Hemodynamic Characteristics of Sodium-Sensitive Human Subjects

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SUMMARY Fifty-eight normal subjects and 51 subjects with borderline hypertension underwent microvascular and hemodynamic studies while on an ad libitum diet and during periods of sodium depletion (10 mEq/day) and repletion (200 mEq/day). Hemodynamic measurements included arterial blood pressure, cardiac index, total peripheral resistance, forearm blood flow, vascular resistance, venous compliance, and capillary filtration fraction. Studies of the microcirculation consisted of macrophotography of the bulbar conjunctiva with measurement of arteriolar, venular, and capillary density and diameter. During sodium repletion, cardiac index increased significantly in the normal subjects (2.35 ± 0.7 vs 2.44 ± 0.7 L/min/m²; p<0.01) and in the borderline hypertensive subjects (2.50 ± 0.7 vs 2.70 ± 0.8 L/min/m²; p<0.01). However, mean blood pressure rose by more than 5% in only 33 subjects, 13 with normal and 20 with borderline hypertension. When these sodium-sensitive subjects were compared with those whose blood pressure did not rise, the former were found to have significantly higher forearm vascular resistance (32.2 ± 21 vs 17.9 ± 12 mm Hg/ml/min/100g; p<0.01), lower forearm blood flow (4.42 ± 2.7 vs 7.47 ± 5.0 ml/min/100 g) and lower conjunctival capillary density (3.72 ± 1.7 vs 5.18 ± 2.1 [SD] mm/mm²; p<0.05). These results indicate that sodium sensitivity in humans is accompanied by elevation of forearm vascular resistance and attenuation of the microcirculation. (Hypertension 9: 398-406, 1987)

KEY WORDS • hypertension • sodium • vascular resistance • hemodynamics • microcirculation

The conclusion that certain individuals are sodium-sensitive is supported by two main lines of evidence, experimental and epidemiological. Meneely et al. found that rats fed a high sodium diet displayed a wide spectrum of blood pressure responses: some became severely hypertensive, some remained normotensive, and others manifested intermediate levels of blood pressure elevation. After several generations of selective inbreeding, Dahl et al. were able produce strains of genetically sodium-sensitive and sodium-resistant rats.

While studies within populations have not shown a direct relationship between individual sodium intake and blood pressure, possibly because of a saturation effect, studies of human populations have also supported the concept of individual susceptibility to the hypertensive effects of sodium. Several surveys have demonstrated a positive relationship between sodium intake and the prevalence of hypertension. However, normotensive persons can be found even in populations ingesting large quantities of sodium, suggesting that some humans are sodium-resistant while others are sodium-sensitive.

A number of investigators have observed abnormalities in the vascular resistance of patients with early, mild hypertension that might underlie sodium sensitivity. The purpose of the present study was to identify persons whose blood pressure rises with increases in dietary sodium, to determine the hemodynamic mechanism of the increase in blood pressure, and to seek identifying characteristics of sodium-sensitive subjects, other than blood pressure response, that might allow prospective identification.
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Subjects and Methods

The protocol for this study was approved by the Institutional Review Board of the University of Tennessee Center for the Health Sciences. All participants gave their informed consent. The subjects of our study included 58 normal subjects and 51 borderline hypertensive (BHT; i.e., diastolic pressures > 90 mm Hg on 3 occasions and < 90 mm Hg the rest of the time) subjects. 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 Vital Signs Monitor (Critikon, Tampa, FL, USA) after a 5-minute rest in the supine position. Plasma renin activity, aldosterone concentration, and 24-hour urinary excretion of sodium, potassium, and creatinine were measured on the first day of the study while the subjects followed their usual diet and at the end of each period of dietary intervention. Hemodynamic studies were performed on the same day. Plasma renin activity and plasma aldosterone were measured by radioimmunoassay.13, 14 Urinary sodium and potassium were measured with a flame photometer. The hemodynamic studies included echocardiography and venous occlusion plethysmography.

To estimate the proportion of our subjects who were sodium-sensitive and to determine which variables were associated with sodium sensitivity, all normal and BHT subjects were studied while they followed their usual diet, after 4 days of a 10 mEq Na, 60 mEq K diet, and again after 2 days of an ad libitum diet and a 4-day 200-mEq sodium repletion diet, also containing 60 mEq K.

