Dietary Salt Produces Abnormal Renal Vasoconstrictor Responses to Upright Posture in Borderline Hypertensive Subjects

William J. Lawton, Christine A. Sinkey, Annette E. Fitz, and Allyn L. Mark

SUMMARY We studied the effect of high and low NaCl diets in normotensive and borderline hypertensive subjects to determine if a high NaCl diet produces abnormal renal vasoconstriction during the stress of upright posture in borderline hypertensive subjects. We studied 13 normotensive young men with diastolic blood pressures below 85 mm Hg and nine borderline hypertensive young men defined by diastolic blood pressures intermittently above 90 mm Hg. The subjects achieved comparable sodium balance during 6 days of low NaCl (10 mEq Na, 40 mEq Cl, 100 mEq K) and high NaCl (400 mEq Na, 400 mEq Cl, 100 mEq K) diets. In the normotensive subjects, standing for 30 minutes resulted in a tendency for diastolic blood pressure to fall during both diets. In contrast, during standing borderline hypertensive subjects showed no change in diastolic blood pressure during the low salt diet and a tendency for diastolic blood pressure to increase after the high salt diet. Standing reduced renal plasma flow in both groups during both diets. However, only during the high NaCl diet did the absolute decrease and percent decrease in renal plasma flow during standing differ significantly \((p<0.05\) and \(p<0.01\), respectively) between the borderline hypertensive \((-151 \pm 24 \text{ ml/min/1.73m}^2; -29 \pm 4\%\) and normotensive subjects \((-79 \pm 17 \text{ ml/min/1.73m}^2; -15 \pm 3\%)\). The resultant increase in the renal vascular resistance index with standing did not differ between the two groups during the low NaCl diet. In contrast, during the high NaCl diet, standing increased the renal vascular resistance index by 48 ± 12% in borderline hypertensive subjects but only by 14 ± 5% in normotensive subjects \((p<0.01)\). Standing also reduced free water clearance to a greater extent in the borderline hypertensive subjects compared with normotensive subjects during both diets \((\text{low NaCl, } p<0.05; \text{ high NaCl, } p<0.01)\). In summary, dietary NaCl loading in borderline hypertensive subjects produces greater decreases in renal blood flow, enhanced renal vasoconstriction, and enhanced water retention during standing. A high NaCl diet appears to unmask an abnormality in the neurohumoral control of the renal circulation in borderline hypertensive subjects.

KEY WORDS • renal function • borderline hypertension • salt loading • diastolic blood pressure

THE relationship of dietary salt (NaCl) intake to blood pressure (BP) has been of interest to clinicians and investigators for many years. Normal subjects have a remarkable ability to maintain normal BP during wide changes in NaCl intake.1-4 In hypertensive persons, increased NaCl intake is associated with increased BP in susceptible individuals. In addition, in hypertensive persons, the relationship between NaCl and BP elevation is supported by epidemiological data, by direct salt loading studies, and by beneficial clinical responses to marked restrictions in dietary NaCl.5-9 The remarkable differences in the response to dietary NaCl between normotensive (NT) and hypertensive subjects were further defined by our earlier studies. Abboud10 showed that salt loading in normal subjects was accompanied by striking decreases in forearm vascular resistance without change in arterial pressure. In contrast, we found that borderline hypertensive (BHT) subjects responded to a high salt intake with increases in forearm vascular resistance and arterial pressure.11 The present study was designed to test the hypothesis that high NaCl diets produce abnormalities in the
control of the renal circulation in BHT subjects compared with NT subjects. Subjects were studied while fed high NaCl (400 mEq Na, 400 mEq Cl) and low NaCl (10 mEq Na, 40 mEq Cl) diets. Studies of renal function and the renal circulation were performed with subjects in the supine position and during the stress of standing.

