Hemodynamic, Fluid, and Electrolyte Changes in Sodium-Depleted, One-Kidney, Renal Hypertensive Dogs

GREGORY A. STEPHENS, JAMES O. DAVIS, RONALD H. FREEMAN, JACK M. DEFORREST, AND DAVID M. EARLY

SUMMARY We evaluated the role of increased cardiac output in the development of experimental renal hypertension. The studies were made in five uninephrectomized, sodium-depleted dogs; renal blood flow was reduced by 55-60% by renal artery constriction (RAC). Blood pressure (BP), plasma renin activity (PRA), heart rate (HR), cardiac output (CO), stroke volume (SV), and plasma volume (PV) were determined in conscious dogs before and on days 2, 4, 6, 10, 14, 21, and 28 after RAC. After RAC, BP increased from a control mean value of 96 mm Hg to 118-147 mm Hg. CO fell from a control mean value of 1.92 liters/min to 1.42 and 1.63 liters/min ($P < 0.05$) on days 2 and 4 after RAC. After four days of RAC, CO was not significantly different from the control mean value. During hypertension, HR was consistently lower than the control mean value of 94 beats/min. Water balance was positive on days 1 and 4, but no change in PV was detected. During the control period, PRA was elevated 4- to 8-fold above sodium replete values. After RAC, PRA increased transiently on days 2 and 4 and then returned to the normal level. Three of the five dogs were sodium repleted 28 days after RAC; arterial pressure was unchanged but CO increased, peripheral resistance fell, and PRA returned to the normal level. The results demonstrate that sodium retention and a consequent increase in cardiac output were unnecessary for the development of one-kidney experimental renal hypertension. Also, the level of chronic hypertension was unaffected by sodium and volume repletion.

LEDINGHAM and Cohen (1964) reported transient increases in plasma volume, extracellular fluid volume, and cardiac output following renal artery constriction in uninephrectomized rats. They hypothesized that salt and water retention resulted in increased cardiac output which was inappropriate for the metabolic needs of the tissues and led to autoregulation of the resistance vessels. They suggested further that this autoregulation might explain the increased peripheral resistance in chronic hypertension. This idea is now commonly known as the theory of whole body autoregulation. Also, this hypothesis was suggested by Guyton and colleagues (Coleman and Guyton, 1969; Guyton et al., 1972) as an explanation for the hypertension produced by volume loading. Several investigators have reported results similar to those of Ledingham and Cohen (1964) during the development of several types of experimental hypertension in dogs (Bianchi et al., 1970; Bianchi et al., 1972; Coleman and Guyton, 1969; Ferrario, 1974; Ferrario et al., 1970), and these findings are consistent with the hypothesis of whole body autoregulation. On the other hand, Olmsted and Page (1965) reported a transient fall in cardiac output in unilaterally nephrectomized dogs after renal artery constriction. Also, Brown et al. (1966) and Conway (1968) produced chronic, benign hypertension after renal artery constriction in sodium-depleted, one-kidney dogs, and Freeman et al. (1977) produced chronic perinephritic hypertension in one-kidney, sodium-depleted dogs. In addition, Thurston and Swales (1976) produced chronic hypertension by renal artery constriction in both one- and two-kidney, sodium-depleted rats. These studies in sodium-depleted animals raise some question about the importance of expanded extracellular fluid volume and increased cardiac output in the development of experimental renal hypertension. In light of this evidence on body fluid volume and cardiac output during the development of experimental hypertension, the present study was undertaken to measure hemodynamic, volume, and electrolyte changes during the first 28 days of renovascular hypertension in sodium-depleted, uninephrectomized dogs. Subsequently, the dogs were sodium and volume repleted and hemodynamic studies continued.

