Renal and Endocrine Response to Saline Infusion in Essential Hypertension

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SUMMARY To assess the contribution of the renin-angiotensin-aldosterone system and renal hemodynamics to acute renal sodium handling in essential hypertension we studied 21 subjects who had essential hypertension (16 with normal renin, 5 with low renin) and 9 normal subjects. All were in balance on a 10 mEq sodium intake before receiving a small sodium load, 60 mEq intravenously over 1 hour. Hypertensive subjects with low renin showed the anticipated exaggerated natriuresis, which was transient and occurred without a rise in blood pressure. Natriuresis in hypertensive subjects with normal renin was either normal or blunted; delayed sodium excretion occurred in a subset, along with delayed suppression of the renin-angiotensin-aldosterone system by the saline load. Neither renal plasma flow nor glomerular filtration rate changed during the saline load. After 72 hours of converting enzyme inhibition with enalapril, renal plasma flow increased substantially more in the subjects with a blunted renin response and their natriuretic response to the sodium load returned to normal. These results indicate that when prior sodium intake is controlled, large sodium loads are avoided, and low renin hypertension is removed as a confounding variable, blunted rather than exaggerated natriuresis is the common feature of essential hypertension. This abnormality is reversed by angiotensin converting enzyme inhibition, perhaps because of converting enzyme inhibition-induced renal vasodilatation. (Hypertension 8: 217-222, 1986)

KEY WORDS • natriuresis • renal blood flow • converting enzyme inhibition

FEW phenomena have been more widely documented in hypertension than the exaggerated natriuresis that follows an acute saline load.1-3 Equally well documented has been the sensitivity of hypertension to sodium intake.4 3 It has been difficult to reconcile the two phenomena — accelerated sodium excretion and sensitivity of the hypertension to sodium intake — in a single pathogenetic sequence, in which sodium is responsible for the hypertension. Without exception, however, the acute sodium load employed in earlier studies has been very large, and with few exceptions, the state of sodium balance before administration of the sodium load was uncontrolled. One goal of this study was to assess the rate of sodium excretion after a much more physiological sodium load, 60 mEq, or about the quantity of sodium in a typical meal, in subjects whose sodium balance was controlled before administration of the sodium load.

In response to a large sodium load, suppression of the renin-angiotensin-aldosterone system is delayed in some subjects with normal renin and essential hypertension.6 These subjects also have disordered angiotensin-mediated control of renal perfusion and aldosterone release with shifts in sodium balance.7 A second goal of this study was to examine the response of the renin system to a much smaller sodium load and to relate the magnitude of renin suppression to the rate of sodium excretion following the sodium load. Our working premise was that sodium excretion must reflect, at least in part, the state and responsiveness of the renin-angiotensin-aldosterone system and the renal blood supply.

Because earlier studies have shown especially pronounced exaggerated natriuresis in subjects with low renin essential hypertension,8-10 we included a subgroup in this category as a positive control to assess the capacity of a low dose saline infusion to identify exaggerated natriuresis.

Our findings in the first phase of this study linked a reduction in the rate of sodium excretion with a striking delay in the suppression of the renin-angiotensin-aldosterone system in about half of the hypertensive
subjects. Among possible mechanisms to account for this blunted renin suppression and sodium excretion in the same subject is excessive intrarenal angiotensin II (ANG II) concentrations, a possibility that has also been raised in similar patients by other lines of investigation. For that reason, in a second phase of this study the response to a sodium load was reassessed after treatment with the converting enzyme inhibitor enalapril.

Subjects and Methods

Twenty-one subjects with hypertension (age range, 23–67 years) and nine normotensive subjects (age range, 24–46 years) were studied in the Clinical Research Center at the Brigham and Women’s Hospital. The protocol was approved by the Human Subjects Committee of the Brigham and Women’s Hospital. Written informed consent for the procedures was obtained from all subjects after a full description of the protocol. Each hypertensive subject had an outpatient diagnostic blood pressure measurement in excess of 90 mm Hg on at least three occasions documented for at least 3 months before the study. Secondary hypertension was ruled out by a detailed evaluation.