Subjects and Methods

BHT men (mean age, 24.8 ± 1.1 [SE] years; age range, 20–31 years) were recruited from the clinics of the University of Iowa Hospitals or by advertisement. Normal men (mean age, 24.3 ± 0.6 years; age range, 22–28 years) with documented normal systolic (<140 mm Hg) and diastolic BPs (<85 mm Hg) were recruited as control subjects. All subjects were white men. A medical history was obtained and physical examination was performed on all participants, with emphasis on detecting a personal history of hypertension. Subjects were classified after at least three screening sessions taken 1 week apart in which BP measurements were obtained from the arm of the seated subject using a standard mercury sphygmomanometer. The subject sat quietly for 15 minutes, and then three BPs were taken during 6 minutes. Fifth phase Korotkoff sounds were used for diastolic BP. BHT subjects were those who intermittently had documented sitting diastolic BP recordings of 90 mm Hg or above.

All BHT and NT subjects had normal electrocardiograms and chest roentgenograms. The results of urinalysis, complete blood count, and determinations of blood chemistries for electrolytes and renal and liver functions were also normal.

The studies were approved by the institutional review committee on human investigation, and all subjects voluntarily gave written informed consent to participate.

Diets

Subjects were studied during low and high NaCl diets; the order of the diets was randomized. A 3- to 4-week interval was allowed between dietary periods, during which time the subjects resumed an ad libitum diet.

The diets were developed by the dietitians of the Clinical Research Center. They consisted of liquid formulas plus selected food and were calculated to contain 400 mEq Na, 400 mEq Cl (high NaCl) or 10 mEq Na, 40 mEq Cl (low NaCl), plus 100 mEq of potassium in all diets. Diets were designed to be eucaloric (about 3000 calories/day with 320 mg calcium/1000 kcal) and were adjusted to the individual's projected activity level. Calories were distributed as 15% protein, 40% fat, and 45% carbohydrates. Random samples of the diets were ashed and analyzed for sodium and potassium content. The high NaCl diets contained 380 ± 12 (SE) mEq Na/24 hr and 102 ± 2 mEq K/24 hr (n = 12). The low NaCl diets contained 8.5 ± 1.0 mEq Na/24 hr and 105 ± 4 mEq K/24 hr (n = 6).

Subjects were allowed to continue their normal daily activities but were asked to refrain from strenuous physical exercise. They reported to the Clinical Research Center at least once per day to receive their meals for the day, to be weighed, to deliver urine specimens, and to have measurements of BP and heart rate. Subjects were instructed not to ingest anything other than the diet and distilled water supplied by the Clinical Research Center.

Subjects were maintained on the dietary regimen for 6 days. A 24-hour urine collection for sodium, potassium, and creatinine was obtained daily to ensure that subjects were in comparable sodium balance by Day 5 before beginning the experimental procedures on Day 6. Twenty-four-hour urine collections were also obtained for aldosterone on Day 4. On the evening of Day 5, all subjects were admitted to the Clinical Research Center, where they slept overnight.

On the morning of Day 6, subjects remained supine while two needles were inserted into peripheral veins. One was used to obtain venous blood, and the other was used for infusion of p-aminohippurate (PAH). Subjects then underwent studies of renal function and renal circulation during supine and upright posture.

Studies of Renal Function and Circulation

On Day 6, subjects took only liquids after midnight and received a 1000-ml water load orally followed by 200 ml of water orally per half-hour to maintain urine flow during the renal studies. Standard renal function tests were performed using clearance of endogenous creatinine (Ccr) as a measure of glomerular filtration rate (GFR) and clearance of PAH (CPAH) as a measurement of renal plasma flow. After an initial loading dose of PAH (8 mg/kg), a constant infusion of PAH at 12 mg/min in 5 g dextrose/dl of water was begun at 2 ml/min. Subjects then remained supine for an hour.

Urine collections were obtained by spontaneous voiding. Two sequential 10-minute urine collections were obtained to ensure that urine flow was stable (±15%). When urine flow was stable, the subjects underwent three 30-minute clearance periods. The first two periods were obtained in the supine position, and the third was obtained during quiet standing. Urine was collected every 30 minutes. At the midpoint of each period, a blood sample was obtained. Urine and blood were analyzed for creatinine, PAH, sodium, potassium, and osmolality during each period. Ccr and CPAH, filtration fraction, fractional excretion of sodium (FENa) and potassium, osmolar clearance, and free water clearance (CH2O) were calculated for each period. Measurements of BP using a standard mercury sphygmomanometer and heart rate were performed at 5- to 10-minute intervals throughout the clearance studies. A renal vascular resistance (RVR) index was calculated from mean arterial pressure/CAPAH.

