Sodium susceptibility and potassium effects in young patients with borderline hypertension

TOSHIRO FUJITA, M.D., HIROSHI NODA, M.D., AND KATSUYUKI ANDO, M.D.

ABSTRACT To evaluate sodium susceptibility in subjects with borderline hypertension at increased risk of developing essential hypertension, the effect of salt loading after sodium deprivation with a diuretic was studied in 21 young patients with borderline hypertension and 12 age-matched normal subjects. Treatment with a diuretic caused significant decreases in mean blood pressure (MBP) in subjects with borderline hypertension but not in normotensive subjects. In borderline hypertensives, the subsequent sodium loads resulted in a significant rise in MBP (5.8 ± 1.7%; p < .01), but sodium did not change MBP in normotensives. There is a good correlation between the increments in MBP with sodium loads and the decrements in MBP with a diuretic for each patient (r = −.759, p < .001). After diuretics, cardiac index (CI) as measured echocardiographically fell significantly but calculated total peripheral resistance (TPR) remained unchanged in subjects with borderline hypertension. After 180 meq sodium chloride each day was added for 7 days, CI (9.1 ± 2.1%; p < .01) and stroke index (21.0 ± 3.4%; p < .01) rose significantly but TPR remained unchanged. Overall, the increments of MBP with sodium loads did not correlate with the changes in CI but did correlate with the changes in TPR (r = .567, p < .01). In these young patients with borderline hypertension, plasma norepinephrine and epinephrine concentrations and plasma renin activity (PRA) were significantly higher than in normotensive subjects. These results suggest that young patients with borderline hypertension differ from normal subjects in that they display a blood pressure increase due to a disproportionate rise in CI and inadequate fall in TPR in response to a short-term increase in dietary sodium and that adrenosympathetic overactivity and increased activity of the renin-angiotensin system may be partly involved. Moreover, during salt loading the 11 patients with borderline hypertension who received a dietary supplementation of 96 meq potassium chloride each day had less of an increase in MBP (−1.6 ± 2.1% vs 5.8 ± 1.7%; p < .05) and CI (−1.8 ± 2.0% vs 9.1 ± 2.1%; p < .05) than did the 21 patients who had not taken the potassium supplement. PRA and plasma aldosterone concentration during salt loading were relatively higher in the potassium-supplemented patients as compared with in the ones that did not receive supplements. It is suggested that potassium supplementation may prevent the blood pressure rise with the sodium loading by attenuating the increase in cardiac output possibly as a result of the natriuresis.


YOUNG PATIENTS with borderline hypertension are at least three times more likely to develop established essential hypertension than are age-matched normotensive subjects.1, 2 Thus, young patients with borderline hypertension have been of particular interest to investigators because they may provide insight into the pathogenesis of essential hypertension. Borderline hypertensive subjects have been reported to have abnormalities in volume and/or sodium homeostasis,3, 4 hemodynamic function (i.e., elevated resting cardiac output and heart rate),5, 6 and/or responsiveness of either the renin-angiotensin-aldosterone system or the sympathetic nervous system.7–9

Generally, patients with certain essential hypertension may be specifically sensitive to changes in dietary sodium intake as compared with normotensives.10–12 The increase in blood pressure with sodium loading is associated with hemodynamic changes, i.e., increased cardiac output10, 13, 14 and/or increased peripheral resistance.13, 15 Moreover, abnormalities in the appropriate-ness of circulating components of the renin-angiotensin-aldosterone system16 and the sympathetic nervous system10, 15, 17, 18 in the pressor responses to sodium loading have been identified in essential hypertension. In young patients with borderline hypertension very few detailed studies of hemodynamic and humoral responses to sodium loading or depletion have been re-
ported. To identify some factors that may contribute to sodium susceptibility, we studied the hemodynamic and endocrine responses to sodium depletion or sodium loading in young patients with borderline hypertension who are at risk for the development of essential hypertension. The sodium challenges consisted of the administration of a diuretic and periods of incremental dietary sodium intake for 1 week. In this study we have also evaluated the protective effect of potassium loading against blood pressure-raising action of sodium chloride in young patients with borderline hypertension.

