Sodium and Volume Depletion Activates Neurogenic Mechanisms in Renal Hypertensive Dogs

WILLIAM D. SWEET, RONALD H. FREEMAN, JAMES O. DAVIS, AND DANIEL VILLARREAL

SUMMARY The acute response to ganglionic blockade (hexamethonium bromide, 30 mg/kg, i.v.) was used to evaluate the neurogenic contributions to mean arterial pressure maintenance in the conscious one-kidney, one clip hypertensive dog. Approximately 2 hours (112 minutes) after ganglionic blockade, captopril (10 mg/kg, i.v.) was given to block the renin-angiotensin system. Hypertensive animals were studied 3 days after clipping (group 2) or 2 to 4 weeks after clipping (groups 3 and 4). Groups 2 and 3 were fed a regular sodium diet, but group 4 animals were sodium and volume depleted. Normotensive control animals (group 1) were fed a regular sodium diet. On the day of the acute experiment the baseline blood pressures measured in group 2 (151 ± 10 mm Hg, n = 5), group 3 (154 ± 5 mm Hg, n = 7), and group 4 (160 ± 8 mm Hg, n = 7) were not different (p > 0.05) from each other, but all were elevated (p < 0.05) compared with the group 1 animals (106 ± 3 mm Hg, n = 8). Also, there were no significant differences (p > 0.05) in the baseline plasma catecholamine levels among the three hypertensive groups. Ganglionic blockade produced a greater fall in blood pressure (p < 0.05) in the sodium/volume-depleted dogs of group 4 (−35 mm Hg) than in group 1 (−10 mm Hg), group 2 (−5 mm Hg), or group 3 (−12 mm Hg) animals. Captopril administration decreased (p < 0.05) the blood pressure strikingly in the high-renin sodium/volume-depleted animals of group 4 (−35 mm Hg) and in the high-renin 3-day animals of group 2 (−32 mm Hg); captopril produced a smaller depressor response (p < 0.05) in group 3 (−15 mm Hg) and the group 1 (−9 mm Hg) animals with normal renin levels. These results suggest that sodium/volume depletion activates both adrenergic- and angiotensin-dependent mechanisms to maintain blood pressure at hypertensive levels in conscious dogs with established one-kidney, one clip renal hypertension. (Hypertension 7: 39–46, 1985)

Key Words • sympathetic nervous system • plasma renin activity • renin-angiotensin system • ganglionic blockade • captopril • plasma norepinephrine and epinephrine • heart rate • established hypertension

In 1934 Goldblatt and associates1 produced chronic arterial hypertension in dogs by renal artery constriction. Although still incompletely understood, experimental renal hypertension frequently is analyzed in terms of sodium and volume factors, the renin-angiotensin pressor system, and neural mechanisms that increase the activity of the sympathetic nervous system.2–3 It has been emphasized that the relative importance of these different factors is variable and depends partially on the animal species, the presence or absence of a contralateral nonclipped kidney, and the duration and severity of the hypertension.2–5

The renin-angiotensin pressor mechanism usually is activated for a transient period of 1 week or less in one-kidney, one clip (1K1C) Goldblatt hypertension unless the constriction is severe.4–7 During the established phase of 1K1C hypertension, plasma renin activity (PRA) returns toward or to normal and arterial pressure becomes unresponsive to pharmacological blockade of the renin system.4–8 The mechanism by which the presumed sodium/volume excess maintains or contributes to chronic 1K1C renal hypertension when the angiotensin-pressor component is within normal limits remains unsettled,4 but an increasing body of evidence suggests the participation of both the central and peripheral sympathetic nervous systems in the maintenance of experimental 1K1C renal hypertension.5 Sodium/volume depletion has been shown to activate the renin-angiotensin system, however, and partially restore the renin dependency of the hypertension in these chronically hypertensive 1K1C animals.8

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Experiments in the present study were designed to evaluate the contributions of both the sympathetic nervous system and the renin-angiotensin system for arterial pressure maintenance in conscious sodium-replete and sodium-depleted dogs with established 1K1C hypertension. Experiments also were performed on sodium-replete 1K1C hypertensive dogs on the third day after renal artery stenosis when PRA is still elevated and sodium and water balances are positive. Evaluations were based on the hemodynamic responses to pharmacological blockade of ganglionic transmission and of the renin-angiotensin system.

