Sodium Sensitivity in Human Subjects
Hemodynamic and Hormonal Correlates

JAY M. SULLIVAN AND THOMAS E. RATTS

SUMMARY To investigate factors associated with sodium sensitivity, 157 subjects were studied while receiving 10 and 200 mEq sodium diets. Measurements included blood pressure (BP), forearm vascular resistance, plasma renin activity (PRA), and plasma aldosterone. Sodium repletion was associated with a greater than 5% increase in mean BP in 16% of the normotensive subjects and 29% of the borderline hypertensive subjects. Sodium-sensitive subjects were compared with sodium-resistant subjects in both the normotensive (n = 92) and borderline hypertensive (n = 65) groups. Forearm vascular resistance was significantly higher (p<0.05) during sodium loading in the sodium-sensitive subgroups of both the normotensive and borderline hypertensive groups (35.8 ± 29 vs 23.8 ± 20 [SD] and 37.5 ± 29 vs 22.5 ± 14 mm Hg/ml/min/100 g, respectively. Venous capacitance was lower in the sodium-sensitive than in the sodium-resistant borderline hypertensive subjects (0.8 ± 0.21 vs 1.69 ± 0.24 ml/100 g). During sodium restriction, PRA was significantly lower (p<0.01) in the sodium-sensitive subsets (2.56 ± 1.6 vs 4.04 ± 2.6; 2.65 ± 2.1 vs 3.88 ± 2.6 ng angiotensin I/ml/hr). Aldosterone was lower (p<0.01) during sodium depletion in the sodium-sensitive subsets (17.3 ± 12 vs 26.3 ± 16; 18.5 ± 18 vs 27.9 ± 17 ng/ml). A significant inverse correlation existed between change in BP with sodium repletion and change in PRA or level of PRA during sodium depletion (p<0.003). We conclude that both normotensive and borderline hypertensive sodium-sensitive subjects are characterized by an increase in forearm vascular resistance during high sodium intake and that this characteristic is associated with decreased responsiveness of the renin-aldosterone system during sodium depletion. (Hypertension 11: 717-723, 1988)

KEY WORDS • hypertension • sodium • vascular resistance • hemodynamics • renin • aldosterone

ALTHOUGH considerable evidence links dietary sodium intake with high blood pressure, several observations suggest that all persons are not affected equally by the hypertensive effects of sodium. By selective inbreeding, Dahl et al. 1 have developed strains of rats that become hypertensive when fed a high sodium diet and others that are resistant to the hypertensive effects of sodium. Worldwide studies of sodium intake in various human populations have shown a direct relationship between sodium intake and the prevalence of hypertension, 2 yet in certain populations, the majority of persons remain normotensive despite high sodium intake. 3 Over the past several years, a number of investigators have demonstrated that only a portion of normotensive and hypertensive groups display a change in blood pressure when sodium-depleted or sodium-loaded. 4-12 The mechanisms responsible for sodium sensitivity remain to be clarified.

In previous studies, we have shown that a mixed group of sodium-sensitive normotensive and borderline hypertensive humans were characterized by elevated forearm vascular resistance. 13 The purpose of the present investigation was to compare a larger group of normotensive and borderline hypertensive sodium-sensitive subjects to sodium-resistant normotensive and borderline hypertensive subjects to determine which characteristics were associated with sodium sensitivity and which with hypertension. A further purpose was to examine the association of hormonalpressor systems with elevated forearm resistance in the sodium-sensitive subjects.

