Systemic and Regional Hemodynamics in Patients With Salt-Sensitive Hypertension

Toshiro Fujita, Katsuyuki Ando, and Etsuro Ogata

Twenty-two patients with normal plasma renin and essential hypertension were classified as "salt-sensitive" (SS) (n=9) or "non-salt-sensitive" (NSS) (n=13) from an increase in mean blood pressure with changes in sodium intake from 25 to 250 meq/day. With the high sodium diet, the SS patients gained more weight (p<0.05), retained more sodium (p<0.05), and had a greater increase in cardiac output (p<0.05). Despite the markedly increased cardiac output, systemic vascular resistance did not change with sodium loads in the SS patients, whereas the NSS patients had a significant decrease in systemic vascular resistance. Thus, the greater increase in blood pressure with sodium loads in SS patients can be attributed not only to an increase in cardiac output, possibly resulting from greater sodium retention, but also to inappropriately elevated systemic vascular resistance. Concomitant with a greater increase in cardiac output, the SS patients had a greater increase in forearm blood flow with sodium loading than the NSS patients (p<0.02). In contrast, blood flow to the kidney and the liver was not significantly changed in either group; renal (p<0.05) and hepatic (p<0.01) vascular resistance increased significantly in SS patients but remained unchanged in NSS patients. Thus, evidence presented suggests that the greater increase in blood pressure with sodium loads seems to be characterized by a very inhomogenous distribution of local flow and resistance in SS patients; renal and hepatic blood flow remains essentially unchanged and skeletal muscle blood flow receives almost all of the increase in cardiac output. Moreover, systemic vascular resistance changes did not reflect the resistance of individual beds because vasoconstriction appeared in the kidney and the splanchnic area but was masked by prominent vasodilation in the skeletal muscle. Because this hemodynamic pattern is similar to the pattern evoked during defense reaction, it is suggested that sympathetic overactivity on a selective basis might be involved in the impaired renal function for sodium excretion and the increase in blood pressure with sodium loads in SS patients. (Hypertension 1990;16:235-244)

It is widely believed that excessive sodium intake plays a role in the development of hypertension in humans. However, the mechanisms by which excess salt intake increases blood pressure in humans are not clear.

In previous studies, patients with hypertension were classified as salt-sensitive (SS) or non-salt-sensitive (NSS) as estimated from the rise in blood pressure with the increase in sodium intake. On a high salt diet, the SS hypertensive patients retained more sodium and gained more weight, with a greater increase in cardiac output, than did the NSS patients. Thus, the elevation of blood pressure with salt loading in the SS patients was attributed to the increased cardiac output, possibly by sodium retention. Because glomerular filtration rate was almost normal in the SS patients, there are considerable possibilities that the impaired renal function for sodium excretion, the most characteristic finding in SS hypertension, might be due not only to morphological but also to functional changes in the kidney. Although a number of factors control the renal handling of sodium, neural mechanisms are important in the renal function for sodium excretion and the resultant development of hypertension. In rats with deoxycorticosterone acetate (DOCA)–salt hypertension, a model of salt-dependent hypertension, the increased sympathetic activity in the kidney might contribute, through sodium retention, to the development of hypertension. Accordingly, we and recently Gill et al have hypothesized that the persistence of autonomic "drive" in the SS patients might play an important role in the impaired renal function for sodium excretion and the resultant increases in cardiac output and blood pressure with...
sodium loads. This hypothesis was supported by the studies of Campese et al.11 and Koolen and Van Brummelen12 that reported higher plasma norepinephrine concentrations during salt loading in SS hypertensive patients as compared with the NSS patients.

In general, autonomic activation in essential hypertension is not generalized but is regional.13,14 Because the sympathetic nervous system is the key factor in regulating vasoconstrictor tone, it is not equal in the different organs;15 a defense reaction triggered, for example, by mental arithmetic induced a peculiar hemodynamic pattern of increased vascular resistance in the kidney and the splanchnic area and a decreased vascular resistance in the skeletal muscle vascular bed, suggesting increased sympathetic tone on a selective basis.16,17 Thus, the degree of sympathetic tone in the different tissues can be estimated indirectly by measuring the change in blood flow and the resistance of individual beds. Consequently, if there are abnormal responses of the sympathetic nervous system to sodium loading in the SS patients, the pattern of changes in regional blood flow with sodium loading in the SS patients should differ from that in the NSS patients. Interestingly, the recent study of Lawton et al18 showed that dietary salt loading in borderline hypertensive subjects produced enhanced renal vasoconstriction during standing, suggesting that salt loading might unmask the increased renal sympathetic tone and then cause exaggerated reflex vasoconstrictor responses. However, only a few studies have examined changes in blood flow in the different organs during salt loading in SS hypertensive patients. In the present study, therefore, we studied the changes in systemic and regional hemodynamics with sodium loads in patients with SS hypertension to further assess the role of the sympathetic nervous system in vascular resistance changes and blood pressure increases with sodium loads.

