Effect of Dietary Salt on Hemodynamics of Established Renal Hypertension in the Rabbit
Implications for the Autoregulation Theory of Hypertension

PAUL I. KORNER, M.D., JUDITH R. OLIVER, B.SC., AND DAVID J. CASLEY, MS. APP. SC.

SUMMARY Two groups of 10 rabbits were subjected to renal cellophane wrapping and sham operation. Their initial mean arterial pressures (MAP) were similar, 92 ± 1.5 and 90 ± 2.9 mm Hg. Six weeks later three experimental periods began, each of 2 weeks' duration, on low, normal, and high salt (1, 9, and 50 mmole Na/100 g food) diets. Each group had two subgroups: rabbits with both kidneys, and rabbits with only one kidney and previous nephrectomy. The hemodynamic findings were similar in each group. After sham operation, the range of dietary salt produced no significant circulatory changes. After wrapping, MAP was reduced on low compared with normal and high salt diets (122 ± 132 and 136 mm Hg; p = 0.01). This was entirely due to lowering of cardiac output (CO) on low salt; on normal and high salt CO was higher than in sham-operated rabbits. Total peripheral resistance (TPR) in the wrapped animals was unaffected by diet, i.e., 21.4, 20.5, and 21.2 units on low, normal, and high salt — about 35% above values of sham-operated rabbits. Volume-related CO changes therefore produce long-term changes in MAP without alteration in TPR, which is not in conformity with the autoregulation theory of hypertension. Evidence of impaired capacity of wrapped compared with sham-operated rabbits to handle salt included diet-related hematoctrit changes, lower creatinine clearance, and some differences in renin responses to salt. Giving saralasin reduced TPR while the rabbits were on low salt; the fall was twice as great in wrapped compared with sham-operated rabbits.

Key Words • autoregulation theory • blood pressure • cardiac output • hypertension • renin • salt • saralasin • vascular resistance • volume

EPIDEMIOLOGICAL analysis has suggested a strong association between the average salt intake in different countries and the incidence of hypertension.1-13 However, evidence for such an association has been less striking with data from certain countries (e.g., Dawber et al.). Similarly, in many types of experimental hypertension, altering the salt intake has produced only small effects on blood pressure. Increasing the salt intake in one-kidney renovascular hypertension, perinephritis hypertension, and several types of genetic hypertension produced either small or no rise in blood pressure, except with very high salt loads, dietary protein deficiency, or after markedly reducing the renal mass. Decreasing the level of salt in these models produced only slight, if any, lowering of the blood pressure except if the salt intake was almost zero and the diet was also low in protein.6-7,14-17

In some of the studies above, animals were placed on different regimes before and during development of hypertension (when the kidney's capacity to handle salt may itself change) rather than during stable established hypertension (when the quantitative effects of different salt loads might be easier to assess). The hemodynamic mechanisms involved in the possible long-term effects of salt and fluid loads are also unclear. In some of the experiments with large salt loads or renal impairment, rises in cardiac output (CO) have sometimes preceded elevation of total peripheral resistance (TPR),16-18 This has been explained by the autoregulation theory of the pathogenesis of hypertension as a transformation of "volume" factors (influencing CO) into increased resistance. However, the initial complex sequence of CO and TPR changes has not been uniformly observed, and recently some doubts have been expressed about how far a phase of elevated CO is important in the development of hypertension.18-19,25-28

The purpose of the present investigation has been to study the effects of moderate increases and decreases in dietary salt on the mean arterial pressure (MAP), CO, and TPR in rabbits with established cellophane-wrapped hypertension and in sham-operated rabbits. This has provided a further test of the predictions of the autoregulation theory.

From the Baker Medical Research Institute, Melbourne, Australia.
Supported by a grant from the National Health and Medical Research Council of Australia.
Address for reprints: Professor P. I. Korner, Baker Medical Research Institute, Commercial Road, Prahran, Victoria 3181, Australia.
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794
Methods