Methods

Calm female dogs weighing 16-27 kg (average weight, 20.8 kg) were used in this study. All experiments were performed on conscious dogs that had been trained for 2-4 weeks to lie quietly on a padded
Table. At least 7 days before data collection, the dogs were splenectomized and chronic catheters were placed in the aortic arch through the right carotid artery and in the superior vena cava or right heart through the right external jugular vein. The catheters were exteriorized between the shoulder blades. At the same time, a unilateral nephrectomy was performed after verification of the existence of a single renal artery for the remaining kidney. During the acute studies, blood pressure was recorded continuously from the chronic arterial catheter with a Statham P23Db pressure transducer and a Sanborn 7700 recorder. Heart rate was determined from the blood pressure recording. Cardiac output was determined by dye dilution using indocyanine green dye (Coleman and Guyton, 1969); each value is the mean of three determinations made in rapid succession. Stroke volume was calculated by dividing cardiac output by heart rate, and peripheral resistance was calculated by dividing mean blood pressure in mm Hg by cardiac output in liters per minute. Plasma volume was estimated by injection of Evans blue dye. Hematocrit was measured by a microhematocrit method, and urine and plasma electrolytes were determined by flame photometry. For plasma renin activity (PRA), blood samples were collected in tubes in an ice bath; each tube contained 0.1 ml of 10% ethylenediaminetetraacetate per 10 ml of blood. The tubes were centrifuged in the cold for plasma separation. The plasma was prepared for the angiotensin I generation by dialysis against 0.2 M phosphate buffer (pH 5.4) for 18 hours (three changes), after which 25 μl of a 10 g/liter solution of diisopropylfluorophosphate and 25 μl of normal saline were added to 1 ml of plasma. The plasma was incubated for 60 minutes at 37°C, then was placed in ice water to stop the reaction. Angiotensin I content was determined by radioimmunoassay (Sealey et al., 1974). All data were analyzed by Student's paired or group t-test.

Prior to data collection, the dogs were maintained for at least 7 days on a diet containing 60 mEq sodium and 50 mEq potassium daily. Throughout the study, water was available ad libitum and the volume consumed daily was recorded. The dogs were housed in metabolic cages to allow measurement of fluid and electrolyte balances. After 7 days on the normal diet, the dogs were sodium depleted by maintenance on a low sodium diet (<3 mEq/kg/ day) augmented with intramuscular injections of 2 ml of Mercuhydrin (meralluride sodium and theophylline) on the 1st and 2nd days. This regimen resulted in an average negative sodium balance of approximately 7 mEq/kg body weight over the first 4 days. On the 4th day, the dogs were placed on a padded table for approximately 90 minutes, during which time blood pressure was continuously recorded. After blood pressure and heart rate had stabilized, cardiac output and plasma volume were measured. Heart rate was determined immediately before and after the cardiac output and the average of the two values recorded. Arterial blood samples also were taken for determination of PRA, hematocrit, and plasma sodium (PNa), and potassium (PK) concentrations. The same procedure was repeated 2 days later so that two series of control values were obtained for each dog on the 4th and 6th days of sodium depletion. The following morning, under sterile conditions and during sodium pentobarbital anesthesia, the renal artery of the remaining kidney was exposed retroperitoneally through a flank incision. The renal artery was bathed with 2% lidocaine and an electromagnetic flow probe and an adjustable clamp were placed around the artery. After an interval of 10–20 minutes was allowed for renal blood flow to stabilize, the clamp was constricted to reduce renal blood flow by 55–60%. This procedure has been shown previously to produce benign, one-kidney hypertension in dogs fairly consistently (Watkins et al., 1978). Blood pressure, cardiac output, heart rate, plasma volume, PRA, hematocrit, PNa, and PK were determined 2, 4, 6, 10, 14, 21, and 28 days after renal artery constriction. To ensure that the dogs were sodium depleted throughout the study, intramuscular injections of 1 ml of Mercuhydrin were given on days 2, 6, 13, 20, and 27. After 28 days, three of the dogs were returned to the normal diet (60 mEq Na, 50 mEq K, daily); after sodium repletion three more series of hemodynamic measurements were made.

Results

Hemodynamic measurements were made in five uninephrectomized dogs before and after renal artery constriction which reduced renal blood flow by an average of 57.9 ± 0.5%. During the early training period, arterial pressure and heart rate were unstable but, with training, these functions became much more stable and lower. The study was not undertaken until it was certain that the hemodynamic functions were stable and reproducible, and that the dogs were relaxed and accustomed to the measurement procedures. Table 1 presents the average values (±SEM) for the dogs before and during the development of hypertension.