Methods

Twenty-two patients with essential hypertension (15 men, seven women) were studied. These patients had mild-to-moderate hypertension, with casual (morning) clinic blood pressure from 150 to 180 mm Hg systolic and 90 to 115 mm Hg diastolic. Patients with primary aldosteronism, pheochromocytoma, renal vascular disease, diabetes mellitus, or Cushing's syndrome were excluded by complete history and physical examination, urinalysis, rapid-sequence intravenous pyelograms, plasma potassium and creatinine, plasma renin activity, aldosterone and norepinephrine, and 24-hour urinary 17-hydroxycorticosteroids, metanephrine, and vanillylmandelic acid. There was no evidence of cardiac failure or of liver damage in any of the patients, and none had “malignant” hypertension. The electrocardiogram investigation was done to detect left ventricular hypertrophy. A subject was considered to have a positive family history of hypertension if either or both parents had hypertension. This information, to learn of a “probable genetic background of hypertension” (World Health Organization workshop19), was obtained by questioning the subjects. Twenty-two unselected hypertensive patients were entered into the study. All subjects read and signed an informed consent outlining the details of the tests to be performed.

Protocol

All antihypertensive medications had been discontinued at least 2 weeks before admission. Each subject was maintained on a constant activity pattern and adhered to a daily constant diet containing 25 meq sodium and 70 meq potassium (low sodium diet). Patients were studied for 4 days with this diet to which 140 meq NaCl was added each day (normal sodium diet). Then, the low sodium diet alone was given for 3 days, followed by 6 days of the low sodium diet to which 225 meq NaCl was added each day (high sodium diet). On the first day of the low sodium diet, 40 mg furosemide was injected intravenously.

Body weight was measured each morning at 7:00 AM after the patient had voided. Daily urine collections were made from admission to discharge to assess urinary sodium and creatinine excretion and to determine both creatinine clearance and the completeness of urine collection. Urine collections had to be complete, as judged by a daily creatinine excretion within 10% of the mean for the entire admission. Every 4 hours throughout the study, after the patient had been supine for 5 minutes or longer, blood pressure was measured by sphygmomanometer. Mean blood pressure, calculated for every 4-hour reading (day and night) as diastolic pressure plus one third of pulse pressure, for the third day of the low sodium diet and the sixth day of the high sodium diet was a statistical comparison of the effects of dietary sodium on blood pressure. As in previous studies,4,5 patients whose average mean blood pressure value on day 6 of the high sodium regimen exceeded by 10% or more that on the third day of the low sodium diet were classified as SS, those whose average mean blood pressure decreased, did not change, or increased by less than 10%, as NSS (Figure 1).

With the patient supine, blood was drawn from all subjects on the last day of the normal sodium diet, the furosemide plus low sodium diet, and the high sodium diet for hematocrit, plasma sodium, and plasma potassium determinations. Plasma and urine sodium and potassium concentrations were measured with a flame photometer, and plasma and urinary creatinine was measured by an autoanalyzer method. Radioimmunoassay was used to measure plasma renin activity and aldosterone.20,21 Normal renin essential hypertension, present in all cases, was defined as plasma renin between 2.5 and 15 ng angiotensin 1/ml/hr in a sample drawn from the subjects after they had been in an upright position for 2 hours and after balance had been achieved with a 165 meq sodium intake after oral administration of 40 mg furosemide.

The hemodynamic studies were performed on the third day of the low sodium diet and on the sixth day...
of the high sodium diet. The patients were studied in the resting state in an air-conditioned laboratory, with ambient temperature ranging from 24°C to 27°C. Cardiac output was determined by dye dilution (indocyanine green) as previously described.20-21 Cardiac output was measured at least 20 minutes after each patient had rested supine in the morning, but not before the subject was subjectively relaxed and had a stable pulse rate. Cardiac index was expressed as liters per minute per meters squared. Systemic vascular resistance (SVR) was calculated as the ratio of mean blood pressure to cardiac index, expressed in units of dynes-second-centimeter^-2meters squared. Renal vascular resistance (RVR) was calculated as the ratio of mean blood pressure to RBF (expressed in units of dynes-second-centimeter^-2meters squared).

