Altered Adrenal Sensitivity to Angiotensin II in Low-Renin Essential Hypertension

Naomi D.L. Fisher, Shelley Hurwitz, Claudio Ferri, Xavier Jeunemaitre, Norman K. Hollenberg, Gordon H. Williams

Abstract—Low-renin essential hypertension (LREH) describes a widely recognized classification validated by clinical features, including salt-sensitive blood pressure and diuretic responsiveness. Classic physiological teaching has cited normal plasma aldosterone concentration despite suppressed renin as evidence for adrenal supersensitivity to angiotensin II (Ang II). We studied 94 patients with LREH, 242 normal-renin hypertensives, and 135 normal subjects as controls. Low-renin hypertensives did not differ significantly from the other groups in either basal or Ang II–stimulated aldosterone concentrations on a high-sodium diet. Stimulated with a low-sodium diet, LREH patients demonstrated the smallest rise in basal aldosterone secretion. Ang II responsiveness was also subnormal: the rise in aldosterone after Ang II infusion in LREH (613±39 pmol/L), although greater than in nonmodulators (180±17 pmol/L; P=0.001), was less than either the patients with intact modulation (940±53 pmol/L; P=0.001) or normotensives (804±50 pmol/L; P<0.05). Blacks with LREH demonstrated an even lower response than low-renin whites ((388±50 versus 610±47 pmol/L; P=0.0001). In contrast, the rise in systolic blood pressure with Ang II infusion on a low-salt diet was greatest among LREH patients (P=0.001). Patients with LREH and nonmodulators were equally salt-sensitive. These results indicate that the adrenal response in LREH is normal on a high-salt diet but becomes progressively more abnormal as sodium control mechanisms are stressed. The factors that mediate enhanced adrenal response to Ang II with sodium restriction may be defective, suggesting the existence of alternative physiological mechanisms for sodium homeostasis in the low-renin state. (Hypertension. 1999;34:388-394.)

Key Words: renin ■ sodium ■ angiotensin II ■ aldosterone ■ posture ■ blacks

The term “low-renin essential hypertension” (LREH) describes a widely recognized subset of patients with essential hypertension, characterized by clinical features that support a specific biological and pathophysiological influence of the low-renin state. Low-renin patients are more likely to have hypertension that is salt-sensitive and are more likely to respond to diuretics than to agents that block the renin system. LREH has been found with higher frequency among black and elderly hypertensives. In addition, some data suggest that renin status influences natural history.1

Far less is known about the determinants of sodium homeostasis in this patient population. Among the important roles played by the renin-angiotensin system is control of adrenal aldosterone release. Sodium intake modifies adrenal responsiveness to angiotensin II (Ang II). Aldosterone release is maintained at a low level when subjects consume diets high in sodium but is significantly enhanced on a restricted sodium intake, thus augmenting ultimate sodium retention. We had been led to believe that LREH patients maintain normal basal plasma levels of aldosterone in the face of a suppressed renin system via excessive responsiveness to Ang II, at least on an ad libitum sodium intake. Early studies favored this thesis,2–6 with some suggestion of heterogeneity of response,7 although each included only small numbers of patients.

In an earlier study on regulation of aldosterone secretion in hypertensives analyzed by race and not by renin status, we made an unanticipated observation.8 Adrenal sensitivity to Ang II in low-renin hypertensives, both black and white, showed the same blunting of adrenal responsiveness compared with normal subjects and with normal-renin hypertensives. That study focused on measurements performed when the patients were in balance on a restricted sodium intake, and the low-renin sample size was small. The present study was undertaken to resolve these differences by examining several possible hypotheses, each related to a change in the normal relationship between sodium intake and aldosterone response to Ang II. The first hypothesis predicts that the entire relationship between adrenal responsiveness and concentration of Ang II is shifted upward in LREH, rendering these patients hyperresponsive on both high- and low-salt intakes. However, our earlier study refuted this possibility. The second hypothesis is that sodium intake has very little

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influence on adrenal responsiveness to Ang II in LREH, with responsiveness fixed at a level that translates into a state of normal or high responsiveness in a high-salt state but suppressed responsiveness on a low-salt diet. In addition, the LREH population may be heterogeneous in its response. We tested the hypothesis that shifts in sodium intake, already known to influence adrenal responsiveness, would explain some of the heterogeneity that has been described by examining adrenal responsiveness to changes in sodium intake and to Ang II infusion in a large group of white and black patients with LREH.