After renal artery constriction, all the dogs developed hypertension by the 2 day, and blood pressure continued to rise throughout the 28 days. Cardiac output decreased transiently on days 2 and 4 after constriction. On days 6, 10, 14, 21, and 28 cardiac output was not significantly different from control. The initial decrease in cardiac output was accompanied by a significant increase in peripheral resistance which continued throughout the study. On the 2nd day after constriction, heart rate dropped significantly and remained significantly below control values throughout the study. After renal artery constriction, stroke volume increased slowly with the increase reaching statistical significance on day 28. Changes in plasma volume and hematocrit were not detected throughout the study; when
Table 1  Hemodynamic Changes in Trained, Conscious, Sodium-Depleted Dogs before and after Renal Artery Constriction (Means ± SEM; n = 5)

<table>
<thead>
<tr>
<th>Days</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Cardiac output (liters/min)</th>
<th>Stroke volume (ml)</th>
<th>Peripheral resistance [mm Hg (liters/mm)]</th>
<th>Plasma volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3</td>
<td>94 ± 3</td>
<td>98 ± 7</td>
<td>1.95 ± 0.15</td>
<td>19.5 ± 0.8</td>
<td>49.2 ± 3.3</td>
<td>1126 ± 84</td>
</tr>
<tr>
<td>-1</td>
<td>97 ± 3</td>
<td>89 ± 5</td>
<td>1.85 ± 0.15</td>
<td>21.2 ± 1.5</td>
<td>52.8 ± 4.5</td>
<td>1253 ± 66</td>
</tr>
</tbody>
</table>

Renal artery constriction

<table>
<thead>
<tr>
<th>Days</th>
<th>Water intake (ml/day)</th>
<th>Urine volume (ml/day)</th>
<th>Excreted Na (mEq/day)</th>
<th>PRA (ng A I/ml per hr)</th>
<th>P&lt;Na (mEq/liter)</th>
<th>P&lt; (mEq/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-6</td>
<td>602 ± 75</td>
<td>999 ± 146</td>
<td>112 ± 13.9</td>
<td>13.9 ± 1.4</td>
<td>123 ± 8.7</td>
<td>123 ± 5</td>
</tr>
<tr>
<td>-5</td>
<td>628 ± 126</td>
<td>636 ± 81</td>
<td>27 ± 13.9</td>
<td>25.5 ± 2.8</td>
<td>75.7 ± 3.3</td>
<td>1258 ± 71</td>
</tr>
<tr>
<td>-4</td>
<td>862 ± 202</td>
<td>578 ± 59</td>
<td>1.2 ± 0.4</td>
<td>25.3 ± 1.9</td>
<td>73.8 ± 5.2</td>
<td>1329 ± 104</td>
</tr>
<tr>
<td>-3</td>
<td>700 ± 121</td>
<td>524 ± 97</td>
<td>2.4 ± 1.0</td>
<td>26.0 ± 1.9</td>
<td>76.6 ± 5.6</td>
<td>1243 ± 87</td>
</tr>
<tr>
<td>-2</td>
<td>490 ± 75</td>
<td>590 ± 111</td>
<td>1.9 ± 1.0</td>
<td>27.1 ± 2.7</td>
<td>84.2 ± 8.3</td>
<td>1274 ± 77</td>
</tr>
<tr>
<td>-1</td>
<td>588 ± 88</td>
<td>573 ± 62</td>
<td>1.0 ± 0.3</td>
<td>27.4 ± 2.0</td>
<td>77.1 ± 4.8</td>
<td>1236 ± 95</td>
</tr>
</tbody>
</table>

Na intake <3 mEq/day.

* P < 0.05 compared with control values.

plasma volume was expressed in ml/kg, it ranged from a control mean value of 57.2 ml/kg to 67.1 ml/kg during the experimental period (P > 0.05).