Materials and methods

Forty-four male subjects (32 borderline hypertensives and 12 normotensives) were included in this study. Each subject underwent a physical examination and gave a medical history. Laboratory results, including those of urinalysis, tests for levels of serum electrolytes, creatinine, plasma renin activity (PRA), and aldosterone, and results of electrocardiographic examinations were normal. Thus, there was no evidence of a secondary cause of hypertension in any of the subjects. Most had never been treated and in those few who had, antihypertensive drugs had been discontinued at least 4 weeks before the study. No patient was older than 30 years of age, and none had electrocardiographic or radiographic evidence of left ventricular hypertrophy, hypertensive retinopathy, or renal involvement. Each subject was informed of the nature of the study and gave written consent. Patients were considered to have borderline hypertension if, on examination in the outpatient department, their diastolic pressures at times exceeded but at other times were lower than 90 mm Hg. A subject was considered to have a positive family history of hypertension if either or both parents had hypertension. This information was obtained by asking the subjects (“probable genetic background of hypertension” in WHO workshop).

Protocol. The patients were studied on an outpatient basis. Each subject attended a special research clinic at a fixed hour and day of the week for each visit. After four screening visits, patients and normal subjects were admitted to the trial. Each subject underwent three consecutive studies. Hemodynamic and endocrine measurements were made while subjects maintained regular customary diets (normal-sodium diet), after sodium depletion with the administration of a diuretic (25 mg/day metru-side) for 1 week (diuretic treatment), and subsequently after 180 meq sodium chloride each day was added as 10 meq sodium chloride tablets for 1 week (high-sodium diet). In 11 of 32 borderline hypertensive patients, 96 meq/day potassium chloride as “Slow K” (CIBA Laboratories) was added during the high-sodium diet (group C). Twenty-one of 32 borderline hypertensives received 180 meq/day sodium chloride alone (group B). A dietitian advised them on their diets based on their previous dietary histories and their 24 hr sodium and potassium excretions. The aim was to keep up a constant sodium and potassium intake without altering caloric intake. At every visit throughout the trial subjects brought with them two complete 24 hr urine samples for the determination of sodium, potassium, and creatinine levels. Body weight was recorded at each visit. When patients were supine, subjectively relaxed, and had a stable pulse rate, blood pressure was measured by sphygmomanometer.

Hemodynamic studies. Since invasive techniques were not acceptable, hemodynamic assessment was performed by echocardiography, as previously reported. Briefly, in each subject the ultrasonic beams were introduced from the third or fourth intercostal space into the left ventricle, where the endocardial echoes of the interventricular septum and the posterior wall could be clearly identified, and the tips of both leaflets of the mitral valve were recorded between them. Photographic recordings were obtained at a paper speed of 100 mm/sec with simultaneous recordings of the electrocardiogram and phonocardiogram; the pericardial echo was identified at the end of each recording with the use of dapping procedure. Five consecutive beats were averaged. The left ventricular diameter at end-diastole (LVDd) was measured at the peak of R wave of the simultaneously recorded electrocardiogram. The left ventricular diameter at end-systole (LVDs) was taken to occur at the onset of the second heart sound of the phonocardiogram. Stroke index (SI) was calculated as: SI = (LVDd - LVDs)/body surface area. The cube method was used because the hearts of the subjects examined in our study were not in asynergy and could therefore be assumed to be symmetrically contracting. In our previous study, to assess the reliability of this method, measurements of cardiac output by echocardiography and by a thermodilution technique in 11 patients without left ventricular asynergy demonstrated a good correlation between the methods. Cardiac index (CI) was calculated with the formula: CI = SI × heart rate. CI was expressed in liters per minute per square meter by correcting for body surface area. Total peripheral resistance (TPR) index was calculated from the following formula: TPR (dyne·sec·cm⁻²·m⁻²) = mean blood pressure (MBP)/CI × 79.32. Ejection time (ET) was measured by the simultaneous recording of indirect carotid artery pulse tracing and an electrocardiogram at a paper speed of 100 mm/sec. Mean velocity of circumferential fiber shortening (VCF) was calculated from the formula: mean VCF = (LVDd - LVDs)/LVDd·ET. Mean VCF was used as an index of myocardial contractility.

Laboratory procedures. Adequacy of urine collection was checked by daily creatinine determinations. Sodium and potassium concentrations in the urine were determined by flame photometry, with the use of lithium as an internal standard. For each test procedure the subject was supine and had an indwelling catheter inserted in an arm vein. At least 30 min after insertion of the indwelling catheter, but not before the patient was subjectively relaxed and had a stable pulse rate, blood for the determination of catecholamines, PRA, and plasma aldosterone concentrations (PACs) was drawn. This procedure was repeated in each patient while on the normal-sodium diet, on the seventh day of the diuretic treatment, and on the seventh day of sodium loading. Circulating norepinephrine and epinephrine were determined by the modification method of Schwedt, with high-pressure liquid chromatography combined with an automatic fluorimetric detector. PRA and PAC were measured by radioimmunoassay as previously reported. Urinary kalikrein was measured with a fluorogenic peptide substrate, Pro-Phe-Arg-MCA, as previously reported.