Echocardiographic Studies

Echocardiographic images were obtained using Toshiba SSH-10 phased-array, real-time and combined M-mode ultrasonography (Tustin, CA, USA). The transducer was placed on the subject’s chest wall and oriented to display the long-axis view, which represents a sagittal cut through the heart from left ventricular apex to aortic root. The M-mode cursor was then positioned to intersect the maximum diameter of the left ventricle below the mitral valve leaflets and superior to the papillary muscles. This step ensures that the same dimensions are identified on subsequent studies. The motion mode ultrasound information was then recorded on a strip chart recorder (Model 1856; Honeywell, Denver, CO, USA) at 25 to 50 mm/sec through three or four respiratory cycles.

The records were then measured using conventional measuring sites for left ventricular end-diastolic dimension and end-systolic dimension.15 Systolic and diastolic volumes were calculated using the regression equation derived by Meyer et al.16: left ventricle = - 19.1 + 14.6 Be + 0.62 Be², where Be represents the echo-determined left ventricular dimension.

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 simultaneous with the echocardiographic studies: Resistance (dyn · sec · cm⁻⁵) = [mean arterial pressure (mm Hg) × 1330]/cardiac output (ml/sec).

In separate experiments we have analyzed our method for reproducibility.15 Fifty-three subjects with normal ventricles were studied on two occasions after a 30-minute rest in the supine position. At the time of each study triplicate measurements were made over a 20-minute period. The average variation of cardiac outputs calculated by this method was 11.6%. The accuracy and reproducibility of echocardiographic measurement of left ventricular volume in subjects with normal hearts have been confirmed in several studies.17

Forearm Hemodynamic Studies

Plethysmography was employed to measure forearm blood flow (FBF) and vascular resistance (FVR),18 capillary filtration coefficient (CFC),19 and venous capacitance (VC).20 A mercury-filled, single-strand strain gauge was connected to an impedance-matching circuit, a high-sensitivity, alternating current, carrier preamplifier, and an 8-channel Hewlett-Packard 7788A recorder (Palo Alto, CA, USA) and activated by a constant current. Subjects were examined, while supine, after a 10-minute rest. Arterial blood pressure was measured with a Dinamap Vital Signs Monitor at the time the plethysmographic tracing was made. The strain-gauge-to-pen deflection ratio was determined by dividing the stretch distance of the strain gauge by the pen deflection. The strain gauge was wrapped around the left forearm approximately 10 cm below the elbow, stretched 2% past its resting length, and secured with tape. A blood pressure cuff was placed on the upper left arm and inflated to 40 mm Hg to block venous return at the time of the tracings in triplicate.

The initial slope of the plethysmographic record results from the veins filling with blood. The FBF (in ml/min/100 g) was calculated from this first slope by the formula $FBF = [2(1st \ slope) \times \ calibration \ ratio \ \times \ chart \ speed (mm/min) \ \times 100]/Lo$, where $Lo$ is forearm circumference (in millimeters).

As the veins become fully distended, a second slope is recorded as fluid leaves the capillaries. CFC (in ml/min/mm Hg/100 g) was calculated from the second slope using the formula $CFC = [2(2nd \ slope) \times \ calibration \ ratio \ \times \ chart \ speed \ \times \ (1 + 0.25) \ \times 100]/40 \ Lo$, where 0.25 is taken to be the ratio of postcappillary to precapillary resistance in human subjects.

If a tangent is drawn from the second slope back to an erect perpendicular line drawn at the time the cuff was inflated, the height of the line where it meets the tangent (h) represents the VC (in ml/100 g) at 40 mm Hg. VC was calculated from the formula $VC = [(h) \ \times \ calibration \ ratio \ \times 100]/Lo$.

An automatic blood pressure reading was taken dur-
arterioles were grouped under three orders of branching: the terminal arterioles, the ones giving rise to terminal arterioles were called preterminal arterioles, and the vessels from which they arose were called large arterioles.

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 DEC 20/60 computer (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. The significance of differences (α = 0.05) in distribution of vessels was analyzed by Fisher’s exact test. Values are expressed as means ± SD.