Forearm blood flow (FBF) was measured by a plethysmographic technique, as described previously.22 Changes in forearm blood volume were determined by means of a mercury-in-rubber strain-gauge plethysmograph placed on the mid forearm. With the subject comfortable in the supine position and his arms supported at a 45° angle from the long axis of the body, a strain-gauge was mounted so that its maximal tension was less than 10 g, to prevent the gauge from obstructing even the superficial veins beneath it. To eliminate the vessels in the hand from these determinations, a sphygmomanometric cuff 7 cm wide was placed around the upper arm, and forearm venous occlusion was produced by suddenly inflating this cuff to a pressure below the diastolic arterial pressure (40 mm Hg).24 using a tank of compressed air to provide a constant pressure source. FBF was taken as the average of 4-8 flow measurements made at 15-second intervals. Calculation of FBF was done independently by two of the authors from the copied records, and the average value was used for statistical analysis. The blood pressure was measured in the other arm with a sphygmomanometer. FBF, expressed as milliliters per 100 milliliters forearm volume per minute, was calculated from the change in forearm circumference during venous occlusion. Forearm vascular resistance (FVR) was calculated by dividing mean blood pressure (mm Hg) by forearm blood flow (ml/100 ml forearm volume/min); these values are expressed as "units" throughout this report.

In this method of FBF measurements, a within-observer variability is 2.8%, and a between-observer variability is 3.6%. Under these experimental conditions, repeated FBF measurements (on two different days) in a separate group of 10 normal subjects when sodium intake remained constant gave a 13.2±15.8% variation coefficient.

Renal blood flow (RBF) was determined by the single injection clearance of iodine-131 para-aminohippurate (131I-PAH)25 on the basis of the model proposed by Sapirstein et al.26 The fasting patients were recumbent for 30 minutes before the injection of 131I-PAH. 131I-PAH (60 Ci/1.73 m²) was injected intravenously and heparinized blood samples (5 ml) were drawn at 5, 10, 15, 20, 30, 40, 50, and 60 minutes after injection. Renal plasma flow was calculated as proposed by Sapirstein et al.26 This value was corrected for hematocrit and body surface area, and RBF was expressed in milliliters per minute per meter squared. Renal vascular resistance (RVR) was calculated as the ratio of mean blood pressure to RBF (expressed in units of dynes-second-centimeter^-2meters squared).

In a group of 10 normal subjects in whom duplicate determinations of 131I-PAH clearance were obtained by this method on two different days while the subjects were maintained on the same diet, the mean estimated RBF was 1,106±54 ml/min/m². The absolute day-to-day variation was 40±44 ml/min/m², an average of 3.6±4.0%.

131I-PAH clearance was compared in a group of seven normal subjects on a high (250 meq/day) versus a low (25 meq/day) sodium diet. There was a significant increase (163±36 ml/min/m², p<0.01, by paired t test) in 131I-PAH clearance with salt loading (1,076±41 versus 913±46 ml/min/m²). The results obtained provide evidence that the method for measurement of RBF, as performed in our laboratory, is significantly sensitive enough to detect small changes in blood flow.

In the present study, indocyanine green was used to estimate hepatic blood flow (HBF).27 A bolus of indocyanine green (50 mg) was rapidly injected into an antecubital vein and a 2 ml sample of blood was drawn at 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22 minutes after the injection. Indocyanine green concentrations in the serum were estimated with a Beckman DU-2 spectrophotometer (Beckman Instruments, Inc., Irvine, Calif.) at a wavelength of 805 nm. Concentrations were read off a standard calibration curve prepared with solutions of known concentrations of the dye made up in pooled human serum. The values, when plotted against time on semilogarithmic paper, fell in a straight line. This exponential disappearance...
permitted extrapolation back to zero time. Optical density units were converted to plasma concentrations by reference to standard curves of dye in plasma constructed with each dye lot and found to be linear in the concentration range used in these studies. Plasma volume was estimated from the volume of distribution of indocyanine green, which was calculated as the ratio of the amount of dye injected (mg) to extrapolated concentration at zero time (mg/ml). Fractional clearance was calculated using the method of least squares for the natural logarithmic values of the serum concentration. Subsequently, the fractional clearance was multiplied by the plasma volume to obtain plasma clearance of indocyanine green. This value was corrected for hematocrit to obtain the total blood clearance, that is, HBF (expressed in ml/min/m²). Hepatic vascular resistance (HVR) was calculated as ratio of mean blood pressure to HBF (expressed in units of dynes·sec·cm⁻⁵·m⁻².) The absolute average difference in paired indocyanine green measurements on a single sample on the same run is less than 1%. The internal standards vary by 1% or less on different days. In a group of nine normal subjects in whom duplicate determinations of indocyanine green clearance were obtained by this method on two different days while they were ingesting the same diet, the mean estimated HBF was 1,116±76 ml/min/m². The absolute day-to-day variation was 52±66%, an average of 4.7±5.9%.