Subjects and Methods

The protocol for this study was approved by the Institutional Review Board of the University of Tennessee, Memphis. All participants gave their informed
consent. The subjects of our study included 92 normal subjects and 65 with borderline hypertension (i.e., diastolic pressures >90 mm Hg on at least three occasions and <90 mm Hg most of the time). Few of the borderline hypertensive subjects had ever received antihypertensive therapy, and all were untreated for at least 1 month before the study. All subjects were admitted to a clinical research center for interview, physical examination, and clinical laboratory studies. Blood pressure was measured in triplicate before each meal with a Dinamap sphygmomanometer (Critikon, Tampa, FL, USA) after a 5-minute rest in the supine position. Plasma renin activity; aldosterone, noradrenaline, adrenaline, and dopamine concentrations; and 24-hour urinary excretion of sodium, potassium, and creatinine were measured on the first day of the study while the patients followed their usual diet and again at the end of each period of dietary intervention. Hemodynamic studies were performed on the same day and included echocardiography and venous occlusion plethysmography. Plasma renin activity and plasma aldosterone were measured by radioimmunoassay and fractionated plasma catecholamines were measured by radioenzymatic assay. Urinary sodium and potassium were measured with a flame photometer.

To estimate the proportion of our subjects who were sodium-sensitive and to determine which variables were associated with sodium sensitivity, all normal and borderline hypertensive subjects were studied on the first day of the protocol while following their usual diet and subsequent sodium depletion. After 4 days of a 10 mEq sodium, 60 mEq potassium diet, and again after 2 days of ad libitum diet and a 4-day 200 mEq sodium repletion diet, also containing 60 mEq potassium.

Echocardiographic Studies
Echocardiographic images were obtained as described previously. Stroke volume was determined by subtracting the systolic from diastolic volumes. Cardiac output was calculated as the product of simultaneous heart rate and stroke volume averaged over 10 seconds. Mean arterial blood pressure equaled the sum of the diastolic pressure plus one third of the pulse pressure. Total peripheral resistance was calculated from the Frank formula using auscultatory blood pressure measurements simultaneously with the echocardiographic studies: resistance (dyn·sec·cm⁻²) = mean arterial pressure (mm Hg) × 1330/cardiac output (mL/sec).

Forearm Hemodynamic Studies
Plethysmography was employed to measure forearm blood flow and vascular resistance, capillary filtration coefficient, and venous capacitance, as described in detail in earlier reports. The reproducibility of our method has been evaluated in 20 normal subjects. On triplicate determination several minutes apart, mean arterial pressure varied by 3%, forearm blood flow and resistance by 16.5%, venous capacitance by 11.4%, and capillary filtration coefficient by 22.3%.

Data Handling
The data were tabulated in original and translated forms and entered in a computerized data base. Data were tested for significance by analysis of variance, taking into account repeated measures using a VAX computer (Digital Equipment Corporation, Maynard, MA, USA). A Newman-Keuls a posteriori test was used to determine where differences lie when significant differences (α = 0.05) are found during analysis of variance. Pearson's correlation coefficients were used to examine the relationship among changes in variables. All data are presented as means ± SE.

Results
Subject Characteristics
The study cohort included 157 volunteers: 92 were normotensive, and 65 had borderline hypertension. One hundred ten were men, 140 were white, and 94 had a family history of hypertension. Their average age was 28 ± 0.6 years.

Effect of Diet on Blood Pressure
On changing from an ad libitum (average sodium excretion, 156 ± 5.8 mEq/24 hr) to a sodium-restricted diet (sodium excretion, 26 ± 1.6 mEq/24 hr), mean arterial blood pressure fell from 82.7 ± 0.82 to 84.0 ± 0.68 mm Hg in the normal subjects and from 98.6 ± 1.02 to 94.6 ± 1.06 mm Hg in the borderline hypertensive patients. A decrease in mean blood pressure of 5% or more was observed in 40% of the normotensive subjects and 42% of the borderline hypertensive subjects. During subsequent sodium repletion, sodium excretion rose to 196 ± 6.5 mEq/24 hr. The effect of sodium repletion on blood pressure is shown in Figure 1. An increase in mean blood pressure of 5% or greater was seen in 16.3% of normotensive subjects and 29.2% of borderline hypertensive subjects and was adopted as a definition of sodium sensitivity for the purpose of this study.