**Materials and Methods**

Female hounds weighing 16 to 24 kg were laparotomized during sodium pentobarbital anesthesia (30 mg/kg), and a unilateral nephrectomy was performed after ascertaining that there was a single renal artery to the other kidney. A permanent femoral arterial catheter was inserted and the other end was passed subcutaneously to the back of the neck where it was exteriorized. The dogs were allowed to recover for at least 2 weeks before hypertension was induced. During this period the animals were brought routinely to a quiet room where they were trained to lie calmly on a padded table. Arterial pressure and heart rate were measured from the femoral arterial catheters. The dogs were routinely fed a daily diet that provided 70 to 75 mEq sodium; drinking water was available ad libitum. The dogs were housed individually in stainless steel metabolism cages. Daily urinary sodium output was measured so that sodium balance could be estimated. Urinary electrolyte levels were determined by flame photometry (Instrumentation Laboratory, Model 443, Lexington, MA).

**Constriction of the Renal Artery**

At least 2 weeks after uninephrectomy, the dogs were again anesthetized with sodium pentobarbital (30 mg/kg) and the renal artery of the remaining kidney was exposed retroperitoneally through a flank incision. After bathing the area around the renal vessels with a 2% lidocaine solution to minimize vasospasms, an adjustable constricting device and an electromagnetic flow probe (Carolina Medical Electronics, King, NC) were placed around the renal artery. Renal blood flow was allowed to stabilize for approximately 10 to 15 minutes. The renal artery was then constricted to reduce renal blood flow by 55% to 60%. This degree of renal artery constriction has been shown to produce chronic benign 1K1C renal hypertension in the dog.

**Short-term Experimental Protocol**

On the day of the short-term experiment the dogs were brought to the laboratory, placed on a padded table, and allowed to rest for approximately 1 hour before control measurements of arterial pressure and heart rate were made at 15-minute intervals for an additional hour. Blood samples for determinations of baseline PRA and plasma norepinephrine and epinephrine levels were obtained at 30 and 60 minutes of the control period. After these control measurements were taken, hexamethonium bromide (30 mg/kg; Sigma Chemical Co., St. Louis, MO) was infused intravenously over 5 minutes to block ganglionic transmission. Blood pressure and heart rate measurements were made immediately after completion of hexamethonium administration and at 15-minute intervals for an additional 90 minutes; blood samples for PRA and plasma norepinephrine and epinephrine were drawn 30, 60, and 90 minutes after ganglionic blockade. Approximately 2 hours (112 minutes) after hexamethonium administration, a bolus injection of captopril (10 mg/kg, i.v.; E. R. Squibb & Sons, Princeton, NJ) was given to inhibit angiotensin-converting enzyme. Measurements of blood pressure and heart rate were made immediately (3 minutes) after captopril infusion and at 15 and 30 minutes postinjection; blood samples for PRA and plasma norepinephrine and epinephrine determinations were drawn 30 minutes after captopril administration. This sequence of drug administration was chosen to avoid any reflex activation of the sympathetic system during blockade of the renin-angiotensin cascade and a subsequent decrease in arterial pressure. Also, preliminary results indicated the absence of any consistent compensatory increase in PRA following ganglionic blockade.