Animals and Operations

Female rabbits bred from a colony developed from several multicolored English strains underwent renal cellophane wrapping or sham operation under halothane anesthesia after induction with propanolol. A thermistor catheter (for measuring CO) was inserted into the descending abdominal aorta through the iliolumbar artery, with its tip about 5 mm below the renal artery; in this location there are no detectable losses of thermal indicator injected at room temperature into the right atrium. Perivascular balloons had also been placed around the descending aorta and inferior vena cava for studying the properties of the baroreceptor-heart rate reflex, unrelated to temperature into the right atrium. Each group of rabbits had two subgroups: one in which both kidneys were either wrapped in cellophane or merely exposed through the iliolumbar artery, with its tip about 5 mm below the renal artery; in this location there are no detectable losses of thermal indicator injected at room temperature into the right atrium. Each group of rabbits had two subgroups: one in which both kidneys were either wrapped in cellophane or merely exposed through the same type of flank incision during sham operation; and one in which one kidney was removed and the second either wrapped or exposed. The rabbits were studied on 3 experimental days, when minor operative procedures (e.g., catheterization of the central ear artery and vein) were performed under local 0.5% lidocaine anesthesia.

Measurements

Ear artery pressure, right artery pressure (RAP), and heart rate were recorded as described previously. Cardiac output was determined by thermodilution after rapid injection of a known volume (about 0.4 ml) of 5.5% dextrose into the right atrium using the injection apparatus and computer for determining the area of the primary curve described previously. Urine was collected through a funnel and mesh from the animal's metabolic cage into a glass cylinder containing a known amount of HCl and a small quantity of mineral oil. The urine volume was measured, the urine further acidified to dissolve urates and sodium, and the potassium concentrations determined by flame photometry. Creatinine was determined by autoanalyzer.

On the day of the experiment, fresh arterial blood was collected for microhematocrit estimation, for measuring plasma sodium, potassium, and creatinine concentration, and for determining plasma renin activity (PRA) and plasma renin concentration (PRC). The latter was measured by radioimmunoassay into 0.1 ml cold BAL/EDTA solution and immediately centrifuged cold; 100 μl aliquots were frozen and stored for subsequent radioimmunoassay.

Plan of Experiment

The rabbits remained in individual metabolic cages from the time before the operation throughout the study. For the first 6 weeks after operation, they were given their ordinary pellet diet of normal sodium composition. The main part of the experiment then began in three periods, each of 2 weeks, in which the rabbits received pellets of either low, normal, or high salt composition plus tap water ad libitum. A Latin Square experimental design was used to eliminate bias in the order of their administration.

The sodium and potassium concentrations of the pellets were as follows: low salt = Na 1.1, K 25.6 mmol/100 g pellets; normal salt = Na 8.9, K 25.2 mmol/100 g; and high salt = Na 50, K 26.4 mmol/100 g. Their composition was otherwise the same, i.e., approximately 20% protein, 4% fat, 65% carbohydrate (starch), 10% fiber, plus vitamins and salt-free minerals; the energy value was about 260 kcal/100 g.

Urine was collected for the last 4 days of each 2-week period on each diet. Collections were made over Days 3 and 4 and Days 1 and 2 before the hemodynamic study. In each group there were no significant differences in urine volume, sodium, potassium, and creatinine excretions over the two collection periods, suggesting that the animals were in a stable state of fluid balance. The results reported here refer to Days 1 and 2 before the hemodynamic study. Blood samples for creatinine (and other) estimations were taken only at the time of the latter study to avoid excessive sampling in the rabbit, and we have used this value and the urinary excretion data to estimate creatinine clearance.

On the day of the experiment, the rabbit rested for 30 minutes in its box after completion of the minor operative procedures. An arterial blood sample of about 2.5 ml was then taken followed by another 20-minute rest period. Five sets of measurements of MAP, RAP, and CO were then obtained at 2-minute intervals, and TPR was calculated as (MAP — RAP, mm Hg)/(CO, ml/min) units; the average of each variable was taken as the animal's value for that part of the experiment. About 30 minutes later (following tests of baroreceptor-heart rate reflex function not relevant to this paper) a second 1.3 ml sample of arterial blood was taken for a second set of PRA and PRC determinations. The animals then received an infusion of saralasin (sarcosine — alanine — angiotensin II) 6 μg/kg/min i.v. This produced an approximately 100-fold shift to the right in the angiotensin II (A II) — MAP dose response curve to bolus injections of synthetic volasine A II (Hypertensin, Ciba) and completely blocked the pressor effect of a bolus of 0.25 μg/kg/i.v. of A II. Saralasin was infused for 60 minutes before obtaining another five sets of hemodynamic measurements as before.

After the last experiment the animals were killed with an overdose of sodium pentobarbital and the organs rapidly removed, drained of blood, and weighed after washing in saline. Kidney and heart were also examined histologically after fixation in 10% formalin-saline.

