Numerous investigations have provided evidence involving the renin-angiotensin system in the etiology of two-kidney Goldblatt hypertension. The early blood pressure (BP) elevation in this condition correlates with an increase in plasma renin and vasoconstrictor activity, and angiotensin antagonists or angiotensin converting enzyme inhibitors decrease BP of animals with experimental two-kidney, one clip Goldblatt hypertension (2K-1C).

Factors other than the renin-angiotensin system are believed responsible for maintaining the hypertension beyond the initial stage, but these remain unclear. Strong evidence of a contribution of increased sympathetic activity to the increase in BP or peripheral resistance in some forms of renovascular hypertension have been presented in several studies; yet little or no sympathetic component of the hypertension has been detected in some instances. The majority of these investigations have offered evidence of an increase in sympathetic tone in renal hypertension, at least in the one-kidney, one clip (1K-1C) model.

Conflicting results have been reported concerning the ability of adrenergic blockade or depletion with 6-hydroxydopamine or guanethidine to affect development of renovascular hypertension. When 6-hydroxydopamine was given intracisternally in doses of 250 µg two to three times before clamping, it prevented 1K-1C Goldblatt hypertension from developing, but had no effect on 2K-1C hypertension. When administered systemically, 6-hydroxydopamine combined with adrenal medullectomy inhibited the development of 2K-1C hypertension in adult and weanling rats, but only delayed the full complement of 1K-1C hypertension. Large-dose guanethidine treatment of newborn rats, not combined with adrenalectomy, failed to alter the development of 1K-1C or 2K-1C hypertension. Dorr and Brody found evidence of sympathetic involvement in the maintenance phase of 1K-1C hypertension in rats. Based on the ability of 6-hydroxydopamine given intracisternally to prevent induction of 1K-1C, but not...
2K-1C, Goldblatt hypertension, and the finding of an increased plasma catecholamine level in the former but not latter model, it was concluded that neither the central nor peripheral sympathetic nervous system participates in 2K-1C Goldblatt hypertension in the rat.

Because of previous suggestions in the literature for sympathetic involvement in 2K-1C Goldblatt hypertension, and the known interactions of angiotensin with both central and peripheral components of the sympathetic nervous system, we initiated this investigation. We wished to determine the influence of the sympathetic and renin-angiotensin systems on the blood pressure and renal blood flow in the 2K-1C Goldblatt hypertensive dog. Our approach was to employ conscious normotensive and Goldblatt hypertensive dogs in which we could monitor BP and renal blood flow to study the hypotensive and renal vascular response to the angiotensin antagonist saralasin, given alone, or after adrenergic blockade with guanethidine. Another series of experiments was conducted in normotensive and hypertensive dogs to determine the effect of angiotensin blockade with saralasin when the renin-angiotensin system is activated by administration of a large dose of furosemide.

Methods

In various experiments, 30 dogs of both sexes weighing 18.0 to 27.3 kg were studied: eight when normotensive and hypertensive, 16 only when hypertensive, and six only when normotensive. Prior to the surgical procedures that have been previously described, the dogs were quarantined and treated with canine distemper-hepatitis-parainfluenza vaccine (Pitman-Moore). Their diet consisted of standard dog chow. They were anesthetized with sodium pentobarbital, 30 mg/kg, and Tygon tubing catheters were implanted under sterile conditions in the abdominal aorta by cannulating the carotid artery and into the jugular vein. The arterial catheter was used to record systemic arterial BP, to inject angiotensin (5-10 μg) intraarterially, and to withdraw blood samples. Drugs were injected or infused through the venous catheter.

After training the animals to lie quietly on their sides, BP measurements and blood samples were taken during several recording sessions. When stable BP readings were obtained, a pre-calibrated Zepeda (Seattle) blood flow probe (4 or 5 mm in diameter) was placed on the left renal artery, which was exposed under anesthesia through a retroperitoneal incision in the flank area. It was assumed that the probe calibration factor remained constant throughout the experimental period since probes used repeatedly after termination of the animals showed little or no change in calibration. Renal nerves accompanying the artery were left intact, and the majority of the renal nerve plexus was untouched since it reaches the kidney distal to placement of the probe. A dog jacket (Alice Chatham, Los Angeles) covered and protected the probe leads and catheters that had been tunneled under the skin to emerge high on the back. Renal blood flow was monitored with either a Carolina or Zepeda flowmeter coupled to the implanted flow probe by connectors on the leads. Zero flow was checked in each animal at the end of various recording sessions by intraaortic administration of 5-10 μg of angiotensin II. This dose of angiotensin injected close to the origin of the renal arteries caused a rapid fall in renal blood flow to zero, during which time the reference was verified. Balance adjustments were made periodically. In three animals in which the Zepeda flowmeter was employed, the zero flow reference obtained by injection of angiotensin agreed with the electrical zero of the flowmeter.