Table 2 presents the changes in water and sodium balances, PRA, and plasma electrolytes. The control PRA levels of 7.6 ± 1.9 and 6.0 ± 1.4 ng angiotensin I/ml per hr (ng A I/ml per hr) are typical of those observed previously in this laboratory for sodium-depleted dogs and are considerably higher than normal sodium replete values (0.5-1.0 ng A I/ml per hr). After renal artery constriction, PRA increased further to 13.2 ± 2.8 ng A I/ml per hr on day 2 and 10.4 ± 2.0 ng A I/ml per hr on day 4 (P < 0.05 for both values). By day 6, PRA had
returned to the control level and was unchanged from control for the remainder of the 28-day period of study.

After renal artery constriction, water intake was significantly elevated above the control intake on days 1 and 4 (P < 0.05), and on days 1 and 4 water balance was positive (P < 0.05). After this transient positive water balance, which coincided with the transient rise in PRA, water balance was not significantly different from control for the remainder of the study. The high rates of sodium excretion on days −6 and −5 resulted from Mercuhydrin given on the first 2 days of the low sodium diet; also, the high rates of excreted sodium on days 2, 6, 13, 20, and 27 occurred in response to a diuretic given to ensure a sodium-depleted state throughout the study. On the 2nd day after constriction, PNa was 136.8 mEq/liter (P < 0.05) in association with a positive water balance on day 1. For the duration of the study, the PNa values were not significantly different from the mean value obtained immediately prior to renal artery constriction. PK showed no significant change after constriction.

On day 29 after renal artery constriction, three of the dogs were returned to the normal diet of 60 mEq sodium and 50 mEq potassium daily. Excreted sodium increased with the higher sodium intake to normal sodium replete levels. On the 7th, 10th, and 13th days after beginning sodium repletion, the hemodynamic measurements were repeated and the results are presented in Table 3. Arterial pressure was not significantly changed from the sodium-depleted value on day 28. In the last two determinations in the sodium-repleted state, cardiac output was elevated in comparison with the sodium-depleted value on the 28th day; the mean values for heart rate and stroke volume were numerically different from the mean value obtained immediately prior to renal artery constriction. PK showed no significant change after constriction.

The early, short-term effects of renal artery constriction have been studied by Bianchi et al. (1970); they observed a significant elevation in peripheral resistance at 35–45 minutes, 2 hours, and 1 day after renal artery constriction. Also, these workers observed transient increases in blood and extracellular fluid volume and cardiac output during this initial phase of hypertension. In rabbits, Fletcher et al. (1975) reported inconsistent increases in cardiac output 4 days after either bilateral renal cellophane wrapping or after a sham operation in the control group. Fletcher and his colleagues concluded that the changes in cardiac output during the 1st week after cellophane wrapping were a "nonspecific con-