Methods

We studied 94 low-renin hypertensive patients (64 men). Thirteen of the patients were black (14%), the remainder white. Race was determined by self-identification and supported by physical appearance. Two hundred forty-two normal-renin hypertensives and 135 normotensive subjects who underwent the same protocol served as the comparison group.

Patients were studied at 3 collaborating centers: Boston, Massachusetts; Rome, Italy; and Paris, France. Similar protocols were approved by the Human Subjects Committees at each site, and informed written consent was obtained from each subject. All subjects were free of cardiovascular and overt renal disease, except for blood pressure elevation in the hypertensive subjects, whose untreated seated blood pressures were >90 mm Hg diastolic and 140 mm Hg systolic, measured manually with a standard mercury sphygmomanometer on ≥2 visits. All subjects were screened with a physical examination; laboratory tests, including serum electrolytes, liver function tests, and complete blood count; and ECG. Subjects with known or suspected secondary hypertension or with renal insufficiency (creatinine clearance <70 mL/min) were excluded from the study. All antihypertensive medications were discontinued at least 2 weeks before study. Diabetes mellitus type II was diagnosed either by fasting blood glucose >140 mg/dL or because of ongoing treatment with insulin or oral hypoglycemic agents.

Protocols

On admission to the metabolic ward, each subject was placed on a constant isocaloric diet including 10 mmol sodium and 100 mmol potassium, with 2000 mL/d water. Some subjects began their low-sodium diet as outpatients. From the time of admission, daily 24-hour urine collections were obtained for measurement of sodium, potassium, and creatinine. After 5 to 7 days, when external sodium balance had been achieved (urinary sodium equaling dietary sodium), upright posture studies and Ang II infusions were performed on separate days. Hormonal responses to a postural stimulus were assessed in each subject after 1 or 2 hours in the standing position for the measurement of plasma renin activity (PRA) and plasma aldosterone concentration.

While remaining in low-salt balance, on a separate study day each patient received an infusion of Ang II amide (CIBA-Geigy) at 3 ng·kg⁻¹·min⁻¹ for 40 minutes, delivered by an infusion pump (Baxter Corp). This dose has been found to stimulate aldosterone release with minimal pressor effects. Each study began at 8:00 AM, after the subjects had been fasting and recumbent overnight. During the infusion, blood pressure was monitored every 2 minutes with an indirect recording sphygmomanometer. PRA and aldosterone were measured in all patients at the beginning and end of the Ang II infusion. In a subset of patients, Ang II infusions were also performed after 3 to 4 days of high-salt intake (200 mmol Na+).

Laboratory Procedures

Blood samples were collected on ice and spun immediately, and the plasma was frozen until the time of assay. Serum and urine sodium and potassium levels were measured by flame photometry, with lithium as an internal standard. Serum and urine creatinine were assayed by radioimmunoassay techniques previously described. Sodium-lithium countertransport was measured as the sodium-dependent lithium efflux, as recently described.

Group Definitions

All hypertensive patients were classified by upright-posture PRA value as either low-renin or normal/high-renin. LREH was defined by conventional criteria, with subjects in low-salt balance; PRA was measured after upright posture of 1 to 2 hours’ duration. Normal/high-renin hypertensives were further classified as modulators or nonmodulators (NMs) on the basis of formal analyses that have demonstrated NMs to be a distinct subgroup of essential hypertension. NMs are patients in whom sodium intake fails to modify the responsiveness of the renal vasculature and the adrenal gland to Ang II. Specific abnormalities defined in this subset include failure of sodium loading to increase basal renal blood flow or to enhance the renal vascular response to Ang II and failure of sodium restriction to enhance adrenal responsiveness to Ang II. Normal-renin patients were categorized by their increment in plasma aldosterone after infusion of Ang II in low-salt balance, a parameter shown to fit a bimodal distribution in the general hypertensive population, with modulators having a rise in aldosterone similar to that of normotensive subjects and NMs having a much smaller increase (defined as <416 pmol/L; <15 ng/dL). Some of these patients have been reported in previous publications. Potential subjects who had a second measure of NM assessed, namely the fall in renal plasma flow with Ang II on a high-salt intake, were excluded if the indices were discordant.