This experimental protocol was administered to four groups of dogs: group 1 (n = 8) consisted of one-kidney normotensive dogs; group 2 (n = 5) of 1K1C hypertensive dogs, which were studied on Day 3 after renal artery constriction; group 3 (n = 7) of 1K1C hypertensive dogs, which were studied 2 to 4 weeks after renal artery constriction; and group 4 (n = 7) consisted of sodium/volume-depleted 1K1C hypertensive dogs, which were studied 2 to 4 weeks following renal artery constriction. The animals in groups 1, 2, and 3 were fed the regular sodium diet that provided 70 to 75 mEq sodium daily. The dogs in group 4 were sodium depleted immediately before the short-term experiment. Sodium/volume depletion was produced by feeding the dogs a low sodium diet that provided less than 9 mEq sodium daily and by giving a potent diuretic (50 mg sodium ethacrynate, i.v.; Merck Sharp & Dohme, West Point, PA) on each of the first 2 days of the low sodium diet. This regimen produced a cumulative sodium deficit of 103 ± 14 mEq during the 4-day depletion period. The short-term experiment was performed on the fifth day of sodium depletion. In addition to these four groups, there were two individual dogs that developed a rapidly accelerating hypertension and resembled 1K1C malignant hypertensive dogs. The experimental protocol was followed in these two dogs also, but the results are reported separately.

Completeness of ganglionic blockade and angiotensin-converting enzyme inhibition was assessed by intravenous bolus injections of norepinephrine (1 μg/kg) and angiotensin I (4 μg). The pressor and heart rate changes produced by norepinephrine and angiotensin I were evaluated before and after the administration of hexamethonium and captopril. Before ganglionic
blockade both norepinephrine and angiotensin I pressor responses resulted in baroreceptor-mediated reflex slowing of the heart rate. After the administration of hexamethonium, the total absence of a reflex slowing of the heart rate in response to the acute pressure elevation elicited by norepinephrine and angiotensin I infusions was the criterion for complete ganglionic blockade. Similarly, the criterion for complete inhibition of the angiotensin-converting enzyme was indicated by the total absence of any pressor response to exogenous angiotensin I (4 μg) after captopril infusion.

**Analytical Methods**

Blood samples for PRA measurements were collected in chilled tubes containing ethylenediaminetetraacetic acid (EDTA). The samples were centrifuged immediately (1400 g for 10 minutes) and the plasma was frozen and stored (−20 °C) until the time of the radioimmunoassay. The PRA is expressed as nanograms of angiotensin I generated per milliliter of plasma per hour of incubation. Blood samples for plasma norepinephrine and epinephrine measurements were obtained in a chilled syringe containing 20 μl of an additive solution for each milliliter of whole blood to be drawn. This solution contains 95 μg of ethyleneglycol-bis(β-aminoethyl ether)-N,N,N′,N′-tetraacetic acid (EGTA) and 60 μg of reduced glutathione per milliliter, and the pH was adjusted to 6 to 7 with 6N NaOH. The samples were centrifuged immediately (1400 g for 10 minutes) and the plasma frozen and stored (−20 °C) until assayed at a later date by the radioenzymatic method of Peuler and Johnson. Plasma norepinephrine and epinephrine levels are expressed as picograms per milliliter of plasma.

The data are expressed as mean ± SEM. Analysis of variance with the split-plot design and Duncan’s multiple range test were used to determine whether statistically significant (p < 0.05) changes occurred within individual series and between groups. The Student’s t test for paired or unpaired observations was used to evaluate the pressor and heart rate responses to angiotensin I and norepinephrine infusions.

**Results**

**Hemodynamic Responses to Hexamethonium and Captopril Administration**

Figure 1 summarizes the data for average mean arterial pressure (upper panel) and the average heart rate (lower panel) in the four groups of dogs. On the day of the short-term experiment, the baseline mean arterial pressures measured during the 60-minute control period in groups 2, 3, and 4 (151 ± 10, 154 ± 5, and 160 ± 8 mm Hg respectively) were not significantly different (p > 0.05) from each other; however, baseline pressure of the normotensive group 1 dogs (106 ± 3 mm Hg) was significantly lower (p < 0.05) when compared with all three hypertensive groups. With regard to baseline heart rates among groups, the only significant difference (p < 0.05) was the slower heart rate of the group 2 hypertensive dogs (75 ± 7 beats/minute) compared with groups 1, 3, and 4 (89 ± 6, 91 ± 7, and 95 ± 9 beats/minute respectively).