To assess humoral factors potentially related to vascular resistance, forearm venous blood was obtained for measurements of plasma renin activity (PRA), noradrenaline, and arginine vasopressin (AVP) during the second supine period and at the midpoint of the standing period. In patients receiving the high NaCl...
diet, urinary prostaglandins E₂ (PGE₂) and F₂α (PGF₂α) were measured during the second supine control period and during the upright period.

Chemical Measurements

PAH and PRA were measured using standard methods in our laboratory. A Beckman DU-20 spectrophotometer (Arlington Heights, IL, USA) was used for PAH measurements. Creatinine was measured in our laboratory by the autoanalyzer method, a modification of the Jaffé reaction. These measurements were made on a Technicon AutoAnalyzer II (Tarrytown, NY, USA). Sodium and potassium were measured by ion-selective electrodes (Beckman E2A Na/K electrode system). Osmolalities were measured by the freezing point depression method (Micro-Osmette, Precision Systems, Sudbury, MA, USA). Total calcium was measured by the CPC (creosolphthalein Complexone) calcium method using a Hitachi 737 (Nissui Sango of Japan, distributed by Boehringer-Mannheim Diagnostics, Indianapolis, IN, USA). Ionized calcium was measured by ion-selective electrode (Nova Biochemical, Waltham, MA, USA). Urinary aldosterone was measured by radioimmunoassay, and urine and plasma catecholamine concentrations were measured by high performance liquid chromatography (BioScience, Van Nuys, CA, USA).

Plasma AVP and prostaglandins (PGE₂ and PGF₂α) were determined by radioimmunoassay in the Cardiovascular Center Core Laboratories, University of Iowa, Iowa City, IA, USA. The vasopressin assay uses rabbit antibody with the following cross-reactivities: AVP, 100%; lysine vasopressin, 47%; oxytocin, less than 0.1%. The sensitivity is 0.31 μU. The assay range is 0.1 to 19.2 μU. Intra-assay coefficient of variation is 4.7%; interassay coefficient of variation is 12.2%.

The PGE₂ assay uses a rabbit antibody with the following cross-reactivities: PGE₂, 100%; prostaglandin E₁, 100%; 0% with prostaglandin F₁α, PGF₂α, prostaglandin A₁, A₂, and 15-keto-PGE₂; and less than 1% with 13,14-dihydro-15-keto-prostaglandin E₁, 13,14-dihydro-15-keto-PGE₂, and 13,14-dihydro-15-keto-prostaglandin F₂. The sensitivity is 6.4 pg (range, 6-400 pg). Intra-assay coefficient of variation is 4.6%; interassay coefficient of variation is 8.6%; recovery from urine is 82.1%.

The PGF₂α assay uses a rabbit antibody with the following cross-reactivities: PGF₂α, 100%; prostaglandin F₁α, 128%; prostaglandin E₁, 15.7%; PGE₂, 3.9%; 0% with prostaglandins A₁, A₂, 15-keto-prostaglandin F₂, 13,14-dihydro-15-keto-prostaglandin E₁, 13,14-dihydro-15-keto-PGE₂, and 13,14-dihyro-15-keto-prostaglandin F₂. The sensitivity is 2.15 pg (range, 3-200 pg). Intra-assay coefficient of variation is 3.3%; interassay coefficient of variation is 10.5%; recovery in urine is 76.0%.

Statistical Analysis

Data from the first two supine (control) periods were averaged. Comparisons between the two groups were performed by unpaired t tests. The Wilk-Shapiro test for normality was applied, and data were normally distributed. Comparisons within the same group were performed by paired t tests. Significance was considered at a p level below 0.05. Data are presented as means ± SE.

