Clinical Studies

Prolonged Converting Enzyme Inhibition in Non-modulating Hypertension

Robert G. Dluhy, Kenneth Smith, Terry Taylor, Norman K. Hollenberg, and Gordon H. Williams

Patients with normal- or high-renin non-modulating essential hypertension fail to shift their adrenal sensitivity on a low sodium diet in response to an infusion of angiotensin II (Ang II). In a prior study, 72 hours of converting enzyme inhibition (CEI) partially corrected this subnormal aldosterone response to Ang II in patients with non-modulating hypertension. Since it was uncertain whether the failure to restore normal adrenal responsiveness reflected a continued abnormality or an insufficient duration of CEI, the present study was performed wherein subjects were studied before CEI and then 72 hours and 6 weeks after CEI. Adrenal and renovascular responses were assessed in 13 subjects with normal- or high-renin hypertension in response to an infusion of Ang II (0.3, 1.0, and 3.0 ng/kg/min) in balance on a 10 meq Na+/100 meq K+ diet. Eight of 13 had a normal plasma aldosterone increment above control levels (≥15 ng/dl) and were classified as modulators; the remaining subjects (five of 13) were classified as non-modulators. Enalapril was then administered for 72 hours and 6 weeks, and the assessment of the Ang II dose–response relations was repeated. In the modulators, there was no change compared with levels before CEI in the aldosterone dose–response curve or threshold sensitivity to infused Ang II at either 3 days or 6 weeks after CEI administration. In the non-modulators, CEI for 72 hours partially restored aldosterone responsiveness, but more prolonged CEI for 6 weeks completely corrected the defect, restoring aldosterone responsiveness on a sodium-restricted diet to that seen in modulators and in normotensive control subjects. The threshold dose for a significant increase in plasma aldosterone above control levels progressively shifted from 3 ng/kg/min (72 hours of CEI) to 1 ng/kg/min (6 weeks of CEI). After CEI, basal p-aminohippurate clearance progressively increased in both groups, but a significant increment above control levels was only observed in non-modulators at 6 weeks; CEI enhanced renovascular responsiveness to infused Ang II equally in the two hypertensive subgroups. Complete correction of the renal abnormality in a previous study and the adrenal defect in the present study by CEI without demonstrable changes in circulating Ang II levels provide support for a tissue defect in the renin-angiotensin system in non-modulating hypertensive subjects. (Hypertension 1989;13:371–377)

In normal subjects, sodium intake has a reciprocal influence on adrenal and vascular responsiveness to angiotensin II (Ang II), with sodium restriction reducing the vascular while enhancing the adrenal responses.1,2 We have reported that approximately 40% of patients with essential hypert...
hypertensive subjects is more complex. In an early report, captopril enhanced the adrenal response to Ang II in a small group of sodium-restricted patients with essential hypertension. Since it was unclear whether this was a phenomenon present in all patients with essential hypertension or only a subset, a subsequent study was designed to examine the influence of CEI in essential hypertensive patients with normal (modulators) or abnormal (non-modulators) adrenal responsiveness to infused Ang II in the sodium-restricted state. After 72 hours of CEI, no change in adrenal responsiveness was seen in normotensive control subjects or the hypertensive modulators. In the hypertensive non-modulators, both the entire dose–response curve and threshold sensitivity were significantly enhanced after 72 hours of CEI. However, in this study only partial correction of the abnormality was observed in non-modulators.

The present study was designed to determine whether more prolonged CEI not only maintained the correction of the altered adrenal response to Ang II in non-modulators, but also whether the incomplete correction of abnormal adrenal responsiveness seen at 72 hours could be further corrected and restored to that seen in normotensive control and in modulator essential hypertensive subjects.

