Renal Vascular Response to Sodium Loading in Sons of Hypertensive Parents

S.C. Textor and S.T. Turner

Studies of normotensive offspring of hypertensive parents offer the potential to identify inherited abnormalities that contribute to essential hypertension. We compared renal and systemic hemodynamic responses to saline infusion between normotensive sons of two hypertensive parents (SOHT) and sons of two normotensive parents (SONT) selected from the general population of Rochester, Minn. Hemodynamic measurements were performed after a week of low sodium intake (10 meq/day) and were repeated after a week of high sodium intake (200 meq/day). Despite being in the normotensive range, blood pressures in SOHT were higher than those in SONT during low sodium (124±3/85±3 versus 118±2/71±2 mm Hg, p<0.01) and high sodium (122±3/80±3 versus 112±2/70±2 mm Hg, p<0.05) conditions. Higher pressures in SOHT were associated with elevated systemic and renal vascular resistance. After a high sodium diet, renal vascular resistance in SOHT rose further during acute saline infusion, whereas systemic vascular resistance did not change. After a low sodium diet, this renal vasoconstrictor response to saline infusion in SOHT was not present, and renal vascular resistance fell to levels not different from SONT. Plasma renin activity, aldosterone, and atrial natriuretic peptide did not differ between SONT and SOHT. Circulating levels of norepinephrine were higher in SOHT. These data demonstrate a renal vasoconstrictor response to saline infusion in normotensive SOHT, which depends on prior sodium intake. This alteration in renal hemodynamics may represent an inherited abnormality related to the development of hypertension. (Hypertension 1991;17:982–988)
RENAL HEMODYNAMIC MEASUREMENTS

On the morning of the hemodynamic studies, an oral water load of 15-20 ml/kg was given over 30 minutes. After administration of priming doses of para-aminohippurate (PAH) (100 mg/kg) and inulin (25 mg/kg), 45 minutes was allowed for equilibration during infusion of maintenance doses (15 mg/min PAH and 12.5 mg/min inulin in 2.5% dextrose), which were continued throughout the clearance protocol. Urine was obtained during three timed urinary collection periods of 30 minutes each. Clearance values for each period were calculated, and the average was taken as the mean basal level. Thereafter, 2 L of 0.9% sodium chloride was infused intravenously over 2 hours. Blood and urine samples were collected at 30-minute intervals for determination of clearance markers. Effective renal plasma flow (ERPF) was calculated as the clearance of PAH, [U] / [V] / [P], where [U] and [P] are the urinary and plasma concentrations of PAH, respectively, and [V] is the urinary flow rate expressed as milliliters per minute. Renal blood flow (RBF) was calculated as ERPF / (1 - hematocrit). Plasma samples were obtained before and at the end of each hour during saline infusion for measurement of plasma renin activity, aldosterone, atrial natriuretic peptide, and norepinephrine. Blood pressure was determined by an automated oscillometric recorder (Acutorr, Datascope, Paramus, N.J.) at 5-minute intervals throughout the clearance protocol. Mean arterial pressure (MAP) was determined as diastolic pressure + (systolic - diastolic) / 3. Renal vascular resistance index was calculated as the MAP / RBF indexed for 1.73 m² of body surface area and expressed as dyne/cm/sec².

SYSTEMIC HEMODYNAMIC MEASUREMENTS

Determination of cardiac stroke volume was performed by measurement of thoracic electrical bioimpedance gated during electrical systole using a commercially available unit (NCCOM-3, BoMed Medical Manufacturing, Irvine, Calif.). This instrument uses surface electrocardiographic electrodes applied at the base of the neck and at the base of the thorax. Care was taken to replace the electrodes at the same surface sites for each dietary study period. Average values were obtained for 12 cardiac cycles at midexpiration for heart rate, stroke volume, cardiac output, and thoracic impedance (Z, ohms). Stroke volume was derived from dZ/dt measured during electrical systole using the formula of Kubicek et al with modifications by Skramek et al. Thoracic size was estimated using a nomogram based on body weight, height, and sex; a single value for thoracic dimension was used throughout the study for each patient. Preinfusion values of stroke volume were confirmed by comparison with values obtained by suprasternal Doppler ultrasound (Velcom, Waters Instruments, Inc., Rochester, Minn.). Cardiac output was displayed as heart rate x stroke volume. Hemodynamic values were indexed for body surface area. Systemic vascular resistance was calculated by standard formulas.

