Renal Sodium Excretion in Sons of Hypertensive Parents

Stephen T. Turner, Sharon L. Reilly

The objective of this study was to evaluate whether renal excretion of sodium is impaired and whether tubular reabsorption of sodium is increased in normotensive white men with a familial predisposition to develop essential hypertension. We compared 11 normotensive sons of two hypertensive parents (SOHT) with 11 normotensive sons of two normotensive parents (SONT); renal sodium handling was assessed after 1 week of low-sodium diet (10 mmol/d) and after 1 week of high-sodium diet (200 mmol/d). The SOHT were on average 5.5 years older than the SONT (46.9±5.2 [SD] vs 41.4±4.1, P=.012). On the sixth day of each diet, mean urinary sodium excretion did not differ between the two groups (12.9±6.3 vs 12.7±6.7 mmol/d on low-sodium diet, P=.930; 197±25 vs 200±27 mmol/d on high-sodium diet, P=.817). On the seventh day of each diet, baseline means for filtered load of sodium, absolute excretion of sodium, fractional excretion of sodium (an index of total tubular sodium reabsorption), and fractional excretion of lithium (an inverse index of proximal tubular sodium reabsorption) also did not differ between the groups. To assess renal sodium handling under non-steady-state conditions, we infused 2 L normal saline intravenously over a 2-hour period. The means for absolute excretion of sodium, fractional excretion of sodium, and fractional excretion of lithium increased from baseline, but the increases did not differ in magnitude between the groups. With both diets, mean blood pressure was 7 mm Hg greater in the SOHT than in the SONT (P=.046) and did not change significantly during saline infusion. These results provide no evidence that renal excretion of sodium is impaired or that tubular reabsorption of sodium is increased in normotensive white men who have a familial predisposition to develop essential hypertension. If such alterations are underlying characteristics of the familial predisposition to develop essential hypertension, then higher blood pressure in the offspring of hypertensive parents may have compensatory renal effects that restore renal sodium handling to normal. (Hypertension. 1993;22:323-330.)

KEY WORDS • sodium • lithium • hypertension, genetic

A prevailing hypothesis to explain the familial predisposition to essential hypertension (hypertension) is that inherited factors have effects that impair the kidneys' ability to excrete sodium chloride (sodium).1 Sodium excretion may be impaired either because less sodium is filtered by the kidneys or because more filtered sodium is reabsorbed by the renal tubules. Either alteration might result from an abnormality that is intrinsic to the kidneys or one that is secondary to extrarenal factors. Because plasma sodium concentration and glomerular filtration rate—the determinants of the filtered load of sodium—are not decreased early in the course of uncomplicated hypertension,2 increased tubular reabsorption of sodium has been the renal alteration most often postulated to impair sodium excretion and contribute to the development of hypertension.

Despite compelling arguments presented by Guyton and others that impairment of renal sodium excretion is a sine qua non for hypertension to develop,3 studies that have assessed renal excretion and tubular reabsorption of sodium in normotensive humans with a familial predisposition to develop hypertension have been inconsistent in their results. For example, the natriuretic response to intravenous saline infusion has been reported to be either decreased or increased in normotensive first-degree relatives of hypertensive patients.4-6 and the fractional excretion of lithium—an inverse indicator of proximal tubular reabsorption of sodium—has been reported to be either increased or no different in normotensive offspring of hypertensive patients.7,8 The reasons for these inconsistencies may include differences between studies in methods used to select subjects with contrasting predispositions to develop hypertension, differences in the level of dietary sodium intake before assessment of renal sodium handling, and differences in the measures used to assess renal sodium handling.

We undertook the present study in search of evidence to support the hypothesis that renal excretion of sodium is impaired and that tubular reabsorption of sodium is increased in normotensive white men with a familial predisposition to develop hypertension. To maximize the likelihood of detecting such evidence, we first selected two groups of normotensive individuals with markedly different predispositions to develop hypertension—namely, sons of two normotensive parents...
(SONT) and sons of two hypertensive parents (SOHT). Second, we controlled dietary sodium intake before the assessment of renal sodium handling and studied the groups after adaptation to low- and high-sodium diets. Third, with each diet, we assessed differences between the groups in multiple measures of renal sodium handling under baseline conditions and during an acute natriuresis induced by intravenous saline infusion. To identify differences in extrarenal factors that might account for differences in sodium handling between the groups, we also assessed indexes of sympathetic nervous system activity and circulating natriuretic and antinatriuretic substances.