Results
Comparison of Normal and Borderline Hypertensive Subjects
To identify potentially sodium-sensitive persons, we have recruited 109 subjects with and without a history of transient elevation of blood pressure. To date, 58 normal subjects have been studied. Their average age was 27.8 years. Thirty-five were men, 23 were women, 53 were white, and 5 were black. A family history of hypertension was present in 27 (46.6%). Fifty-one BHT subjects have been studied. Their average age was 29.6 years, 44 were men, 7 were women, 45 were white, 6 were black, and 37 (72.5%) had a family history of hypertension. Both systolic and diastolic blood pressure were significantly higher in the BHT subjects (129.5 ± 10.4/84.9 ± 9.6 vs 114.5 ± 11.1/75.8 ± 7.2 mm Hg; p < 0.00001), reflecting the criteria for their selection (Table 1).

The BHT subjects were heavier (79.1 ± 13.9 vs 69.8 ± 12.9 kg; p < 0.025) and had a higher cardiac index (5.61 ± 1.5 vs 4.62 ± 1.4 L/min; p < 0.006), which did not differ significantly when corrected for body surface area (2.87 ± 0.7 vs 2.51 ± 0.8 L/min/m²; p = 0.07). The BHT subjects also had a higher hematocrit (43.5 ± 2.7 vs 41.0 ± 3.8%; p < 0.002). CFC was significantly lower in the BHT subjects (Table 2). Serum sodium, urine potassium, and urine creatinine were slightly higher in the BHT subjects than in normal subjects. The other hemodynamic and metabolic variables measured did not differ significantly between groups.

When the participants with a family history of hypertension were compared with those who did not have a family history of hypertension, no significant differences were found in any of the variables studied.

Response to Sodium Depletion and Repletion
In hypertensive subjects, a number of variables changed significantly with sodium depletion (see Table 1). Weight, blood pressure, and cardiac index fell significantly, while total peripheral resistance rose. The fall in cardiac index was associated with a
fall in stroke volume, which in turn was due to a significant decrease in diastolic but not systolic left ventricular size. Ejection fraction did not change, although heart rate fell significantly with sodium repletion.

Several metabolic and hormonal variables changed predictably. With sodium depletion, serum sodium fell while plasma renin activity, aldosterone, and serum creatinine all rose significantly. Urinary potassium excretion fell insignificantly with sodium depletion.

When the response to sodium depletion and repletion of the BHT subjects as a group was compared with that of the normal subjects, no significant differences were found. However, when individual responses were examined, it was found that the majority of subjects in both groups experienced a slight decrease in mean blood pressure during dietary sodium repletion. A small group was found to have a greater than 5% increase in mean arterial pressure when sodium-replete; these subjects represented 39% of the BHT group but only 22% of the normal subjects (\(\chi^2 = 2.88, p = 0.089\); Figure 1). The mechanism of the increase in blood pressure was an increased cardiac index in 13 subjects, increased total peripheral resistance in 16, and an increase of both cardiac index and total peripheral resistance in four. For the purposes of this study, these subjects were designated sodium-sensitive. Fifty-six of the 76 subjects whose blood pressure rose less than 3% with sodium repletion had an increase in cardiac index, but in contrast to the sodium-sensitive su-
Comparison of Sodium-Sensitive and Sodium-Resistant Subjects

The effect of sodium on mean blood pressure in the sodium-resistant and sodium-sensitive normal subjects was contrasted with that of comparable BHT subgroups (Figure 2). Although arterial blood pressure was significantly higher in the BHT subjects, the response to sodium depletion and repletion was similar in the normal and BHT sodium-resistant subjects and the normotensive and BHT sodium-sensitive subjects.

When the effect of sodium depletion and repletion on all variables measured was compared in normotensive and BHT sodium-resistant and sodium-sensitive subgroups, only two significant differences were found. Both diastolic blood pressure during echocardiography and hematocrit fell to a greater degree during sodium repletion in BHT than in normotensive sodium-resistant subjects.

Because the responses of the four subgroups were so similar, all subjects whose mean arterial pressure rose by more than 5% during sodium repletion were then contrasted with those whose pressure did not to determine if any hemodynamic or endocrine characteristic served to identify the sodium-sensitive individual. The characteristics of the two groups of subjects are listed in Table 3. Baseline blood pressure did not differ significantly. Mean blood pressure rose significantly in the sodium-sensitive subjects, while it fell slightly in the sodium-resistant subjects (Table 4). Although cardiac index rose to approximately the same degree with sodium repletion in both groups, the fall in total peripheral resistance was twofold greater in the sodium-resistant subjects (10.8 vs 5.3%). Additionally, initial FVR was significantly higher in the sodium-sensitive subjects than in the sodium-resistant subjects and remained higher during sodium depletion and repletion (Table 5).