Statistical Analyses

Descriptive statistics by group are presented as mean±SEM or as percentage. The 4 study groups were compared by ANCOVA, with age as a covariate. Dunnett’s multiple comparison procedure was used to test the pairwise differences between LREH and each of the 3 other groups. The Dunnett procedure is applicable to this set of 3 a priori nonorthogonal comparisons in which the correlation between each pair of contrasts is 0.5. The experiment-wide probability of incorrectly rejecting the null hypothesis was limited to 0.05. Within subject groups, t tests were used to compare observed subgroups (by race, gender, age, and diabetes). Pearson correlations were used to test associations between continuous variables. The assumptions underlying the statistical tests were satisfied by the raw data, except for the ratio of aldosterone to PRA, for which the natural logarithmic transformation was applied to achieve normality before analysis. Data analyses were performed with the SAS system.

Results

Demographics

Patients with LREH were significantly older than normotensives and modulating hypertensives (P=0.001, Table 1) as well as NMs (P=0.05), with a corresponding later age at diagnosis. There was no discernable difference in body mass index (kg/m²) among the hypertensive groups; the normotensives were lean. The proportion of all female hypertensives with LREH (29%) was similar to that of males (27%). In this study sample, the percentage of hypertensive blacks with LREH was nearly identical to that of whites (29% versus 28%). Blood pressure on admission was comparable among the hypertensives, as were serum creatinine and potassium. Urinary potassium was significantly lower among all groups of hypertensives than among the normal subjects. Twenty-four-hour urinary sodium values, conversely, were significantly higher among the LREH patients than either the modulators (P=0.01) or the normotensives (P=0.001). Diabetics mellitus type II was diagnosed in 20 hypertensives (6%) and in none of the normal subjects. LREH was not more
Adrenal Responses

High-salt Ang II infusions were performed in 29 patients with LREH. Reflecting overall suppression of the renin-angiotensin system, these patients had low concentrations of aldosterone at baseline (166 ± 19 pmol/L; 6.0 ± 0.7 ng/dL), which were essentially identical to those of the other groups (Figure 1). With Ang II stimulation, patients with LREH again had responses that did not differ significantly from any other group [aldosterone increment of 305 ± 58 versus 388 ± 55 pmol/L (10.7 ± 2.1 versus 14.1 ± 2.4 ng/dL) in patients with intact modulation, 194 ± 55 pmol/L (7 ± 2 ng/dL) in NMs, and 250 ± 111 pmol/L (8 ± 4 ng/dL) in normotensives]. However, when the renin-angiotensin system was stimulated with a low-sodium diet, patients with LREH demonstrated the least augmentation of basal aldosterone secretion, with an increment of only 222 ± 28 pmol/L (8 ± 1 ng/dL), compared with 361 ± 55 pmol/L (13 ± 2 ng/dL) in the modulators (P = NS), 472 ± 111 pmol/L (17 ± 4 ng/dL) in the NMs (P < 0.05), and 499 ± 28 pmol/L (18 ± 2 ng/dL) in the normal subjects (P = 0.01). Basal aldosterone concentration on a low-sodium diet was statistically lower among LREH than either modulating hypertensives or normotensives (P = 0.001) but not statistically different from NMs.