All antihypertensive medications were discontinued for at least 2 weeks before the study. Subjects were fed constant, isocaloric diets containing 10 mEq of sodium and 100 mEq of potassium during their hospitalization. Fluid intake was maintained at 2500 ml/day. Daily 24-hour urine collections were analyzed for sodium, potassium, and creatinine. Each study was begun at 0800 after the subjects had been fasting and recumbent for at least 8 hours.

Renin Profile

Five subjects with low renin hypertension were identified on the basis of a plasma renin activity (PRA) response to upright posture on a 10 mEq sodium intake that was less than 2.4 ng of angiotensin I per milliliter per hour. The remaining 16 hypertensive subjects had normal renin, defined as an increase in PRA in response to upright posture that was between 2.5 and 15 ng of angiotensin I per milliliter per hour. Our working premise in this study was that suppression of the renin-angiotensin-aldosterone system in response to the small saline load would resemble that documented earlier for a larger saline load, revealing two groups, one similar to the normotensive subjects and the other showing minimal or no suppression with saline infusion. For purposes of presentation we have defined “nonresponders” as hypertensive subjects in whom PRA failed to fall by more than 20% in the 2 hours following the initiation of the saline infusion.

p-Aminohippurate and Inulin Infusion

Renal plasma flow was assessed after metabolic balance had been achieved on the sodium-restricted intake, as previously described. In brief, intravenous catheters were placed in each arm, one for infusion and the other for blood sampling. A control blood sample was obtained, and a loading dose of p-aminohippurate (PAH), 8 mg/kg, and inulin, 50 mg/kg, then was given. A constant infusion of PAH (12 mg/min) and inulin (30 mg/min) was begun immediately with an IMED pump (San Diego, CA, USA). This infusion rate achieved a plasma PAH concentration in the middle of the range in which tubular secretion dominates excretion. At this level, PAH clearance is independent of plasma concentration and represents about 90% of renal plasma flow. Inulin and PAH clearances were calculated from the plasma concentration and the infusion rate and corrected for body surface area. Plasma samples were obtained 45 and 60 minutes after the start of the constant infusion when a steady state was achieved, and the mean values were used for presentation.

Saline Infusion

On the morning of saline infusion, the subjects were asked to void at 0700 to complete the previous 24-hour collection. At 0800 the subjects received a loading dose of PAH and inulin. They also ingested distilled water, 5 ml/kg body weight, over 30 minutes to maintain a brisk urine flow. After basal PAH and inulin clearance was measured, a 0.45% saline infusion was started and 500 ml was administered over 1 hour using an IMED pump. Thus, the total sodium infused from the saline and PAH was 60 mEq. At -15, 0, 60, and 120 minutes blood samples were drawn for measurement of PRA, ANG II, aldosterone, cortisol, sodium, potassium, inulin, and PAH. Before the saline infusion was begun, subjects were asked to void. Spontaneously voided urines were collected thereafter for 9 hours, and the urine voided plus 40 ml/hr for insensible loss was replaced with distilled water by mouth; maximal replacement was 400 ml/hr. Fractional sodium excretion was calculated from the serum sodium concentration, the inulin clearance, and the rate of sodium excretion as the percentage of filtered load that was excreted.

Converting Enzyme Inhibition

The 16 subjects with normal renin essential hypertension then received enalapril (MK 421) in escalating daily doses of 2.5, 5.0, 10.0, and 20.0 mg on consecutive mornings for a total of 72 hours. At 0800, 72 hours after the control saline infusion, the last dose of enalapril was administered; 2 hours later, a PAH-inulin infusion was instituted, as described previously. After baseline measurements of PAH and inulin clearance, the saline infusion was repeated for 1 hour, precisely as already described.