Statistical analysis. Two-tailed Student’s t tests (paired for within group and unpaired for between group comparisons), regression analysis, and analysis of variance were carried out with the use of the Statistical Package from the University of Tsukuba Computer Center. The results are expressed as mean ± SEM. The null hypothesis was rejected when p < .05.

Results

Table 1 summarizes clinical and laboratory findings of borderline hypertensive and age-matched normal subjects. There were no significant differences in age.
TABLE 1
Clinical findings (mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12 Normotensives</td>
<td>21 BHT</td>
<td>11 BHT</td>
</tr>
<tr>
<td>Positive family history of essential hypertension</td>
<td>5/12</td>
<td>11/21</td>
<td>6/11</td>
</tr>
<tr>
<td>Age (years)</td>
<td>22 ± 1</td>
<td>23 ± 1</td>
<td>23 ± 1</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>70 ± 2</td>
<td>69 ± 3</td>
<td>67 ± 3</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>123 ± 2</td>
<td>138 ± 2 ( ^a )</td>
<td>138 ± 4 ( ^b )</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>69 ± 1</td>
<td>85 ± 3 ( ^a )</td>
<td>82 ± 4 ( ^b )</td>
</tr>
<tr>
<td>Plasma sodium (meq/l)</td>
<td>138 ± 1</td>
<td>139 ± 1</td>
<td>139 ± 1</td>
</tr>
<tr>
<td>Plasma potassium (meq/l)</td>
<td>4.2 ± 0.1</td>
<td>4.1 ± 0.2</td>
<td>4.2 ± 0.2</td>
</tr>
<tr>
<td>Plasma creatinine (mg/dl)</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>1.1 ± 0.1</td>
</tr>
</tbody>
</table>

All subjects were men.
BHT = borderline hypertensives; BP = blood pressure.
\(^a\) \( p < .01 \) (vs group A).

or body weight between the groups. Borderline hypertensive subjects of both group B and group C had a significant increase in systolic and diastolic blood pressures as compared with the normotensives. There were no significant differences in plasma creatinine, sodium, or potassium levels between the borderline hypertensive and the normotensive subjects. Five of the 12 normotensives have a family history of essential hypertension, and 17 of 32 borderline hypertensives have such a history.

Effects of a diuretic or sodium loads in borderline hypertensive and normotensive subjects. Figure 1 shows the course of systolic and diastolic blood pressures during the normal-sodium diet, after the treatment with a diuretic, and after the subsequent sodium loading in 12 normotensive (group A) and 21 borderline hypertensive subjects (group B).