ANALYTICAL METHODS AND HORMONAL ASSAYS

Inulin and PAH were determined by colorimetric assays as described previously. Urine and plasma electrolytes were measured by flame photometry. Plasma renin activity, aldosterone, and atrial natriuretic peptide were measured by radioimmunoassay as described previously. Plasma norepinephrine was measured by high-performance liquid chromatography. Urinary thromboxane B₂ and 6-ketoprostaglandin F₁α were determined by sensitive radioimmunoassay after column extraction of 24-hour urine samples on each dietary intake.

STATISTICAL METHODS

Results are expressed as mean±SEM. Differences between patient groups were made by nonpaired t tests or Mann-Whitney tests for parametric or nonparametric comparisons as appropriate. Changes in parameters during saline infusion and between dietary periods were evaluated by repeated measures analysis of variance. Individual differences then were tested using the Bonferroni correction or Dunnett's multiple range test.

RESULTS

The mean age of SONT was 41.4±1.2 years, and the mean age of SOHT was 46.7±1.7 years (p<0.05). Body weight of SOHT was slightly higher than that of SONT (Table 1). Prestudy laboratory values, includ-
TABLE 1. Body Weight and Sodium, Potassium, and Prostaglandin Excretion at the End of Low and High Sodium Balance Periods

<table>
<thead>
<tr>
<th></th>
<th>Low sodium diet</th>
<th>High sodium diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body wt (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SONT</td>
<td>85.9±4.6</td>
<td>86.0±4.4</td>
</tr>
<tr>
<td>SOHT</td>
<td>92.1±4.8*</td>
<td>92.1±4.7*</td>
</tr>
<tr>
<td>24° U\textsubscript{Na}V (meq/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SONT</td>
<td>13±2</td>
<td>193±8</td>
</tr>
<tr>
<td>SOHT</td>
<td>13±2</td>
<td>193±5</td>
</tr>
<tr>
<td>24° U\textsubscript{K}V (meq/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SONT</td>
<td>93±5</td>
<td>94±6</td>
</tr>
<tr>
<td>SOHT</td>
<td>94±5</td>
<td>95±4</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SONT</td>
<td>123±4</td>
<td>120±3</td>
</tr>
<tr>
<td>SOHT</td>
<td>125±4</td>
<td>129±4</td>
</tr>
<tr>
<td>Urinary 6-keto (ng/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SONT</td>
<td>2,635±329</td>
<td>2,302±309</td>
</tr>
<tr>
<td>SOHT</td>
<td>3,217±684</td>
<td>2,178±193</td>
</tr>
<tr>
<td>Urinary TXB\textsubscript{2} (ng/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SONT</td>
<td>754±114</td>
<td>909±152</td>
</tr>
<tr>
<td>SOHT</td>
<td>927±174</td>
<td>1,421±270</td>
</tr>
</tbody>
</table>

Values are mean±SEM. SONT, sons of normotensive parents (n=11); SOHT, sons of hypertensive parents (n=11); U\textsubscript{Na}V, urinary sodium excretion; U\textsubscript{K}V, urinary potassium excretion; GFR, glomerular filtration rate; 6-keto, 6-ketoprostaglandin F\textsubscript{1α}; TXB\textsubscript{2}, thromboxane B\textsubscript{2}. *p<0.05, SONT vs. SOHT.

...ing hematocrit, calcium, electrolytes, and creatinine, did not differ between groups. Both groups reached sodium balance on the respective diets by the day of hemodynamic measurements. As summarized in Table 1, urinary excretion of 6-ketoprostaglandin F\textsubscript{1α} (the stable urinary metabolite of prostacyclin) and thromboxane B\textsubscript{2} (the stable urinary metabolite of thromboxane A\textsubscript{2}) were not different between the two groups.