Of the normotensive subjects who were sodium-sensitive by our definition, 73.3% also had a fall in mean arterial pressure during sodium depletion of more than 5% compared with baseline. However, although blood pressure increased in 63% of the borderline hypertensive sodium-sensitive subjects, only

![Figure 1](https://example.com/fig1.jpg)
TABLE 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na-resistant</td>
<td>Na-sensitive</td>
</tr>
<tr>
<td>Men (%)(n=77)</td>
<td>61.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Women (%)(n=15)</td>
<td>39.0</td>
<td>40.0</td>
</tr>
<tr>
<td>White (%)</td>
<td>89.6</td>
<td>80.0</td>
</tr>
<tr>
<td>Black (%)</td>
<td>10.4</td>
<td>20.0</td>
</tr>
<tr>
<td>Family history of hypertension</td>
<td>54.6</td>
<td>46.7</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>27.3</td>
<td>25.4</td>
</tr>
</tbody>
</table>

36.8% had a fall greater than 5%, whereas 34.6% of the borderline hypertensive sodium-resistant participants and 33.8% of the sodium-resistant normotensive subjects had a fall in mean arterial pressure of more than 5%.

Differences Between Sodium-Resistant and Sodium-Sensitive Subjects

Hemodynamic Differences

In an attempt to distinguish changes associated with sodium sensitivity from those due to hypertension, the normotensive and borderline hypertensive groups were divided into sodium-resistant and sodium-sensitive subsets. The characteristics of these groups are listed in Table 1, showing a relatively greater proportion of men in the hypertensive subsets and of blacks in the sodium-sensitive subsets.

The contrasting effects of diet on blood pressure in the four groups are shown in Figure 2; the sodium-resistant subjects showed a downward trend with repeated measurements, while the sodium-sensitive groups showed an increase in blood pressure with sodium repletion to levels significantly higher than those observed in the sodium-resistant subjects. Blood pressure was significantly higher in the hypertensive subjects (p<0.0001). During sodium depletion, blood pressure was significantly lower in the sodium-sensitive than in the sodium-resistant normotensive subjects.

The changes observed in mean arterial blood pressure were paralleled by changes in forearm vascular resistance, which was significantly higher during sodium repletion in the sodium-sensitive subjects (Figure 3). In contrast to blood pressure, which was significantly higher in the borderline hypertensive group, forearm vascular resistance was not significantly different between the normotensive and borderline hypertensive groups, but it was significantly higher in the sodium-sensitive subsets (p<0.001).

Venous capacitance was significantly lower (p<0.05) in sodium-sensitive hypertensive subjects than in sodium-resistant hypertensive subjects (Table 2). Although a similar trend was seen in normotensive subjects, the differences were not significant, nor did the changes in capacitance accompany changes in sodium intake. Although capillary filtration coefficient tended to be lower in hypertensive subjects, no significant differences were noted among the four groups (see Table 2).

Echocardiographic studies of the four subsets showed that left ventricular dimensions were significantly smaller in the hypertensive sodium-sensitive subjects (p<0.05), but the difference between the normotensive groups was not significant. Ejection fraction was significantly higher in the hypertensive compared with the normotensive sodium-sensitive subjects (p<0.01). No significant differences were seen in stroke volume, cardiac index, peripheral vascular resistance, or left ventricular diastolic dimensions.

Hormonal Differences

During sodium depletion, supine plasma renin activity was significantly lower in sodium-sensitive than in sodium-resistant subsets, and it remained signifi-
TABLE 2. Venous Capacitance and Capillary Filtration Coefficient in Normotensive and Hypertensive Subjects