Statistical Analysis

Significance of differences within rabbits was assessed by two-way analysis of variance, with orthogonal partitioning of the "between salt diets" sums of squares into individual degrees of freedom.
For estimating the significance of differences of PRA, PRC, and urinary sodium excretion, logarithmic transformation of the data was employed. Comparison of CO values between normotensive and hypertensive animals and the different weights were assessed by unpaired t test and by the Mann-Whitney U test.21

Results

Hemodynamic Findings

The preoperative MAP levels and body weights were similar in rabbits subsequently subjected to renal wrapping (MAP = 91.5 ± 1.45 (SEM) mm Hg; 2.59 ± 0.11 kg; n = 10) and sham operation (89.6 ± 2.88 mm Hg; 2.51 ± 0.08 kg; n = 10). In both groups, body weight had altered little from initial values during the main part of the experiment from 6 to 12 weeks postoperatively, and there was no effect due to dietary salt (table 1).

In sham-operated rabbits, MAP also remained close to the preoperative value on all three levels of salt (fig. 1). In this group the different diets had no

Figure 1. Average values of mean arterial pressure (MAP), cardiac output (CO), total peripheral resistance (TPR), and hematocrit (H’CRIT) in 10 sham-operated and 10 renal-wrapped rabbits using pooled data of rabbits with two kidneys and with only one kidney. Each animal was studied after 2 weeks on low (L), normal (N), and high (H) salt. Horizontal interrupted line is preoperative MAP. Asterisk denotes significant change (p < 0.05) within animals from the value on normal salt. Standard error of mean (within animals) of each column is SD (from table 1).

Table 1. Average Hemodynamic, Hematocrit and Body Weight Values on Low, Normal, and High Salt Diets in Sham-Operated and Renal-Wrapped Rabbits with both Kidneys (2K) and with only one Kidney plus Nephrectomy (1K)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Rabbit</th>
<th>Low</th>
<th>Normal</th>
<th>High</th>
<th>sd</th>
<th>Low</th>
<th>Normal</th>
<th>High</th>
<th>sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure</td>
<td>2K</td>
<td>87.6</td>
<td>89</td>
<td>89.8</td>
<td>(±5.0)</td>
<td>126</td>
<td>133</td>
<td>137.6</td>
<td>(±11.0)</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>1K</td>
<td>80.6</td>
<td>89.9</td>
<td>89.5</td>
<td></td>
<td>118.2</td>
<td>131.8</td>
<td>135.2</td>
<td></td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>2K</td>
<td>660</td>
<td>688</td>
<td>579</td>
<td>(±84.4)</td>
<td>614</td>
<td>712</td>
<td>766</td>
<td>(±104.2)</td>
</tr>
<tr>
<td></td>
<td>1K</td>
<td>517</td>
<td>573</td>
<td>569</td>
<td></td>
<td>593</td>
<td>609</td>
<td>709</td>
<td></td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td>2K</td>
<td>-0.7</td>
<td>-1.6</td>
<td>-2.5</td>
<td>(±1.1)</td>
<td>-1.8</td>
<td>-2.1</td>
<td>-1.2</td>
<td>(±0.9)</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>1K</td>
<td>-2.0</td>
<td>-2.7</td>
<td>-1.7</td>
<td></td>
<td>-1.7</td>
<td>-1.0</td>
<td>-1.6</td>
<td>(±0.9)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>2K</td>
<td>271</td>
<td>268</td>
<td>274</td>
<td>(±28.7)</td>
<td>269</td>
<td>259</td>
<td>276</td>
<td>(±33.3)</td>
</tr>
<tr>
<td></td>
<td>1K</td>
<td>249</td>
<td>262</td>
<td>275</td>
<td></td>
<td>226</td>
<td>240</td>
<td>262</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>2K</td>
<td>2.69</td>
<td>2.71</td>
<td>2.69</td>
<td>(±0.12)</td>
<td>2.55</td>
<td>2.53</td>
<td>2.59</td>
<td>(±0.11)</td>
</tr>
<tr>
<td></td>
<td>1K</td>
<td>2.38</td>
<td>2.43</td>
<td>2.37</td>
<td></td>
<td>2.51</td>
<td>2.58</td>
<td>2.58</td>
<td></td>
</tr>
</tbody>
</table>

n = 5 each subgroup; Low, Normal, High refer to dietary salt. Figures in parentheses are SD obtained from analysis of variance as (error mean square)². *Low compared with average of normal + high salt, p < 0.05, using pooled data of both subgroups.
significant effects on CO, TPR, and heart rate, and the findings were similar in the two subgroups of rabbits with two and only one kidney (table 1).