**Patients and Methods**

Thirteen patients with normal- or high-renin essential hypertension were studied in the Clinical Research Center at the Brigham and Women’s Hospital. The results of CEI in some of these same patients at 72 hours and in normal subjects have been previously reported. Patients with low-renin essential hypertension were excluded. Patients had outpatient diastolic blood pressure measurements in excess of 90 mm Hg on at least three occasions and documented hypertension for at least 6 months before study. Secondary forms of hypertension were excluded by serum creatinine, urinalysis, plasma aldosterone, plasma norepinephrine and epinephrine, and 24-hour vanillylmandelic acid, norepinephrine, epinephrine, and hydroxycorticoid steroid levels. Renal vascular hypertension was excluded by rapid sequence intravenous pyelography in all patients. In some subjects, renal arteriography was performed to exclude this possibility definitively. All antihypertensive medications were discontinued for at least 2 weeks before study. During their hospitalization, subjects were fed constant isocaloric diets that contained 10 meq of sodium and 100 meq of potassium. Fluid intake was maintained at 2,500 ml/day. Daily 24-hour urine collections were analyzed for sodium, potassium, and creatinine. Each study was begun at 8:00 AM after the subjects had been fasting and recumbent for 8 hours.

**p-Aminohippurate Infusion**

Renal plasma flow was assessed after metabolic balance had been achieved on the sodium-restricted intake, as previously described. After assessment of basal p-aminohippurate (PAH) clearance, the 13 hypertensive subjects received an infusion of Ang IIamide at successive doses of 0.3, 1, and 3 ng/kg/min for 45 minutes each, using a Harvard infusion pump. PAH was infused continuously at a constant rate throughout the Ang II infusion to assess changes in PAH clearance with increasing Ang II doses. Blood pressure was monitored every 2 minutes with an indirect recording sphygmomanometer (Arteriosonde, Roche Diagnostics Division, Hoffman LaRoche, Inc., Nutley, New Jersey) with the cuff position over the brachial artery of the arm containing the sampling catheter. Basal blood pressure was recorded for 1 hour during the basal PAH clearance study. Blood samples were drawn at the end of the control period and after each incremental infusion dose of Ang II and were analyzed for PAH, aldosterone, Ang II, plasma renin activity, cortisol, sodium, and potassium. A normal response under these circumstances is a plasma aldosterone increment greater than 15 ng/dl in response to a 3 ng/kg/min infusion of Ang II. The hypertensive subjects were divided into modulators or non-modulators according to this definition.

**Converting Enzyme Inhibition**

On the afternoon after the control Ang II infusions were completed, the 13 patients were given their first dose of a converting enzyme inhibitor. Enalapril in escalating doses of 2.5, 5, 10, and 20 mg at 8:00 AM on consecutive mornings was administered for a total of 72 hours. At 8:00 AM, 72 hours after the control Ang II infusion, the last dose of the converting enzyme inhibitor was administered. Two and a half hours later, the Ang II dose–response relation was defined as above. The subjects were then discharged and CEI was continued. Daily doses were titrated to control diastolic blood pressure at or below 90 mm Hg. Six to 10 weeks after the initial study, the subjects were readmitted, placed on a 10 meq sodium, 100 meq potassium diet and restudied in an identical fashion 2½ hours after their morning dose of enalapril. Five days of sodium restriction preceded the Ang II infusions during the two admissions.

**Laboratory Procedures**

Blood samples were collected on ice, spun immediately, and the plasma separated and 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 creatinine was measured by an autoanalyzer technique. Ang II, aldosterone, plasma renin activity, and cortisol were assayed by radioimmunoassay techniques that have been previously described. Cross-reactivity of the Ang II antibody with angiotensin I (Ang I) is 0.2%. All Ang II values were corrected for Ang I content (maximum correction was 5 pg/ml). Ang II levels in charcoal stripped plasma were less than sensitivity of the assay (7 pg/
ml). PAH concentration was measured by a Technicon autoanalyzer spectrophotometric technique. The absolute difference in paired PAH measurements on a single sample on the same run was less than 1%. Internal standards varied by 1% or less on different days.