**Methods**

**Subjects**

We studied 22 adult white men distributed in two groups of 11 individuals: SOHT and SONT. Both groups were recruited from the middle generation of 276 three-generation pedigrees that participated in the Rochester Family Heart Study (RFHS) between 1985 and 1988. These pedigrees were ascertained through households having two or more children enrolled in the schools of Rochester, Minn, in 1984. The diagnosis of normotension or hypertension in parents of the sons in this study was determined by physical examination of the parents or review of their complete medical records if the parents were not examined. To ensure accuracy of the diagnostic determinations based only on review of medical records, we required that blood pressure readings were recorded in each parent’s medical records during the year before the family’s participation in the RFHS or the parent’s death. Parents of the SOND had systolic blood pressure less than 140 mm Hg and diastolic blood pressure greater than 94 mm Hg, or they were taking antihypertensive medications because hypertension was documented; they had no acute or chronic illnesses and were taking no medications that could lower blood pressure. Parents of the SOHT had systolic blood pressure greater than 159 mm Hg, or diastolic blood pressure greater than 94 mm Hg, or they were taking antihypertensive medications because hypertension had been previously diagnosed. Their mean age when hypertension was documented was 64±13 years (range, 36 to 83 years). At the time normotension was documented, they had no acute or chronic illnesses and were taking no medications. Parents of the SOHT had systolic blood pressure less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg. Their mean age (±SD) when normotension was documented was 66±7 years (range, 55 to 83 years). At the time normotension was documented, they had no acute or chronic illnesses and were taking no medications that could lower blood pressure.

**Screening Visit Before Experimental Protocol**

Procedures involving participation of human subjects were approved by the Institutional Review Board of the Mayo Clinic and were carried out in accordance with institutional guidelines. Within 1 month before study participation, each subject signed a consent form and underwent a physical examination and screening laboratory tests that included chemistry and hematology profiles, urinalysis, chest x-ray, and electrocardiogram. As part of the physical examination, three blood pressure readings, at least 2 minutes apart, were measured with a random-zero sphygmomanometer (Hawksley and Sons, Ltd, West Sussex, England) after the subject had been sitting quietly for 5 minutes. These readings were averaged to determine the subject’s office blood pressure before the study protocol (Table 1).

**Experimental Protocol**

The experimental protocol lasted 2 weeks. During the first week, subjects ate a low-sodium diet containing 10 mmol sodium per day; during the second week, they ate a high-sodium diet containing 200 mmol sodium per day. Although food items differed between the diets, both diets contained the same daily amounts of protein (79 g), potassium (100 mmol), calcium (900 mg), magnesium (345 mg), and phosphorus (1200 mg); the amounts of carbohydrate and fat were adjusted to maintain each subject’s usual caloric intake. Supplementation of the low-sodium diet with calcium carbonate (Tums, Norclift Thayer, Tarrytown, NY) was required to match the calcium content of the low-sodium diet to that of the high-sodium diet. All meals were prepared and eaten in the General Clinical Research Center (GCRC). Adherence to the diet was confirmed by measuring the amount of sodium and potassium excreted in the urine each day; completeness of the collection was assessed by measuring the amount of creatinine excreted each day.

On the 6th day of each diet—days 6 and 13 of the experimental protocol—subjects underwent 24-hour ambulatory monitoring of blood pressure and heart rate. Analyses of those data have been published separately.10 The 24-hour urine collections on days 6 and 13 were analyzed for aldosterone, norepinephrine, prostaglandin E2, 6-ketoprostaglandin F1α, and thromboxane B2 contents. Subjects slept overnight in the GCRC these days. At 10 PM, they received 600 mg lithium carbonate orally. Thereafter, they remained horizontal until blood was drawn the next morning, and they fasted until the renal clearance protocol (described below) was completed.