Statistical Analysis
Mean±SEM and correlation coefficients were calculated by the standard statistical method. Regression analyses were carried out by the least-squares method. Differences in means between two groups were assessed by Student’s t test. A p value less than 0.05 was accepted as statistically significant.

Results
Nine patients fell into the SS group and 13 into the NSS group by our criteria (Figure 1). Their distribution by age and sex is given in Table 1. There was no significant difference in age, sex distribution, or known duration of hypertension. Also, there were no significant differences in systolic and diastolic blood pressure levels, in secondary effects of hypertension as revealed by serum creatinine, or in the incidence of left ventricular hypertrophy or retinopathy (Table 1). Indexes of the state of the renin-angiotensin-aldosterone system and plasma and urinary electrolytes also did not differ when external sodium balance had been achieved on a low sodium diet (Table 2). The average mean blood pressure values for the SS patients taking the normal sodium diet, the low sodium diet, and the high sodium diet were 111±2, 101±2, and 116±2 mm Hg, respectively (Table 3). Corresponding averages of mean blood pressure values for the NSS patients were 110±3, 104±2, and 110±2 mm Hg, respectively. The mean decrement of mean blood pressure between the normal sodium and low sodium diets was significantly (p<0.05) greater in the SS than in the NSS patients (−8.9±1.5% versus −5.5±0.8%). Also, the mean increment of mean blood pressure with sodium loading differed significantly (p<0.01) between the SS and NSS groups (14.8±1.5% versus 6.2±0.7%) (Figure 1).

Sodium Balance
Urinary sodium during the normal sodium diet was not significantly different in either group, as shown in Table 2. On the third day of sodium restriction, urinary sodium decreased equally in both groups (Table 2 and Figure 2). On the last day of the high

<table>
<thead>
<tr>
<th>Variables</th>
<th>Salt-sensitive</th>
<th>Non-salt-sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>48±4</td>
<td>44±3</td>
</tr>
<tr>
<td>Gender (female: male)</td>
<td>4:5</td>
<td>3:10</td>
</tr>
<tr>
<td>Prior drug therapy</td>
<td>5/9</td>
<td>10/13</td>
</tr>
<tr>
<td>Family history positive</td>
<td>5/9</td>
<td>11/13</td>
</tr>
<tr>
<td>Duration of hypertension (yr)</td>
<td>7.8±0.6</td>
<td>7.3±1.3</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>5/9</td>
<td>6/13</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>4/9</td>
<td>5/13</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>Highest recorded</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>166±5</td>
<td>165±5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>113±3</td>
<td>112±2</td>
</tr>
<tr>
<td>Admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>152±3</td>
<td>151±2</td>
</tr>
<tr>
<td>Diastolic</td>
<td>100±2</td>
<td>99±2</td>
</tr>
<tr>
<td>Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>147±2</td>
<td>146±4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>93±2</td>
<td>92±2</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.0±0.1</td>
<td>1.0±0.1</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Salt-sensitive</th>
<th>Non-salt-sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>63.7±2.6</td>
<td>66.5±2.7</td>
</tr>
<tr>
<td>Plasma renin activity (ng Ang/l/ml/hr)</td>
<td>6.4±1.9</td>
<td>8.9±1.1</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>19.8±3.2</td>
<td>24.2±5.8</td>
</tr>
<tr>
<td>Sodium concentration, serum (meq/l)</td>
<td>139±2</td>
<td>138±2</td>
</tr>
<tr>
<td>Potassium concentration, serum (meq/l)</td>
<td>4.2±0.1</td>
<td>4.2±0.1</td>
</tr>
<tr>
<td>Sodium excretion (meq/24 hr)</td>
<td>25±6</td>
<td>28±4</td>
</tr>
<tr>
<td>Potassium excretion (meq/24 hr)</td>
<td>65±7</td>
<td>62±6</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m²)</td>
<td>113±12</td>
<td>110±14</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Data refer to values obtained when balance had been achieved with a 25 meq sodium intake. Blood samples were obtained between 7:00 and 8:00 AM with subjects in a recumbent position. Ang I, angiotensin I.
TABLE 3. Systemic and Regional Hemodynamics in Salt-Sensitive and Non-Salt-Sensitive Hypertensive Patients