The average MBPs for the borderline hypertensives (group B) on the normal-sodium diet, at the end of a diuretic treatment, and after sodium loading were 101.9 ± 2.2, 96.8 ± 2.0, and 102.1 ± 2.1 mm Hg, respectively (table 2). Corresponding averages of MBPs for normotensive patients were 87.8 ± 1.2, 86.2 ± 1.6, and 88.2 ± 1.5 mm Hg, respectively. With the administration of a diuretic, MBP in the borderline hypertensive subjects decreased significantly...
TABLE 2
Hemodynamic data (mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Diuretics</th>
<th>NaCl load</th>
<th>Control</th>
<th>Diuretics</th>
<th>NaCl load</th>
<th>Control</th>
<th>Diuretics</th>
<th>NaCl + KCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>72.1 ± 2.2</td>
<td>71.8 ± 2.3</td>
<td>72.5 ± 2.3</td>
<td>69.2 ± 2.8</td>
<td>68.2 ± 2.9</td>
<td>69.3 ± 2.9</td>
<td>66.8 ± 2.7</td>
<td>66.1 ± 2.8</td>
<td>68.8 ± 3.5</td>
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<tr>
<td>Difference (%)</td>
<td>-0.49 ± 0.50</td>
<td>1.03 ± 0.16</td>
<td>-1.51 ± 0.30</td>
<td>1.63 ± 0.25</td>
<td>-1.07 ± 0.28</td>
<td>1.39 ± 0.24</td>
<td>-1.42 ± 0.10</td>
<td>1.39 ± 0.24</td>
<td>-1.42 ± 0.10</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>87.8 ± 1.2</td>
<td>86.2 ± 1.6</td>
<td>88.2 ± 1.5</td>
<td>101.9 ± 2.2A</td>
<td>96.8 ± 2.0B</td>
<td>102.1 ± 2.1B</td>
<td>100.4 ± 2.8</td>
<td>98.0 ± 2.1</td>
<td>96.5 ± 3.0A</td>
</tr>
<tr>
<td>Difference (%)</td>
<td>-1.72 ± 1.86</td>
<td>2.71 ± 2.35</td>
<td>-4.73 ± 1.42</td>
<td>5.76 ± 1.66</td>
<td>-2.16 ± 1.40</td>
<td>-1.60 ± 2.06A</td>
<td></td>
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<tr>
<td>Heart rate</td>
<td>54.6 ± 2.4</td>
<td>59.4 ± 2.4</td>
<td>54.7 ± 2.5</td>
<td>72.3 ± 2.2A</td>
<td>73.0 ± 2.9B</td>
<td>66.3 ± 2.2B</td>
<td>71.2 ± 4.0</td>
<td>74.8 ± 3.2</td>
<td>67.7 ± 2.9</td>
</tr>
<tr>
<td>(beats/min)</td>
<td>9.34 ± 3.23</td>
<td>-7.60 ± 2.95</td>
<td>0.89 ± 2.00A</td>
<td>-8.16 ± 2.73</td>
<td>6.24 ± 3.54</td>
<td>-9.39 ± 1.72</td>
<td></td>
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<tr>
<td>LVDD (mm)</td>
<td>53.4 ± 0.6</td>
<td>52.5 ± 0.7</td>
<td>53.6 ± 0.7</td>
<td>49.8 ± 1.0B</td>
<td>48.6 ± 1.0A</td>
<td>51.3 ± 1.0</td>
<td>50.0 ± 0.7</td>
<td>48.4 ± 0.8</td>
<td>49.7 ± 0.7</td>
</tr>
<tr>
<td>Difference (%)</td>
<td>-1.70 ± 0.81</td>
<td>1.92 ± 0.49</td>
<td>-2.45 ± 0.37</td>
<td>5.61 ± 0.71B</td>
<td>-3.21 ± 0.59</td>
<td>2.75 ± 0.44A</td>
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<tr>
<td>LVDs (mm)</td>
<td>33.9 ± 0.9</td>
<td>33.7 ± 1.2</td>
<td>33.8 ± 1.0</td>
<td>30.7 ± 0.9B</td>
<td>29.4 ± 0.8B</td>
<td>30.2 ± 0.9B</td>
<td>31.0 ± 0.8</td>
<td>29.5 ± 0.9</td>
<td>30.2 ± 0.9</td>
</tr>
<tr>
<td>Difference (%)</td>
<td>-0.31 ± 0.47</td>
<td>0.14 ± 1.13</td>
<td>-3.90 ± 1.12</td>
<td>2.91 ± 1.00</td>
<td>-5.04 ± 1.54</td>
<td>2.74 ± 1.45</td>
<td></td>
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<tr>
<td>Stroke index</td>
<td>61.1 ± 1.9</td>
<td>56.9 ± 1.6</td>
<td>61.8 ± 1.4</td>
<td>53.1 ± 2.3A</td>
<td>50.6 ± 2.3</td>
<td>60.5 ± 2.6</td>
<td>53.2 ± 2.0</td>
<td>49.4 ± 2.2</td>
<td>53.3 ± 1.8</td>
</tr>
<tr>
<td>(ml/m²)</td>
<td>9.62 ± 2.80</td>
<td>8.96 ± 2.14</td>
<td>-4.74 ± 1.72</td>
<td>21.00 ± 3.38A</td>
<td>-7.30 ± 1.60</td>
<td>8.60 ± 2.41A</td>
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<tr>
<td>CI (l/min/m²)</td>
<td>3.29 ± 0.08</td>
<td>3.35 ± 0.10</td>
<td>3.37 ± 0.16</td>
<td>3.79 ± 0.15A</td>
<td>3.62 ± 0.16</td>
<td>3.97 ± 0.19A</td>
<td>3.73 ± 0.16</td>
<td>3.64 ± 0.11</td>
<td>3.57 ± 0.12</td>
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<tr>
<td>Difference (%)</td>
<td>1.66 ± 1.77</td>
<td>1.25 ± 3.20</td>
<td>-4.27 ± 1.75A</td>
<td>9.14 ± 2.06A</td>
<td>-0.71 ± 3.23</td>
<td>-1.79 ± 1.97B</td>
<td></td>
<td></td>
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<tr>
<td>TPR (dyne·sec⁻¹)</td>
<td>2098 ± 49</td>
<td>2060 ± 71</td>
<td>2099 ± 98</td>
<td>2144 ± 81</td>
<td>2160 ± 94</td>
<td>2080 ± 82</td>
<td>2159 ± 126</td>
<td>2133 ± 92</td>
<td>2130 ± 75</td>
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<tr>
<td>cm⁻³·m⁻²·min⁻¹</td>
<td>-2.94 ± 2.68</td>
<td>2.98 ± 2.81</td>
<td>0.54 ± 1.96</td>
<td>-2.89 ± 2.22</td>
<td>1.30 ± 3.57</td>
<td>0.65 ± 3.04</td>
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<tr>
<td>Mean VCF</td>
<td>1.22 ± 0.04</td>
<td>1.24 ± 0.05</td>
<td>1.24 ± 0.04</td>
<td>1.42 ± 0.04B</td>
<td>1.48 ± 0.04B</td>
<td>1.45 ± 0.04B</td>
<td>1.37 ± 0.06</td>
<td>1.51 ± 0.07</td>
<td>1.43 ± 0.06</td>
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</tbody>
</table>