Administration of hexamethonium over 5 minutes to produce ganglionic blockade resulted in an immediate and striking fall in the mean arterial pressure in the hypertensive sodium/volume-depleted animals of group 4 (Figure 1). Before ganglionic blockade mean arterial pressure in group 4 averaged 160 ± 8 mm Hg and decreased by 35 mm Hg to average only 125 ± 9 mm Hg (p < 0.05) for the entire 90 minutes after hexamethonium. In contrast, the mean arterial pressure failed to decrease significantly (p > 0.05) at any time after ganglionic blockade in the 3-day hypertensive animals in group 2. Smaller but significant (p < 0.05) decreases occurred in the arterial pressure of the sodium-replete hypertensive dogs in group 3, from 154 ± 5 to 142 ± 6 mm Hg, and of the normotensive group 1 animals, from 106 ± 3 to 96 ± 3 mm Hg, following ganglionic blockade. After the administration of hexamethonium, the arterial pressure of the sodium-depleted hypertensive dogs in group 4 was significantly less than the arterial pressure in the other
two hypertensive groups at all times, with the exception of the initial response and the 30-minute posthexamethonium administration pressure in group 3. Heart rate (Figure 1, lower panel) increased significantly ($p < 0.05$) in all four groups after ganglionic blockade. The greatest heart rate increases were observed in the 3-day hypertensive and the sodium-replete hypertensive animals; the heart rate in both groups of animals was significantly faster ($p < 0.05$) than the heart rate in the normotensive group at all times after ganglionic blockade. The heart rate in groups 2 and 3 also was faster ($p < 0.05$) than the heart rate in the sodium/volume-depleted hypertensive animals of group 4 for the initial 45 minutes after hexamethonium administration.

The infusion of captopril ($10 \text{ mg/kg, iv}$) to block the renin-angiotensin system produced only a small transient fall ($p < 0.05$) in the mean arterial pressure of the normotensive group 1 animals, and this depressor response was not sustained after 15 and 30 minutes ($p > 0.05$). In striking contrast, captopril produced a large initial depressor response 3 minutes postinjection in all three hypertensive groups, and this fall in the arterial pressure remained statistically significant ($p < 0.05$) at all times after captopril infusion. The greatest depressor response to captopril occurred in the 1K1C sodium-depleted animals of group 4 in which arterial pressure fell immediately within 3 minutes from a post-hexamethonium infusion average of 125 ± 9 to 85 ± 8 mm Hg ($p < 0.05$) and remained decreased at 90 ± 5 and 93 ± 7 mm Hg after 15 and 30 minutes ($p < 0.05$ for both values) respectively. Thus, the decrease in mean arterial pressure after captopril averaged approximately $35 \text{ mm Hg}$ in the sodium-depleted hypertensive animals of group 4. There was no statistical difference ($p > 0.05$) for arterial pressure between the normotensive and the sodium/volume-depleted hypertensive animals at any time after captopril administration. Captopril infusion also decreased ($p < 0.05$) arterial pressure by approximately $32 \text{ mm Hg}$ in group 2 animals, from 145 ± 10 to 113 ± 5 and 113 ± 8 mm Hg after 15 and 30 minutes respectively. Arterial pressure decreased in group 3 animals from 143 ± 6 to 126 ± 9 and 126 ± 6 mm Hg ($p < 0.05$ for both values) 15 and 30 minutes after captopril administration. Compared with the normotensive and the sodium/volume-depleted hypertensive animals, however, the mean arterial pressures of both the 3-day hypertensive and the hypertensive sodium/volume-replete groups remained significantly higher ($p < 0.05$) at all times after captopril infusion. Heart rates failed to change in any group following captopril administration despite the marked depressor responses.