Peak adrenal Ang II responsiveness on a low-sodium intake was also low in LREH (Figure 1). As anticipated, the increment in serum aldosterone concentration on a low-salt diet was smallest among the NMs, by definition (180 ± 17 pmol/L; 6.5 ± 0.6 ng/dL). Patients with LREH had a larger response (613 ± 39 pmol/L; 22.1 ± 1.5 ng/dL; P = 0.001), but one significantly lower than that seen in either the modulators (940 ± 53 pmol/L; 33.9 ± 1.9 ng/dL; P = 0.001) or the normo-

![Figure 1. Aldosterone responsiveness to increasing stimulation of the renin-angiotensin system. Left, Patients with LREH did not differ significantly from any other group in either basal or Ang II-stimulated responsiveness on a high-salt diet. All 4 subgroups had similar basal plasma aldosterone on a high-salt diet. Right, On achieving a state of low-salt balance, patients with LREH had the smallest rise in aldosterone. In response to Ang II, the increment in aldosterone concentration among LREH (613 ± 39 pmol/L; 22.1 ± 1.5 ng/dL), although higher than in nonmodulators (180 ± 17 pmol/L; 6.5 ± 0.6 ng/dL), was significantly lower than in either modulators (940 ± 53 pmol/L; 33.9 ± 1.9 ng/dL; P = 0.001) or normotensives (804 ± 50 pmol/L; 29 ± 1.8 ng/dL; P < 0.05).](http://hyper.ahajournals.org/)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Renin</th>
<th>NMs</th>
<th>Modulators</th>
<th>Normals</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>94</td>
<td>112</td>
<td>130</td>
<td>135</td>
</tr>
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<td>Age, y</td>
<td>51 ± 1</td>
<td>47 ± 1.2</td>
<td>41 ± 1.1</td>
<td>33 ± 0.8</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>45 ± 1.2</td>
<td>38 ± 1.5†</td>
<td>36 ± 1.7†</td>
<td>...</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>7.6 ± 0.8</td>
<td>7.5 ± 0.9</td>
<td>8.4 ± 1.4</td>
<td>...</td>
</tr>
<tr>
<td>Women, %</td>
<td>33</td>
<td>20</td>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>Black, %</td>
<td>14</td>
<td>19</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.5 ± 0.5</td>
<td>27.8 ± 0.5</td>
<td>26.9 ± 0.5</td>
<td>23 ± 0.3 §</td>
</tr>
<tr>
<td>LS UNa, mmol/24 h</td>
<td>11.4 ± 0.5</td>
<td>10.1 ± 0.5</td>
<td>8.8 ± 0.5‡</td>
<td>8.1 ± 0.4‡</td>
</tr>
<tr>
<td>LS UK, mmol/24 h</td>
<td>73 ± 5.8</td>
<td>70 ± 2.9</td>
<td>78 ± 2.6</td>
<td>89 ± 2.4†</td>
</tr>
<tr>
<td>Serum K⁺, mmol/L</td>
<td>4.2 ± 0.06</td>
<td>4.2 ± 0.04</td>
<td>4.2 ± 0.03</td>
<td>4.2 ± 0.04</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.2 ± 0.06</td>
<td>1.2 ± 0.04</td>
<td>1.1 ± 0.05</td>
<td>1.1 ± 0.02</td>
</tr>
<tr>
<td>Adm DBP, mm Hg</td>
<td>98 ± 2</td>
<td>100 ± 1.2</td>
<td>98 ± 1.4</td>
<td>72 ± 2†</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>5.3</td>
<td>9.8</td>
<td>3.1</td>
<td>0</td>
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<tr>
<td>NaLi CTT</td>
<td>0.34 ± 0.02</td>
<td>0.41 ± 0.04</td>
<td>0.27 ± 0.02</td>
<td>0.22 ± 0.02†</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; LS, low sodium; UNa, urinary sodium excretion; UK, urinary potassium excretion; Adm DBP, diastolic blood pressure on admission; and NaLi CTT, sodium-lithium countertransport.

*P = 0.05 vs low renin.
†P = 0.01 vs low renin.
‡P = 0.001 vs low renin.

frequent in the small set of diabetics (5 were LREH, 4 modulating, and 11 NM hypertensives). Sodium-lithium countertransport (NaLi CTT) was higher in LREH than in normal subjects.