<table>
<thead>
<tr>
<th>Diet</th>
<th>Venous capacitance (ml/100 g)</th>
<th>Capillary filtration coefficient (ml/min/mm Hg/100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na-resistant (n = 66)</td>
<td>Na-resistant (n = 40)</td>
</tr>
<tr>
<td></td>
<td>Na-sensitive (n = 13)</td>
<td>Na-sensitive (n = 11)</td>
</tr>
<tr>
<td>Ad libitum</td>
<td>1.29 ± 0.22</td>
<td>1.69 ± 0.24</td>
</tr>
<tr>
<td>10 mEq Na</td>
<td>1.39 ± 0.22</td>
<td>1.75 ± 0.22</td>
</tr>
<tr>
<td>200 mEq Na</td>
<td>1.28 ± 0.25</td>
<td>1.59 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>110.5 ± 20.5</td>
<td>82.2 ± 8.9</td>
</tr>
<tr>
<td></td>
<td>149.9 ± 47.5</td>
<td>84.8 ± 8.9</td>
</tr>
<tr>
<td></td>
<td>100.9 ± 20.8</td>
<td>84.2 ± 13.2</td>
</tr>
<tr>
<td></td>
<td>123.4 ± 26.8</td>
<td>97.1 ± 13.0</td>
</tr>
</tbody>
</table>

Values are means ± SE.

* p < 0.05, compared with respective Na-resistant values.

significantly lower, even with the added stimulus of upright posture (Figure 4). Plasma aldosterone concentration was also significantly lower in the sodium-sensitive participants during sodium depletion (Figure 5). A significant positive correlation was noted between the increase in plasma renin activity with sodium depletion while subjects were supine with the increase observed while they were standing (r = 0.701, p = 0.0001). The increase in plasma renin activity also correlated positively with the increase in plasma aldosterone during sodium depletion (r = 0.558, p = 0.001). Conversely, a significant negative correlation was noted between the change in blood pressure with sodium depletion and either plasma renin activity during sodium depletion (r = 0.248, p = 0.003) or the increment in plasma renin activity during sodium depletion (r = 0.260, p = 0.0016).

No significant differences in plasma norepinephrine, epinephrine, or dopamine were observed among the four groups.

Other Differences

During all dietary states, the hypertensive sodium-sensitive patients were significantly heavier than the sodium-resistant hypertensive subjects, although the changes in weight with diet were parallel. No differences were noted between the normotensive subsets. There were no significant differences between the sodium-resistant and sodium-sensitive subsets regarding hematocrit; serum creatinine, sodium or potassium; urinary excretion of sodium, potassium, or creatinine; or volume.

Discussion

The response to sodium varies from person to person. In the present study, we found the prevalence of sodium sensitivity to be approximately 16% in normotensive subjects and 29% in subjects with borderline hypertension. Subsequently, Weinberger et al. and Luft and Weinberger noted that the prevalence of sodium sensitivity was higher in hypertensive than in normotensive groups. Fujita et al. observed a 10% or greater increase in blood pressure with sodium depletion in 50% of a group of 18 patients with essential hypertension. Miller et al. observed a heterogeneous response to sodium restriction in normotensive subjects; the prevalence of sodium sensitivity increased with age. In the present study, we noted a decline in mean blood pressure of more than 5% during sodium depletion in many subjects whose sensitivity to sodium could not be confirmed by an increase in mean pressure of more than 5% when sodium-replete. Therefore, we chose to use the latter criterion to define sodium sensitivity.

Several laboratories have examined the interplay of blood flow and vascular resistance in normal and borderline hypertensive subjects. Studies by Kirkendall et al. have found that sodium loading of normotensive
volunteers is accompanied by increased forearm blood flow without an increase in blood pressure, suggesting local vasodilation. Luft et al.\(^\text{24}\) found that a sodium intake of 800 mEq or more was associated with a significant increase in blood pressure and cardiac index without a change in vascular resistance. Julius et al.\(^\text{3}\) and Sannerstedt\(^\text{26}\) have studied the degree to which cardiac output and vascular resistance change with various interventions in patients with labile hypertension in comparison with normal subjects and have found that the slope of the line relating output to resistance was shifted, indicating that peripheral vascular resistance was actually inappropriately elevated in persons with mild labile hypertension. In studies of borderline hypertensive subjects, Mark et al.\(^\text{27}\) noted decreased forearm blood flow during sodium loading, suggesting vasoconstriction. Takeshita and Mark\(^\text{28}\) have studied the effect of stimuli causing maximum reactive hyperemia on forearm blood flow and resistance in borderline hypertension and have demonstrated that forearm vascular resistance does not fall as greatly in labile hypertensive subjects.