<table>
<thead>
<tr>
<th>Hemodynamic measurements</th>
<th>Salt-sensitive Low Na</th>
<th>Salt-sensitive High Na</th>
<th>Non-salt-sensitive Low Na</th>
<th>Non-salt-sensitive High Na</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>133±2</td>
<td>153±3*</td>
<td>134±3</td>
<td>146±4*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>85±2</td>
<td>98±2*</td>
<td>89±2</td>
<td>92±2*</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>101±2</td>
<td>116±2*</td>
<td>104±2</td>
<td>110±2*†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>69±2</td>
<td>65±2</td>
<td>72±2</td>
<td>67±2‡</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>3.4±0.4</td>
<td>4.0±0.4*</td>
<td>3.1±0.2</td>
<td>3.4±0.2*</td>
</tr>
<tr>
<td>Systemic vascular resistance (units)</td>
<td>2,674±269</td>
<td>2,469±204</td>
<td>2,891±197</td>
<td>2,682±176*</td>
</tr>
<tr>
<td>Forearm blood flow (ml/100 ml/min)</td>
<td>3.0±0.3</td>
<td>3.8±0.3‡</td>
<td>2.8±0.3</td>
<td>2.7±0.1§</td>
</tr>
<tr>
<td>Forearm vascular resistance (units)</td>
<td>37.6±3.4</td>
<td>31.7±2.9‡</td>
<td>41.7±3.3</td>
<td>41.0±1.5§</td>
</tr>
<tr>
<td>Hepatic blood flow (ml/min/m²)</td>
<td>1,135±97</td>
<td>1,029±82</td>
<td>1,200±77</td>
<td>1,190±76</td>
</tr>
<tr>
<td>Hepatic vascular resistance (units)</td>
<td>7.8±0.7</td>
<td>9.2±0.6*</td>
<td>7.3±0.5</td>
<td>7.7±0.5</td>
</tr>
<tr>
<td>Renal blood flow (ml/min/m²)</td>
<td>726±42</td>
<td>751±31</td>
<td>896±41</td>
<td>906±43†</td>
</tr>
<tr>
<td>Renal vascular resistance (units)</td>
<td>12.5±0.7</td>
<td>13.6±0.7‡</td>
<td>10.4±0.6</td>
<td>10.8±0.6‡</td>
</tr>
</tbody>
</table>

*p<0.01 versus patients on the low sodium diet, by paired t test.
†p<0.05 versus salt-sensitive patients, by unpaired t test.
‡p<0.05 versus patients on the low sodium diet, by paired t test.
§p<0.01 versus salt-sensitive patients, by unpaired t test.

Sodium diet, urinary sodium was quite close between the SS and NSS patients (248±14 meq/day versus 250±13 meq/day, respectively) despite the significantly (p<0.05) higher level of blood pressure in the SS than in the NSS patients (116±2 mm Hg versus 110±2 mm Hg, respectively) (Table 3 and Figure 2). Therefore, the slope of the blood pressure/urinary sodium excretion curve for the kidneys of the SS hypertensive patients apparently decreased as compared with that of the NSS patients (Figure 2).

An estimate of the mean cumulative sodium retention (intake sodium minus urinary sodium) over the 6 days of the high sodium diet was 204±32 meq in the SS patients and 125±26 meq (p<0.05) in the NSS patients; the SS patients retained significantly more sodium over the 6 days of high sodium diet than had the NSS patients. These differences in sodium excretion could not be explained by a difference in filtered sodium load as estimated by creatinine clearance and serum sodium concentration (Table 2). Body weight changes showed the anticipated increase from the data on external sodium balance by 0.7±0.1 kg in the SS patients and 1.2±0.2 kg (p<0.05) in the SS patients. Concomitantly, the SS patients had a greater increase in plasma volume than the NSS ones (693±157 versus 195±135 ml, p<0.05).