Laboratory Procedures

All blood samples were collected on ice and spun immediately, and the plasma was separated and frozen until the time of assay. Serum and urine sodium and potassium levels were measured by flame photometry using lithium as an internal standard. Serum creatinine was measured by an autoanalyzer technique. Aldosterone, cortisol, ANG II, and PRA were assayed by radioimmunoassay techniques that have been pre-
viously described.13,16 The ANG II levels in charcoal stripped plasma are less than the sensitivity of the assay (7 pg/ml).

Plasma PAH and inulin concentrations were measured by a Technicon autoanalyzer (Tarrytown, NY, USA) spectrophotometric technique. The absolute average difference in paired PAH measurements of a single sample on the Technicon autoanalyzer on the same run is less than 1%. The internal standards vary by 1% or less on different days.

Analysis of Data

Group means have been presented with the standard error of the mean (SEM) as the index of dispersion. Statistical probability, where appropriate, was assessed by analysis of variance and with the t test for normally distributed data or the Fisher exact or Wilcoxon signed rank test for nonhomogeneously distributed data. Differences are significant at a p level of less than 0.05 unless otherwise stated. Missing data points were estimated by linear regression.

Results

Renin and Aldosterone Suppression After Saline Infusion

In the normal subjects both PRA (p < 0.02) and plasma aldosterone concentration (p < 0.02) had fallen within 60 minutes after initiating the saline infusion, and little further change occurred in the second hour (Figure 1). As a group, the subjects with normal renin essential hypertension, showed a blunted response in both indices (p < 0.01). Indeed, plasma aldosterone concentration did not fall significantly in this group until 1 hour after cessation of the saline infusion (see Figure 1).

As anticipated, the fall in PRA was compatible with a bimodal distribution (Figure 2).6 An appropriate response, essentially identical to that seen in the normal subjects, occurred in nine of the 16 subjects with normal renin essential hypertension (responders). The response was clearly blunted in the other seven subjects (nonresponders), with an indication of a secondary mode (see Figure 2). The PRA of three of these seven subjects was within 5% of baseline, which is probably within the reproducibility of the method. The nine subjects who responded appropriately to saline and the seven nonresponders did not differ in any baseline clinical, biochemical, or physiological indices (Tables 1-3).

Natriuresis After Saline Infusion

Following saline infusion, all subjects had a prompt and sustained increase in sodium excretion (Figure 3). In the normal subjects, sodium excretion had doubled by the end of the infusion (17.7 ± 1.7 vs 40.9 ± 8.7

![Figure 1. Change in plasma renin activity and plasma aldosterone concentration in nine normal subjects and 16 subjects with normal renin essential hypertension following the administration of 60 mEq of sodium intravenously. Values are means ± SEM.](image)

![Figure 2. Frequency distribution of the fall in plasma renin activity (PRA) in nine normal subjects (inset) and in 16 subjects with normal renin essential hypertension.](image)

| TABLE 1. Characteristics of Responding and Nonresponding Patients with Normal Renin Essential Hypertension |
|---------------------------------------------------------------|------------------|------------------|
| Indices                                                      | Responders      | Nonresponders   |
| No. of subjects                                              | 9               | 7                |
| Sex (M/F)                                                   | 6:3             | 7:0              |
| Age (yr)                                                    | 40±5            | 47±5             |
| Duration of hypertension (yr)                               | 6±1             | 9±3              |
| Admission systolic BP (mm Hg)                               | 142±6           | 148±8            |
| Admission diastolic BP (mm Hg)                              | 95±5            | 95±5             |
| Admission serum creatinine (mg/dl)                          | 1.13±0.09       | 1.06±0.02        |
| Admission 12-hr urinary Na\(^+\) excretion (mEq)             | 44.5±13         | 34.6±11          |
| Admission 12-hr urinary K\(^+\) excretion (mEq)              | 23±3            | 19±3             |

Values are means ± SEM. BP = blood pressure.
excreted sodium at a rate that exceeded that of any of the normal subjects. The rate of sodium excretion was essentially identical to that found in the normal subjects by the third hour.