More recently, a number of investigators have examined the problem of sodium sensitivity. Our earlier studies\(^\text{13}\) demonstrated that mean arterial blood pressure rose more than 5\% when sodium-sensitive subjects became sodium-replete; the average change in sodium-resistant subjects was zero. Cardiac index increased equally in the two groups; however, the fall in peripheral resistance was twofold greater in the sodium-resistant subjects. Thus, during periods of high sodium intake, sodium-resistant subjects accommodate increases in cardiac index by a proportionate fall in total peripheral resistance that our previous studies indicate can be maintained for at least 1 year.\(^\text{29}\) Omvik and Lund-Johansen\(^\text{30}\) have found that decreased blood pressure during long-term sodium depletion (9 months) was due to a sustained fall in cardiac output and an increase in vascular resistance. Our earlier data\(^\text{12}\) also indicated that forearm vascular resistance was significantly higher in a mixed group of normotensive and borderline hypertensive sodium-sensitive subjects than in sodium-resistant subjects. However, sodium-sensitive subjects were able to decrease resistance significantly after isotonic exercise to levels near those of sodium-resistant subjects, indicating that the elevated resistance could not be accounted for entirely by permanent structural changes in the resistance arterioles. However, the residual elevation of resistance in the sodium-sensitive subjects during reactive hyperemia was consistent with a degree of structural damage. Our observations are consistent with the reports of Takeshita et al.\(^\text{3}\) and Koolen and van Brummelen,\(^\text{8}\) who found that the forearm vascular resistance of sodium-sensitive hypertensive subjects rose significantly when daily sodium intake was increased to 345 and 300 mEq, respectively. Our present study shows that sodium repletion to a level of only 200 mEq/day causes a further increase in the already elevated forearm vascular resistance of both normotensive and hypertensive sodium-sensitive subjects.

Several studies have observed decreased venous distensibility in patients with borderline or chronic essential hypertension.\(^\text{31-35}\) Fitzgerald et al.\(^\text{39}\) have presented evidence that decreased venous distensibility is associated with reduced renin responsiveness, possibly because a less compliant venous system allows less pooling of blood in the lower extremities during upright posture or thigh cuff inflation. We have found venous capacitance to be lowest in sodium-sensitive borderline hypertensive subjects, and these subjects also had lower renin and aldosterone levels.

Our present data do not provide an explanation for the increased vascular resistance in sodium-sensitive persons, but our earlier studies indicate that it is not entirely structural,\(^\text{13}\) suggesting that the abnormal resistance was due to hormonal or autonomic pressor stimuli. A number of investigators have studied the renin-angiotensin system in relation to sodium sensitivity in human subjects. Fujita et al.\(^\text{11}\) reported that sodium-sensitive patients with essential hypertension showed a lesser decrement of plasma renin activity and plasma aldosterone during sodium loading (244 mEq/day) than did non-sodium-sensitive subjects. Weinberger et al.\(^\text{3}\) observed relatively low plasma renin activity in both normotensive and hypertensive sodium-sensitive subjects. Koolen et al.\(^\text{12}\) found that the change in blood pressure between high and low salt diets was inversely related to plasma aldosterone during low sodium intake in patients with essential hypertension. Ishii et al.\(^\text{36}\) also found changes in plasma aldosterone to be inversely proportional to changes in blood pressure in similar patients. Fraser et al.\(^\text{37}\) found that patients with essential hypertension showing the greatest fall in blood pressure with sodium depletion (10 mEq) had the least rise in plasma aldosterone. In contrast, Gudmundsson et al.\(^\text{38}\) found no significant changes in blood pressure, forearm blood flow, or resistance among normotensive men with and without a family history of hypertension subjected to a high sodium intake, and no differences in the degree of suppression of plasma renin activity or aldosterone concentration in those genetically predisposed to become hypertensive. Fujita et al.\(^\text{39}\) observed that patients with essential hypertension had greater changes in blood pressure than did normal subjects after receiving diuretics or sodium supplements; however, plasma norepinephrine, epinephrine, and renin activity were significantly higher than those of normotensive subjects. The increase in blood pressure was due to an increase in cardiac output with an inadequate fall in total peripheral resistance.