Dogs were made hypertensive by constraining the right renal artery with a Goldblatt clamp to reduce flow by 60%-80% after allowing for flow stabilization. Flow was monitored during the clamping procedure with an acute 10 mm Carolina blood flow probe placed distal to the clamp. If hypertension did not develop satisfactorily in 1 week or less, the operation was repeated and the clamp readjusted.

Arterial blood was withdrawn for measurement of plasma renin activity (PRA) in each animal. After incubation of the plasma for 1 hour, we measured the angiotensin 1 concentration in diluted or undiluted aliquots by radioimmunoassay, using the New England Nuclear kit as previously reported. When dilution of the plasma was necessary, use of buffer was found to be satisfactory. The only other modification in our radioimmunoassay procedure was inclusion of 0.3% bovine serum albumin in the buffer.

Catecholamine content of 50–160 mg samples of the plantar branch of the saphenous artery was determined by fluorometric analysis. The arterial sample in one paw was removed while the animal was anesthetized prior to administration of guanethidine, and an arterial sample from the opposite paw was taken approximately 24 hours after guanethidine administration, after completion of the experiment. The tissue was frozen on dry ice, crushed by a mortar, and extracted with 0.4 N perchloric acid.

Guanethidine and Saralasin Experiments

In this series, experiments were carried out on eight normotensive and 20 hypertensive dogs to determine the effects of an i.v. infusion of saralasin, 1 μg/kg/min for 15 minutes, on BP, renal blood flow, PRA, and on the response to the i.v. injection of angiotensin (0.05 μg/kg). The saralasin experiment was carried out 1–7 days (X = 4) before another one with guanethidine plus saralasin. The animals were treated with guanethidine, 5 mg/kg i.v., 24 hours before being given saralasin in the same dose, and the same parameters were measured. The 24-hour interval was allowed for maximal depletion of norepinephrine from the adrenergic nerves, and for the initial sympathomimetic effect of guanethidine to completely dissipate. Selection of this interval was based on the knowledge that the maximal depletion of adrenergic transmitter in rat heart and salivary glands occurs...
between 4 and 24 hours after a single dose of another depleting agent, reserpine.  

**Furosemide and Saralasin Experiments**

These experiments were conducted on 10 hypertensive and nine normotensive dogs. Renal blood flow in two of the hypertensive animals was recorded from one artery of a pair supplying the kidney, and therefore renal blood flow in these animals was approximately 50% of normal. Hypertensive and normotensive animals were given furosemide, 20–25 mg/kg, but one hypertensive was given only 10 mg/kg. Two or 3 hours later an experiment similar to that described above was run. Three experiments on normotensive dogs treated with furosemide, 20 mg/kg, were conducted the next day 2 hours after they had received a boosting dose of 5 mg/kg of the diuretic. The results of the latter experiments did not differ from those obtained in the other six normotensive dogs.

Data were evaluated statistically by Student’s t test for paired or unpaired values or by one-way analysis of variance and Duncan’s new multiple range test.  

**Results**

**Response to Saralasin Alone and Saralasin Following Guanethidine Treatment**

Blood pressure and renal vascular response to saralasin alone and following guanethidine treatment were measured in conscious hypertensive and normotensive dogs. Experiments on the hypertensive dogs were carried out between 2 to 26 days after constriction of the right renal artery. Based on multiple measurements in this group of 20 animals prior to renal artery constriction, the mean BP was 107 ± 3.1 mm Hg, and PRA was 1.5 ± 0.2 ng/ml/hr of angiotensin I. The hypertension established in these animals represented a mean increase in BP of 34.8 ± 4.4 mm Hg at the time of the experiments with saralasin alone, and 37.8 ± 3.9 mm Hg at the time of the experiments utilizing guanethidine plus saralasin. Corresponding increments in PRA were 4.4 ± 1.0 and 5.7 ± 2.6 ng/ml/hr of angiotensin I. In eight of these 20 hypertensive dogs, blood flow and vascular resistance of the contralateral kidney were measured both before and after constriction of the opposite renal artery.