To determine whether the increased FVR was reversible, we studied the response to three interventions: isometric exercise, isotonic exercise, and cold pressor stimulation (Table 6). We found that resistance remained significantly higher in the sodium-sensitive subjects after isometric exercise, but the differences observed after isometric exercise or during cold pressor stress were not significant. Despite the higher resting values obtained in the sodium-sensitive subjects, these individuals were able to reduce resistance during partial reactive hyperemia to levels near those of the sodium-resistant subjects.

Table 7 examines the trends that emerged when the plethysmographic studies of normotensive sodium-resistant subjects were compared with those of normotensive sodium-sensitive subjects and similar comparisons were made in the hypertensive subgroups. FVR was significantly higher in sodium-sensitive subjects in the normotensive group during all dietary states and during high sodium intake in the BHT subjects. Although the FVR of the latter group was higher than that in the BHT sodium-resistant subjects during ad libitum
TABLE 4. Comparison of Sodium-Sensitive and Sodium-Resistant Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sodium-sensitive (n = 33)</th>
<th>Sodium-resistant (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mEq Na</td>
<td>200 mEq Na</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>73.6 ± 15*†</td>
<td>71.9 ± 13*†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>87.5 ± 10.7*</td>
<td>89.8 ± 13.7</td>
</tr>
<tr>
<td>LV diastolic dimension (mm)</td>
<td>47.0 ± 6.4‡</td>
<td>48.6 ± 5.6*</td>
</tr>
<tr>
<td>LV systolic dimension (mm)</td>
<td>30.4 ± 6.2</td>
<td>30.7 ± 4.5</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>71.5 ± 24.4</td>
<td>68.5 ± 20.8*</td>
</tr>
<tr>
<td>Cardiac index (mEq/L)</td>
<td>139.1 ± 2.49</td>
<td>140.4 ± 2.32</td>
</tr>
<tr>
<td>Plasma Na (mEq/L)</td>
<td>17.0 ± 16.4*</td>
<td>21.2 ± 11.6*</td>
</tr>
<tr>
<td>Plasma renin activity, supine (ng ANG I/ml/hr)</td>
<td>28.0 ± 16.02*</td>
<td>24.8 ± 14.5*</td>
</tr>
<tr>
<td>Urine Na (mEq/24 hr)</td>
<td>1574 ± 592</td>
<td>1691 ± 667*</td>
</tr>
<tr>
<td>Urine K (mEq/24 hr)</td>
<td>138.6 ± 2.67*</td>
<td>140.1 ± 2.37</td>
</tr>
</tbody>
</table>

Values are means ± SD. See Table 1 for key to abbreviations.
* p < 0.01, † p < 0.05, compared with values for 200 mEq Na.
* p < 0.01, † p < 0.05, compared with values for sodium-resistant subjects.

TABLE 5. Forearm Hemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sodium-resistant (n = 62)</th>
<th>Sodium-sensitive (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ad libitum Na</td>
<td>10 mEq Na</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>91.9 ± 10.9</td>
<td>89.2 ± 10.87</td>
</tr>
<tr>
<td>FBF (ml/min/100 g)</td>
<td>7.47 ± 5.02</td>
<td>4.42 ± 2.69*</td>
</tr>
<tr>
<td>FVR (mm Hg/ml/min/100 g)</td>
<td>17.9 ± 11.6</td>
<td>32.2 ± 21.3*</td>
</tr>
<tr>
<td>VC (ml/100 g)</td>
<td>1.02 ± 0.69</td>
<td>0.85 ± 0.48</td>
</tr>
<tr>
<td>CFC (ml/min/mm Hg/100 g)</td>
<td>115.6 ± 67.2</td>
<td>91.4 ± 33.7</td>
</tr>
</tbody>
</table>

Values are means ± SD. See Table 2 for key to abbreviations.
* p < 0.01, † p < 0.05, compared with values for sodium-resistant subjects.
* p < 0.01, † p < 0.05, compared with resting value.

