs with chronic hypertension due to application of a Goldblatt clamp and contralateral nephrectomy. Again in contrast...
with its effect on normal dogs, anesthesia caused lowering of arterial pressure and the effect was more pronounced than in the dogs with perinephritis hypertension. Because of the development of extensive collateral arterial blood supply to the kidney it was not possible to measure the total renal blood flow.

Samples of renal venous plasma incubated for one hour revealed that increased pressor activity appeared in three of the four dogs when aortic pressure was still above the range at which renin secretion increased in normal dogs. These data suggest that renin secretion is increased at aortic pressures higher than those at which it occurs in normal dogs, but the pressure drop across the clamp on the renal artery results in a significantly lower actual perfusion pressure. This was measured directly by needle and strain gauge transducer during aortic constriction; the values at the time of increased renin release are presented in table 3. They all fall well within the range for normal dogs. The perfusion pressures beyond the clamp before aortic constriction are also within the normal range.

Simultaneous measurements of pressure on either side of the clamp during reductions of pressure induced by aortic constriction, and during rises induced by carotid occlusion, revealed that the pressure gradient across the clamp did not alter by more than 5 mm Hg when aortic pressures were made to vary over a range of 120 to 200 mm Hg.

**NEUROGENIC HYPERTENSIVE DOGS**

Table 4 presents the data from 8 experiments on dogs with chronic neurogenic hypertension due to section of the carotid sinus and aortic depressor nerves. As in the renal hypertensive dogs, pentobarbital anesthesi...
themia usually caused a fall in arterial pressure; in experiments no. 3 and 6 this effect was marked and resulted in normal arterial pressure. On reducing renal perfusion pressure, increased renin secretion was detected over a fairly wide range of pressures, and in three experiments secretion increased at pressures slightly higher than in normal dogs. In none of the experiments, however, did 4-hour incubation of the plasma samples reveal renin secretion at perfusion pressures above 130 mm Hg. This is in contrast with five of the six perinephritis hypertensive dogs which secreted renin at perfusion pressures of 140 mm Hg or above.

**PRESSOR ACTIVITY IN CONTROL RENAL VENOUS PLASMAS**

Four hours of incubation of renal venous plasma collected before aortic constriction caused some pressor activity to appear in nearly all samples, and in those from normotensive as well as hypertensive dogs. Since incubation of plasma may generate pressor material unrelated to the renin-angiotensin system, electrophoresis and the other criteria described were used to establish that the active material was angiotensin. Apart from the one dog with accelerated hypertension, the amount of angiotensin generated was less than 20 ng/ml in both normal and hypertensive dogs. Because of the number of dogs and the design of the experiments, it is not possible to make a quantitative comparison to determine whether resting plasmas from one group of dogs generate more angiotensin on incubation than those from another. The experiments were concerned exclusively with the range of pressures at which a significant increase in renin secretion could be detected in individual animals.

**Discussion**

The renal baroreceptor mechanism controlling secretion of renin is operative at the higher systemic arterial pressure levels found in dogs with hypertension due to perinephritis. Decreases of aortic perfusion pressure caused the usual release of renin into renal venous blood, but at pressure levels well above those causing release in normal dogs. In dogs made hypertensive by a clamp on a renal artery, although systemic arterial pressure was elevated, actual renal perfusion pressure beyond the clamp was in the normal range, which is in accord with observations of Mason, Robinson and Blalock. Not only were perfusion pressures normal, but small decreases caused release of renin in the same range of pressure as in normal dogs. Thus, in this type of hypertension there is no apparent change in sensitivity of the mechanism that initiates release of renin. The constricting clamp on the renal artery protects the renal baroreceptor from the higher systemic pressure and, since the pressure drop across the clamp was found to be essentially the same over a fairly wide range of pressures, a fall in the elevated systemic arterial pressure produces a lower than normal perfusion pressure.