**Plasma Renin and Catecholamine Responses to Hexamethonium and Captopril Administration**

Figure 2 (bottom panel) summarizes the data for the average PRA in the four groups of dogs. On the day of the experiment baseline PRA was statistically elevated ($p < 0.05$) in both the 3-day hypertensive (6.31 ± 2.05 and 5.10 ± 1.60 ng/ml/hr) and the sodium/volume-depleted hypertensive (9.27 ± 2.20 and 8.60 ± 2.45 ng/ml/hr) groups compared with the PRA of the normotensive group 1 (0.75 ± 0.31 and 0.78 ± 0.30 ng/ml/hr) and the sodium-replete hypertensive group 3 (1.60 ± 0.47 and 1.68 ± 0.55 ng/ml/hr). The PRA failed to change significantly ($p > 0.05$) in any group after hexamethonium administration, except for a transient increase to 15.0 ± 4.4 ng/ml/hour ($p < 0.05$) in the hypertensive sodium/volume-depleted animals of group 4 after 35 minutes when the arterial pressure fell sharply. Conversely, PRA increased significantly ($p < 0.05$) in all three hypertensive groups after captopril infusion; PRA appeared to increase slightly in group 1 after captopril administration but the change was not significant ($p > 0.05$).

Figure 2 also summarizes the data for plasma epinephrine levels (top panel) and plasma norepinephrine levels (middle panel) in the four experimental groups. The day of the experiment baseline plasma epinephrine levels were elevated ($p < 0.05$) in all three hypertensive groups compared with baseline normotensive plasma epinephrine levels of 121 ± 45 and 141 ± 21 pg/ml. Baseline plasma norepinephrine levels (Figure...
2, middle panel) averaged 263 ± 39 and 230 ± 33 pg/ml in the normotensive animals of group 1 and were elevated to 330 ± 32 and 325 ± 42 pg/ml (p < 0.05 for both values) in the 3-day hypertensive animals of group 2. Baseline plasma norepinephrine levels averaged 309 ± 21 and 310 ± 48 pg/ml in group 4, and there were no significant differences for both values) in the 3-day hypertensive animals of the same group.

TABLE 1 Response to Bolus Injection of Norepinephrine (1 μg/kg, i.v.) Before and After Sequential Administration of Hexamethonium and Captopril in the Conscious Dog

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>Control</th>
<th>Hexamethonium (30 mg/kg, i.v.)</th>
<th>Captopril (10 mg/kg, i.v.)</th>
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</thead>
<tbody>
<tr>
<td>Group 1 (n = 8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔHR (minute⁻¹)</td>
<td>–42 ± 7</td>
<td>24 ± 9*</td>
<td>0 ± 12*</td>
</tr>
<tr>
<td>ΔMAP (mm Hg)</td>
<td>45 ± 5</td>
<td>119 ± 9*</td>
<td>113 ± 8*</td>
</tr>
<tr>
<td>Group 2 (n = 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔHR (minute⁻¹)</td>
<td>–9 ± 11†</td>
<td>65 ± 10*</td>
<td>34 ± 4*</td>
</tr>
<tr>
<td>ΔMAP (mm Hg)</td>
<td>50 ± 10</td>
<td>101 ± 26*</td>
<td>83 ± 24</td>
</tr>
<tr>
<td>Group 3 (n = 7)</td>
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</tr>
<tr>
<td>ΔHR (minute⁻¹)</td>
<td>–28 ± 7</td>
<td>47 ± 12*</td>
<td>32 ± 12*</td>
</tr>
<tr>
<td>ΔMAP (mm Hg)</td>
<td>46 ± 5</td>
<td>131 ± 8*</td>
<td>118 ± 16*</td>
</tr>
<tr>
<td>Group 4 (n = 7)</td>
<td></td>
<td></td>
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<tr>
<td>ΔHR (minute⁻¹)</td>
<td>–39 ± 9</td>
<td>44 ± 17*</td>
<td>13 ± 8*</td>
</tr>
<tr>
<td>ΔMAP (mm Hg)</td>
<td>36 ± 14</td>
<td>122 ± 11*</td>
<td>124 ± 13*</td>
</tr>
</tbody>
</table>

*p < 0.05 compared with the predrug control response within the same group.  †p < 0.05 compared with the response in the normotensive (group 1) animals. ΔHR = change in heart rate, ΔMAP = change in mean arterial pressure. Values are means ± SEM.