At 5:30 AM on days 7 and 14, an intravenous catheter was inserted into a forearm vein of each subject. Blood was sampled one-half hour later to determine plasma concentrations of norepinephrine, renin activity, aldosterone, atrial natriuretic peptide, and endothelin. At 7 AM, a second intravenous catheter was inserted into a forearm vein of the subject’s other arm to permit fluids to be infused into one arm and blood to be sampled from the other arm. At 7:30 AM, the renal clearance protocol began with intravenous infusion of loading doses of inulin (25 mg/kg body wt) and para-aminohippurate (PAH, 10 mg/kg) in a 2.5% dextrose solution (50 mL total volume), followed by a 1 mL/min infusion of a 2.5% dextrose solution containing 12.5 mg/mL inulin and 15 mg/mL PAH. After a 45-minute equilibration period, urine and blood samples were collected every 30 minutes for a total of seven clearance periods. After the first three clearance periods (baseline clearance periods), normal saline was infused at a rate of 1 L/h over the subsequent four clearance periods (saline infusion periods); thus, 308 mmol sodium was infused over 2 hours. Throughout the clearance protocol, urine flow rate was maintained at 5 to 10 mL/min by giving water orally. The sustaining infusion of inulin and PAH contained 0.05 μCi/mL of [131I]iodohippurate, which permitted monitoring of bladder emptying by comparing radioactive counts over the bladder before and after...
voiding. A urinary catheter was inserted when necessary to achieve complete emptying of the bladder.

Blood was sampled to determine plasma concentrations of norepinephrine, renin activity, aldosterone, atrial natriuretic peptide, and endothelin just before, 1 hour after, and at the end of the saline infusion. Mean blood pressure was measured every 5 minutes during the clearance protocol by a noninvasive oscillometric method (Accutor 1A, Datascopc Corp, Parnasus, NJ), and cardiac output was estimated every 12 cardiac cycles by a noninvasive thoracic electrical bioimpedence method (NCCOM-3, BoMed Medical Manufacturing Ltd, Irvine, Calif). Analyses of the cardiac output data; urinary 6-ketoprostaglandin $F_{1\alpha}$ and thromboxane $B_2$ contents; and plasma concentrations of norepinephrine, renin activity, aldosterone, and atrial natriuretic peptide have been reported separately.12

Laboratory Methods

The screening laboratory tests before the study protocol were carried out in the clinical laboratories of the Mayo Clinic. Sodium concentrations in the plasma and urine samples collected during the experimental protocol were measured with a flame photometer (model 1943, Instrumentation Laboratories, Lexington, Mass); lithium concentrations were measured with an atomic absorption spectrophotometer (model 1000, Perkin-Elmer, Norwalk, Conn); inulin and PAH concentrations were measured by colorimetric methods.11 Plasma and urine norepinephrine were determined by high-performance liquid chromatography.1 Plasma renin activity, aldosterone, atrial natriuretic peptide, and endothelin as well as urinary aldosterone, prostaglandin $E_2$, 6-ketoprostaglandin $F_{1\alpha}$, and thromboxane $B_2$ were measured by radioimmunoassays.14-17

Data Analysis

The clearances of inulin, PAH, sodium, and lithium were calculated for each 30-minute collection period as $\frac{U_x V}{P_x}$, where $U_x$ and $P_x$ denote the urinary and plasma concentrations of $X$, the substance of interest, and $V$ denotes the urine flow rate during the period. The clearance of inulin was taken as a measure of glomerular filtration rate and the clearance of PAH as a measure of effective renal plasma flow. The fractional excretions of sodium and lithium were calculated by dividing the clearances of these substances by the clearance of inulin. Because the clearance of lithium provides a measure of isotonic fluid delivery out of the proximal tubule,18 the fractional excretion of lithium was taken as an inverse indicator of proximal tubular reabsorption of sodium. Clearances and fractional excretions for the first three collection periods (before saline infusion) were averaged to estimate baseline values.