Results

The values for the outpatient screening BPs obtained during the subjects' ad libitum diet were as follows: The mean (±SE) BP for all NT subjects, using all screening pressures, was 112 ± 2/74 ± 2 mm Hg and for BHT subjects was 127 ± 4/85 ± 2 mm Hg (systolic BP: BHT vs NT subjects, p<0.01; diastolic BP: BHT vs NT subjects, p<0.001). The mean BP for the single highest screening pressure for NT subjects was 115 ± 2/79 ± 2 mm Hg and for BHT subjects was 131 ± 4/93 ± 2 mm Hg (systolic BP: BHT vs NT subjects, p<0.01; diastolic BP: BHT vs NT subjects, p<0.001).

BP at the end of the diet periods on Day 5 in seated subjects was as follows: on the low NaCl diet, BP was 107 ± 3/72 ± 2 mm Hg in NT subjects and 124 ± 3/86 ± 3 mm Hg in BHT subjects (systolic and diastolic BP, p<0.001); on the high NaCl diet, BP was 109 ± 2/70 ± 2 mm Hg in NT subjects and 125 ± 4/82 ± 4 mm Hg in BHT subjects (systolic and diastolic BP, p<0.01).

Balance Data

All subjects achieved comparable sodium balance during each diet before studies of their renal circulation, as indicated by their 24-hour urinary sodium excretion values at the end of the diet periods (Table 1). There were no significant differences between the groups for sodium or potassium excretion. Urinary aldosterone obtained on Day 4 was increased by low NaCl and suppressed by high NaCl diets to a comparable degree in both groups (see Table 1). Urinary calcium excretion on Day 5 increased in both groups during the high NaCl diet, but there were no differences between the groups during either diet. Serum ionized calcium levels measured while the subjects were receiving an ad libitum diet were not different in the two groups; 4.89 ± 0.15 mg/dl in NT subjects and 4.96 ± 0.16 mg/dl in BHT subjects.

TABLE 1. 24-Hour Urinary Electrolyte and Aldosterone Excretion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low NaCl diet</th>
<th>High NaCl diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=13)</td>
<td>(n=9)</td>
</tr>
<tr>
<td>Na (mEq/24 hr)</td>
<td>13±1</td>
<td>15±3</td>
</tr>
<tr>
<td>K (mEq/24 hr)</td>
<td>79±4</td>
<td>68±4</td>
</tr>
<tr>
<td>Aldosterone (μg/24 hr)</td>
<td>59±7</td>
<td>52±8</td>
</tr>
<tr>
<td>Ca (mg/24 hr)</td>
<td>163±17</td>
<td>192±22</td>
</tr>
</tbody>
</table>

Values are means ± SE. There were no significant differences between NT and BHT subjects in these variables. NT = normotensive; BHT = borderline hypertensive.
5.19 ± 0.05 mg/dl in BHT subjects. The BHT subjects were heavier than the NT subjects (p<0.01), but the modest weight gain during high NaCl diet did not differ between the groups. Body weights were as follows: 74.5 ± 1.7 and 86.1 ± 3.6 kg on low NaCl diet and 75.2 ± 1.6 and 86.9 ± 3.7 kg on high NaCl diet for NT and BHT subjects, respectively.

Blood Pressure and Renal Hemodynamic Responses to Standing

On Day 6 of both the low and high NaCl diets, diastolic BP was significantly higher in BHT compared with NT subjects in upright periods (p<0.05, low NaCl diet; p<0.01, high NaCl diet; Table 2). During the high NaCl diet, diastolic BP in NT subjects declined slightly during the 30 minutes of quiet standing (−2 ± 2 mm Hg) but directionally increased in BHT subjects (+4 ± 3 mm Hg; see Table 2). This increase in diastolic pressure during standing was observed in five of nine BHT but in only four of 13 NT subjects during the high NaCl diet. Heart rate increased during standing in both groups on both diets without a difference between groups.

The effect of upright posture on renal hemodynamics is shown in Table 3 and Figures 1 and 2. At the end of each diet, the $C_{PAH}$ in the supine position were not different between the groups. $C_{PAH}$ increased in nine of 13 NT subjects and in seven of nine BHT subjects in the supine position after the high NaCl diet compared with the low NaCl diet. The absolute and percent decreases in the $C_{PAH}$ from supine to upright posture are shown in Table 3 and Figure 1. A significantly greater decrease in $C_{PAH}$ (in ml/min/1.73 m²) occurred in NaCl-restricted and NaCl-loaded normotensive (NT; n = 13) and borderline hypertensive (BHT; n = 9) subjects.