Systemic Hemodynamics

The average cardiac indexes for the SS patients on the low sodium and high sodium diets were 3.4±0.4 and 4.0±0.4 l/min/m², respectively (p<0.01, by paired t test) (Table 3). Corresponding averages of cardiac index were 3.1±0.2 and 3.4±0.2 l/min/m² (p<0.01, by paired t test) for the NSS patients on the low sodium and the high sodium diets, respectively (Table 3). The mean increments of cardiac output between the low sodium and the high sodium diets, calculated for each patient, differ significantly between the groups (19.4±4.5% versus 9.5±1.5%, p<0.05) (Figure 3). In contrast, there was no significant change of SVR with sodium loads in the SS patients (-5.2±3.9%, NS), although SVR was significantly decreased in the NSS patients (-7.0±1.4%, p<0.01) (Figure 3).

Regional Hemodynamics

The average FBF for the SS patients on the low sodium and high sodium diets were 3.0±0.3 and 3.8±0.3 ml/100 ml/min, respectively (p<0.05, by paired t test) (Table 3). Corresponding averages of FBF were 2.8±0.3 and 2.7±0.1 ml/100 ml/min (NS, by paired t test) for the NSS patients on the low sodium and the high sodium diets, respectively. The mean increments of FBF between the low sodium and the high sodium diets, calculated for each patient, differed significantly between the groups.
FIGURE 3. Bar graph showing percent changes in cardiac output (%ΔCO) and systemic vascular resistance (%ΔSVR) with sodium load in salt-sensitive (SS) (n=9) and non-salt-sensitive (NSS) (n=13) patients. Despite the markedly increased CO, SVR remained unchanged with sodium load in SS patients, but it decreased significantly in NSS patients. *p<0.01 (paired t test); §p<0.05 (versus NSS, by unpaired t test).

(31.9±8.6% versus 1.6±7.3%, p<0.02) (Figure 4). Thus, FBF in those patients on the high sodium diet was significantly greater in those that were SS than in those that were NSS (3.8±0.3 versus 2.7±0.1 ml/100 ml/min, p<0.01); FBF in those patients on the low sodium diet did not differ between the two groups. Overall, there was a direct positive correlation between the increments of FBF and those of cardiac output with sodium loads in all SS and NSS patients (r=0.540, p<0.01) (Figure 5).

The SS patients had significantly lower RBF as compared with the NSS patients whether on the low sodium diet (726±42 versus 896±41 ml/min/m², p<0.05) or on the high sodium diet (751±31 versus 906±43 ml/min/m², p<0.05) (Table 3). However, there were no significant differences in cardiac index or HBF between the SS and the NSS patients. There was no significant change of RBF with sodium loads in the SS patients (4.6±3.9%, NS) or in the NSS patients (1.6±3.8%, NS); nor did HBF change with sodium loads in the SS patients (−7.4±5.9%, NS) or in the NSS patients (0.3±4.7%, NS) (Figure 4).

The SS patients had significantly higher RVR as compared with the NSS patients whether on the low sodium diet (12.5±0.7 versus 10.4±0.6 units, p<0.05) or on the high sodium diet (13.6±0.7 versus 10.8±0.6 units, p<0.05) (Table 3). However, RBF or RVR did not correlate with mean blood pressure in the patients overall. There were no significant differences in SVR or HVR between the SS and NSS patients. With sodium loads, both RVR (11.0±4.7%, p<0.05) and HVR (22.1±7.0%, p<0.01) were significantly increased in the SS patients, whereas the NSS patients had insignificant changes of RVR (6.3±4.0%, NS) and HVR (5.9±4.8%, NS) with sodium loads (Figure 6). In contrast, the SS patients had a significantly decreased FVR with sodium loads (−14.0±5.6%, p<0.05), although FVR did not significantly change in the NSS patients (5.1±7.6%, NS) (Figure 6). Thus, FVR in patients on the high sodium diet was significantly less in those that were SS than in those patients that were NSS (31.7±2.9 units
versus 41.0±1.5 units, p<0.01), although FVR on the low sodium diet did not differ between the two groups (Table 3). There was no significant difference in changes of FVR, RVR, or HVR with the sodium load between the two groups.