TABLE 6. Forearm Vascular Resistance

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Sodium-resistant</th>
<th>Sodium-sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>17.9 ± 11.6</td>
<td>32.2 ± 21.3*</td>
</tr>
<tr>
<td>Isometric exercise</td>
<td>24.1 ± 17.8†</td>
<td>39.1 ± 28.5*</td>
</tr>
<tr>
<td>Isotonic exercise</td>
<td>5.9 ± 5.2†‡</td>
<td>7.0 ± 3.2†‡</td>
</tr>
<tr>
<td>Cold pressor stress</td>
<td>34.1 ± 32.8‡</td>
<td>26.5 ± 20.0</td>
</tr>
</tbody>
</table>

Values are means ± SD. Forearm vascular resistance is expressed as mm Hg/ml/min/100 g.
* p < 0.01, † p < 0.05, compared with values in sodium-resistant subjects.
† p < 0.01, compared with resting value.

and sodium depletion diets, the differences between the relatively small subgroups were not statistically significant.

Studies of the Conjunctival Microvasculature

To seek an anatomical explanation for the differences uncovered by our measurements of forearm and systemic hemodynamics, macrophotographs were taken of the conjunctival microvasculature and 50-fold enlargements were printed for measurement of arterio-

lar, capillary, and venular length-density and diameter by a stereological technique. In our preliminary studies, which involved few sodium-sensitive subjects, we found that capillary and venous density were significantly reduced in BHT subjects (5.43 ± 0.38 vs 3.31 ± 0.63 mm/mm²; p < 0.01; and 3.24 ± 0.21 vs 2.49 ± 0.30 mm/mm²; p < 0.05, respectively). The BHT subjects had a higher cardiac index than the normal subjects (3.13 ± 0.15 vs 2.79 ± 1.4 L/min/m²; p < 0.05), and the capillary density was inversely related to the cardiac index (r = -0.482, p < 0.01) but was not related to the level of arterial pressure (r = -0.207).

We have obtained conjunctival macrophotographs from 28 normal subjects and 16 BHT subjects. Thirty-six of those subjects were sodium-resistant, while nine were sodium-sensitive. We found that capillary length-density was significantly reduced in the sodium-sensitive subjects in comparison with those who were sodium-resistant (3.72 ± 1.71 vs 5.18 ± 2.07 mm/mm²; p < 0.05). No significant differences were found between arteriolar or venular length-density or in the diameter of large, preterminal, or terminal arterioles (Table 8).
Table 7. Forearm Hemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sodium-resistant (n = 35)</th>
<th>Sodium-sensitive (n = 11)</th>
<th>Sodium-resistant (n = 27)</th>
<th>Sodium-sensitive (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad libitum Na</td>
<td>86.7 ± 9.2</td>
<td>90.1 ± 7.4</td>
<td>98.7 ± 9.2</td>
<td>101.5 ± 8.0</td>
</tr>
<tr>
<td>10 mEq Na</td>
<td>87.0 ± 10.1</td>
<td>83.1 ± 6.0</td>
<td>96.6 ± 6.6</td>
<td>95.9 ± 11.0</td>
</tr>
<tr>
<td>200 mEq Na</td>
<td>84.7 ± 9.8</td>
<td>89.2 ± 4.7</td>
<td>93.8 ± 8.2</td>
<td>100.9 ± 14.2*</td>
</tr>
<tr>
<td>FBF (ml/min/100 g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad libitum Na</td>
<td>8.54 ± 5.95</td>
<td>3.93 ± 2.62*</td>
<td>6.08 ± 3.06</td>
<td>4.96 ± 2.81</td>
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<tr>
<td>10 mEq</td>
<td>7.63 ± 4.84</td>
<td>4.76 ± 4.10</td>
<td>6.45 ± 3.46</td>
<td>3.97 ± 1.73</td>
</tr>
<tr>
<td>200 mEq</td>
<td>7.75 ± 4.97</td>
<td>4.60 ± 3.44</td>
<td>7.05 ± 4.29</td>
<td>4.19 ± 2.41</td>
</tr>
<tr>
<td>FVR (mm Hg/ml/min/100 g)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ad libitum Na</td>
<td>15.9 ± 10.9</td>
<td>36.5 ± 25.0*</td>
<td>20.6 ± 12.1</td>
<td>27.6 ± 16.3</td>
</tr>
<tr>
<td>10 mEq</td>
<td>16.8 ± 12.6</td>
<td>32.2 ± 23.2*</td>
<td>19.4 ± 10.4</td>
<td>28.7 ± 12.9</td>
</tr>
<tr>
<td>200 mEq</td>
<td>15.8 ± 10.4</td>
<td>37.0 ± 31.9*</td>
<td>17.1 ± 8.6</td>
<td>30.0 ± 15.0†</td>
</tr>
<tr>
<td>VC (ml/100 g)</td>
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<td></td>
</tr>
<tr>
<td>Ad libitum Na</td>
<td>0.98 ± 0.70</td>
<td>1.05 ± 0.54</td>
<td>1.07 ± 0.69</td>
<td>0.63 ± 0.30*</td>
</tr>
<tr>
<td>10 mEq</td>
<td>1.00 ± 0.65</td>
<td>1.14 ± 0.54</td>
<td>1.14 ± 0.72</td>
<td>0.60 ± 0.36*</td>
</tr>
<tr>
<td>200 mEq</td>
<td>0.95 ± 0.63</td>
<td>1.18 ± 0.62</td>
<td>0.99 ± 0.52</td>
<td>0.72 ± 0.52</td>
</tr>
<tr>
<td>CFC (ml/min/mm Hg/100 g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad libitum Na</td>
<td>130.2 ± 71.5</td>
<td>105.6 ± 34.2</td>
<td>98.2 ± 58.2</td>
<td>75.7 ± 26.6</td>
</tr>
<tr>
<td>10 mEq</td>
<td>150.6 ± 92.3</td>
<td>102.3 ± 80.9</td>
<td>102.5 ± 58.3</td>
<td>90.0 ± 41.5</td>
</tr>
<tr>
<td>200 mEq</td>
<td>160.6 ± 112.4</td>
<td>96.7 ± 37.8†</td>
<td>107.0 ± 79.1</td>
<td>82.8 ± 46.1</td>
</tr>
</tbody>
</table>