In the two subgroups of renal hypertensive rabbits, the findings were again closely similar (table 1). After pooling the results (fig. 1) MAP was not significantly different on normal and high salt diets (means 132.4 and 136.4 mm Hg respectively) but was reduced on low salt (122 mm Hg; p within animals = 0.01). This fall in MAP was entirely accounted for by reduction in CO on low salt (p < 0.05). The TPR remained closely similar on low, normal, and high salt, with values of 21.4, 20.5, and 21.2 units respectively.

In the hypertensive rabbits, the CO values on normal (705 ml/min) and high (738 ml/min) salt diets were above the average value (601 ml/min) and range observed in sham-operated rabbits (p < 0.05 by Mann-Whitney U test) (fig. 1). Heart rates were variable and not significantly different on the three diets (table 1). Stroke volumes were higher in the wrapped rabbits on normal and high salt (2.8 ± 0.21 ml) than in sham-operated rabbits on the same diet (2.26 ± 0.11 ml; p = 0.05). Low salt brought the CO of the wrapped rabbits (604 ml/min) into the range of the sham-operated animals, but had a less pronounced effect on stroke volume (2.53 ± 0.21 ml).

Hematocrit did not alter significantly in sham-operated rabbits on low, normal, and high salt (34.8, 35.3, and 34.8% respectively). By contrast, in the renal-wrapped group, the hematocrit on low sodium (32.8%) was 2.3% ± 0.7% (p < 0.01) greater than the average on normal (31.5%) and high (29.6%) salt; on high salt it was significantly less than on normal salt (SED ± 0.86; p < 0.05) (fig. 1, table 1).

Effect of Saralasin

In sham-operated rabbits, 1 hour of saralasin infusion reduced MAP in animals on low and normal salt, but not on high salt (table 2). However, it was only on low salt that the fall in MAP was consistently associated with reduction in TPR. In the renal-wrapped group, saralasin infusion was associated with a fall in MAP on all three diets, but again it was only on low salt that TPR was also reduced, a reduction about twice as great as that in sham-operated rabbits (table 2). Saralasin produced no significant changes in heart rate in either group on low and normal salt, but on high salt there was a small reduction in beats/min of 14.4 ± 5.3 (wrapped) and 14.9 ± 6.1 (sham) (p = 0.05). In both sham-operated and renal-wrapped rabbits, the changes in RAP after saralasin were variable on all diets and were not significant.

After AII blockade, the pattern of absolute "AII-independent" values of MAP, CO, and TPR on the different diets differed from that observed before blockade (table 2). In sham-operated rabbits, the difference in MAP between low and high salt was slightly greater than before saralasin (0.1 > p > 0.05), while TPR was about 7% greater on high salt than on the other diets (p = 0.05). In the renal-wrapped rabbits, the absolute MAP values after saralasin were somewhat lower than before blockade on all diets, but the difference between low salt on the one hand and normal and high on the other was the same as before (table 2). However, the more marked reduction in MAP on low salt was now no longer solely accounted for by reduction in CO, which had in-