*p < .05 (group B vs group A or group C vs group B); p < .01 (group B vs group A or group C vs group B).

(-4.73 ± 1.42%; p < .01), but it did not decrease significantly (-1.72 ± 1.86%) in the normotensive subjects (figure 2). Correspondingly, MBP increased significantly with sodium loading in those with hypertension (5.76 ± 1.66%; p < .01), but not in those without it (2.71 ± 2.35%). The decrement in MBP after diuretic in each patient is plotted against the increase in MBP after sodium loading in that patient in figure 3 (r = -0.759, p < .001).

Urinary sodium was not significantly different during the normal-sodium diet vs diuretic treatment in either group. During salt loading, urinary sodium increased equally in both groups. During the three experimental periods mean values and SEMs for urinary sodium excretion were quite close in the normotensive and the borderline hypertensive subjects, with similar distributions of urinary sodium in the two groups. These changes in urinary sodium indicate good compliance with therapy.

Hemodynamics. The young patients with borderline hypertension had significantly increased heart rates, stroke volumes, cardiac outputs, and mean VCFs (table 2), suggesting a hyperkinetic circulatory state. The average CIs for the hypertensive subjects on the normal-sodium diet and a diuretic were 3.79 ± 0.15 and 3.62 ± 0.16 l/min/m², respectively (p < .01, paired t test). Corresponding CIs for the normotensive subjects were 3.29 ± 0.08 and 3.35 ± 0.10 l/min/m², respectively (NS, paired t test). The mean decrements in cardiac output during the normal-sodium diet and the diuretic treatment periods, calculated for each patient, differed significantly between the groups (−4.27 ± 1.75 vs 1.66 ± 1.77%; p < .05). There were no significant differences in TPR between the groups (table 2 and figure 2).

The average CIs for the borderline hypertensive subjects taking the diuretic and after sodium loading were 3.62 ± 0.16 and 3.97 ± 0.19 l/min/m² (p < .01, paired t test). Corresponding CIs for the normotensive subjects were 3.35 ± 0.10 and 3.37 ± 0.16 l/min/m² (NS, paired t test). The mean increments in cardiac output during periods of diuretic treatment and sodium loading, calculated for each patient, differ significantly between the groups (9.14 ± 2.06 vs 1.25 ± 3.20%; p < .05). Correspondingly, the mean increments in LVDd and those in stroke volume after sodium loading were significantly greater in hypertensives compared with normotensives (5.61 ± 0.71% vs 1.92 ± 0.49%; p < .05 and 21.00 ± 3.38% vs 8.96 ± 2.14%; p < .05, respectively; table 2 and figure 2). Mean calculated TPR did not significantly change in either group. In borderline hypertensive subjects the
nephrine was also significantly higher in the borderline hypertensives, both during the normal-sodium diet and the diuretic treatment periods. During the three experimental periods urinary kallikrein was not significantly different in the two groups.