Statistical Analyses

Data for each variable were summarized by calculating group means±SD for the SONT and SOHT. For the variables measured at the screening visit before the study protocol (Table 1), we used the Student’s unpaired t test to assess the statistical significance of differences in means between groups. For the variables measured under baseline conditions after adaption to low- and high-sodium diets (Tables 2 and 3), we used the repeated-measures analysis of variance with group stratification to assess the statistical significance of interactions between the effects of group classification and dietary sodium intake. When tests for interactions were not statistically significant, we concluded that the differences between groups were independent of dietary sodium intake and, conversely, that the effects of dietary sodium intake were independent of group classification. Thus, when there was no interaction, we assessed the significance of differences between the groups by contrasting group means pooled across diets and the significance of differences between the diets by contrasting diet means pooled across groups. When there was interaction, we assessed the significance of differences between the groups on each diet separately and the significance of differences between diets for each group separately. In this case, the Student’s unpaired t test was used to contrast means between groups on each diet, and the Student’s paired t test was used to contrast means between diets for each group.

For those variables also measured during saline infusion (Fig 2), we used the repeated-measures analysis of variance with group stratification to assess the statistical significance of interactions between the effects of group classification and saline infusion on each diet separately. Here, the “effects of saline infusion” refers to changes in the mean value of a variable across the average baseline period and the four saline infusion periods. When tests for interaction were not statistically significant, we concluded that the differences between groups were independent of the effects of saline infusion and, conversely, that the effects of saline infusion were independent of group classification. Thus, when there was no interaction, we assessed the significance of differences between groups by contrasting group means pooled across clearance periods and the significance of differences between clearance periods by contrasting clearance period means pooled across groups.

Results of the statistical tests outlined above were considered significant if the associated probability values ($P$) were less than .05.

Results

Description of the Sample

The SOHT were on average 5.5 years older than the SONT ($P=.012$) (Table 1). At the screening visit before the study protocol, the SOHT had higher mean fasting levels of serum glucose ($P=.005$) and plasma total cholesterol ($P=.026$) than the SONT. In both groups, means for systolic and diastolic blood pressures were within the normotensive range (<140/90 mm Hg).

Daily Urinary Sodium Excretion

Throughout the experimental protocol, daily (24-hour) mean sodium excretion did not differ between SONT and SOHT (Fig 1). During the first week when subjects ate the low-sodium diet, sodium excretion decreased in both groups, reaching on day 6 a mean (±SD) of $12.9±6.3$ mmol/d in SONT and $12.7±6.7$ mmol/d in SOHT ($P=.930$). On day 7, when 2 L normal saline was infused, mean sodium excretion increased by $59.4±34.3$ mmol/d in SONT and by $68.4±28.3$ mmol/d in SOHT ($P=.512$). During the second week when subjects ate the high-sodium diet, sodium excretion rose
TABLE 1. Description of the Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>SONT (n=11)</th>
<th>SOHT (n=11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td>.012</td>
</tr>
<tr>
<td>Sodium</td>
<td>141±2</td>
<td>140±1</td>
<td>.099</td>
</tr>
<tr>
<td>Glucose</td>
<td>5.2±0.4</td>
<td>6.1±0.8</td>
<td>.005</td>
</tr>
<tr>
<td>Creatinine</td>
<td>339±71</td>
<td>351±54</td>
<td>.734</td>
</tr>
<tr>
<td>Uric acid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>43.1±1.3</td>
<td>43.5±1.7</td>
<td>.629</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>87.2±12.8</td>
<td>92.9±14.1</td>
<td>.332</td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>4.58±0.65</td>
<td>5.38±0.88</td>
<td>.026</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.14±0.36</td>
<td>1.78±0.98</td>
<td>.062</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>117±15</td>
<td>124±11</td>
<td>.219</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>79±9</td>
<td>85±8</td>
<td>.092</td>
</tr>
</tbody>
</table>

SONT, sons of two normotensive parents; SOHT, sons of two hypertensive parents; HDL, high-density lipoprotein; BP, blood pressure. Values are mean±SD. P values are for differences in means between groups.

Further, reaching on day 13 a mean of 197±25 mmol/d in SONT and 200±27 mmol/d in SOHT (P=.817). On day 14, when 2 L normal saline was again infused, mean sodium excretion rose by 138±65 mmol/d in SONT and by 131±67 mmol/d in SOHT (P=.805).