### Table 3  Hemodynamic, Fluid, and Electrolyte Changes in Conscious Dogs During Sodium Repletion (Means ± SEM; n = 3)

<table>
<thead>
<tr>
<th>Days</th>
<th>Mean blood pressure (mm/Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Cardiac output (liters/min)</th>
<th>Stroke volume (ml)</th>
<th>Peripheral resistance (mm Hg liters/min)*</th>
<th>Plasma volume (ml)</th>
<th>PRA (ng/A I per ml per hr)</th>
<th>H₂O intake (ml/day)</th>
<th>Urine volume (ml/day)</th>
<th>Excreted Na (mEq/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>142±6 70±3</td>
<td>2.02±0.18</td>
<td>28.8±1.5</td>
<td>70.7±3.5</td>
<td>1540±249</td>
<td>380±20</td>
<td>2.2±0.5</td>
<td>380±20</td>
<td>2.2±0.5</td>
<td>380±20</td>
</tr>
<tr>
<td>2</td>
<td>413±37</td>
<td>367±67</td>
<td>320±125</td>
<td>273±88</td>
<td>467±169</td>
<td>305±125</td>
<td>30±11</td>
<td>413±37</td>
<td>30±11</td>
<td>413±37</td>
</tr>
<tr>
<td>3</td>
<td>473±38</td>
<td>363±71</td>
<td>330±86</td>
<td>283±54</td>
<td>470±10</td>
<td>330±86</td>
<td>43±15</td>
<td>473±38</td>
<td>43±15</td>
<td>473±38</td>
</tr>
<tr>
<td>4</td>
<td>760±330</td>
<td>403±84</td>
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<td>500±129</td>
<td>470±47</td>
<td>470±122</td>
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<td>52±8.3</td>
<td>470±10</td>
<td>52±8.3</td>
<td>500±129</td>
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<td>500±129</td>
</tr>
<tr>
<td>6</td>
<td>283±54</td>
<td>330±86</td>
<td>437±38</td>
<td>367±67</td>
<td>62±15</td>
<td>367±67</td>
<td>62±15</td>
<td>283±54</td>
<td>62±15</td>
<td>283±54</td>
</tr>
<tr>
<td>7</td>
<td>143±9 80±8</td>
<td>2.50±0.19</td>
<td>32.5±1.1</td>
<td>55.8±4.0†</td>
<td>1462±130</td>
<td>420±47</td>
<td>57±11</td>
<td>143±9</td>
<td>57±11</td>
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<tr>
<td>8</td>
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<td>55±8.3</td>
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<td>467±169</td>
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<tr>
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<td>372±69</td>
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<td>59±7.1</td>
<td>450±85</td>
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<td>470±10</td>
<td>59±7.1</td>
<td>470±10</td>
</tr>
<tr>
<td>10</td>
<td>143±9 80±8</td>
<td>2.50±0.19</td>
<td>32.5±1.1</td>
<td>55.8±4.0†</td>
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<td>456±115</td>
<td>26±19</td>
<td>456±115</td>
</tr>
<tr>
<td>13</td>
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<td>2.56±0.22*</td>
<td>31.8±2.6</td>
<td>56.1±5.2†</td>
<td>1517±161</td>
<td>325±85</td>
<td>42±4.7</td>
<td>142±6</td>
<td>42±4.7</td>
<td>142±6</td>
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<tr>
<td>14</td>
<td>380±60</td>
<td>325±85</td>
<td>380±60</td>
<td>380±60</td>
<td>53±17</td>
<td>380±60</td>
<td>53±17</td>
<td>380±60</td>
<td>53±17</td>
<td>380±60</td>
</tr>
</tbody>
</table>

Na intake = 60 mEq/day.

* P < 0.005 and † P < 0.05, in comparison with values on day 28.
sequence" of the surgical procedure and were not necessary for the development of hypertension.

The long-term effects (weeks 1–4) after renal artery constriction have also been investigated in both the rat and the dog. In one-kidney hypertensive rats, Ledingham and Cohen (1964) found that extracellular fluid volume and cardiac output were elevated initially and then returned to the control level 10–15 days after renal artery constriction. In a later study, Ledingham and Pelling (1967) made comparisons between a group of uninephrectomized rats developing hypertension and a sham-operated group. For 3 days after renal artery constriction, cardiac output was lower in the hypertensive group but subsequently increased and, after day 6, was maintained approximately 10% above that of the sham group. The transient volume expansion and increased cardiac output observed in the rats in the earlier study (Ledingham and Cohen, 1964) are consistent with the theory of whole body autoregulation, but the failure of cardiac output to return to the control level in the later study suggests a possible direct role for cardiac output in the maintenance of the hypertension. In the dog, Ferrario (1974) reported that cardiac output increased during the first few days after renal artery constriction and then declined toward control values after 3 weeks; by this time peripheral resistance had increased significantly and remained elevated until the end of the 7-week study. Ferrario concluded that this elevated cardiac output followed by a rise in peripheral resistance is consistent with the theory of whole body autoregulation. Transient increases in cardiac output and plasma volume also have been reported by Ferrario and associates (1970) during the development of cellophane perinephritis hypertension in one-kidney dogs and by Coleman and Guyton (1969) after salt loading in dogs with reduced renal mass.

Thus, some investigators have found volume expansion and cardiac output increases early in the development of experimental renal hypertension, but others have reported no increase in cardiac output or increases in both hypertensive and sham groups. It should be emphasized that, although volume expansion and increased cardiac output have been described during the early development of experimental hypertension, in none of the studies has a definite causal relationship been established between these changes and the rise in blood pressure.