### TABLE 2. Supine and Standing BP and Heart Rate

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low NaCl Diet (10 mEq Na, 100 mEq K)</th>
<th>High NaCl Diet (400 mEq Na, 100 mEq K)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NT (n = 13)</td>
<td>BHT (n = 9)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>110 ± 2</td>
<td>119 ± 3*</td>
</tr>
<tr>
<td>Standing</td>
<td>104 ± 3</td>
<td>112 ± 4</td>
</tr>
<tr>
<td>Change</td>
<td>−6 ± 2</td>
<td>−7 ± 1</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>78 ± 1</td>
<td>84 ± 3</td>
</tr>
<tr>
<td>Standing</td>
<td>73 ± 3</td>
<td>84 ± 3*</td>
</tr>
<tr>
<td>Change</td>
<td>−4 ± 2</td>
<td>−0.2 ± 3</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>89 ± 1</td>
<td>96 ± 3*</td>
</tr>
<tr>
<td>Standing</td>
<td>84 ± 3</td>
<td>94 ± 3*</td>
</tr>
<tr>
<td>Change</td>
<td>−4 ± 2</td>
<td>−2 ± 2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>56 ± 2</td>
<td>60 ± 2</td>
</tr>
<tr>
<td>Standing</td>
<td>74 ± 3</td>
<td>77 ± 3</td>
</tr>
<tr>
<td>Change</td>
<td>18 ± 3</td>
<td>17 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SE. Mean BP equals diastolic BP plus pulse pressure.

NT = normotensive; BHT = borderline hypertensive.

*p < 0.05, †p < 0.01 compared with respective value for NT subjects.

### FIGURE 1. Percent change in p-aminohippurate (PAH) clearance when subjects changed from a supine to a standing position, measured in NaCl-restricted and NaCl-loaded normotensive (NT; n = 13) and borderline hypertensive (BHT; n = 9) subjects.

During the low NaCl diet, the percent by which $C_{PAH}$ decreased was also greater in the BHT (−28.7 ± 4.2%) than in the NT subjects (−14.9 ± 2.7%; p < 0.01). In the NaCl-loaded NT subjects, the maximum percent decrease in $C_{PAH}$ induced by standing was −29%; five of nine NaCl-loaded BHT subjects exceeded the 29% decrease in $C_{PAH}$ elicited by standing. During the low NaCl diet, $C_{PAH}$ decreased by 24.1 ± 4.5% in BHT and by 20.4 ± 4.0% in NT subjects. These responses to posture during low NaCl did not differ significantly between groups.

RVR index increased with standing in both groups (see Table 3 and Figure 2). During the low NaCl diet, NT subjects increased RVR by 23 ± 8% during standing while the BHT subjects increased RVR by 32 ± 8% (p = NS; see Figure 2). During the high NaCl diet, the RVR response to standing remained the same in NT subjects (14 ± 5%) as compared with the response on the low NaCl diet. In contrast, the increase in RVR during standing in BHT subjects was augmented during the high NaCl diet to 48 ± 12% (p < 0.01, BHT vs NT subjects). During the high NaCl diet, RVR increased more than 20% in three of 13 NT and in seven of nine BHT subjects during standing. Thus,
Renal Function Responses to Standing

The effect of upright posture on water and sodium handling was examined (Table 4). \( C_{\text{H,O}} \) was calculated from the standard formula \( C_{\text{H,O}} = \frac{\text{urine flow rate} \times \text{osmolar clearance}}{\text{GFR}} \). The fall in \( C_{\text{H,O}} \) was greater (\( p < 0.01 \)) in BHT than in NT subjects with both diets (see Table 4), and these changes persisted after adjustment for GFR. In fact, NT subjects showed only very modest reductions in \( C_{\text{H,O}} \) when assuming the upright posture (see Table 4). After adjustment for GFR, on the low NaCl diet, upright CH\( _2O/dl \) GFR in NT subjects was 6.9 ± 0.3% and in BHT subjects 4.5 ± 0.9% (\( p < 0.05 \)). During the high NaCl diet, the difference was accentuated: upright CH\( _2O/dl \) GFR was 8.3 ± 0.3% in NT subjects and was 5.1 ± 0.9% (\( p < 0.01 \)) in BHT subjects.