Our studies did not show differences in plasma catecholamines in the four groups, especially in relation to salt intake, as suggested by Campese et al.\(^\text{7}\) Koolen and van Brummelen,\(^\text{8}\) and Fujita et al.,\(^\text{11}\) but at present we have no indirect suggestion that sympathetic nervous system activity differs between the two groups, as heart rate and cardiac index were not significantly different. We have no data relative to other vasoactive agents, such as vasopressin, prostaglandins, bradykinin, atrial natriuretic factor, renomedullary vaso-
depressor lipids, or circulating inhibitors of Na⁺,K⁺-adenosine triphosphatase (ATPase).

The hemodynamic and hormonal characteristics of the sodium-sensitive subjects observed in the present study resemble those described by studies of the Dahl sodium-sensitive rat (DS). Ishii et al. reported significantly lower plasma and kidney renin activity in DS than in the Dahl sodium-resistant strain of rat (DR). These observations were confirmed by Rapp et al., who also found that plasma 18-hydroxy-deoxycorticosterone was increased in DS.

Ganguli et al. studied the hemodynamic response to sodium loading in DS and DR. After 3 days, cardiac output rose in both groups. Pressure did not rise in the DR because of a fall in vascular resistance. In contrast, vascular resistance rose in the DS and continued to rise with continued salt loading, leading to an elevation of blood pressure and a return of cardiac output to control levels. Rodriguez-Sargent et al. measured plasma renin activity, aldosterone, and renal Na⁺,K⁺-ATPase in DS and DR and found a reduction of plasma renin activity, aldosterone, and Na⁺,K⁺-ATPase during sodium restriction in the DS as compared with the DR. Hirata et al. observed that the serum of hypertensive, sodium-fed DS resulted in an elevation of blood pressure when injected into normotensive, sodium-restricted DS. The hypertensive effect was lost if the kidneys of the donor rats had been removed previously. Baba et al. found adrenal zona glomerulosa renin and plasma aldosterone to be reduced in the DS, even during sodium depletion, leading them to conclude that the decreased levels were not due to volume expansion. Similarly, we have not been able to demonstrate volume expansion in sodium-sensitive humans in earlier studies in which plasma volume was measured. Thus, the reason for the suppressed renin activity was not apparent, but as in the DS, this finding could be due to genetic factors, such as increased 18-hydroxylation of deoxycorticosterone controlled by a single genetic locus, as demonstrated by Rapp and Dahl.

Although deficiency of either atrial natriuretic factor or renomedullary vasodepressor lipids could explain elevated vascular resistance and failure to vasodilate during sodium loading, a deficiency of atrial natriuretic factor would not explain suppressed plasma renin activity and aldosterone concentration in the absence of volume expansion. The effect of renomedullary vasodepressor lipids on renin activity has not been established. An abnormality of arachidonic acid metabolism remains a possible explanation of the findings reported herein, as local prostaglandin formation is involved in both vascular tone and renin release.

In summary, we found that mean blood pressure rose by more than 5% during periods of relatively high sodium intake in approximately 16% of normotensive and 29% of borderline hypertensive subjects. We found four factors to characterize sodium-sensitive persons, whether normotensive or hypertensive. Forearm vascular resistance was higher and venous compliance was lower in the sodium-sensitive subsets of the normotensive and borderline hypertensive groups, especially during periods of high sodium intake. The sodium-sensitive subsets were characterized further by relatively low levels of plasma renin activity and aldosterone concentration, particularly during the stimulus of sodium depletion. The rise in blood pressure during sodium repletion was predicted by the level of plasma renin activity during sodium depletion.

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