Renal Sodium Handling Assessed by Clearance Methods

Baseline measurements. For the measures of renal sodium handling and hemodynamics assessed under baseline conditions, tests for interactions between the effects of group classification and dietary sodium intake were not statistically significant (Table 2). The filtered load of sodium, absolute excretion of sodium, fractional excretions of sodium and lithium, and glomerular filtration rate did not differ between SOHT and SONT. Renal plasma flow tended to be lower in SOHT than in SONT (498±56 vs 552±103 mL/min per 1.73 m², P=.129), and the calculated filtration fraction was higher in SOHT than in SONT (21.1±2.3% vs 19.1±2.3%, P=.045). Mean blood pressure was also higher in SOHT than in SONT (99±8 vs 92±3 mm Hg, P=.046).

The filtered load of sodium, absolute excretion of sodium, fractional excretions of sodium and lithium, and renal plasma flow were greater on high-sodium than on low-sodium diet (Table 2). Mean blood pressure was lower on high-sodium than on low-sodium diet (94±9 vs 97±8 mm Hg, P=.004).

Effects of saline infusion. For each measure of renal sodium handling assessed during saline infusion (Fig 2), tests for interactions between the effects of group classification and clearance period were not statistically significant with either diet. The filtered load of sodium, absolute excretion of sodium, and fractional excretions of sodium and lithium did not differ between SOHT and SONT. The absolute and fractional excretions of sodium and the fractional excretion of lithium increased during saline infusion.

For mean blood pressure (data not shown), the test for interaction between the effects of group classification and clearance period was not statistically significant on low-sodium diet (P=.772) or on high-sodium diet (P=.144). Mean blood pressure tended to be higher in SOHT than in SONT (100±8 vs 93±8 mm Hg on low-sodium diet, P=.053; 98±9 vs 91±8 mm Hg on high-sodium diet, P=.064). Although mean blood pressure did not change during saline infusion on low-sodium diet (P=.631), it tended to increase on high-sodium diet (P=.061).

Sympathetic Nervous System Activity and Natriuretic and Antinatriuretic Substances

For urinary norepinephrine excretion on days 6 and 13, the test for interaction between the effects of group classification and dietary sodium intake was statistically significant (P=.044) (Table 3). On low-sodium diet, mean urinary norepinephrine excretion was 139 nmol/d greater in SOHT than in SONT (466±171 vs 327±60 nmol/d, P=.020); but on high-sodium diet, it was only 53 nmol/d greater in SOHT than in SONT (289±66 vs 236±79 nmol/d, P=.103). With the shift from low- to high-sodium diet, mean urinary norepinephrine excretion decreased 177 nmol/d in SOHT (P<.001) but only decreased 91 nmol/d in SONT (P<.001).

For the other urinary variables measured on days 6 and 13 — namely, aldosterone and prostaglandin E₂ (Table 3) — tests for interactions between the effects of group classification and dietary sodium intake were not statistically significant. Neither variable differed between groups. Urinary aldosterone excretion was greater on low- than on high-sodium diet.