![Table 1. Demographics](http://hyper.ahajournals.org/)
tensives (804 ± 50 pmol/L; 29 ± 1.8 ng/dL; *P* < 0.05); Figure 1. In response to the stimulus of upright posture, the rise in aldosterone was significantly smaller among both the low-renin patients (644 ± 78 pmol/L; 23.2 ± 2.8 ng/dL) and NMs (752 ± 91 pmol/L; 27.1 ± 3.3 ng/dL) compared with modulators (1576 ± 169 pmol/L; 56.8 ± 6.1 ng/dL; *P* < 0.001) and normotensives (1620 ± 194 pmol/L; 58.4 ± 7 ng/dL; *P* < 0.01) (Figure 2).

For NaLi CTT, the pattern of results is similar to that of aldosterone release. The highest values were found in NMs, followed by LREH patients, whose values were significantly higher than in normal subjects (*P* < 0.01; Table 1).

**Analyses Within LREH Patients**

Adrenal responsiveness was analyzed within the group of LREH patients to explore heterogeneity of responses. Because of our previous reports of a blunted adrenal aldosterone release in hypertensive blacks,8 we analyzed the data within LREH according to race. The analysis was restricted to the Boston and Paris sets, because no blacks were studied in Rome.

For white subjects, in the subset studied in the condition of a suppressed renin-angiotensin system, namely on a high-salt diet, there was no significant difference in either basal or Ang II–stimulated PRA between LREH patients and any other group (Table 2, top). Similarly, black low-renin hypertensives had high-salt PRA values that were very similar to those of NMs and normotensives. Because this is a subset analysis, the observations within certain samples are few (Table 2, bottom). With the stimulation of a low-salt diet, both black and white LREH patients had PRA responses that were significantly smaller than in any other group. The ratio of basal aldosterone to PRA in low-salt balance was higher among LREH than any other group among both whites (*P* < 0.001) and blacks (*P* < 0.01) The PRA response to posture among patients with LREH was no higher than the supine value, in contrast to every other group.

**TABLE 2. Plasma Renin Activity**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Low Renin (n)</th>
<th>Nonmodulators (n)</th>
<th>Modulators (n)</th>
<th>Normals (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High salt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>0.14 ± 0.02 (14)</td>
<td>0.28 ± 0.03 (23)</td>
<td>0.25 ± 0.05 (23)</td>
<td>0.19 ± 0.02 (44)</td>
</tr>
<tr>
<td>Post Ang II</td>
<td>0.14 ± 0.05 (11)</td>
<td>0.33 ± 0.1 (19)</td>
<td>0.22 ± 0.05 (22)</td>
<td>0.17 ± 0.02 (32)</td>
</tr>
<tr>
<td>Low salt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>0.25 ± 0.02 (44)</td>
<td>1.0 ± 0.1 (69)</td>
<td>1.0 ± 0.05† (93)</td>
<td>1.0 ± 0.08† (89)</td>
</tr>
<tr>
<td>Post Ang II</td>
<td>0.25 ± 0.12 (34)</td>
<td>0.85 ± 0.08‡ (62)</td>
<td>0.8 ± 0.05† (89)</td>
<td>0.66 ± 0.08* (76)</td>
</tr>
<tr>
<td>Upright posture</td>
<td>0.36 ± 0.02 (45)</td>
<td>2.5 ± 0.12 (69)</td>
<td>2.7 ± 0.12† (93)</td>
<td>2.5 ± 0.2† (36)</td>
</tr>
<tr>
<td>Blacks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High salt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>0.1 ± 0.03 (4)</td>
<td>0.1 ± 0.03 (12)</td>
<td>...</td>
<td>0.3 ± 0.05 (12)</td>
</tr>
<tr>
<td>Post Ang II</td>
<td>0.14 ± 0.03 (3)</td>
<td>0.1 ± 0.03 (10)</td>
<td>...</td>
<td>0.1 ± 0.02 (9)</td>
</tr>
<tr>
<td>Low salt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>0.3 ± 0.1 (12)</td>
<td>0.8 ± 0.1 (21)</td>
<td>1.5 ± 0.1† (9)</td>
<td>1.2 ± 0.2* (16)</td>
</tr>
<tr>
<td>Post Ang II</td>
<td>0.28 ± 0.1 (10)</td>
<td>0.74 ± 0.2 (18)</td>
<td>1.3 ± 0.4‡ (9)</td>
<td>0.8 ± 0.2 (14)</td>
</tr>
<tr>
<td>Upright posture</td>
<td>0.28 ± 0.05 (13)</td>
<td>2.4 ± 0.2† (21)</td>
<td>2.7 ± 0.6† (10)</td>
<td>3.6 ± 0.6† (13)</td>
</tr>
</tbody>
</table>