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**Table 2. Pooled Hemodynamic Data on Different Dietary Salt in 10 Sham-Operated and 10 Renal-Wrapped Rabbits Before and During Infusion of Saralasin**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sham-operated</th>
<th></th>
<th></th>
<th>Renal-wrapped</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Normal</td>
<td>High</td>
<td>SEM</td>
<td>Low</td>
<td>Normal</td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
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<tr>
<td>S</td>
<td>B 86.6 89.0 89.5 (±1.6)</td>
<td>123† 132.4 136.6 (±3.4)</td>
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<tr>
<td></td>
<td>S 76.7 80.0 85.6 (±3.2)</td>
<td>110† 125.4 128.0 (±6.8)</td>
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<tr>
<td></td>
<td>Δ -9.9 -9.9 -3.9</td>
<td>-12 -7.0 -10.4</td>
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<tr>
<td></td>
<td>± SED ±2.0* ±3.0* ±2.7*</td>
<td>±4.6* ±3.0* ±3.3*</td>
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<tr>
<td>Cardiac output (ml/min)</td>
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<tr>
<td>S</td>
<td>B 592 636 574 (±26.7)</td>
<td>604† 705 737 (±44.3)</td>
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<tr>
<td></td>
<td>S 600 604 580 (±33.3)</td>
<td>665 704 718 (±54.8)</td>
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<tr>
<td></td>
<td>Δ 17 -32 +6</td>
<td>61 -1 -19</td>
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<tr>
<td></td>
<td>± SED ±16.4 ±35.1 ±24.0</td>
<td>±29.8* ±2.6 ±25.0</td>
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<tr>
<td>Total peripheral resistance (units)</td>
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<td></td>
</tr>
<tr>
<td>S</td>
<td>B 15.3 15.5 16.3 (±0.76)</td>
<td>21.4 20.5 21.2 (±1.7)</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>S 13.6 14.4 15.9 (±0.75)</td>
<td>17.9 19.4 19.6 (±1.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Δ -1.7 -1.1 -0.4</td>
<td>-3.5 -1.1 -1.6</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>± SED ±0.6* ±0.7 ±0.9</td>
<td>±0.6* ±0.9 ±1.4</td>
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</tbody>
</table>

B = before saralasin; S = during saralasin; values in parentheses are standard error of mean (SEM) from analysis of variance.
Δ is (S - B); * ± SED is standard error of difference within rabbits; *p < 0.05 for change after saralasin.
†p ≤ 0.05 for within animal difference low compared with average of normal + high salt.
§p ≤ 0.01 for within animal difference of low compared with average of normal + high salt.
§§p < 0.05 high compared with average of normal and low salt.
creased in this group after saralasin. Thus, in the hypertensive animals on low salt, CO levels were not brought as effectively into the range of CO values of normotensive rabbits as before giving the AII antagonist (table 2).

**Plasma Renin**

Both PRA and PRC increased on low compared with normal salt intake and fell slightly on high salt (table 3). For each diet the difference in average values of PRA and PRC between sham-operated and renal-wrapped groups was not statistically significant. However, in the wrapped group, PRA and PRC values tended to be somewhat higher on low sodium and somewhat lower on high sodium than in sham-operated rabbits, so that the difference in logarithmically transformed renin values on these two diets was greater than in sham-operated animals (table 3; \( p = 0.05 \)).

**Plasma and Urine Sodium and Creatinine**

In sham-operated rabbits, urinary sodium excretion was least on low salt and greatest on high salt, but plasma sodium concentration did not change (table 4). Plasma and urinary creatinine did not alter with salt intake (table 4). Urinary sodium and creatinine excretion was the same in both subgroups of rabbits, but in rabbits with only one kidney plasma creatinine was about 50% higher than in those with both kidneys, i.e., their creatinine clearance was lower.

In renal-wrapped rabbits the daily sodium excretion on normal and high salt was less than in sham-operated rabbits (table 4; \( p = 0.05 \); see Discussion). Another difference was that in the hypertensive rabbits on low salt the plasma sodium was about 2 mmoles/liter lower than in those on normal and high salt (\( p = 0.05 \)), while in sham-operated rabbits it did not change (table 4). In addition, in each subgroup of hypertensive rabbits plasma creatinine levels were significantly higher than in the corresponding subgroup of sham-operated normotensive animals (table 4). Urinary creatinine excretion did not alter with the different levels of salt in each group. However, it was slightly smaller in the wrapped rabbits, so that the estimated creatinine clearance was about 30% lower in the sham-operated group.

**Organ Weight**

Heart and left ventricular weights were about 50% higher in the wrapped rabbits (7.92 ± 0.65, 5.0 ± 0.33 g respectively) than in sham-operated animals (5.50 ± 0.18, 3.30 ± 0.16 g). There were no significant differences between the renal parenchymal weights (after removing the capsule) of the two groups. The fibrous capsule of the hypertensive animals weighed approximately 25-30% of the weight of the renal parenchyma. In rabbits with only one kidney there was little evidence of "compensatory" hypertrophy following removal of the other kidney, so that in uninephrectomized rabbits renal weight was about 50% of that of rabbits with two kidneys.