Values are means ± SD. See Table 2 for key to abbreviations.

Discussion

Our studies suggest that the prevalence of sodium sensitivity is approximately 39% in BHT subjects and 22% in normotensive subjects. Because of the relatively large proportion of young white male participants in this investigation, we cannot ascertain whether the same prevalence would obtain among women or blacks or whether age plays a role.

Our data show that FVR is significantly higher in sodium-sensitive subjects than in sodium-resistant subjects, at three levels of sodium intake. Higher FVR was found in sodium-sensitive subjects, even when dietary sodium intake was restricted and arterial blood pressure did not differ significantly from that of sodium-resistant subjects. Further, FVR was significantly higher in sodium-sensitive subjects after isometric exercise, and the same trend was present during isotonic exercise, although the difference did not reach statistical significance. While sodium-sensitive subjects did not show an increase in FVR from their already elevated resting values during cold pressor stress, they were able to lower 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 arteriole. Whether induction of maximum reactive hyperemia by occlusion of arterial blood flow for 10 minutes could alter the differences between the two groups is not known.12

No significant differences in arteriolar diameter or density could be measured at the level of the microvasculature. A significant reduction was found in conjunctival capillary density, which was consistent with the trend toward a reduction in CFC, an index of
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Sodium repletion with a 6.9% increase in cardiac index and a 13% fall in total peripheral resistance. However, the fall in peripheral resistance was twofold greater in the sodium-resistant subjects (10.8 vs 5.3%), which explained the rise in blood pressure, as cardiac output rose with increased sodium intake in the sodium-sensitive participants.

Previous studies of small numbers of normotensive volunteers have shown that sodium loading is accompanied by increased FBF without an increase in blood pressure, suggesting that local vasodilation takes place. Luft et al. have studied the hemodynamic and metabolic response of normal subjects to extremes of sodium intake, 10 to 1500 mEq/day. They found that an intake of 800 mEq was associated with a significant increase in blood pressure and cardiac index without a significant change in vascular resistance. In contrast, Mark et al. found that in six patients with borderline hypertension, FBF decreased during sodium loading, suggesting that sodium causes vasoconstriction.