Values are ng·L⁻¹·s⁻¹.

*P* = 0.01 vs low renin.

†*P* = 0.01 vs low renin.

‡*P* = 0.05 vs low renin.

**Figure 2.** Aldosterone response to the stimulus of upright posture on a low sodium intake. The rise among both the low-renin patients, although similar to that in NMs, was less than in modulators (*P* = 0.001) or normotensives (*P* = 0.01).
Among white patients, the mean aldosterone increment among LREH (533 ± 58 pmol/L; 19.2 ± 2 ng/dL), although higher than among NMs (175 ± 25 pmol/L; 6.3 ± 0.9 ng/dL; P = 0.01), was still significantly lower than the modulator response (993 ± 69 pmol/L; 35.8 ± 2.5 ng/dL; P = 0.001). Among the 44 hypertensive blacks, as expected by classification, NMs had the lowest responses (194 ± 139 pmol/L; 7 ± 1.6 ng/dL). Aldosterone release among LREH patients was lower than among the modulators (388 ± 50 versus 699 ± 69 pmol/L; 14 ± 1.8 versus 25 ± 2.5 ng/dL), although the difference did not reach significance. As anticipated, black modulators showed responses that were lower than in their white counterparts (P = 0.006). Even within the LREH, however, there was a smaller response in blacks (388 ± 50 versus 610 ± 47 pmol/L; 14 ± 1.8 versus 22 ± 1.7 ng/dL; P = 0.0006). There was no significant difference in urinary potassium excretion between whites and blacks of either the low-renin or NM subsets. Normotensive blacks and whites showed no statistically significant difference in their responsiveness (624 ± 139 versus 818 ± 55 pmol/L; 22 ± 5 versus 29 ± 2 ng/dL).

Gender also contributed to variation in adrenal responsiveness, with the low-salt aldosterone response to Ang II among low-renin women trending higher than in men (746 ± 94 versus 549 ± 42 pmol/L (26.9 ± 3.4 versus 19.8 ± 1.5 ng/dL; t test, P = 0.07). The low-renin state was found in 23% of women < 45 years old; this was similar to the frequency found in young men (21%).

The increased frequency of LREH with increasing age was significant in both men and women (P = 0.001 and P = 0.007). Within the low-renin group, however, there was no correlation between age and low-salt aldosterone response (P = 0.8). This finding is in contrast to the significant negative correlations within both the modulating hypertensives (r = −0.26, P = 0.003) and the normotensives (r = −0.18, P = 0.04).

Diabetes mellitus had no significant impact on aldosterone responsiveness to Ang II in low-salt balance. Nondiabetic LREH patients had an aldosterone increment that was very similar to that in diabetics (619 ± 50 versus 560 ± 55 pmol/L (22 ± 2 versus 20 ± 2 ng/dL)].

**Blood Pressure Responses**

Systolic blood pressure was assessed by the difference in systolic and diastolic blood pressures on changing from high- to low-salt diet. LREH is widely recognized to be a salt-sensitive form of hypertension, which was confirmed in this study (Figure 3). In the normal subjects, diastolic blood pressure changed by only 1.0 ± 1.5 mm Hg, in contrast to LREH response of 11.7 ± 1.3; P = 0.001. Similarly, the change in systolic blood pressure was significantly less in the normal subjects than in low-renin patients (P = 0.01). The NMs showed a blood pressure sensitivity to change in salt intake that was essentially identical to the low-renin patients.