TABLE 2. Response to Bolus Injection of Angiotensin I (4 μg, i.v.) Before and After Sequential Administration of Hexamethonium and Captopril in the Conscious Dog

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>Control</th>
<th>Hexamethonium (30 mg/kg, i.v.)</th>
<th>Captopril (10 mg/kg, i.v.)</th>
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</thead>
<tbody>
<tr>
<td>Group 1 (n = 8)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ΔHR (minute⁻¹)</td>
<td>–34 ± 3</td>
<td>11 ± 8*</td>
<td>3 ± 3*</td>
</tr>
<tr>
<td>ΔMAP (mm Hg)</td>
<td>53 ± 6</td>
<td>78 ± 7*</td>
<td>0 ± 3*</td>
</tr>
<tr>
<td>Group 2 (n = 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔHR (minute⁻¹)</td>
<td>–17 ± 6†</td>
<td>46 ± 13*</td>
<td>2 ± 2*</td>
</tr>
<tr>
<td>ΔMAP (mm Hg)</td>
<td>47 ± 8</td>
<td>83 ± 15*</td>
<td>4 ± 1*</td>
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<tr>
<td>Group 3 (n = 7)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ΔHR (minute⁻¹)</td>
<td>–23 ± 6†</td>
<td>24 ± 26*</td>
<td>3 ± 4*</td>
</tr>
<tr>
<td>ΔMAP (mm Hg)</td>
<td>53 ± 7</td>
<td>74 ± 9*</td>
<td>1 ± 1*</td>
</tr>
<tr>
<td>Group 4 (n = 7)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ΔHR (minute⁻¹)</td>
<td>–20 ± 11</td>
<td>33 ± 6*</td>
<td>1 ± 1</td>
</tr>
<tr>
<td>ΔMAP (mm Hg)</td>
<td>51 ± 3</td>
<td>84 ± 9*</td>
<td>3 ± 2*</td>
</tr>
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</table>

*p < 0.05 compared with the predrug control response within the same group.  †p < 0.05 compared with the response in the normotensive (group 1) animals. ΔHR = change in heart rate, ΔMAP = change in mean arterial pressure. Values are means ± SEM.

Responses in Two Dogs with Accelerated Hypertension

Figure 3 summarizes the results in two dogs that developed severe, accelerated hypertension after renal artery constriction. Both dogs had severe renal artery constriction.
The plasma epinephrine concentration, plasma norepinephrine concentration, plasma renin activity, and mean arterial pressure before and after the intravenous administration of hexamethonium and captopril to two conscious dogs with accelerated hypertension. Hexamethonium (↑↑) was administered between 60 and 65 minutes and captopril (↑) was given as a bolus injection 3 minutes before the measurement of arterial pressure at Minute 180.

Discussion

The major finding of the present study is that chronic sodium/volume depletion activated efferent sympathetic activity to provide an important mechanism for maintaining blood pressure in conscious dogs with established one-kidney renovascular hypertension. Ganglionic blockade in these sodium/volume–depleted 1K1C hypertensive animals produced a striking 35 mm Hg fall in arterial pressure from the baseline of approximately 160 mm Hg to an average of 125 mm Hg. In contrast, ganglionic blockade failed to decrease pressure appreciably in the 3-day 1K1C dogs with hyperreninemia and produced only a small sustained depressor response of 10 to 15 mm Hg in the sodium-replete chronically hypertensive 1K1C dogs with similar levels of hypertension. Ganglionic blockade produced greater heart rate increases in these latter two groups than in the sodium/volume–depleted hypertensive groups. These heart rate and blood pressure responses to ganglionic blockade are consistent with the concept that there is greater peripheral sympathetic drive and less cardiac vagal tone in the sodium/volume–depleted hypertensive dogs than in the dogs of the other two hypertensive groups with presumed sodium/volume excess. These findings suggest that the sympathetic nervous system contributes minimally to the maintenance of established benign 1K1C renal hypertension in the conscious dog, unless sodium depletion is first produced to activate this system. The findings in the 3-day 1K1C dogs also indicate a minimal role for the sympathetic nervous system during the early developmental high-renin phase of experimental renovascular hypertension.