Table 1 shows the BP, renal blood flow, and vascular resistance values obtained on the day of Goldblatt clamp application, 2–3 days later, and on the days of the saralasin (X = 9 days post-Goldblatt clamping) and guanethidine (X = 11 days post-Goldblatt clamping) experiments. At 2–3 days, there were increases in BP (8 dogs) and blood flow (5 of 8 dogs), but renal vascular resistance was unchanged. At the time of the saralasin (9 days post-Goldblatt clamping) and guanethidine-plus-saralasin (11 days post-Goldblatt clamping) experiments, renal blood flow tended to return toward the control levels, and renal vascular resistance increased. Thus, the renal blood flow of the contralateral kidney was not altered in the hypertensive state, and renal vascular resistance tended to be increased compared to the normal state.

Administration of saralasin and guanethidine plus saralasin provided the results in figures 1 and 2. Saralasin given alone to the hypertensives (X = 12 days post-Goldblatt clamping) decreased BP by a mean of 11 mm Hg (p < 0.01), but did not change PRA, renal blood flow, and renal vascular resistance. During the recovery period, BP returned to the control level, and the other parameters were not changed. Treatment of these hypertensive animals with guanethidine (X = 16 days post-Goldblatt clamping) caused a fall in BP of 14 mm Hg (p < 0.01), as measured 24 hours later, but no changes in PRA, renal blood flow, or renal vascular resistance.

Saralasin administration after guanethidine evoked a further decrease in BP of 9 mm Hg (p < 0.05), but not in PRA, renal blood flow, or renal vascular resistance. Again, in the recovery period BP returned to the level that had existed prior to saralasin, and the other parameters exhibited no changes. The combined effect of guanethidine and saralasin on BP surpassed that of saralasin alone, as described above. This result was also verified by subtraction of the BP change caused by guanethidine plus saralasin from that of saralasin alone for each animal, and performing Student’s t test on the paired differences (12.1 ± 2.6 mm Hg, p < 0.001).

The degree of angiotensin blockade by saralasin was assessed in all experiments, and the results are in table 2. The mean BP increase and percent decrease in renal blood flow produced by angiotensin 0.05 μg/kg injected i.v. before and after saralasin, and in the recovery period, are shown. There was a marked decrease in renal blood flow (range, 53% to 79%) and

<table>
<thead>
<tr>
<th>Goldblatt dog</th>
<th>BP (mm Hg)</th>
<th>RBF (ml/min)</th>
<th>RVR (mm Hg/ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>98 ± 6.0</td>
<td>190 = 24</td>
<td>0.52 ± 0.05</td>
</tr>
<tr>
<td>2-3 days post clamping</td>
<td>144 = 7.7</td>
<td>273 = 32</td>
<td>0.61 ± 0.11</td>
</tr>
<tr>
<td>9 days post clamping</td>
<td>135 = 7.9</td>
<td>224 = 24</td>
<td>0.64 ± 0.07</td>
</tr>
<tr>
<td>11 days post clamping</td>
<td>147 = 5.5</td>
<td>216 = 24</td>
<td>0.74 ± 0.08</td>
</tr>
</tbody>
</table>

Mean values *=* sem.
moderate increase in BP (range, 31 to 36 mm Hg) due to this dose of angiotensin. Saralasin antagonized almost completely the renal vascular and BP response to angiotensin ($p < 0.001$, for the paired differences).

Eight normotensive dogs, two of which had Goldblatt clamps implanted but failed to develop hypertension, were employed in experiments with saralasin and guanethidine plus saralasin similar to those described above. At the time of the experiments in which saralasin alone or guanethidine followed by saralasin were conducted, the BP and PRA of the normotensive dogs (fig. 3) were quite similar to the mean BP and PRA that were routinely monitored in these animals. The deviations from their average BP readings were $X = 2 \pm 4.9$ (SEM) mm Hg for the experiments with saralasin alone and $-3 \pm 4.5$ mm Hg for guanethidine plus saralasin. Saralasin administration caused no significant changes in BP, PRA, renal blood flow, or renal vascular resistance immediately after termination of the infusion (figs. 3 and 4), although there was a tendency for renal blood flow to decrease as a result of a slight agonist effect of saralasin. Guanethidine treatment had no significant effect on BP, renal blood flow, renal vascular resistance, or PRA in the normotensives. Saralasin after guanethidine treatment had, as in the untreated normotensives, no significant effect on BP, PRA, renal blood flow, or renal vascular resistance. The degree of angiotensin blockade by saralasin was assessed in the normotensive animals (table 2). In both groups of experiments, saralasin antagonized the BP and renal vascular response to angiotensin ($p < 0.001$) to approximately the same degree as in the hypertensive animals.