The subjects with normal renin essential hypertension showed a delay in sodium excretion after the sodium load, rather than exaggerated natriuresis (p < 0.001; see Figure 3). Because inulin clearance and serum sodium concentration were essentially identical in all of the groups studied and did not change during the sodium load, calculated fractional sodium excretion showed identical intergroup differences.

The normal subjects excreted 24 ± 4 mEq in the first 9 hours and 40 ± 5 mEq of sodium in the 24 hours following the saline infusion (see Table 3). The responders excreted an essentially identical 22 ± 5 and 40 ± 7 mEq of sodium in these two intervals, while the nonresponders excreted significantly less sodium in the first 9 hours: 12 ± 2 mEq (p < 0.03; see Table 3). Indeed, the blunted natriuretic response was evident from the initiation of the saline infusion (Figure 4).

Renal plasma flow and glomerular filtration rate did not change in response to the saline infusion in the normal subjects or in any of the hypertensive subgroups (see Table 3). Arterial blood pressure also did not change during or after the saline load.

**Responses to Converting Enzyme Inhibition**

After 72 hours of converting enzyme inhibition, sodium excretion induced by the saline load was not modified in the responders; however, the nonresponders showed a significant increase in sodium excretion following the saline load, to 26 ± 7 mEq/9 hr which was virtually identical to that in the normotensive subjects and the responders (p < 0.05; Figure 5). Although basal blood pressure and sodium and potassium excretion before the saline load did not differ in the two subgroups of hypertensive subjects, renal plas-
TABLE 4. Baseline Data 24 Hours Before Saline Infusion After 72 Hours of Enalapril in Responders and Nonresponders with Normal Renin Essential Hypertension

<table>
<thead>
<tr>
<th>Indices</th>
<th>Responders</th>
<th>Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hr urinary Na⁺ excretion (mEq)</td>
<td>22.0 ± 3</td>
<td>20.0 ± 3</td>
</tr>
<tr>
<td>24-hr urinary K⁺ excretion (mEq)</td>
<td>77 ± 4</td>
<td>78 ± 4</td>
</tr>
<tr>
<td>Serum Na⁺ (mEq/L)</td>
<td>136 ± 1</td>
<td>137 ± 1</td>
</tr>
<tr>
<td>Serum K⁺ (mEq/L)</td>
<td>4.3 ± 0.1</td>
<td>4.2 ± 0.1</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>79.3 ± 3.8</td>
<td>83.7 ± 3.8</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>117 ± 4*</td>
<td>114 ± 3</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>78 ± 3*</td>
<td>72 ± 3</td>
</tr>
<tr>
<td>Basal PAH clearance (ml/min/1.73 m²)</td>
<td>581 ± 41</td>
<td>709 ± 20**†</td>
</tr>
<tr>
<td>Basal inulin clearance (ml/min/1.73 m²)</td>
<td>107 ± 8.1</td>
<td>109 ± 7.1</td>
</tr>
<tr>
<td>Basal supine PRA (ng ANG I/ml/hr)</td>
<td>18.1 ± 6*</td>
<td>11.7 ± 3*</td>
</tr>
<tr>
<td>Basal supine plasma ANG II (pg/ml)</td>
<td>28 ± 2</td>
<td>26 ± 3</td>
</tr>
<tr>
<td>Basal supine aldosterone (ng/dl)</td>
<td>14 ± 3*</td>
<td>13 ± 3*</td>
</tr>
<tr>
<td>Basal supine cortisol (µg/dl)</td>
<td>11 ± 2</td>
<td>13 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SEM. BP = blood pressure; PAH = p-aminohippurate; PRA = plasma renin activity; ANG = angiotensin.