In agreement with earlier reports of increased plasma norepinephrine levels in chronic 1K1C hypertension in the rat, the present data indicate increased circulating levels of plasma catecholamines in all three of the 1K1C hypertensive dog groups. It is interesting that no significant differences in baseline plasma norepinephrine and epinephrine levels were found among the three hypertensive groups of the present study despite the fact that ganglionic blockade produced a greater depressor response in the sodium/volume–depleted hypertensive group. The sensitivity of circulating plasma norepinephrine as a marker for increased activity of the sympathetic nervous system in hypertension and sodium depletion is questionable, however. Following ganglionic blockade there were no significant differences in the plasma catecholamine levels of the three hypertensive groups. The striking decreases in plasma catecholamine levels in all experimental groups together with the total absence of reflex adjustments to pressor injections of norepinephrine and angiotensin I after hexamethonium administration demonstrate the efficacy of ganglionic blockade in the present study.

There is some evidence consistent with the concept of an enhanced contribution of the sympathetic nervous system to the maintenance of chronic 1K1C hypertension in the rat. Not only are plasma norepinephrine levels and hypothalamic norepinephrine.
content, reported to be elevated, but ganglionic blockade is reported to have decreased substantially the arterial pressure during the chronic phase of 1K1C hypertension in this species; and pretreatment with intracisternal 6-hydroxydopamine reportedly prevented both the rise in plasma norepinephrine levels and the hypertension. A species variation in the contribution of different mechanisms to the maintenance of experimental renovascular hypertension is not unexpected. Thus, the results of the present study indicate a minimal contribution of the adrenergic system to the maintenance of established renal hypertension in trained, conscious sodium-replete dogs. Zimmerman and Largent found no evidence of increased sympathetic tone in the conscious dog with chronic two-kidney, one clip renal hypertension through the use of the ß-adrenergic receptor antagonists propranolol and urapidil. Finally, it is of interest that sodium excess, not sodium depletion, has been reported to increase the participation of the sympathetic system to arterial pressure maintenance in the chronic 1K1C hypertensive rat. It should be appreciated that quiet, docile dogs were selected initially in the present study and then underwent prolonged training to achieve a reasonably basal state. Under these conditions the resting adrenergic tone for blood pressure in these hypertensive dogs may be rather minimal until activated by sodium/volume depletion.

The mechanisms by which sodium/volume depletion activated efferent sympathetic drive in the 1K1C hypertensive dog model used in the present study remain unknown. One possible mechanism might be the increased activity of the renin-angiotensin system produced by sodium depletion. In addition to its direct vasoconstrictor actions on the peripheral arterioles, angiotensin II has been demonstrated to influence blood pressure indirectly by its interactions with both peripheral and central adrenergic mechanisms. Conceivably, increased levels of endogenous angiotensin II may have evoked peripheral and central adrenergic facilitation in the sodium/volume-depleted 1K1C hypertensive groups to intensify sympathetic drive and thereby help to maintain the elevated blood pressure. Alternatively, sodium/volume depletion may have provided a decreased stimulus for the cardiopulmonary receptors with vagal afferent fibers that normally function to exert a tonic restraint on the vasomotor center to inhibit peripheral adrenergic outflow. This study provides no direct evidence to support or refute either of these potential mechanisms. Relevant to this consideration, however, is the finding that ganglionic blockade did not decrease arterial pressure significantly in the sodium/volume-expanded, 3-day constricted dogs with elevated baseline levels of renin activity and hypertension similar to those achieved in the sodium/volume-depleted animals. This finding suggests that circulating angiotensin probably is not the only signal for increased sympathetic activity. Wong and Zimmerman reported recently that bilateral nephrectomy, but not captopril nor saralasin administration, abolished the enhanced vasoconstriction response to sympathetic nerve stimulation in sodium-depleted dogs. They suggested that some renal factor other than renin is responsible for inducing adrenergic potentiation in sodium depletion.