For plasma endothelin (data not shown) measured at baseline before saline infusion on days 7 (low-sodium diet) and 14 (high-sodium diet), the test for interaction
TABLE 2. Baseline Renal Clearance Measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Low-sodium diet</th>
<th>High-sodium diet</th>
<th>Diets pooled</th>
<th>( P )</th>
<th>Group</th>
<th>Diet</th>
<th>Group × diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filtered load of Na(^+) (mmol/min)</td>
<td>SONT</td>
<td>16.1±2.7</td>
<td>16.9±2.9</td>
<td>16.5±2.8</td>
<td>.436</td>
<td>.045</td>
<td>.953</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SOHT</td>
<td>16.8±1.6</td>
<td>17.6±1.5</td>
<td>17.2±1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pooled</td>
<td>16.4±2.2</td>
<td>17.2±2.3</td>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute excretion of Na(^+) (µmol/min)</td>
<td>SONT</td>
<td>63±22</td>
<td>275±75</td>
<td>169±121</td>
<td>.690</td>
<td>&lt;.001</td>
<td>.299</td>
<td></td>
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<tr>
<td></td>
<td>SOHT</td>
<td>71±40</td>
<td>251±71</td>
<td>161±108</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Pooled</td>
<td>67±32</td>
<td>263±72</td>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractional excretion of Na(^+) (%)</td>
<td>SONT</td>
<td>0.41±0.10</td>
<td>1.56±0.56</td>
<td>0.98±0.71</td>
<td>.735</td>
<td>&lt;.001</td>
<td>.649</td>
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<tr>
<td></td>
<td>SOHT</td>
<td>0.41±0.26</td>
<td>1.46±0.48</td>
<td>0.94±0.66</td>
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<tr>
<td></td>
<td>Pooled</td>
<td>0.41±0.19</td>
<td>1.51±0.51</td>
<td>...</td>
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<td></td>
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<tr>
<td>Fractional excretion of Li(^+) (%)</td>
<td>SONT</td>
<td>24.8±3.5</td>
<td>27.2±3.5</td>
<td>26.0±3.6</td>
<td>.585</td>
<td>.003</td>
<td>.356</td>
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<tr>
<td></td>
<td>SOHT</td>
<td>23.1±3.4</td>
<td>27.3±5.7</td>
<td>25.2±5.0</td>
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<tr>
<td></td>
<td>Pooled</td>
<td>24.0±3.5</td>
<td>27.2±4.6</td>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerular filtration rate (mL/min/1.73 m(^2))</td>
<td>SONT</td>
<td>103±14</td>
<td>105±18</td>
<td>104±16</td>
<td>.951</td>
<td>.117</td>
<td>.482</td>
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<tr>
<td></td>
<td>SOHT</td>
<td>102±7</td>
<td>106±9</td>
<td>104±8</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Pooled</td>
<td>102±11</td>
<td>106±14</td>
<td>...</td>
<td></td>
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</tr>
<tr>
<td>Renal plasma flow (mL/min/1.73 m(^2))</td>
<td>SONT</td>
<td>540±100</td>
<td>563±109</td>
<td>552±103</td>
<td>.129</td>
<td>.003</td>
<td>.413</td>
<td></td>
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<tr>
<td></td>
<td>SOHT</td>
<td>478±41</td>
<td>517±63</td>
<td>498±56</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pooled</td>
<td>509±81</td>
<td>540±90</td>
<td>...</td>
<td></td>
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<td></td>
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<tr>
<td>Filtration fraction (%)</td>
<td>SONT</td>
<td>19.3±2.2</td>
<td>19.0±2.4</td>
<td>19.1±2.3</td>
<td>.045</td>
<td>.222</td>
<td>.724</td>
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<tr>
<td></td>
<td>SOHT</td>
<td>21.4±1.8</td>
<td>20.8±2.8</td>
<td>21.1±2.3</td>
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<tr>
<td></td>
<td>Pooled</td>
<td>20.3±2.2</td>
<td>19.9±2.8</td>
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<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>SONT</td>
<td>93±8</td>
<td>90±8</td>
<td>92±8</td>
<td>.046</td>
<td>.004</td>
<td>.820</td>
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<tr>
<td></td>
<td>SOHT</td>
<td>100±7</td>
<td>97±9</td>
<td>99±8</td>
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<tr>
<td></td>
<td>Pooled</td>
<td>97±8</td>
<td>94±9</td>
<td>...</td>
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</table>

SONT, sons of two normotensive parents; SOHT, sons of two hypertensive parents. Values are mean±SD after 1 week of low-sodium diet (10 mEq/d) and 1 week of high-sodium diet (200 mEq/d). \( P \) values are for effects of group classification (Group), dietary sodium intake (Diet), and interactions between these effects (Group × diet).

Discussion

Results of this study do not support the hypothesis that renal excretion of sodium is impaired or that tubular reabsorption of sodium is increased in normotensive individuals with a familial predisposition to develop hypertension. Daily sodium excretion did not differ between the SONT and SOHT on any day of the low- or high-sodium diets (Fig 1). Moreover, at each level of dietary sodium intake, the rate of sodium excretion did not differ between the SOHT and SONT under baseline conditions (Table 2) or during acute natriuresis induced by saline infusion (Fig 2). Because the filtered load of sodium and the fractional excretions of sodium and lithium were the same in the two groups throughout the renal clearances, we infer that total tubular reabsorption of sodium as well as segmental reabsorption at proximal and distal tubular sites did not differ between SONT and SOHT. Thus, under the conditions of the present study, we detected no evidence that any measure of renal sodium handling—filtration, reabsorption, or excretion—was altered in normotensive men predisposed to develop hypertension.