Systemic and renal hemodynamic measurements obtained during the infusion studies at the end of each period of dietary sodium intake are summarized in Figures 1–4. Arterial pressure and systemic hemodynamic measurements before and during saline infusion are shown in Figures 1 and 2. Although all subjects were normotensive (<140/90 mm Hg during screening clinic visits), SOHT had consistently higher preinfusion pressures under both low and high sodium diet conditions (124±3/85±3 versus 118±2/71±2 mm Hg, p<0.01, low sodium diet; 122±3/80±3 versus 112±2/70±2 mm Hg, p<0.05, high sodium diet). Only minor changes in arterial pressure were evident between diets in each group, although SONT systolic pressures fell after adaptation to a high sodium diet (118±2 to 112±2 mm Hg, p<0.05).

Blood pressure rose during saline loading in SOHT after the high sodium diet (123±3/80±4 versus 128±4/85±3 mm Hg, p<0.01).

Bioimpedance-derived measurements of cardiac output did not differ between SONT and SOHT at baseline under low sodium conditions (Figure 2). After high sodium intake, SONT had slightly higher cardiac output than SOHT (6.9±0.4 versus 5.4±0.3 l/min, p<0.05). During saline infusion, cardiac outputs tended to rise in both groups. This increase was statistically significant after high prior sodium intake (Figure 2).

Based on these differences in blood pressure and cardiac output, calculated systemic resistance index was therefore elevated in SOHT under basal low sodium conditions (2,825±245 versus 2,171±170 dyne/cm/sec\textsuperscript{5}, p<0.05). This difference persisted under both diets and throughout saline infusions. SONT developed a fall in systemic resistance during saline infusion, whereas SOHT did not.

RBF and renal vascular resistance index are summarized in Figure 3. Preinfusion RBF of SOHT was slightly lower than SONT after low sodium intake (1,044±35 versus 1,144±40 ml/min/1.73 m\textsuperscript{2}, p=0.07) but rose to levels not different from SONT during acute saline infusion. After high dietary sodium intake, preinfusion levels of blood flow in SOHT rose above the low sodium period (1,044±35 versus

![Fig. 1](http://hyper.ahajournals.org/)
Low sodium diet  

High sodium diet  

Mean ± SEM

*P<0.01 SONT vs. SOHT

**P<0.05

Before Hr 1 Hr 2

Sodium and Renal Resistance in Prehypertension

1,146±48 ml/min/1.73 m², p<0.01), which was not different from SONT. Renal vascular resistance was higher in SOHT than SONT after both diets. During saline loading after a low sodium diet, renal resistance in SOHT fell to levels not different from those of SONT. By contrast, during saline loading after high prior sodium intake, renal vascular resistance of SOHT rose above baseline levels and well above those of SONT (6,167±528 versus 4,810±316 dyne/cm/sec², p<0.05).

These changes in renal vascular resistance from baseline during saline loading are summarized in Figure 4. SONT had a decrement in renal resistance during saline loading under both dietary conditions. SOHT had markedly different responses depending on the prior sodium intake. Saline loading after a high prior sodium intake induced a rise in renal vascular resistance. This renal response during saline loading was not present after the period of low sodium intake. Hence, the renal vascular response in SOHT depended on the conditions of prior sodium intake. Moreover, the renal response was different from changes in systemic vascular resistance under the same conditions (Figure 2).

Measurements of plasma renin activity, aldosterone, atrial natriuretic peptide, and glomerular filtration rate before and during acute saline infusion are summarized in Table 2. Preinfusion levels of renin and aldosterone fell in both SONT and SOHT after the change from low to high sodium intake. These hormones also fell during saline infusion under low sodium conditions. Although preinfusion levels of atrial natriuretic peptide were similar after both dietary periods, saline infusion after high sodium intake produced a greater rise in atrial natriuretic peptide than after the low sodium diet. Levels of these hormones did not differ between SONT and SOHT during this study. Glomerular filtration rates and sodium excretion during acute saline infusion did not differ between groups of subjects.