**Discussion**

Moderate increases and decreases of dietary salt produced no circulatory changes in sham-operated rabbits. However, in rabbits with established hypertension, low salt reduced MAP by about 12 mm Hg; i.e., by 25% of the rise in blood pressure in rabbits on normal salt after cellophane wrapping. In the wrapped rabbits, TPR was about 34% above the value of sham-operated rabbits but did not alter with dietary salt intake. The lowering of MAP on low salt was entirely due to reduction in CO, which was brought from its elevated value on the other diets into the "normal" range of sham-operated rabbits. The probable mechanisms by which CO fell in hypertensive rabbits on low salt included 1) reduction in blood volume, estimated from the hematocrit changes (see below), and 2) the peripheral constrictor action of AII assessed from the saralasin experiments (table 2).

The conclusion, based on hematocrit changes, that in the hypertensive rabbits blood volume decreased on low salt and increased on high salt must be interpreted with caution. We have regarded them as directional indicators (but not quantitative) of changes in blood volume. They only occurred in hypertensive rabbits, but not in sham-operated animals subjected to the same protocol. The relatively higher stroke volumes in the former group and the somewhat greater renin suppression on the high salt diet both favor the conclusion of an elevated central blood volume. However,

| Table 3. Average Values of Plasma Renin Activity (PRA) and Plasma Renin Concentration (PRC) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                 | Sham-operated (n = 10) | Renal-wrapped (n = 10) |
|                                 | Low               | Normal           | High             | Low               | Normal           | High             | ae               | ae               |
| PRA (ng/ml/hr)                  |                   |                  |                  |                   |                  |                  |                  |                  |
| (0.445)*                        | 2.91              | 2.21             | 1.90             | 4.45              | 2.37             | 1.51             |                   |                   |
| (0.339)*                        | (0.206)*          | (0.041)          | (0.548)*         | (0.309)*          | (0.114)*         | (0.082)          |                   |                   |
| PRC (ng/ml/hr)                  |                   |                  |                  |                   |                  |                  |                  |                  |
| (0.826)*                        | 7.10              | 5.38             | 4.29             | 8.07              | 4.47             | 3.22             |                   |                   |
| (0.714)*                        | (0.593)*          | (0.044)          | (0.840)*         | (0.617)           | (0.458)*         | (0.068)          |                   |                   |

Analysis of logarithmic transformation of data shown in brackets.

*Significantly different from normal salt value.
diet-related changes in osmolality (e.g., related to the fall in plasma sodium on low salt) could have contributed to the changes in hemocrit.

In wrapped rabbits, PRA (and PRC) increased slightly more on low salt and decreased slightly more on high salt than in sham-operated animals. The work of Swales and colleagues\(^6\) suggests that in these rabbits there may have been a greater change in body sodium on altering diets than in sham-operated rabbits which probably maintained normal sodium on all diets.\(^6\) The fall in plasma sodium, the diet-induced changes in hematocrit, and somewhat exaggerated renin responses of the wrapped animals are consistent with this view. It should be noted that on normal and high salt the PRA (and PRC) levels of rabbits of both subgroups with one and two kidneys. Only on low salt was there consistent blockade of All-mediated vascular constriction since this diet alone was associated with significant reduction in TPR. The fall in TPR was about twice as great in hypertensive as in normotensive rabbits, similar to the previously observed difference in constrictor sensitivity of the hindlimb vessels to norepinephrine, All, and vasopressin between the groups.\(^10\) Therefore, the difference of the constrictor sensitivity to endogenous All in wrapped and sham-operated rabbits on low salt in the present study was probably nonspecific and mainly determined by structural changes in the hypertensive resistance vessels.\(^10\) This seems more likely to account for the twofold difference in TPR response than the small differences in PRA and PRC between the hypertensive and normotensive rabbits on low salt. The significant rise in CO after giving saralasin to hypertensive rabbits on low salt differs from findings in man where CO either does not change or falls.\(^41\) The small degree of bradycardia that developed on saralasin in both wrapped and sham-operated rabbits on high salt is similar to that recently reported with Sar\(^1\)Thr\(^2\)-All.\(^41\) Its significance is uncertain.

In the two subgroups of wrapped rabbits the creatinine clearance was about 30% less than in the corresponding subgroup of sham-operated animals. The work of Brace and colleagues\(^42\) suggests that it is the increase in renal tissue pressure that occurs after cellophane wrapping that is the major factor in altering renal function. They found that in dogs the pressure that developed 4 weeks after cellophane wrapping was 30 mm Hg. This could have been even greater in the present experiments because of their longer duration. The intrarenal mechanisms contributing to greater salt and fluid retention were not examined in our study; they were clearly not just a reduction in renal mass since the hemodynamic and blood volume changes were similar in the wrapped subgroups with one and two kidneys.