If impaired renal excretion of sodium or increased tubular reabsorption of sodium were underlying characteristics of the familial predisposition to develop hypertension, this study should have provided opportunities to demonstrate these alterations. We selected subjects to maximize the predisposition to hypertension in the SOHT and to minimize the predisposition in the SONT. We required that both parents of the SOHT were hypertensive and that both parents of the SONT were normotensive; and to be certain of their diagnoses, we measured the parents' blood pressures or examined their complete medical records. In addition, we studied the two offspring groups on low- and high-sodium diets.
because differences in renal sodium handling might manifest at one extreme of sodium intake but not at the other. Finally, to detect differences that might manifest only under non-steady-state conditions, we assessed sodium excretion during the adaptation to low-sodium diet, during the transition from low- to high-sodium diet, and during the acute natriuresis induced by intravenous saline infusion on each diet. That we failed to detect differences in renal sodium handling between the SOHT and SONT despite these efforts suggests that impaired renal excretion of sodium and increased tubular reabsorption of sodium are not characteristics of the familial predisposition to develop hypertension.

In reaching this conclusion, we must be cautious. First, if true differences in the means of traits measuring renal sodium handling are small relative to within-group differences, the power to detect these differences will be low when the number of subjects in each group is small. Because the predisposition to hypertension is multifactorial and no single predisposing factor is either sufficient or necessary for hypertension to develop, it is possible that each SOHT has a different set of predisposing factors and that some of these factors may be present in the SONT. Consequently, even if the traits we studied were influenced by factors predisposing to the development of hypertension, differences between groups in the means of these traits may be small and within-group differences may be large. In this study, in which the probability of a type I error was set at .05, if a true difference in the means of a trait were equal to 1 within-group SD, the probability of rejecting the null hypothesis of no difference between the SOHT and SONT would be only .65. Thus, because the power of the present study to detect small differences was low, it may be appropriate to conclude only that large differences in renal sodium handling are unlikely to be characteristic of a large proportion of men with a familial predisposition to develop hypertension.

Another explanation that might be offered for our inability to detect an impairment of sodium excretion in the SOHT is that higher blood pressure levels in the SOHT may have had compensatory renal effects that restored sodium excretion to normal. Because in vitro systems demonstrate a positive relation between the level of blood pressure perfusing the kidneys and the amount of sodium excreted—a relation referred to as pressure-natriuresis—the same sodium excretion at a higher blood pressure level might be interpreted as prima facie evidence of an underlying impairment of sodium excretion in the SOHT. However, if the renal pressure-natriuresis relation were the dominant, long-term regulator of blood pressure level, as hypothesized by Guyton and colleagues,3 and if an underlying impairment of the renal capacity for sodium excretion were the chief determinant of higher blood pressure in the SOHT, we might have expected the difference in blood pressure between the SOHT and SONT to be greatest on high-sodium diet and to decrease on low-sodium diet. Moreover, during saline infusion, we might have expected blood pressure to rise more in the SOHT than in the SONT. Contrary to these expectations, the difference in blood pressure between the groups was independent of dietary sodium intake; blood pressure decreased, not increased, as subjects shifted from the low- to the high-sodium diet, and blood pressure did not rise more in one group than the other during saline infusion. These findings suggest, at least under the conditions of the present study, that factors other than alteration in the renal pressure-natriuresis relation or impairment of sodium excretory capacity are responsible for higher blood pressure in the SOHT than in the SONT.

Our previous analysis of systemic and renal vascular resistances in the SOHT and SONT12 suggests that generalized vasoconstriction, independent of dietary sodium intake, is the basis of higher blood pressure in the SOHT. The only correlates of increased vascular resistances in SOHT were increased urinary excretion and plasma concentrations of norepinephrine (Table 3; also see Fig 5 of Reference 12). There were no differences between the groups in urinary excretion of aldosterone, prostaglandin E2, 6-ketoprostaglandin F1α, and
thromboxane B₂ as well as plasma concentrations of renin activity, aldosterone, atrial natriuretic peptide, and endothelin (Table 3; also see Tables 1 and 2 of Reference 12). Thus, increased sympathetic nervous system activity may mediate the increased vascular resistances and higher blood pressure in SOHT. If impairment of sodium excretion were the original underlying abnormality that led to blood pressure elevation in the SOHT, our previous 12 and present results suggest that blood pressure elevation in SOHT is subsequently maintained by factors other than simply the need to excrete sodium. Otherwise, the changes in sodium load imposed in this study might have been successful in reversing differences in blood pressure between SOHT and SONT and in revealing the underlying impairment of renal sodium excretion in SOHT.