Group means have been presented with the standard error of the mean as the index of dispersion. Statistical probability was assessed with the Student's t test for paired data that were normally distributed. The Wilcoxon Rank Sum Test or the Wilcoxon Signed Rank Test were used for nonhomogeneously distributed data. Significant differences were at p<0.05 unless otherwise stated. Written informed consent was obtained after a full description of the protocol. The protocol was approved by the Human Subjects Committee of the Brigham and Women's Hospital.

Results

Baseline Comparison

The modulator and non-modulator hypertensive subjects did not differ according to a number of clinical parameters (i.e., age, sex, duration of hypertension, evidence of secondary effects of hypertension, or admission blood pressure) (Table 1). Furthermore, there were no significant differences on the day of the study, before administration of the converting enzyme inhibitor enalapril, in either plasma renin activity, cortisol, aldosterone, Ang II, sodium, potassium, systolic or diastolic blood pressure, PAH clearance, or 24-hour urine sodium and potassium levels in the modulators and non-modulators (Table 2).

Control Response to Angiotensin II

Aldosterone increments in response to Ang II infusion in the two subgroups of hypertensive patients before CEI are shown in Figure 1. Adrenal responsiveness to Ang II was less in the non-modulators than in the modulators over the entire dose–response curve, with a highly significant difference at 1.0 (p<0.01) and 3.0 ng/kg/min (p<0.002). The threshold sensitivity (determined as a significant difference between basal and infusion levels) in the modulators was 1.0 ng/kg/min (p<0.02), while in the non-modulators, the increment from baseline was not significant at any dose. In addition, the aldosterone response fell in modulators to within the range observed in normotensive subjects infused with Ang II on a 10 meq sodium diet.

The mean increment of Ang II achieved before CEI was significantly higher in modulators at 0.3 ng/kg/min, but there were no significant differences in Ang II increments achieved at the 1.0 or 3.0 ng/kg/min doses.

In the two hypertensive subgroups, there were no significant differences in the renal vascular responses to Ang II (Figure 1). In both modulators and non-modulators, Ang II at a dose of 3.0 ng/kg/min significantly reduced PAH clearance from baseline (p<0.04).

Hormonal and Vascular Response to Converting Enzyme Inhibition at 3 Days and 6 Weeks

In response to administration of enalapril, both modulators and non-modulators had significant

### Table 1. Characteristics of Hypertensive Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Modulators</th>
<th>Non-modulators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>37±4</td>
<td>51±7</td>
</tr>
<tr>
<td>Subjects (n)</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Men (n)</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Duration of hypertension (yr)</td>
<td>9±3</td>
<td>12±7</td>
</tr>
<tr>
<td>Admission systolic BP (mm Hg)</td>
<td>151±7</td>
<td>164±7</td>
</tr>
<tr>
<td>Admission diastolic BP (mm Hg)</td>
<td>102±3</td>
<td>98±4</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.1±0.1</td>
<td>1.2±0.1</td>
</tr>
</tbody>
</table>

Values are mean±SEM. BP, blood pressure.