Total catecholamine content of saphenous artery segments before and after guanethidine treatment was determined in eight dogs (three normotensive and five
RENAL VASCULAR TONE IN HYPERTENSION/Zimmerman et al.

NORMOTENSIVES (8)

<table>
<thead>
<tr>
<th>Control</th>
<th>Saralasin</th>
<th>Guanethidine</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PRA ng Ang I·ml⁻¹·hr⁻¹ SEM 0.20 0.16 0.30 0.23 0.12 0.39 0.77

FIGURE 3. Blood pressure and PRA for normotensive dogs (mean ± SEM). See figure 1 for details.

In five hypertensive dogs that had been treated with guanethidine, the 1 μg/kg/min infusion of saralasin was immediately followed by a second infusion of the drug for 10 minutes at 2 μg/kg/min to test for a maximal effect. The second dose of saralasin further decreased BP by a mean of 6.2 ± 1.9 mm Hg. This effect, although small, was statistically significant (p < 0.05).

Results from six hypertensive animals studied for at least 3 weeks after they had been made hypertensive were analyzed separately. Control BP was only slightly lower in this group (mean, 138 mm Hg) compared to the other 14 hypertensives (mean, 145 mm Hg) at the time of the experiment with saralasin alone and guanethidine plus saralasin. The increase in BP due to renal artery constriction was from a mean of 112 to 138 mm Hg in these animals and from 105 to 145 mm Hg in the other 14 hypertensive dogs. These BP increments of 26.2 ± 8.6 and 39.6 ± 4.4 mm Hg were not significantly different. Saralasin alone had no effect on the control BP, 140 to 138 mm Hg; however, guanethidine plus saralasin decreased BP significantly from 138 to 124 mm Hg (p < 0.05, by analysis of variance and Duncan’s multiple range test). The change in control BP from 138 to 129 mm Hg obtained after guanethidine alone was not statistically significant.

Response to Saralasin Following Furosemide Treatment

The BP of hypertensive animals at the time of the furosemide experiments was 139 ± 4.7 mm Hg, which represented an increase of 30.2 ± 4.8 mm Hg (p < 0.001) above the BP prior to renal artery constriction. The PRA averaged 2.5 ± 0.6 ng/ml/hr of angiotensin I before furosemide administration, and this represented a mean increase over the control level of 1.6 ± 0.3 ng/ml/hr (p < 0.001). This increase in PRA caused by the clamping procedure tended to be less than that seen in the guanethidine experiments because the majority of the experiments with

hypertensive). The mean arterial catecholamine content, in norepinephrine equivalents, was 1.00 ± 0.15 μg/g wet weight before and 0.22 ± 0.06 μg/g after guanethidine treatment. Comparison of the paired values indicated a 75.5% ± 5% depletion of catecholamine, 24 hours after guanethidine administration. This result indicates that guanethidine had a substantial depleting effect on the adrenergic transmitter in the vasculature at the time of the experiments with saralasin.

FIGURE 4. Renal blood flow and renal vascular resistance for normotensive dogs (mean ± SEM). In six of the eight normotensives, renal blood flow and renal vascular resistance were measured. See figure 1 for details.
Table 2. Effect of Saralasin (1 μg/kg/min for 15 min) on Blood Pressure (Δ mm Hg) and Renal Blood Flow Responses (%Δ) to Angiotensin (0.05 μg/kg/iv) in Untreated and Guanethidine-treated Dogs

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Saralasin</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔBP</td>
<td>%ΔRBF</td>
<td>ΔBP</td>
</tr>
<tr>
<td>Untreated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyper.</td>
<td>35.8 ± 3.6 (20)</td>
<td>5.2 ± 1.2* (20)</td>
<td>30.6 ± 2.9 (20)</td>
</tr>
<tr>
<td>Norm.</td>
<td>30.8 ± 2.2 (8)</td>
<td>6.4 ± 2.0* (8)</td>
<td>27.5 ± 4.4 (8)</td>
</tr>
<tr>
<td>Guanethidine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyper.</td>
<td>35.8 ± 3.4 (20)</td>
<td>4.7 ± 1.4* (20)</td>
<td>32.4 ± 3.2 (20)</td>
</tr>
<tr>
<td>Norm.</td>
<td>33.4 ± 3.3 (8)</td>
<td>4.6 ± 1.8* (8)</td>
<td>25.4 ± 1.9 (8)</td>
</tr>
</tbody>
</table>

Mean values ± SEM. *p < 0.001, compared to control by paired t test. In two experiments in the hypertensives, responses after saralasin were obtained following infusion of the larger dose, 2 μg/kg/min for 10 minutes.