Results of three previous studies have been cited in support of the hypothesis that renal capacity for sodium excretion is diminished in normotensive individuals predisposed to develop hypertension.14,16,19 In two studies, diminished sodium excretion was found in the first-degree relatives of hypertensive patients after intravenous saline infusion.6,8; in the other study, it was found during mental stress.19 Whether decreased glomerular filtration or increased tubular reabsorption was responsible for the reported decreases in sodium excretion is not clear, because glomerular filtration was not measured in these studies. In the present study, we infused saline at two controlled levels of dietary sodium and detected no difference between SOHT and SONT in the rate of sodium excretion during the infusions or in the total amount of sodium excreted the day of the infusions. Furthermore, during the infusions, we detected no difference between the groups in the filtered load or tubular reabsorption of sodium (assessed by the fractional excretion of sodium). To our knowledge, the only other study in which dietary sodium intake was controlled and glomerular filtration rate was measured during intravenous saline infusion found greater sodium excretion and less tubular reabsorption of sodium in the offspring of hypertensive parents than in the offspring of normotensive parents.5 Because the preceding level of dietary sodium intake has a profound influence on sodium excretion (Table 2 and Fig 2), we speculate that sodium excretion may have been impaired in the offspring of hypertensive parents in some previous studies because those subjects were restricting their sodium intakes before the studies. Because reliable comparisons of renal sodium handling between offspring of hypertensive and normotensive parents require that both groups be stabilized on the same dietary sodium intake, we judge the previously cited evidence that renal sodium excretion is impaired in the normotensive offspring of hypertensive parents to be unconvincing.

Also questionable is the notion that increased proximal tubular reabsorption of sodium is a characteristic of the familial predisposition to develop hypertension. Weder7 reported that the fractional excretion of lithium, an inverse indicator of proximal tubular reabsorption of sodium, was lower in 11 young normotensive subjects with a positive family history of hypertension than in 20 normotensive subjects with a negative family history of hypertension. In that study, dietary sodium intake was not controlled, and the fractional excretion of lithium was estimated from the clearances of lithium and creatinine over 6-hour periods while subjects were ambulating freely. Three subsequent studies, including the present one, that controlled dietary sodium intake and used more precise renal clearance methods to estimate fractional excretion of lithium have found no difference in the fractional excretion of lithium between the normotensive offspring of hypertensive and normotensive parents.8,20 In our study and that of Städdler and colleagues,8 the fractional excretion of lithium did not differ between the offspring groups on low- or on high-sodium diet; furthermore, in our study, it did not differ between the groups during acute natriuresis induced by intravenous saline infusion. Judged against these more thorough and carefully controlled investigations, the initial report of Weder may represent a false-positive result. Unless additional studies corroborate that result, claims that increased proximal tubular reabsorption of sodium is a characteristic of the familial predisposition to develop hypertension are unjustified.
Although the present study failed to confirm differences in measures of renal sodium handling between SOHT and SONT, it did identify differences in other traits that have been associated with differences in blood pressure and the risk of developing hypertension. At the screening visit, fasting concentrations of serum glucose and plasma cholesterol were greater in SOHT than in SONT (Table 1); and during the study protocol, the urinary excretion and plasma concentration of noradrenaline were greater in SOHT than in SONT (Table 3; also see Fig 5 of Reference 12). These findings are consistent with previous reports of impaired glucose utilization, dyslipidemia, and increased sympathetic nervous system activity in normotensive offspring of hypertensive parents.21-23

In summary, the results of the present study do not support the hypothesis that renal sodium excretion is impaired or that tubular reabsorption of sodium is increased in normotensive white men with a familial predisposition to develop essential hypertension.

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