### Table 2. Control Data Before Angiotensin II Infusion in Modulating and Non-Modulating Hypertensive Subjects

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Modulators Before CEI</th>
<th>Modulators 3 days CEI</th>
<th>Modulators 6 wk CEI</th>
<th>Non-modulators Before CEI</th>
<th>Non-modulators 3 days CEI</th>
<th>Non-modulators 6 wk CEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>1.7±0.5</td>
<td>11.4±4.9</td>
<td>17.5±6.2</td>
<td>1.6±0.6</td>
<td>8.5±2.7</td>
<td>14.1±7</td>
</tr>
<tr>
<td>Plasma Ang II (pg/ml)</td>
<td>31±3</td>
<td>25±3</td>
<td>27±4</td>
<td>31±5</td>
<td>27±2</td>
<td>30±4</td>
</tr>
<tr>
<td>PA (ng/dl)</td>
<td>24±5</td>
<td>18±4</td>
<td>16±3</td>
<td>23±5</td>
<td>11±4</td>
<td>10±2</td>
</tr>
<tr>
<td>Plasma cortisol (μg/dl)</td>
<td>11±1</td>
<td>10±1</td>
<td>9±1</td>
<td>11.5±1</td>
<td>11±1</td>
<td>11±1</td>
</tr>
<tr>
<td>Serum Na (meq/l)</td>
<td>137±1</td>
<td>137±0</td>
<td>137±1</td>
<td>139±2</td>
<td>136±1</td>
<td>135±0</td>
</tr>
<tr>
<td>Serum K (meq/l)</td>
<td>4.0±0.2</td>
<td>4.1±0.1</td>
<td>4.1±0.1</td>
<td>4.3±0.1</td>
<td>4.3±0.1</td>
<td>4.4±0.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>87.3±5.8</td>
<td>86.4±5.8</td>
<td>83.1±4.8</td>
<td>75.8±2.4</td>
<td>75.6±2.8</td>
<td>74.2±2.8</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>128±5</td>
<td>...</td>
<td>109±2</td>
<td>139±11</td>
<td>...</td>
<td>111±14</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>89±3</td>
<td>...</td>
<td>77±2</td>
<td>90±4</td>
<td>...</td>
<td>74±8</td>
</tr>
<tr>
<td>PAH clearance (cc/min/1.73 m²)</td>
<td>531±31</td>
<td>545±43</td>
<td>587±45</td>
<td>476±36</td>
<td>553±56</td>
<td>575±40</td>
</tr>
<tr>
<td>24-hour urine Na (meq)</td>
<td>18±4</td>
<td>23±3</td>
<td>26±5</td>
<td>23±3</td>
<td>18±3</td>
<td>24±10</td>
</tr>
<tr>
<td>24-hour urine K (meq)</td>
<td>69±6</td>
<td>78±9</td>
<td>70±7</td>
<td>72±7</td>
<td>73±5</td>
<td>60±14</td>
</tr>
<tr>
<td>Enalapril dose (mg/day)</td>
<td>...</td>
<td>17±2</td>
<td>25±5</td>
<td>...</td>
<td>17±7</td>
<td>33±5</td>
</tr>
</tbody>
</table>

All values are mean±SEM. CEI, converting enzyme inhibition; PRA, plasma renin activity; Ang II, angiotensin II; PA, plasma aldosterone; Na, sodium; K, potassium; BP, blood pressure; PAH, p-aminohippurate.
RE5P0NSE TO HFUSED ANOOTCNSIN 0
A PLASUA ALDOSTCRONE
• •  MODULATORS
O O  NONUOOUATOfa
A PAH CLEARANCE
FIGURE 1. Line graphs showing plasma aldosterone and angiotensin II (Ang II) increments and the decrement in p-aminohippurate (PAH) clearance below control levels in 13 subjects with normal-renin essential hypertension in balance on a 10 meq sodium, 100 meq potassium diet in response to infused Ang II (0.3, 1.0, and 3.0 ng/kg/min). Subjects were classified as modulators (n=8) if their plasma aldosterone increments at the 3 ng/kg/min Ang II dose were ≥15 ng/dl, a response previously established in normotensive control subjects.10 Non-modulators (n=5) had plasma aldosterone increments <15 ng/dl.