Prior to the administration of saralasin, renal blood flow was recorded for a sufficient period of time to insure its stability, and saralasin was then administered. It can be seen in figure 5 that saralasin decreased BP and increased renal blood flow compared to the values after furosemide; both of these effects were statistically significant, as determined by one-way analysis of variance and Duncan's multiple range test. The mean percent increase in renal blood flow produced by saralasin after furosemide was 16.1% ± 3.7% (p < 0.001). There was also a marked effect of saralasin on renal vascular resistance. The renal vascular resistance in the hypertensives after furosemide was 0.80 ± 0.18 mm Hg/ml/min, and it was decreased by saralasin to 0.58 ± 0.12 mm Hg/ml/min. The change of 0.21 ± 0.064 mm Hg/ml/min produced by saralasin was highly significant (p < 0.01). In the recovery period, BP and renal blood flow returned to levels not statistically different from those after furosemide. After saralasin administration, PRA increased to 18.3 ± 4.0 ng/ml/hr of angiotensin I but the level was not statistically greater than that caused by furosemide alone. The PRA was variably affected in the recovery period, equalling 16.8 ± 3.2 ng/ml/hr of angiotensin I.

Results of similar experiments in normotensive dogs treated with furosemide differed strikingly from the experiments in the hypertensives. Furosemide caused a lesser, but still significant, increase in PRA in the normotensives. The PRA increased from a control level before treatment of 0.8 ± 0.13 to 4.5 ± 0.70 ng/ml/hr of angiotensin I (p < 0.001) after furosemide. The increase of 11.1 ± 3.6 ng/ml/hr obtained in the hypertensives exceeded the increase of 3.7 ± 0.61 found in the normotensives (p < 0.05).

Individual values were converted to logarithms in order to equalize the variances so that the t test for unpaired values could be performed. Saralasin caused a further increase in PRA to 15.2 ± 4.7 ng/ml/hr of angiotensin I. This effect of saralasin was presumably...
the result of blockade of the short angiotensin negative feedback loop. The BP was not changed by furosemide, but renal blood flow was increased in six of nine dogs at 2-3 hours (fig. 6); this increase was not statistically significant. In all animals, however, there was an immediate effect of furosemide on renal blood flow seen during its i.v. administration, which subsided after 2-3 hours. In contrast to the consistent decrease in BP and increase in renal blood flow produced by saralasin in the hypertensives, the decrease in BP seen in the normotensives was not significant, and only variable changes in renal blood flow were obtained (fig. 6). There was no effect of saralasin on renal vascular resistance in the normotensives after furosemide. Renal vascular resistance was 0.37 ± 0.06 and 0.35 ± 0.08 mm Hg/ml/min after furosemide and furosemide plus saralasin respectively. No further changes in BP and renal blood flow were seen in the recovery period. As a result of the elevation in PRA, the BP and renal vascular responses to angiotensin were depressed after furosemide in both normotensive and hypertensive animals (table 3). Saralasin almost totally abolished the BP and renal blood flow response to angiotensin that remained after furosemide (p < 0.001).

Renal Pathology of Hypertensive Dogs

Goldblatt kidneys of 22 of the 24 hypertensive dogs at autopsy revealed no infarction, infection, or necrosis. Two kidneys exhibited some medullary necrosis. The mean weights of the Goldblatt and contralateral kidneys were 53.8 and 67.7 g respectively, and the contralateral kidneys were hypertrophied in all but six instances. The contralateral kidneys revealed no gross abnormalities in 18 of 24 dogs, and there were no clots or fibrin on the tip of the aortic catheter placed above the origin of the renal artery. In six animals some pathology of the contralateral kidney was observed; two kidneys had small infected areas, three kidneys were partially infarcted (possibly due to the flow probe), and one kidney in a dog with malignant hypertension developed nephrosclerosis (its weight was not included in the mean cited above).