As expected PRA was elevated in both the 3-day postconstricted and the sodium/volume-depleted hypertensive groups, but not in the sodium/volume-replete hypertensive animals. The vasoconstrictor contribution of the renin-angiotensin system to blood pressure maintenance was evaluated in these animals by the administration of captopril to inhibit the angiotensin-converting enzyme. Blockade of the renin-angiotensin system decreased arterial pressure transiently in the normotensive dogs and produced a moderate, sustained blood pressure fall of approximately 17 mm Hg in the sodium/volume-replete hypertensive dogs of group 3. In contrast, captopril produced a pronounced and sustained depressor response of 30 to 35 mm Hg in the hypertensive dogs of groups 2 and 4 with elevated renin levels. The final blood pressures after captopril administration were not significantly different from each other in the sodium/volume-replete hypertensive dogs of groups 2 and 3, however. These results are in good agreement with earlier studies that demonstrated the importance of the renin-angiotensin system for blood pressure maintenance during the early, high-renin phase of 1K1C renal hypertension and in the chronic phase of 1K1C hypertension during sodium depletion. These results together with the lack of consistent changes in PRA after hexamethonium administration suggest that there was little activation of the renin-angiotensin system in response to ganglionic blockade in the present study.

Interestingly, there was no difference in blood pressure between the normotensive and the sodium/volume-depleted hypertensive groups at any time after the administration of both hexamethonium and captopril. The results suggest that the pressor contributions of the adrenergic and angiotensin systems were similar quantitatively in the sodium/volume-depleted 1K1C hypertensive dogs, and together these two systems accounted for nearly all of the blood pressure elevation of approximately 70 mm Hg. Presumably, volume factors such as cardiac output were responsible for the continued higher blood pressure in the 3-day postconstricted and the sodium/volume-replete hypertensive groups following blockade of the adrenergic and angiotensin systems. Alternatively, vasopressin might play a role in blood pressure maintenance following blockade of both the adrenergic and angiotensin systems, but we have no evidence for this in the present study.

It is well known that accelerated hypertension in the 1K1C dog is characterized by increased activity of the renin-angiotensin system, which acts to elevate arterial pressure. It has been suggested that other pathogenic factors also are involved, because the infusion of a competitive angiotensin II antagonist, saralasin, failed to normalize pressure completely in these dogs. The present results demonstrated that ganglionic blockade decreased circulating plasma norepinephrine
to very low levels but failed to decrease arterial pressure in either of two dogs with accelerated hypertension and high renin levels. Thus, the present data provide no evidence to suggest that the adrenergic nervous system contributed substantially to the hypertension in these two dogs. In contrast, blockade of the renin-angiotensin system with captopril normalized arterial pressure in both dogs. It appears that the intense vasoconstriction in these two dogs with accelerated hypertension was mediated entirely by increased activity of the renin-angiotensin system.

Conclusion

The present results indicate that in dogs with established one-kidney renovascular hypertension sodium/volume depletion activates both the sympathetically nervous system and the renin-angiotensin system to maintain the elevated blood pressure. The data fail to demonstrate an important pathogenic role for the adrenergic system in the early, high-renin developmental phase of benign 1K1C hypertension. Accelerated renovascular hypertension appears to be mediated primarily by the renin-angiotensin system.

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W D Sweet, R H Freeman, J O Davis and D Villarreal

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