The sodium excretion was not different between the two groups for the same diet periods (see Table 4). However, the absolute decrease in sodium excretion when changing from supine to upright posture was greater in NaCl-restricted BHT subjects than in NT subjects (\( p < 0.05 \); see Table 4). The FEN, was not significantly different during standing between the two groups after each diet.

We also estimated the FEN, at the end of the proximal tubule using the following formula:

\[
\text{proximal FEN}_n = \frac{(U_{\text{Na} + \text{K}}/P_{\text{Na}} + C_{\text{H},0}) \times 100}{\text{GFR}}
\]

where \( U_{\text{Na} + \text{K}} \) is urinary sodium and potassium excretion, \( V \) is urine flow rate, and \( P_{\text{Na}} \) is serum sodium concentration. After both diets, there were no differences in the proximal FEN, between BHT and NT subjects when supine. In contrast, after both diets standing produced a significant reduction in the proximal FEN, in BHT subjects compared with NT subjects (\( p < 0.01 \), low NaCl diet; \( p < 0.05 \), high NaCl diet), as shown in Table 4.

During the low NaCl diet, potassium excretion decreased in both groups with standing (NT subjects: from 96.6 ± 12.7 μEq/min supine to 71.2 ± 5.8 μEq/min standing; BHT subjects: from 76.0 ± 13.0 μEq/min supine to 55.3 ± 5.0 μEq/min standing). During the high NaCl diet, potassium excretion also fell slightly with standing in both groups but values for NT and BHT subjects were not different after either diet.

### Table 3. Renal Hemodynamic Responses to Standing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low NaCl diet (10 mEq Na, 100 mEq K)</th>
<th>High NaCl diet (400 mEq Na, 100 mEq K)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NT (n=13)</td>
<td>BHT (n=9)</td>
</tr>
<tr>
<td></td>
<td>NT (n=13)</td>
<td>BHT (n=9)</td>
</tr>
<tr>
<td>( C_{\text{PAH}} ) (ml/min/1.73 m\text{^2})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>488 ± 24</td>
<td>509 ± 27</td>
</tr>
<tr>
<td>Standing</td>
<td>389 ± 26</td>
<td>430 ± 22</td>
</tr>
<tr>
<td>Change</td>
<td>-99 ± 18</td>
<td>-79 ± 17</td>
</tr>
<tr>
<td>RVR index (units)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>0.19 ± 0.01</td>
<td>0.18 ± 0.01</td>
</tr>
<tr>
<td>Standing</td>
<td>0.23 ± 0.02</td>
<td>0.21 ± 0.01</td>
</tr>
<tr>
<td>Change</td>
<td>0.04 ± 0.02</td>
<td>0.02 ± 0.01</td>
</tr>
<tr>
<td>( C_{\text{c}} ) (ml/min/1.73 m\text{^2})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>117 ± 5</td>
<td>128 ± 5</td>
</tr>
<tr>
<td>Standing</td>
<td>111 ± 4</td>
<td>124 ± 5</td>
</tr>
<tr>
<td>Change</td>
<td>-6 ± 6</td>
<td>-5 ± 4</td>
</tr>
<tr>
<td>FF</td>
<td>0.25 ± 0.01</td>
<td>0.26 ± 0.01</td>
</tr>
<tr>
<td>Standing</td>
<td>0.30 ± 0.02</td>
<td>0.29 ± 0.01</td>
</tr>
<tr>
<td>Change</td>
<td>0.05 ± 0.01</td>
<td>0.03 ± 0.01</td>
</tr>
</tbody>
</table>

Values are means ± SE. NT = normotensive; BHT = borderline hypertensive; \( C_{\text{PAH}} \) = \( p \)-aminobipyrurate clearance; RVR index = renal vascular resistance index, calculated from mean blood pressure/\( C_{\text{PAH}} \); \( C_{\text{c}} \) = creatinine clearance; FF = filtration fraction, calculated as \( C_{\text{v}}/C_{\text{PAH}} \).