Overall, there was a direct positive correlation between the increments of HVR and those of mean blood pressure with the sodium load (r=0.595, p<0.01), although the increments of mean blood pressure did not correlate with the changes in SVR, RVR, or FVR.

Discussion

In this study, we arbitrarily divided hypertensive patients into two groups based on blood pressure response to the salt load and examined the difference between the two groups in systemic and regional hemodynamics during salt loading. The first observation indicates confirmation of sodium sensitivity in 40% of a hypertensive population.29,30 In keeping with our previous study,5 moreover, the present finding is that the extent of the increase in cardiac output with salt loading was significantly greater in the SS patients than in the NSS patients. Thus, the increase in blood pressure with sodium loading in the SS patients may be attributed to the concomitant increase in cardiac output. With increased cardiac output, the NSS patients had the significantly decreased SVR with sodium loading. In contrast, SVR remained unchanged with sodium loading in the SS patients, in spite of the pronounced increase in cardiac output. Thus, we suggest that the fall in peripheral resistance was not adequate to maintain pressure homeostasis when the magnitude of the increase in cardiac output with sodium loading was relatively greater in the SS patients. It has been suggested that autoregulation may contribute to an increase in vascular resistance during exposure to salt and water in excess.31 Autoregulation in the setting is considered to represent a response to inappropriately high blood flow produced by increases in blood volume and cardiac output. It seems that an autoregulatory adjustment to high blood flow in patients with SS hypertension might be greater than in the NSS patients and contribute to the increase in SVR during salt loading. Because our study was a short-term one that did not include serial measurements of hemodynamic parameters, we could not examine the possibility of total body autoregulation as postulated by Guyton and his group.31,32

Despite unchanged SVR, a high salt intake in SS patients was associated with increases in HVR and RVR but a decrease in FVR. Although the mechanism of this phenomenon is not clear, this result suggests that analysis of SVR alone is inadequate for understanding the vascular changes that take place during elevation of blood pressure with sodium loading.

A peculiar hemodynamic pattern such as increased vascular resistance in the kidney and the splanchnic area and a decreased vascular resistance in the skeletal muscle vascular bed in the salt-loaded SS patients suggests a very inhomogeneous distribution of local flows and resistances. This hemodynamic pattern was also observed in dogs with salt and water loading after renal mass reduction33 and in rats with DOCA-salt hypertension.34 The inhomogeneous nature of the resistance changes that were observed makes it unlikely that the elevation of blood pressure with sodium loads occurred as a result of the operation of a single generalized vasoconstrictor mechanism such as humoral factor. The occurrence of these regional hemodynamic changes could be partly explained by local vascular mechanisms.

The current finding that FBF increased profoundly and FVR decreased with salt loading in the SS patients is consistent with the result of a recent study35 using a sodium loading period of 4 days and a modest increase in sodium intake (200 meq/day). These findings are opposite to those reported earlier: Takeshita et al36 and Koolen and Van Brummelen12 observed that SS patients responded to a high salt intake with a decrease in FBF and an increase in FVR. Our study differed from the two early studies in that we used both a short duration of increased sodium load (6 versus 14 days) and a smaller sodium load (250 versus 345 meq/day) after a greater sodium restriction (25 versus 70–100 meq/day). These differences might account for the absence of increased FVR during salt loading in the SS patients observed in the present study, possibly because of the lesser or slower autoregulatory adjustment to high blood flow. More prolonged exposure to a larger sodium load might have uncovered such a tendency in the SS patients, but more data will be required.

Alternatively, the mechanisms of vasodilation in skeletal muscle could be related to nervous control or...
to some physical or functional characteristic of this vascular bed. During the initial stage of salt loading, high and low pressure mechanoreceptors are stimulated, prompting reflex alterations in the effector segments of the circulation. Abboud et al. found that carotid and cardiopulmonary baroreceptors produced nonuniform regional vascular responses during venous pooling by lower body suction: cardiopulmonary baroreceptors exert the predominant influence on FVR but appear to have only minor influence on splanchnic vascular resistance. Therefore, it might be that some of these reflexes affect more particularly the skeletal muscle vascular bed during salt loading. Otherwise, skeletal muscle vasodilation might actively be effected by sympathetic cholinergic vasodilators.