*p < 0.05, compared with values before converting enzyme inhibition; †p < 0.05, compared with values in responders.

sodium load, did not occur in any subject with normal renin essential hypertension in this study. Indeed, the opposite occurred in a subset of these subjects. Our methods were not too insensitive to identify the phenomenon, as the anticipated early exaggerated natriuresis occurred in the subjects with low renin essential hypertension.

Several alternative explanations exist for the difference between our results and earlier reports. The earlier studies often were performed in severely hypertensive subjects, and the exaggerated natriuresis could have reflected a pressure diuresis. Indeed, a correlation was reported between the blood pressure level and the natriuretic response. Earlier studies employed a very large sodium load, sufficient to have been acutely pressor, that increased the influence of the pressure diuresis. Moreover, the state of prior sodium intake influences the rate of sodium excretion following an acute load; sodium intake, often uncontrolled in earlier studies, was controlled and low in this trial. Finally, many of the earlier studies, often performed in older or black subjects, failed to exclude low renin hypertension. We have confirmed and extended observations on exaggerated natriuresis in these subjects; transient accelerated natriuresis occurred in response to a small sodium load in this study without a parallel pressor response.

Renal hemodynamics, another determinant of renal sodium excretion, did not change in response to the acute sodium load in any subject. The time required for renal blood flow to increase after a sodium load is long (often involving many hours), substantially longer than that required for a fall in PRA and plasma aldosterone.

Discussion

Exaggerated natriuresis, which is defined as a supranormal rate of sodium excretion following an acute sodium load, did not occur in any subject with normal renin essential hypertension in this study. Indeed, the opposite occurred in a subset of these subjects. Our methods were not too insensitive to identify the phenomenon, as the anticipated early exaggerated natriuresis occurred in the subjects with low renin essential hypertension.

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sterone concentration. Multiple lines of evidence have suggested that ANG II is the major determinant of renal blood flow with shifts in the state of sodium balance. In that context, the delay in the renal vascular response to an acute saline load raises the intriguing possibility that there is differential control of renin release and intrarenal ANG II formation, a possibility suggested by other lines of investigation.

The influence of converting enzyme inhibition makes it clear that the blunted sodium excretion in the nonresponders did not reflect a fixed organic renal lesion. Within 72 hours of initiating enalapril administration the kidney's capacity to handle an acute sodium load in the nonresponders returned precisely to normal and was accompanied by a substantially larger increase in renal plasma flow. The increase in renal blood flow could have contributed to the increased acute natriuresis following the sodium load. Certainly, compelling evidence supports a role for renal hemodynamics in normal renal sodium handling.

We and others have shown that suppression of renin release in response to multiple maneuvers, including sodium load and ANG II infusion, is abnormal in some subjects with essential hypertension. Blunted suppression occurs, at least in some subjects, for both maneuvers. Converting enzyme inhibition was shown in an earlier study to correct the abnormality in ANG II–mediated suppression of renin release. That observation also raised the intriguing possibility that inappropriate intrarenal concentrations of ANG II contributed to the sluggish response of renin release to increments in plasma ANG II concentration created by an infusion. This study has brought together hitherto unrelated lines of investigation. Because constraints imposed by the volume of blood required for sampling made it impossible to infuse ANG II in this study, we cannot be certain that the nonresponders were "nonmodulators"; the nonresponders in this study, however, shared a number of features with the nonmodulators, including delayed suppression of plasma renin with a sodium load, an inability to handle a sodium load normally, a larger increase in renal plasma flow with converting enzyme inhibition, and a smaller increase in PRA following converting enzyme inhibition. The action of converting enzyme inhibition, facilitating renal sodium handling in these subjects, suggests an abnormality in the control of intrarenal ANG II concentration underlying their altered sodium handling and, perhaps, renin release. Such an abnormality obviously could contribute to the pathogenesis of hypertension and may account for part of the salutary action of converting enzyme inhibitors.

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