In the present study, FVR tended to rise in sodium-sensitive subjects in both the normotensive and BHT subgroups and to fall in the sodium-resistant subjects (see Table 7), although the differences did not reach statistical significance. These observations are consistent with the reports of Takeshita et al. and of Koolen and van Brummelen, who found that the FVR of sodium-sensitive hypertensive subjects rose significantly when daily sodium intake was increased to 345 and 300 mEq, respectively.

Earlier studies in this laboratory have found that a 200-mEq sodium diet, given after a period of salt restriction, results in an increase in diastolic blood pressure in 14 of 19 labile BHT subjects but in only 4 of 27 normal subjects. The normal subjects responded to sodium repletion with a 6.9% increase in cardiac index and a 13% fall in total peripheral resistance. However, the response in the hypertensive subjects was considerably more varied, suggesting that the group was not homogeneous. Similarly, Julius et al. have studied borderline hypertensive patients and found a spectrum of hemodynamic changes to be present in subjects with labile hypertension, ranging from those with a very high cardiac output to those whose cardiac output was relatively reduced. Julius et al. studied the effect of various interventions, such as sitting, mild exercise, and infusion of dextran, on the hemodynamic status of subjects with borderline hypertension and found that, although peripheral vascular resistance was ordinarily within normal range at rest, peripheral vascular resistance during any hemodynamic intervention was higher in the labile hypertensive subjects than in the normotensive subjects. Similarly, Sannerstedt has studied the degree to which cardiac output and vascular resistance change with exercise in patients with labile hypertension in comparison with normal subjects and have found that the slope of the line relating output to resistance is shifted, indicating that peripheral vascular resistance is actually inappropriately elevated in subjects with mild labile hypertension. Takeshita and Mark have studied the effect of stimuli causing maximum reactive hyperemia on FBF and resistance in normal subjects and subjects with borderline hypertension and have also demonstrated that FVR fails to fall as greatly during maximum reactive hyperemia in labile hypertensive subjects.

Our data support the concept of Julius et al. that a disproportion between cardiac output and vascular resistance is found in some persons with borderline hypertension, for the basis of blood pressure elevation during sodium repletion in most of the sodium-sensitive subjects encountered in our study was a failure to lower vascular resistance adequately when cardiac output rose. Our BHT subjects did not invariably show an increase in FVR when sodium-replete, in contrast to the observations of Mark et al. We believe this difference to be due to differences in sodium intake: 200 mEq in the present study, 410 mEq in that of Mark et al.

Our data do not provide an explanation for the increased vascular resistance in sodium-sensitive subjects but suggest that it is not entirely structural, as the magnitude of the fall in FVR during reactive hyperemia in the sodium-sensitive subjects was even greater than that in the sodium-resistant subjects. Additional observations after interventions inducing maximal reactive hyperemia are needed to determine if any irreversible changes are present.

We found no evidence that the elevated resistance was due to increased activity of the renin-angiotensin-aldosterone system, as neither plasma aldosterone differed significantly between the sodium-sensitive and sodium-resistant participants. However, plasma renin activity and aldosterone levels were not measured, and individual differences in sensitivity to endogenous angiotensin II were not assessed. Our studies are being extended to examine differences in plasma catecholamines in the two groups, especially in relation to salt intake, as suggested by Campese et al., but at present we have no indirect suggestion that sympathetic nervous system activity differs between the two groups, as heart rate, cardiac index, and venous compliance are not significantly different. We have no data about other vasoactive agents, such as vasopressin, prostaglandins, bradykinin, endoxin, natriuretic peptides, or vasodepressor lipids.

We conclude that high sodium intake is associated with significant increases in left ventricular size, stroke volume, and cardiac index and that mean arterial blood pressure increases 5% or more during periods of high sodium intake in about 39% of BHT subjects and 22% of normal subjects. During periods of high sodium intake, sodium-resistant subjects accommodate increases in cardiac index by a proportionate fall in total peripheral resistance, which our previous stud-
ies indicate can be maintained for at least 1 year. Sodium-sensitive subjects are characterized by significantly higher vascular resistance and significantly lower capillary density than are seen in sodium-resistant subjects — characteristics that may serve to identify those whose sodium intake should be limited.

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