Discussion

This study confirms the participation of the renin-angiotensin system in the early stage of 2K-1C Goldblatt hypertension, i.e., up to 3 weeks after renal artery constriction. Failure of an angiotensin antagonist alone to lower the BP of the hypertensive dog after the 3-week period is also in agreement with results of other studies.31 32 The hypotensive response to saralasin seen in our dogs was obtained in untreated as well as in guanethidine-treated hypertensive animals, and the magnitude of the decrease was quantitatively similar in both types of experiment. This result indicates that: 1) a direct effect of endogenous angiotensin contributes to the rise in BP; and 2) a compensatory sympathetic reflex does not antagonize the hypotensive effect of saralasin.

| TABLE 3. Effect of Saralasin (l μg/kg/min for 15 min) on Blood Pressure (Δ mm Hg) and Renal Blood Flow (%Δ) Responses to Angiotensin in Furosemide-treated Dogs |
|---|---|---|---|---|---|
|     | Control | Furosemide | Saralasin | Recovery |
| Hyper. (10) | 42.3 ± 3.8 | 24.2 ± 4.4 | 2.7 ± 1.1* | 18.1 ± 4.1 |
| Norm. (8)    | 33.9 ± 3.8 | 20.5 ± 2.8 | 2.2 ± 2.8* | 18.4 ± 2.7 |

Mean values = SEM. *p < 0.001, compared to control by paired t test. In two experiments on hypertensive animals and four experiments on normotensive animals, responses after saralasin were obtained following infusion of the larger doses, 2 μg/kg/min, for 10 minutes.
An apparent lack of sympathetic antagonism of the hypotensive response of teprotide, a converting enzyme inhibitor, in conscious salt-depleted dogs has also been observed. In our study there is evidence of increased sympathetic tone contributing to the high BP of the 2K-1C dogs. Guanethidine caused a significant decrease in BP in the hypertensive (approximately a 10% decrease) but not normotensive dog. Neither guanethidine nor saralasin alone decreased BP in six dogs at 3 weeks or more after renal artery constriction, in the maintenance phase of the hypertension. After their combined administration, however, BP did fall significantly. This result suggests that both the angiotensinogen and sympathetic components of the hypertension are of a lesser magnitude in the chronic phase of this form of hypertension. Because this part of our investigation involved only six animals, however, we cannot dismiss the importance of the sympathetic nervous system in hypertension at this stage. Further work must be done to clarify its participation.

To our knowledge, this is the first demonstration of a sympathetic contribution to 2K-1C hypertension in the dog. Our results are compatible with the findings made in the rat by Grewal and Kaul pointing to sympathetic participation in the development of 2K-1C hypertension. Our evidence of increased sympathetic tone in this form of hypertension is not in agreement with the absence of a sympathetic component in the 2K-1C Goldblatt hypertensive rat noted in another study. The contribution of the sympathetic nervous system to the hypertension in our dogs may, in fact, have been underestimated. The mean 75% depletion achieved with the 5 mg/kg dose of guanethidine that we employed may not have produced maximal inhibition of sympathetic tone. Our intent in this initial study was, however, not to give large doses of guanethidine because of deleterious effects that the drug can produce, and it is conceivable that repeated doses of the drug may have lowered BP further by a greater depeting effect. Angiotensin blockade by saralasin was near maximal, since doubling the dose caused only a small additional decrease in BP. Our results in this respect with saralasin resemble closely those obtained with a wider range of doses in salt-depleted dogs. The maximal hypotensive effect of saralasin was reached with a 0.5 μg/kg/min infusion rate in that study.

One of our aims in the present study was to follow renal blood flow and vascular resistance in the contralateral kidney after renal artery constriction, because of "involvement" of the normal kidney in renovascular hypertension. Due to the technically difficult nature of these experiments, paired values of blood flow and vascular resistance in the contralateral kidney before and after renal artery constriction could only be obtained in eight dogs. Nevertheless, there was evidence of an increase in renal blood flow in the majority of animals 2–3 days after constriction of the opposite renal artery. Renal hypertrophy would be expected to be accompanied by an increase in blood flow and probably accounts for this finding. Interestingly, however, contralateral renal blood flow shortly thereafter tended to return to the control level, and renal vascular resistance initially remained the same and then increased with time in the early phase of the hypertension. A recent study also revealed no change in contralateral renal blood flow (PAH clearance) and a marked decrease in flow in the Goldblatt kidney of 2K-1C hypertensive dogs.