Finally, as anticipated and in contrast to aldosterone release, the rise in systolic blood pressure with Ang II infusion on a low-salt diet was greatest among the low-renin patients (26 ± 3 mm Hg). This response was significantly larger than in not only the normal subjects (7 ± 1 mm Hg) but also both the modulating and the NM hypertensives (15 ± 1 and 15 ± 2 mm Hg; P < 0.01). The rise in diastolic blood pressure also was greater than the normal (P < 0.001) and NM (P < 0.05) responses. Patients with LREH did not differ from normal subjects in their blood pressure response to Ang II on a high-salt diet.

**Discussion**

This study represents the largest detailed examination of adrenal responsiveness in low-renin essential hypertension to date. The primary question addressed involved the interaction of sodium balance and adrenal responsiveness to Ang II. In addition, the large group size of low-renin hypertensives allowed us to address the issue of heterogeneity of response and to examine the possible contributions of race, gender, age, and concomitant diabetes mellitus to variability in response within low-renin patients. Finally, a systematic comparison across 4 groups of blood pressure responsiveness was made, confirming the association of LREH with salt sensitivity and with heightened pressor responsiveness to Ang II.

Basal plasma aldosterone concentration and its response to Ang II were essentially normal in all of the hypertensives, including the low-renin subset, when studies were performed on a high-salt diet. When the system was stressed by restriction of salt intake, however, a series of abnormalities emerged in low-renin patients. Despite a high aldosterone/PRA activity ratio among patients with LREH, there was, in general, no heightened sensitivity of the adrenal gland to exogenous Ang II on either a liberal or restricted sodium intake, thus countering a widely held view of LREH.
Low-renin subsets in previous detailed physiological studies were substantially smaller. In addition, protocol differences may account for part of the discrepancy. Wisgerhof and Brown reported an increased adrenal sensitivity to Ang II. In that classic study, Ang II was infused on a 155-mmol-sodium diet in 6 white patients with LREH. Furthermore, renin profiling was performed after short-term Lasix dosing rather than sustained low-salt balance. The study by Marks et al was also performed after several days on a high-sodium diet. We found no difference in basal or stimulated aldosterone concentration on the high-salt diet among all 3 groups of hypertensives studied. In addition, these early studies may have included patients with mild primary hyperaldosteronism caused by bilateral zona glomerulosa hyperplasia, with a high aldosterone-to-renin ratio. This diagnosis may have been difficult to confirm in the era when the studies were performed.

The data in our study confirm heterogeneity of response among LREH. One of the main identifiable determinants of response was race. We have previously reported a significant blunting of the adrenal response to Ang II in normal-renin blacks. This difference could not readily be attributed to weaker stimuli for aldosterone secretion: Ang II was administered at equal doses, mean cortisol concentrations decreased over the course of the infusions in both races, and there was no difference in either serum or urinary potassium. The present analysis identified a smaller response even among blacks with LREH compared with low-renin whites, thus supporting a preliminary observation that began to emerge from our earlier studies. Normotensive blacks and whites were not statistically different in response, but a trend visible in this still relatively small sample indicates the need for further study. Indeed, in a large cross-sectional study, a 40% lower aldosterone excretion rate was reported in black children than in whites.

Race was not responsible for the overall findings in this study, however; even with blacks excluded, no heightened adrenal response was found among white patients with LREH. A second factor contributing to adrenal responsiveness is gender, with female responses trending higher among low-renin hypertensives. We have reported greater adrenal sensitivity to Ang II among women compared with men, but only until the age of menopause. Mechanisms underlying this sexual dimorphism in essential hypertension have been postulated in detail. Estradiol is a likely contributor, possibly via its effects on angiotensinogen transcription or through other modifying roles it plays in the renin-angiotensin system. We have speculated that female sex hormones allow an override of genotypic predisposition to the NM phenotype. Our current data dispel the previously reported increased frequency of LREH among premenopausal women, classified by random renin profiling rather than under rigorous salt-restricted conditions.