Renal hypertension due to perinephritis was associated with release of renin at sharply higher levels of renal perfusion pressure than in normal dogs, but it is not known whether this depends upon an effect similar to that produced by a constricting clamp on the renal artery. It is possible that a drop of arterial pressure occurs at some point within the kidney, resulting in a "protective" action similar to that produced by the clamp. Alternatively, the compressing effect of the perinephritic hull may have a more direct action on the baroreceptor to reduce its sensitivity. In either case, an elevated systemic pressure would eventually be sensed by the baroreceptor as normal, and, as in the case of the carotid sinus buffering mechanism, because of an upward shift in threshold and range of responsiveness in renal hypertension, the renal baroreceptor would oppose any fall in systemic pressure and thus maintain the elevated level.

Because of the possibility that constriction of a main renal artery and a perinephritic hull each influence the renal baroreceptor by a different mechanism, the basic initiating cause of hypertension may not be the same, but in both forms of hypertension the renin-
angiotensin system could be a factor helping to maintain the established pressure.

Renal baroreceptor responsiveness in the group of neurogenic hypertensive dogs differed from that of dogs with perinephritis hypertension. As a group, with but minor deviations, responsiveness was in the same range as in normal dogs. This suggests that change in renal baroreceptor responsiveness does not occur solely as a passive effect of chronically elevated arterial pressure. From results obtained with indirect methods, Forster and Maes calculated that afferent renal arteriolar resistance increases during acute neurogenic hypertension in rabbits. While it is not known if this occurs in the chronic neurogenic hypertensive dog, it does not appear to be a major factor influencing renal baroreceptor responsiveness. It might, however, have accounted for the occasional small rise in threshold of responsiveness in the group of neurogenic hypertensive animals.

The suggestion that the kidney contains some type of receptor sensitive to a hemodynamic change that controls secretion of renin is not new, but previous investigations have necessarily employed indirect methods, and the existence of regulatory receptors has been inferred. Goormaghtigh originally suggested a combination of anoxia and hypotension as the stimulus to renin secretion. The later experiments of Divry and Huidobro and Braun-Menéndez seemed to exclude anoxia as a stimulus; Huidobro and Braun-Menéndez favored renal ischemia as the stimulus and Divry postulated a barosensitive device. The findings of Kohlstaedt and Page also indicated a barosensitive mechanism but pulse pressure rather than mean pressure seemed to be responsible for renin release. More recently Tobian has formulated a concept supported by indirect evidence in which the afferent arteriole acts as a “stretch” receptor; changes in intravascular volume and pressure would alter the rate of renin secretion. Other renal functions apparently sensitive to changes in mean renal perfusion pressure, such as tubular handling of salt and water, may be causally related to renal baroreceptor control of renin secretion but the present data do not assist in clarifying a possible relationship. Now that it is known that renin secretion is increased by very small reductions in perfusion pressure without changes in renal blood flow, it seems clear that the renal baroreceptor control of renin secretion is responsive to change in mean perfusion pressure. This control may be important in governing arterial pressure, the level at which the pressure equilibrates being that at which renin secretion is minimal.

Summary

Graded reductions in mean renal perfusion pressure cause kidneys of normotensive, renal, and neurogenic hypertensive dogs to release renin. In anesthetized normal dogs with mean resting pressures of 110 to 150 mm Hg, increased renin secretion occurred at renal perfusion pressures of 90 to 120 mm Hg. In dogs hypertensive from constriction of a renal artery, pressure beyond the constriction was within the normal range, and lowering of renal perfusion pressure caused release in the same range as in normal dogs. In dogs with neurogenic hypertension due to section of the carotid sinus and aortic depressor nerves, renin was released at perfusion pressures within, or only slightly above, the normal range.

In sharp contrast with these three groups, renin was released in dogs with hypertension due to perinephritis at mean pressures of 140 to 165 mm Hg when lowered from resting levels of 180 to 220 mm Hg. This different range could depend either upon reduced intrarenal pressure which mimicks the effects of a renal artery clamp or upon a change in range of response of the renal baroreceptor due to some more direct effect of the perinephritic hull. No evidence was found that the renal baroreceptor control of renin secretion is nonfunctional in dogs with renal hypertension.

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References

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