We sought an influence of the sympathetic nervous and renin-angiotensin systems on blood flow and vascular resistance of the contralateral kidney by short-term blockade of these systems. No consistent changes in either renal blood flow or vascular resistance were found after guanethidine and saralasin or after either drug alone. These findings suggest that an acute influence of the tonic sympathetic discharge and level of circulating angiotensin present in the conscious 2K-1C hypertensive dog does not increase renal vascular tone under basal conditions. Other factors besides the renin-angiotensin or sympathetic nervous system probably also modulate renal hemodynamics in this form of hypertension. In addition, long-term effects of the renin-angiotensin and sympathetic nervous systems, e.g., on salt and water balance, undoubtedly affect renal vascular tone and function. Increased activity of the renin-angiotensin and sympathetic nervous system is known to augment sodium reabsorption. As a result of an increase in retained sodium, the plasma and extracellular fluid volumes would be expanded and thus could increase arterial BP, especially when sustained over a period of time. Blockade of these two systems for a sufficiently long time, at least several days, would be required to demonstrate such a long-term influence of the renin-angiotensin and sympathetic systems. Just as an example, it was necessary to block the angiotensin converting enzyme with captopril for several days before the maximal hypotensive response of the converting enzyme inhibitor was achieved in 2K-1C Goldblatt hypertensive rats. It is conceivable that hypertension in the 2K-1C Goldblatt dog is being augmented by the long-term salt and water influence of the renin-angiotensin and sympathetic systems on the "normal" contralateral kidney of the hypertensive.

A significant finding is that activation of the renin-angiotensin system by furosemide had a relatively greater effect on the BP and kidney of the hypertensive than the normotensive dog. Saralasin administration decreased BP and increased renal blood flow in the hypertensives without exception, but in the normotensives insignificant changes in BP and renal blood flow were found after furosemide. A greater increment in PRA produced by furosemide in the hypertensive than in the normotensive dog accounted at least in part for these results. The influence of acute administration of furosemide on renin release is complex and is due to a number of factors. Increased sympathetic tone, decreased plasma volume, a direct tubular effect of furosemide, and possibly increased renal prostaglandins may all contribute to the increase in PRA caused by furosemide.
We administered furosemide, however, only as a means of acutely activating the renin-angiotensin system in hypertensive and normotensive dogs. As it turned out, this provided an interesting technique for differentiating the response to saralasin of the contralateral and normal kidney of hypertensive and normotensive animals. The angiotensin component to vascular tone of the contralateral kidney caused by furosemide is attributable to a greater response to furosemide itself or to greater activation of the renin-angiotensin system in the hypertensive animal. This effect of the diuretic provides us with a clue as to how other stimuli of renin release would affect vascular tone in the renal hypertensive’s contralateral kidney. Greater renin release caused by furosemide has also been shown in renal hypertensive humans. Administration of the diuretic produced a higher PRA in renovascular than in several other forms of hypertension, which indicates that the results in dogs may be comparable to what occurs in humans.

Results of our investigation imply that under basal conditions increased vascular resistance of the hypertensive’s contralateral kidney mediated by the renin-angiotensin system is not detectable by use of saralasin. However, when the renin-angiotensin system is activated, for example by furosemide, the renal vessels are acted upon by endogenous angiotensin, and this effect can be discerned by angiotensin blockade. This acute influence, which may occur only intermittently during stressful situations, and the long-term effects of the renin-angiotensin and sympathetic systems may eventually lead to persistent renal vasoconstriction in the contralateral kidney. These interacting influences on the kidney may have accounted for the rise in renal vascular resistance with time in our hypertensive dogs, although structural changes cannot be ruled out. The added factor of elevated systemic BP and renal perfusion pressure would eventually bring about damage to the contralateral kidney, which would act as positive feedback to the hypertensive process. Our observations reinforce the concept that the contralateral as well as the Goldblatt kidney are involved in the maintenance of renovascular hypertension.

Acknowledgments

The author is grateful for the excellent technical assistance of Beverly Ness. I wish to thank Theodora Danielson for the artwork, Jackie Rupp for secretarial assistance, and Dr. Keith Ellis of Eaton Laboratories, Norwich, New York, for supplying saralasin.

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Hypertension. 1980;2:53-62
doi: 10.1161/01.HYP.2.1.53

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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