increases of plasma renin activity above basal levels at 3 days and 6 weeks. Although mean levels were higher at 6 weeks than at 3 days in both groups, this difference was not statistically significant (Table 2). PAH clearance progressively increased after CEI in modulators and non-modulators, with the increments above control levels (before CEI) being greater at 6 weeks than at 3 days; however, significant increments above control were achieved only in the non-modulators at 6 weeks (Table 2). Blood pressure was reduced in modulators and non-modulators at both 3 days and 6 weeks, but significance (p<0.02) was obtained only for modulators. Plasma Ang II was not changed significantly below control after 3 days or 6 weeks of CEI in either subgroup. Plasma aldosterone decreased, though not significantly, at both 3 days and 6 weeks after CEI in modulators and non-modulators (Table 2). In general, the magnitude of Ang II and plasma renin activity responses after CEI were similar in both subgroups whereas that of aldosterone, blood pressure, and PAH clearance were greater in non-modulators than modulators; however, there were no significant differences between modulators and non-modulators in any of these parameters after CEI. There were no differences in mean cortisol levels between modulators and non-modulators before CEI or 3 days or 6 weeks after CEI (Table 2). There also were no significant differences between the decrements in weight or urine sodium and potassium excretion of modulators and non-modulators before versus 3 days or 6 weeks after CEI. However, a significant reduction in weight below control levels was seen at 3 days in modulators after CEI (Table 2).

The previously published responses of normotensive subjects on a low sodium diet 3 days after CEI include mean decrements in plasma Ang II of 15±4 pg/ml and in plasma aldosterone of 17±4 ng/dl, and an increment in PAH clearance of 130±38 cc/min/1.73 m².10

Responses to Infused Angiotensin II After Converting Enzyme Inhibition
There were no changes in the aldosterone dose-response curve or threshold sensitivity to infused Ang II in the modulators when compared with before CEI levels (Figure 2) at either 3 days or 6 weeks after CEI. There also were no significant differences between the aldosterone increments at 3 days and 6 weeks after CEI. The aldosterone response of the modulators was similar to what had previously been reported in normotensive subjects.10 In contrast, the non-modulators showed mean aldosterone increments to infused Ang II over the entire dose-response curve to be higher at 3 days than before CEI, and at 6 weeks higher than 3 days after CEI. Significance for this aldosterone increase over before-CEI levels was achieved for both 3 days (p<0.01) and 6 weeks after CEI (p<0.04) at the 3 ng/kg/min Ang II infusion dose. In addition, in non-modulators a significant difference between the aldosterone increment at 3 days (13±5 ng/dl) and 6 weeks (29±9 ng/dl) after CEI was observed at the 1.0 ng/kg/min Ang II dose (p<0.04). Thus, the non-modulators, who showed significantly lower aldosterone responses to the 1.0 and 3.0 ng/kg/min Ang II doses compared with modulators before CEI, progressively corrected this abnormality after 3 days and then 6 weeks of enalapril therapy. As a result, there were no significant differences between the non-modulators' aldosterone responses to Ang II after 6 weeks of CEI therapy and the responses before or after CEI in the modulators or normotensive control subjects. In addition, the threshold sensitivity to Ang II progressively shifted in non-modulators after 3 days and 6 weeks of CEI treatment. No significant aldosterone increment from baseline levels before CEI was seen in non-
modulators at any dose of infused Ang II; the threshold dose was 3 ng/kg/min after 3 days of CEI and 1.0 ng/kg/min at 6 weeks of CEI therapy. This 1.0 ng/kg/min dose was the same threshold dose seen in modulators before and after CEI.

Serum Ang II increments achieved, compared with the control infusion, tended to be higher in modulators after CEI. At 3 days and 6 weeks after CEI, modulators had significantly higher increments in Ang II at the 1.0 ng/kg/min infusion and 3.0 ng/kg/min infusion doses compared with before CEI. However, there were no significant differences observed in the Ang II levels achieved before CEI or after CEI between modulators or non-modulators after the infusion of Ang II. There were no significant differences in the cortisol or potassium levels in modulators or non-modulators at any dose of infused Ang II at 3 days or 6 weeks after CEI.