The effect of potassium chloride during salt loading in borderline hypertensive subjects. During the salt-loading period, the MBP of the subjects in group C on the high-sodium diet and the potassium supplement (96.5 ± 3.0 mm Hg) differed significantly (p < .05) from the corresponding values in the group B patients who did not receive the potassium supplement (102.1 ± 2.1 mm Hg), although the average values for the MBP during the normal-sodium diet and the diuretic treatment periods did not differ significantly between the two groups (table 2). The mean increments in MBP with sodium loading, as analyzed by paired t test, differed significantly (p < .05) between the groups (5.76 ± 1.66% [p < .01] in group B and −1.60 ± 2.06% [NS] in group C; figure 4), although the mean decrement in MBP with the administration of diuretic was not significantly different between the two groups.

During the three experimental periods urinary sodium did not differ significantly between the subjects in two groups. During the normal-sodium diet and the diuretic treatment periods urinary potassium did not differ between the groups. However, urinary potassium during salt loading was significantly increased in the group C patients (151 ± 8 meq/day; p < .01) as

**FIGURE 2.** The changes in MBP (top), cardiac output (middle panel), and TPR (bottom) with the administration of diuretics (left) and with the subsequent sodium loading (right) in normal subjects (open columns) and borderline hypertensives (closed columns). Data are mean ± SEM. *p < .05 (paired t test); NS (paired t test); †p < .05 (vs normal subjects).

increments in MBP did not correlate with the changes in CI (r = .234, NS), but did correlate with the changes in TPR (r = .567, p < .01). In normal subjects, however, there was no correlation between the changes in blood pressure and those in cardiac output or TPR.

**Hormonal changes.** During the normal-sodium diet period, PRA and PAC were significantly increased in borderline hypertensives, as were plasma norepinephrine and epinephrine concentrations (table 3). After diuretic PRA reached significantly higher values in hypertensives than in normotensives; the increments in PRA after diuretic were significantly greater in hypertensives than in normotensives (4.1 ± 0.4 vs 2.0 ± 0.1 ng/ml/hr; p < .001). On the seventh day of sodium loading PRA values had been reduced to the same low values in the subjects in the two groups. Plasma norepinephrine concentration during the three experimental periods was consistently higher in the borderline hypertensives than in the normotensives. Plasma epinephrine was also significantly higher in the borderline hypertensives, both during the normal-sodium diet and the diuretic treatment periods. During the three experimental periods urinary kallikrein was not significantly different in the two groups.

**FIGURE 3.** There is a good correlation between the decrements in MBP with diuretics (ordinate) and the increments in MBP with sodium loading (abscissa) in borderline hypertensives (closed circles) (r = −.759, p < .001) and in normal subjects (open circles) (r = −.846, p < .001).
TABLE 3

<table>
<thead>
<tr>
<th>Laboratory data (mean ± SEM)</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Diuretics</td>
<td>NaCl load</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>1.6±0.1</td>
<td>3.6±0.1</td>
<td>0.9±0.1</td>
</tr>
<tr>
<td>PAC (ng/dl)</td>
<td>6.9±0.9</td>
<td>20.6±2.5</td>
<td>5.3±0.7</td>
</tr>
<tr>
<td>PNE (pg/ml)</td>
<td>157±11</td>
<td>165±13</td>
<td>103±11</td>
</tr>
<tr>
<td>PE (pg/ml)</td>
<td>24±2</td>
<td>22±3</td>
<td>25±3</td>
</tr>
<tr>
<td>Urinary kaliurein (U/g creatinine)</td>
<td>0.99±0.12</td>
<td>1.41±0.21</td>
<td>1.65±0.24</td>
</tr>
<tr>
<td>Urinary sodium (meq/day)</td>
<td>233±20</td>
<td>221±27</td>
<td>392±23</td>
</tr>
<tr>
<td>Urinary potassium (meq/day)</td>
<td>52±5</td>
<td>56±5</td>
<td>54±4</td>
</tr>
</tbody>
</table>

PNE = plasma norepinephrine concentration; PE = plasma epinephrine concentration.

<sup>a</sup>p < .05 (group B vs group A or group C vs group B)
<sup>b</sup>p < .01 (group B vs group A or group C vs group B)

compared with in group B patients (51 ± 4 meq/day), indicating good compliance to the potassium supplementation program.

**Hemodynamics.** There were no significant increases in cardiac output with the high-sodium diet in the group C (-1.79 ± 1.97%), but there were significant increases in this parameter in the group B subjects (9.14 ± 2.06%; p < .01; figure 4). Accordingly, the mean increments in LVDd and those in stroke volume were significantly less (both p < .05) in the group C than in the group B subjects. There was no significant change in TPR with sodium loading in either group.