In the present study, the low sodium diet (<3 mEq/day) combined with injections of a diuretic produced a negative sodium balance throughout the 28 days of hypertension; this is in contrast to the salt and water retention and volume expansion which has been reported previously in animals on a normal sodium intake (Bianchi et al., 1970; Conway, 1968; Leenen et al., 1975; Swales et al., 1972; Watkins et al., 1978). Also, in the present study, plasma volume, hematocrit, and blood volume were not detectably changed. However, water balance was positive on days 1 and 4 after constriction, and hyponatremia was present on the 2nd day after constriction. It seems likely that these changes were related at least in part to the surgical trauma of the operation. In spite of this initial small increase in body fluid volume on days 1 and 4 after renal artery constriction, cardiac output decreased significantly (by 26% and 20%) on days 2 and 4. Heart rate also fell on the 2nd day after constriction and remained significantly below control levels throughout the study; it seems likely that the bradycardia was mediated by the baroreceptor reflexes. The initial decrease in cardiac output occurred secondary to decreased heart rate, since no change in stroke volume was observed until day 28. The initial fall in cardiac output was accompanied by a marked increase in peripheral resistance which was maintained throughout the 28-day study. In the only previous measurement of cardiac output in sodium-depleted, one-kidney hypertensive dogs, Conway (1968) also found blood volume and cardiac output to be unchanged and peripheral resistance elevated on day 14 after renal artery constriction.

The results of the present study demonstrate that sodium retention with increases in plasma volume and cardiac output are unnecessary for the development of experimental renal hypertension. These findings are consistent with results of other studies of experimental renal hypertension in sodium-depleted animals in which volume expansion was not essential for the development of experimental renal hypertension (Brown et al., 1966; Conway, 1968; Freeman et al., 1977; Thurston and Swales, 1976).

Both the control data on cardiac output and arterial pressure and the degree of hypertension observed after renal artery constriction in the present study are consistent with previous reports (Bianchi et al., 1972; Conway, 1968; Ferrario, 1974; Ferrario and McCubbin 1973). A significant rise in blood pressure occurred on the 2nd day after renal artery constriction and a further rise to 147 ± 6 mm Hg was present after 28 days. In sodium-depleted, one-kidney Goldblatt hypertensive dogs, Brown et al. (1966) reported an increase in blood pressure of approximately 40 mm Hg within 12 days after renal artery constriction, and Conway (1968) observed an increase of 37 mm Hg on the 14th day after renal artery constriction. Similar blood pressure elevations after renal artery constriction have been reported in one-kidney dogs on a normal diet (Bianchi et al., 1970; Ferrario, 1974; Olmstead and Page, 1965; Watkins et al., 1978). It appears, therefore, that the pressor responses to renal artery constriction are similar to those reported previously in uninephrectomized dogs on a normal or low sodium intake.

Sodium repletion was accomplished by returning three of the chronic hypertensive dogs to a normal diet containing 60 mEq sodium daily. This failed to
change the level of hypertension, but PRA returned to the normal level. At the same time, cardiac output increased and was accompanied by a corresponding decrease in peripheral resistance. It seems likely that the striking decrease in PRA from 8.0 to 0.6 ng angiotensin I/ml per hr contributed to the decrease in peripheral resistance (Johnson et al., 1973; Davis, 1975). Since in these renal hypertensive dogs, arterial pressure was unchanged by sodium repletion, the increased cardiac output contributed substantially to the high stable level of arterial pressure. It is also clear that whole body autoregulation did not occur in response to the increased cardiac output, since total peripheral resistance actually fell. Instead, it appears that increased cardiac output exerted a direct influence in the maintenance of hypertension when the animals were fully sodium and volume repleted.

The results of the present study provide no support for the theory of whole body autoregulation to explain the pathogenesis of experimental renal hypertension. The present findings demonstrate that an increase in cardiac output was unnecessary for the development of chronic, experimental renal hypertension. Also, during the chronic phase of one-kidney experimental renal hypertension, the level of arterial pressure was not detectably influenced by sodium repletion and the state of body fluid volume; however, cardiac output increased significantly and contributed directly to the level of hypertension, while peripheral resistance fell.

References
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_Circ Res._ 1979;44:316-321
doi: 10.1161/01.RES.44.3.316

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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