The fall in renin release with age is well accepted; studies have confirmed a diminution of aldosterone secretion in the basal state. We have previously reported an increasing frequency of adrenal unresponsiveness with age among normal renin hypertensives, confirmed again in this study, which, however, revealed no association of age and aldosterone responsiveness within the group of LREH. This contrast is probably explained by the older age of the low-renin hypertensives studied. However, age did not contribute significantly to the overall findings; controlling for age in the ANCOVA did not affect our findings regarding either adrenal or pressor responsiveness in LREH compared with all other groups.

One unanticipated finding was the lack of excessive LREH among patients with diabetes mellitus. Historically, diabetes mellitus has been considered a low-renin state. The stage of disease and extent of renal involvement may underlie the variable responses. Patients in most earlier reports that found the low-renin state to be more frequent in diabetics often had longstanding disease, severe hypertension, and nephropathy. The subjects in this study were without overt proteinuria; most had mild to moderate hypertension, and in many, the duration of diabetes was brief.

Although hormonal responses were lower than normal in LREH, pressor responsiveness was heightened on the low-salt diet. Whereas 1 early report in 8 patients with LREH failed to demonstrate an increased pressor response to Ang II, it has been shown repeatedly that in hypertension marked by sodium retention, like primary aldosteronism, there is a heightened sensitivity of the vasculature to Ang II, attributed to upregulation of vascular Ang II receptors. A positive correlation between plasma renin activity and pressor dose of Ang II within essential hypertension has been reported. In addition, it is well established that the pressor response to Ang II is enhanced on a high salt intake in essential hypertensives and in healthy subjects, with suppression of endogenous Ang II concentration.

Salt-sensitivity of LREH has been one of the most salient clinical features described, and it was reported again in this analysis, as measured by rise in blood pressure of >10 mm Hg when changing from a high to a low sodium intake. Of significance, nonmodulating hypertensives demonstrated a salt-sensitivity equivalent to that of low-renin hypertensives. The similarity in salt sensitivity exposes 1 of several similarities between these patient groups. Both groups showed an elevated NaLi CTT measure, although not to the same degree, confirming our earlier reports of an elevated NaLi CTT in essential hypertension. In addition, each had subnormal peak aldosterone response to Ang II infusion on a low-salt diet.

A comparison and contrast of adrenal responsiveness in LREH patients and NMs is mechanistically revealing. Both groups have low basal aldosterone concentration on a low-salt diet. However, their response characteristics differed once the system became engaged: the slope of response in LREH paralleled the normal, whereas that of the NMs was clearly blunted. In the case of the kidney and the peripheral vasculature, normal Ang II responses are augmented on a high-salt diet because of receptor upregulation. For the adrenal, the scenario is more complex: enhanced adrenal responsiveness to Ang II on a low-salt diet is due not to receptor upregulation but rather to augmentation of an event further downstream, eg, aldosterone synthase activity. The normal response to infusion of Ang II in a low-salt state should be enhanced—ie, follow a steeper slope. Neither the
LREH nor the NM responses, therefore, can be attributed simply to a diminished signal. In NMs, a blunted aldosterone response even with infusion of Ang II suggests an abnormality in synthesis. One possibility raised by this study is that PRA plays a role in normal modulation but via an action not understood and not through the formation of Ang II.

In the case of LREH, conversely, the parallel slope suggests an abnormality in Ang II receptor number or affinity. Genetic linkage studies on the angiotensin AT1 receptor in essential hypertension have thus far been unrevealing in the entire group of essential hypertension. Within the low-renin subgroup, however, it may be that an AT1 receptor abnormality will be uncovered. Such an abnormality might account for both the reduced adrenal response and the heightened pressor response. These mechanistic conclusions are necessarily speculative. Continued hormonal and genetic testing may eventually uncover the mechanisms responsible for maintenance of the low-renin state.

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References


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