**Hormonal changes.** During the normal-sodium diet and the diuretic treatment periods there were no significant differences in PRA or PAC in groups B and C (table 3). During salt loading PRA was significantly (p < .01) higher in group C patients, as was PAC (p < .05). Plasma norepinephrine, epinephrine, and urinary kaliurein during the three experimental periods were not significantly different in the two groups.

**Discussion**

A number of observations have documented the importance of sodium homeostasis in the regulation of blood pressure. Sodium contributes not only to the volume component of blood pressure but also to resistance by modifying vascular reactivity. 26-28 Thus, considerable attention has been paid to factors relevant to the control of blood pressure and sodium balance, including the sympathetic nervous system, the renin-angiotensin-aldosterone system, and cardiac output. 10, 14, 28

Our studies show that, after a period of sodium depletion with a diuretic, short-term sodium loading causes blood pressure to rise significantly in a group of young subjects with borderline hypertension but not in a group of normal subjects of comparable age, sex, and body weight. Kirckendall et al. 30 observed that four normal subjects were able to follow a 410 meq/day
sodium diet for 1 month with average increases in supine blood pressure of only 1 mm Hg. Luft et al.\textsuperscript{14} studied 14 normotensive men at six levels of sodium intake of from 10 to 1500 meq/day, concluding that in a short-term study, blood pressure does not increase significantly until the daily intake of sodium exceeds 800 meq. However, recent studies of the response of hypertensives to sodium loads have indicated that the blood pressure of certain patients with essential hypertension is quite sensitive to dietary sodium loads.\textsuperscript{10-12}

In our present study, hemodynamic responses of borderline hypertensives to sodium loads after sodium restriction showed an increased CI, while in the normal subjects in whom blood pressure was not significantly increased with sodium loading, CI did not change significantly. Calculated TPR did not change in either group. These observations are consistent with those of our previous study in which patients with essential hypertension maintained a high-sodium diet containing 249 meq sodium chloride each day\textsuperscript{10} and with those from a study by Luft et al.\textsuperscript{14} in which normal subjects were exposed to extremely large amounts of sodium. Also, Kirkendall et al.\textsuperscript{31} noted that the forearm vascular resistance of normal subjects fell when dietary sodium was increased. However, Mark et al.\textsuperscript{15} found that forearm vascular resistance increased in hypertensives when they were exposed to a similar sodium intake, during which time MBP rose from 88.7 to 98.0 mm Hg. Since the increments in MBP did not correlate to changes in cardiac output but did correlate to the changes in TPR, as observed in this study, the differences in blood pressure must be attributed to differing responses of peripheral resistance. 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 borderline hypertensives. It has been suggested that autoregulation may contribute to an increase in vascular resistance during exposure to salt and water in excess. Autoregulation in the setting is considered to represent a response to inappropriately high blood flow produced by increases in blood volume and cardiac output.\textsuperscript{33} Although an autoregulatory adjustment to high blood flow did not occur during sodium loading in normotensive subjects, autoregulation in subjects with borderline hypertension might be greater than in normal subjects and contribute to the increase in TPR during salt-loading. Since 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 et al.\textsuperscript{32, 33}

Throughout the study, the blood pressure of borderline hypertensives was associated with high cardiac output and inappropriately elevated TPR, and was significantly higher than that in the normal subjects. Thus, our findings indicate a disturbed relationship between cardiac output and TPR.\textsuperscript{1, 2, 5, 7, 9} This disproportion between cardiac output and vascular resistance has been reported by Julius et al.,\textsuperscript{34} who demonstrated that blockade of the sympathetic nervous system could normalize these abnormal hemodynamics. They concluded that the abnormalities such as increased heart rate, cardiac output, and TPR, which are characteristic features of borderline hypertension, may be attributed to the sympathetic overactivity. In our study young subjects with borderline hypertension also had increased heart rates, SIs, CIs, and mean VCFs, suggesting that they were in the hyperkinetic circulatory state.\textsuperscript{5, 6} Moreover, throughout the study plasma noradrenaline and epinephrine concentrations and PRA were significantly increased in the borderline hypertensives compared with in the normal subjects. It is suggested, therefore, that the augmented neurogenic activity may be partly involved in the inappropriately high TPR relative to the elevated cardiac output with sodium loading.