In our study only urine volume and sodium output were measured, and not intake. In each group urinary output values were stable over the last 4 of the 14 days on each diet (see Methods). This suggests that the animals were in a stable state of fluid and sodium balance at that time. Hence the smaller daily sodium output on normal and high salt of the hypertensive compared with sham-operated groups probably reflected a difference in their intakes, or greater loss

### Table 4. Average Values of Urine Volume, Sodium, and Creatinine Excretion and of Plasma Sodium, and Creatinine Concentrations

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sham-operated</th>
<th>Renal-wrapped</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rabbit</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Urine volume (ml/min)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ave</td>
<td>92</td>
</tr>
<tr>
<td><strong>Plasma sodium (mmole/liter)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ave</td>
<td>139</td>
</tr>
<tr>
<td><strong>Urine sodium (mmole/day)</strong></td>
<td>2K</td>
<td>0.26*</td>
</tr>
<tr>
<td></td>
<td>1K</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Plasma creatinine (mmole/liter)</strong></td>
<td>Ave</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>2K</td>
<td>0.080</td>
</tr>
<tr>
<td></td>
<td>1K</td>
<td>0.120</td>
</tr>
<tr>
<td><strong>Urine creatinine (mmole/day)</strong></td>
<td>Ave</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>2K</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>1K</td>
<td>0.83</td>
</tr>
</tbody>
</table>

*Significantly different from normal salt value p < 0.01.
\(2K, 1K = \) subgroups with both kidneys and with only one kidney.
†Significance assessed after logarithmic transformation.
by the fecal route. Both would tend to make less apparent the true degree of impairment of sodium homeostasis in the hypertensive animals.

Our finding that MAP in the wrapped rabbits on normal and high salt was raised entirely through an increase in CO is at variance with the predictions of the autoregulation theory of the pathogenesis of hypertension. According to these, one would have expected that after 2 weeks on each diet there would be little difference in the CO values but an increasing TPR with increased salt intake.\textsuperscript{51, 54} We did not measure hemodynamics at an earlier stage of each dietary period, and there may have been even larger changes in CO at that time.\textsuperscript{44, 45} However, if long-term "autoregulatory" processes were at work there should have been a demonstrable salt-related difference in TPR after 2 weeks on the different diets.

Our results suggest that CO can exert prolonged effects on MAP independently of TPR. This has also been observed by Bravo et al.\textsuperscript{44} in steroid hypertension in the dog where in about half their animals MAP was raised for several weeks entirely through elevation of CO.

We have previously studied the development of renal-wrap hypertension in another strain of rabbits.\textsuperscript{39} Comparison of the time course of hemodynamic changes in wrapped and sham-operated rabbits maintained throughout on the same normal salt diet suggested that hypertension was entirely TPR-mediated from the beginning; an early rise in CO occurred in both groups and was considered to be a nonspecific accompaniment of surgery unrelated to the subsequent development of hypertension.\textsuperscript{40}

These two studies suggest that in the pathogenesis of renal-wrap hypertension "volume" and "constrictor" factors play a causally independent role and are not interrelated as envisaged by the transformation of CO to TPR postulated by the autoregulation theory. We cannot be certain that the independence of these two factors also applies to other models of experimental hypertension or to different types of human hypertension. However, we believe that to regard them as independent is at present a better working hypothesis than to regard them as closely interrelated, as implied in the concept of long-term autoregulation, and is probably more useful in the search for different pathogenetic causes of hypertension. In many of the earlier studies, the experimental designs would generally not have permitted a distinction as to whether "volume" or "constrictor" factors were independent or interrelated. Many of the studies were performed during development of hypertension, and early CO changes could appear to become transformed into TPR changes even if volume and constrictor factors were altered independently but at different rates. To date, most of the autoregulatory processes described have been fairly rapid processes, of several minutes' duration, ones that play an important role in adjusting tissue blood flow to local requirements.\textsuperscript{44} Their importance in moment-to-moment control is recognized in both normotensive and hypertensive circulations. However, there is at present no firm experimental evidence for a special process of long-term autoregulation envisaged by the autoregulation theory of hypertension.

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