*p < 0.05, compared with respective value for NT subjects.

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Responses of Humoral Vasoconstrictors to Standing

We measured PRA, plasma norepinephrine, and plasma AVP in the supine and upright periods in all subjects (Table 5). Renin and norepinephrine levels increased during standing during both diet periods, but there were no differences between the groups.

Urinary prostaglandins were measured during the high NaCl diet. Supine urinary PGF\textsubscript{2\alpha} was 1.94 ± 0.18 ng/mg creatinine in NT subjects and 1.37 ±0.20 ng/mg creatinine in BHT subjects (p = 0.054). Urinary PGF\textsubscript{2\alpha} collected during standing was 1.85 ± 0.21 ng/mg creatinine in NT subjects and 1.15 ± 0.16 ng/mg creatinine in BHT subjects (p <0.05). Supine urinary PGE\textsubscript{2} was 1.49 ± 0.12 ng/mg creatinine in NT subjects and 1.43 ± 0.21 ng/mg creatinine in BHT subjects. Standing urinary PGE\textsubscript{2} was 1.40 ± 0.18 ng/mg creatinine in NT subjects and 0.98 ± 0.19 ng/mg creatinine in BHT subjects.

Discussion

Orthostatic changes in renal blood flow have long been known to occur in normal humans.\textsuperscript{16} The major new finding in our study is that a high NaCl diet results in an exaggerated reduction in renal plasma flow in response to standing in BHT subjects compared with NT subjects. Since the BP was increasing when NaCl-loaded BHT subjects were standing, our data strongly suggest that the RVR increased more in NaCl-loaded BHT subjects during standing than in NaCl-loaded NT subjects. Homer Smith\textsuperscript{16} originally demonstrated the effect of posture on renal function and showed quite clearly that the normal response of the renal circulation to standing was vasoconstriction. Although resting renal blood flow is normal or only slightly decreased in patients with mild hypertension, the effect of orthostatic stress on the renal circulation in these persons has not been evaluated.\textsuperscript{17-20} Our study shows that the increase in RVR index with standing was significantly augmented in NaCl-loaded BHT subjects compared with NaCl-loaded NT subjects, but it was not different between the groups during NaCl restriction.

Our data regarding supine renal plasma flow and GFR in BHT subjects are similar to those of others, including Temmar et al.\textsuperscript{21} and Reubi et al.\textsuperscript{22} who showed normal CPAH and extraction in patients with benign essential hypertension. In our study, standing decreased renal plasma flow as expected. In NT subjects, the posturally induced reduction in CPAH after a
high NaCl diet remained the same as that found with the low NaCl diet. This finding was not unexpected since sodium loading expands extracellular fluid volume and suppresses plasma catecholamines and renin activity. Surprisingly, dietary NaCl loading produced an exaggerated posturally induced decrease in renal blood flow in BHT subjects compared with NT subjects. Although there was a range in the values of decreased renal plasma flow to upright posture in NaCl-loaded BHT subjects, more than half of the BHT subjects showed a drop in renal plasma flow exceeding that seen in NaCl-loaded NT subjects. During NaCl restriction, the decrease in renal plasma flow with standing was not different between the two groups.

Although renal plasma flow dropped with standing in NT subjects, GFR in NT subjects after both diets remained stable as a reflection of normal autoregulation. In NaCl-loaded BHT subjects, however, GFR fell with standing to a greater degree than in NT subjects, reflecting enhanced vasoconstriction and the greater decrease in renal plasma flow in BHT subjects when standing and suggesting some loss of autoregulation of the GFR.

The cause of the enhanced vasoconstrictor response in the NaCl-loaded BHT subjects during upright posture is not clearly defined. Our measurements of PRA and plasma norepinephrine showed that the BHT subjects had normal responses during upright posture. Our observations relating to renal vascular changes in the upright posture show enhanced renal vasoconstriction and diminished autoregulation of GFR in NaCl-loaded BHT subjects. This effect might be mediated by enhanced sympathetic nervous system activity. Although there were no differences in peripheral vein plasma catecholamines in the two groups, peripheral plasma catecholamines may not reflect changes in sympathetic activity in the renal bed. Alternatively, the augmented renal vasoconstriction in BHT subjects with standing might relate to undetermined humoral vasoactive substances or to altered reactivity of the renal circulation.