In contrast, levels of circulating plasma norepinephrine were higher in SOHT than in SONT at every time point (Figure 5). These differences were largest during high dietary intake but did not change during saline infusion.
Discussion

The results of the present study demonstrate that hemodynamic differences between SOHT and SONT are established before clinical hypertension is manifest. Both total systemic vascular resistance and regional resistance within the kidney were elevated in SOHT. Hence, the small differences in arterial pressure between groups appeared to be mediated by a diffuse increase in vascular tone at this early stage.

Moreover, after a period of high sodium intake, a renal vasoconstrictor response during acute saline infusion in SOHT developed within the kidney but not within the total circulation. Already elevated levels of renal vascular resistance rose further. This renal vasoconstrictor response was no longer present when saline was infused after a period of low sodium intake. Under those conditions, renal vascular resistance fell to levels not different from those of SONT (Figures 3 and 4).

Several previous studies have focused on alterations in the renal circulation in offspring of patients with essential hypertension. Measurements in borderline hypertensive or normotensive offspring of hypertensives have produced widely varied results. Such individuals may have normal or elevated levels of blood flow. Despite normal levels of blood flow, several studies have suggested that renal vascular tone and vasodilation are modulated differently in relatives of hypertensives in response to calcium channel blockade with nifedipine or diltiazem. Another study from Japan demonstrated progressively increased renal vascular resistance in adolescent subjects with differing familial predisposition to hypertension that could be reversed after administration of captopril. Taken together, most of these data suggest that changes in the renal vasculature appear early in those subjects predisposed to elevated blood pressure.

These reports are difficult to compare directly to the present study, because selection of patients, dietary conditions, and protocols differed. Some studies cited above have used patients from hypertension referral clinics or potential kidney transplant donors, which may be subject to important selection bias.

Nevertheless, the present data confirm observations that abnormalities in renal vascular tone are
Although blood pressures in SOHT were not present in SOHT before the onset of clinical hypertension. They further suggest that renal vasoconstriction in response to saline infusion may represent an inherited abnormality related to the development of hypertension. Expression of this abnormality appears to be conditioned by prior dietary sodium intake. Although blood pressures in SOHT were not changed by shifting to a high sodium intake in this study, this transition in the renal circulation may contribute to “salt sensitivity” noted in some essential hypertensive patients at a later stage in the evolution of this disorder.

The precise mechanisms responsible for the rise in renal vascular resistance during saline infusion in SOHT cannot be established with the present data. Circulating levels of plasma renin activity, aldosterone, and atrial natriuretic factor did not differ between groups, nor did the urinary excretion of the eicosanoid metabolites 6-ketoprostaglandin F1α and thromboxane B2. The most consistent difference between SONT and SOHT throughout these studies was the elevation in plasma norepinephrine levels. Similar differences have been observed repeatedly in subjects with borderline and established essential hypertension. It is possible that enhanced adrenergic outflow, both to the kidneys and other regions of the vasculature, mediates the general rise in peripheral resistance and reactivity to exogenous stimuli, such as saline loading, may reflect secondary alterations due to the increased pressure itself. Perhaps such changes are early manifestations of altered baroreflexes. Such an argument would not explain, however, the change in renal response to saline loading between low and high sodium diets, as no change in arterial pressure occurred in the SOHT. Other studies of younger subjects have identified changes within the renal circulation despite similar average pressures. Hence, we believe it is unlikely that these represent only secondary changes to the level of blood pressure.

Taken together, these results suggest that differences in renal and systemic vasomotor tone are present in SOHT and SONT from the general Caucasian population. The regulation of renal vasoconstriction during acute saline loading appears to depend profoundly on the prior sodium intake. This may be one instance in which the manifestations of familial predisposition to hypertension are subject to modification by dietary sodium, an environmental factor long suspected to play a role in essential hypertension.

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References


7. Skramek BB, Rose DM, Miyamoto A: Stroke volume equation with a linear base impedance and its accuracy, as compared to thermodilution and electromagnetic flow meter techniques in animals and humans (abstract). *Proc Sixth Int Conf Electrical Bioimpedance* 1983;1:38


**KEY WORDS** • sodium • kidney • renal circulation • genetics • renin-angiotensin system • atrial natriuretic peptides • catecholamines • essential hypertension
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