How important a role are these regional hemodynamic changes likely to play in the process of increasing cardiac output and blood pressure with sodium loading in the SS patients? On the basis of animal experiments, it seems likely that arteriolar vasodilation of muscles is analogous to opening an arteriovenous fistula. In contrast to the short time constant for venous drainage of the skeletal muscles, the splanchnic bed has a long time constant for venous drainage. If such is the case in humans, there is a considerable possibility that a redistribution of local flows and resistances with vasoconstriction in the splanchnic bed and an increase in muscle blood flow, which was observed in the salt-loaded SS patients, might contribute to the profound increase in cardiac output through a faster average venous return to the heart by means of the shorter time constant pathway. It is suggested that skeletal muscle blood flow receives almost all of the increase in cardiac output with sodium loads in the SS patients to maintain high cardiac output. Moreover, the selective vasoconstriction in the splanchnic bed during salt loading may contribute to the rise in blood pressure, not only by increased vascular resistance but also by increased cardiac output, through increased central blood volume via splanchnic venous constriction.

The present finding that the SS patients retained more sodium and gained more weight during the high sodium–diet period suggests that the SS patients have an impaired renal function for sodium excretion despite a normal glomerular filtration rate, which is consistent with previous studies. Because the SS patients had significantly lower RBF and higher RVR than did the NSS patients, it is suggested that the abnormality of renal hemodynamics in the SS patients might be involved in the impaired renal ability to excrete sodium in the urine. To account for the observation that the SS patients had lower RBF than the NSS patients, one might speculate that the SS patients had suffered from more severe organ damage due to hypertension than the NSS ones. However, the evidence does not support such a suggestion, as there were no significant differences in systolic and diastolic blood pressure or secondary effects of hypertension, as revealed by creatinine clearance and the incidence of left ventricular hypertrophy. In addition, the variances of mean blood pressure (67.6 versus 80.0, F=1.18, NS) were quite close between the SS and NSS patients. Finally, there were no significant correlations of mean blood pressure with RBF or RVR in all the patients. Thus, the increased RVR and reduced RBF in the SS patients did not appear to be a consequence of hypertension. Although many extrarenal factors regulate renal vascular tone, neural mechanisms may play an important role in the control of renal sodium handling. Several investigators demonstrated that long-term intrarenal infusion of low dose norepinephrine in dogs caused not only the decreased RBF but also resulted in an increasingly higher arterial pressure level with progressive increases in sodium intake associated with the shifted renal function curve.

In previous studies, patients with SS hypertension had inappropriately high levels of plasma norepinephrine during sodium loading and greater increments of plasma norepinephrine during standing compared with the NSS patients, thus suggesting the persistence of autonomic “drive” in the sodium-loaded patients with SS hypertension. Therefore, it can be speculated that the increased sympathetic activity with salt loading may contribute to the decreased RBF through increased renal vascular resistance and thus induce the impaired renal function for sodium excretion in SS patients. In general, autonomic activation in essential hypertension is regional rather than generalized, so that the measurement of total plasma norepinephrine and tests for generalized activation are inadequate. In the present study, we measured regional blood flows to further assess changes in the sympathetic activity in individual vascular beds with salt loading. As a result, salt loading caused a defenselike hemodynamic pattern of increased RVR and HVR and decreased FVR in the SS patients, which might reflect an increased neurogenic tone in the renal and splanchnic area on a selective basis. Interestingly, Koepke and DiBona demonstrated that high sodium intake could not only enhance the renal sympathetic nerve activity but also antinatriuretic responses to air stress in the spontaneously hypertensive rat, which might be dependent on a centrally mediated facilitation of sympathetic neural outflow to the kidney. Accordingly, Lawton et al. also demonstrated that salt loading caused an exaggerated renal vasoconstrictor and antinatriuretic response to standing in young patients with essential hypertension. Therefore, there is a considerable possibility that an augmented centrally mediated outflow to the kidney could mediate the altered renovascular response to sodium loading, and thus shift the sodium-loaded renal function curve to the higher pressure levels, resulting in sodium retention and blood pressure rise with sodium loading in patients with SS hypertension. However, further studies are necessary to clarify the primary cause of impaired
renal hemodynamics and blood pressure rise with sodium loading in patients with SS hypertension.

References


**KEY WORDS** • sodium • sympathetic nervous system • vascular resistance • blood pressure
Systemic and regional hemodynamics in patients with salt-sensitive hypertension.

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*Hypertension*. 1990;16:235-244
doi: 10.1161/01.HYP.16.3.235

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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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