The mechanisms by which excessive sodium intake increases cardiac output in borderline hypertensives are not known, but a decreased natriuretic capacity is a characteristic common to all salt-sensitive rats\textsuperscript{35} and to man.\textsuperscript{10, 29} Tobian et al.\textsuperscript{36} performed pressure-natriuresis experiments in sodium-sensitive and sodium-resistant rats and found that kidneys from sensitive rats required greater perfusion pressures to excrete a given amount of sodium than kidneys from resistant rats. In our previous study,\textsuperscript{10} the salt-sensitive patients who had greater increases in cardiac output and blood pressure with sodium loading showed an impaired renal ability to excrete sodium as compared with the nonsalt-sensitive subjects. Since in the present study there is a good correlation between the elevation of blood pressure after sodium loading and its decrease after diuretic in borderline hypertensives (as previously reported in patients with essential hypertension\textsuperscript{10}), it is likely that the sodium that is retained with loading and that is lost after administration of a diuretic is in some way responsible for the increases and decreases in blood pressure. This provides further support for modest volume expansion with sodium loading in borderline hypertensives that is related to retarded renal excretory responses and leads to a resultant increase in cardiac output. In the sodium-sensitive rats of Dahl and his colleagues\textsuperscript{37, 38} the genetic fault that caused hyperten-
sion clearly resided within the kidney, as documented and verified by cross-transplantation experiments. The nature of the intrinsic renal defect in these rats is not known. On the other hand, several findings suggest that extrarenal control mechanisms influencing renal sodium handling may be involved in the decreased natriuretic capacity in hypertensive rats and salt-sensitive hypertensive human subjects. Black people excrete less urinary sodium after salt loading and are more salt-sensitive than white people. In addition, black hypertensive subjects have a deficiency of the kallikrein-kinin renal vasodilatory and natriuretic system. We measured urinary kallikrein in the present study, but there was no significant difference in urinary kallikrein in the young patients with borderline hypertension and the normotensive subjects. The sympathetic nervous system and the renin-angiotensin system have important influences over renal sodium excretion. It was recently reported that the renal ability of stroke-prone spontaneously hypertensive rats to excrete sodium and water was significantly reduced in the prehypertensive stage in which enhanced renal sympathetic nerve activity might be involved. Luft et al. demonstrated that first-degree relatives of patients with essential hypertension who had the impaired natriuretic responses to sodium loading had PRA values greater than those in control subjects. They therefore suggested that in first-degree relatives with hypertension, a regulatory mechanism such as the renin-angiotensin system may be involved, rather than an isolated intrinsic renal defect. In the present study, plasma noradrenaline, epinephrine, and PRA levels were consistently higher in subjects with hypertension. It is therefore possible that in the borderline hypertensives examined here adrenosympathetic overactivity and increased renin-angiotensin system may be involved in the difficulty in the ability to excrete sodium and that this leads to increased cardiac output and the resultant blood pressure rise with sodium loading via sodium retention. Adrenosympathetic overactivity, of course, could directly increase cardiac output by the β-adrenergic chronotropic and inotropic actions. In addition, increased adrenosympathetic activity might produce the contraction of capacitance vessels, relatively increase cardiopulmonary blood volume, and then promote the increase in cardiac output, thus resulting in positive cooperation.

In contrast to the pressor action of sodium, potassium has been known to have antihypertensive properties. Although the precise mechanism of the antihypertensive action of potassium remains controversial, its natriuretic properties are thought to play an important role. Recently, we have demonstrated that dietary potassium supplementation could lessen expansion of extracellular fluid in DOCA-salt rats and as a result counteract the blood pressure-raising effect of DOCA-salt in a dose-related fashion. In patients with essential hypertension, dietary potassium supplementation could prevent the elevation of blood pressure with sodium loading by inhibiting sodium retention. In our study potassium supplementation in borderline hypertensives attenuated increases in ventricular volume, stroke volume, and cardiac output that occurred with sodium loading, and these parameters are clinically available indexes of preload. Moreover, PRA and PAC during salt loading were relatively higher in the group C as compared with in group B patients. Despite the renin-secreting inhibitory effect of potassium, the relatively higher PRA induced by potassium chloride supplementation may be attributable to natriuresis via suppression of sodium retention. It is suggested, therefore, that in these young borderline hypertensives with impaired renal function for sodium excretion, potassium loading could prevent the increases in blood pressure with sodium loading by attenuating the increase in cardiac output, mainly as a result of the natriuresis.

References
44. Meneely GR, Battarbee HD: High-sodium-low potassium environment and hypertension. Am J Cardiol 38: 768, 1976
Sodium susceptibility and potassium effects in young patients with borderline hypertension.
T Fujita, H Noda and K Ando

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