Williams and Hollenberg and colleagues have reported a group of subjects with mild to moderate essential hypertension in whom an oral sodium load did not increase renal blood flow. Since $C_{\text{PAH}}$ increased in seven of nine BHT and in nine of 13 NT subjects after the high NaCl diet, we were not able to distinguish NT from BHT subjects based on the renal plasma flow response to a sodium load. Postural changes, however, did accentuate differences between the groups.

Our studies of water and sodium excretion show clearly that during standing BHT subjects on both diets retain more water than do NT subjects, as indicated by the greater decrease in $C_{\text{H,O}}$. We measured certain factors that might be related to the decreased $C_{\text{H,O}}$ in BHT subjects during standing. We measured plasma AVP concentration, and values were not different between groups. We also speculated that a reduction in renal prostaglandins in BHT subjects during upright posture would influence $C_{\text{H,O}}$, since prostaglandins have been shown to antagonize the hydroosmotic action of AVP on water transport and reduced prostaglandins might enhance AVP action. We observed a reduction in urinary prostaglandins in BHT subjects during standing. We speculate that if the urinary prostaglandins reflect intrarenal prostaglandins, the reduction we observed in prostaglandins may contribute to the decrease in $C_{\text{H,O}}$ by enhancing the activity of AVP in BHT subjects.

Alternatively, a decrease in sodium delivery to the ascending limb may be another factor determining the decreased $C_{\text{H,O}}$ in BHT subjects. We estimated the FE$_{\text{Na}}$ at the end of the proximal tubule from the sodium in the urine plus the sodium removed by the thick ascending limb plus the sodium removed from the distal tubule. This estimate suggests that the sodium reabsorption in the proximal tubule is significantly greater in BHT subjects, when they stand, compared with NT subjects. Hence, a decrease in sodium delivery from the proximal tubule, supported by an indirect estimate of proximal tubule FE$_{\text{Na}}$, could account for the decreased $C_{\text{H,O}}$ in BHT subjects during standing. Enhanced proximal tubular reabsorption of sodium may well be mediated by neurogenic or unmeasured humoral factors.

The neurogenic control of the renal circulation and function has been well studied. Hollenberg et al. demonstrated that the increase in RVR in essential hypertension was mediated in part by increased $\alpha$-adrenergic tone. The role of the renal nerves in regulation of the renal circulation and in renal tubular sodium transport and renin release has been well reviewed. DiBona and Johns have studied the renal response to 60-degree head-up tilt in dogs and found that the renal sympathetic nerves were responsible for decreases in FE$_{\text{Na}}$ and that these changes were mediated by renal tubular $\alpha$-adrenergic receptors. Our data would be compatible with a similar effect in humans.

Our finding that diastolic arterial pressure tends to increase with standing in BHT subjects supports the work of others. Payen et al. stressed the importance of this finding in a 48-month follow-up study of 23 young men with borderline hypertension. They found that persons who showed an increased diastolic BP in response to orthostatic change later exhibited significant increases in systolic and mean arterial pressure. These groups, however, have not reported the orthostatic blood pressure response to NaCl restriction. In our subjects, extreme NaCl restriction prevented or attenuated the rise in diastolic BP during standing in the BHT subjects. Our data, as well as those of Payen et al. and Hull et al., are to some degree at odds with the recent findings of Bakris et al., who reported an increase in mean arterial pressure in normal subjects with standing.

Although the phenomenon of renal vasoconstriction with standing is well known, to our knowledge our observation that NaCl loading produces an exaggerated renal vasoconstrictor response in BHT subjects is new. This finding supports the concept that persons who are predisposed to hypertension respond to dietary NaCl loading and upright posture by exaggerated re-
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Dietary salt produces abnormal renal vasoconstrictor responses to upright posture in borderline hypertensive subjects.

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