In contrast to the effect of CEI on the aldosterone responses to infused Ang II, CEI at 3 days and 6 weeks had similar effects on PAH clearance in the two hypertensive subgroups. Although mean decrements in PAH clearance were not significantly different at 3 days or 6 weeks over before-CEI levels in either modulators or non-modulators, the decrements tended to be greater than before CEI with 6 weeks greater than 3 days greater than before CEI. Also, the threshold response for a significant decrement in PAH clearance below control levels changed from 3.0 ng/kg/min before CEI to 1.0 ng/kg/min at 3 days after CEI (p<0.01) in modulators and non-modulators and to 0.3 ng/kg/min at 6 weeks in modulators. The threshold dose in non-
modulators at 6 weeks was 3 ng/kg/min, probably related to the large standard error of the mean seen at the lower infusion doses.

There were no significant differences in theenalapril doses given to modulators and non-modulators at 3 days or 6 weeks after CEI (Table 2).

**Discussion**

We have previously reported that approximately 50% of patients with normal- or high-renin essential hypertension failed to shift their adrenal sensitivity on a low sodium diet in response to an infusion of Ang II.\(^1\)\(^-\)\(^5\) We coined the term "non-modulators" for these hypertensive subjects. Non-modulators also failed to increase their renal blood flow when shifted from a low to a high salt diet; they also do not show the expected enhanced renal vascular response to infused Ang II in the salt-loaded state.\(^1\)\(^5\) A final characteristic of non-modulating essential hypertension is the partial or complete correction of the above abnormalities by CEI. For example, renal vascular responsiveness to infused Ang II was restored to normal in non-modulating hypertensive subjects after 66 hours of CEI. On the other hand, after 72 hours of CEI, the subnormal aldosterone response to Ang II on a low sodium diet was only partially corrected in the non-modulating hypertensive subjects.\(^10\) In the latter study, it was uncertain whether the failure to fully restore normal responsiveness in non-modulators was a reflection of a continued abnormality or an insufficient duration of CEI. The present study, therefore, extended the duration of CEI from 3 days to 6 weeks to determine whether the subnormal adrenal responsiveness could be fully corrected in non-modulators. The results show that more prolonged CEI restores aldosterone responsiveness in non-modulators on a sodium-restricted diet to that seen in modulating hypertensive and in normotensive control subjects. Not only were the increments in aldosterone above control levels restored to normal after 6 weeks of CEI, but the threshold dose for a significant increase in aldosterone levels above control levels progressively shifted in the non-modulators from 3 ng/kg/min (72 hours of CEI) to 1 ng/kg/min (6 weeks of CEI).

Confounding factors that could have accounted for the differences in aldosterone responsiveness observed between the two patient groups before or after CEI include differences in clinical criteria of the two groups, differences in potassium homeostasis or cortisol secretion, or differences in the degree of CEI or the Ang II level achieved during the Ang II infusions. However, no significant differences in any of these parameters were observed between non-modulating hypertensive and modulating hypertensive subjects before or at 3 days or 6 weeks of CEI.

In this study, non-modulators tended to be older and had a greater duration and severity of hypertension compared with modulators, although these differences were not significant (Table 1). Therefore, the differences observed in response to CEI could possibly reflect the responses in two different populations of hypertensive subjects. However, although non-modulators tend to be older than modulators in some of our previous reports, no differences have ever been observed between modulators and non-modulators in the severity or duration of hypertension.\(^3\)\(^-\)\(^5\)\(^10\)\(^11\)\(^15\)\(^16\) In addition, non-modulation occurs in the young patient with essential hypertension\(^5\) as well as the normotensive offspring of hypertensive parents.\(^17\) Thus, although the small sample size in the present study suggested differences, previous studies in larger numbers of essential hypertensive subjects make it unlikely that age and duration or severity of hypertension can explain the differences observed.

The mechanisms producing subnormal adrenal responsiveness to Ang II in non-modulating subjects, and the correction of the defect with CEI remains speculative. Unlike responsiveness of vascular tissue to Ang II,\(^18\)\(^-\)\(^20\) circulating Ang II levels do not appear to be responsible for the enhanced adrenal response to Ang II after sodium restriction.\(^8\)\(^-\)\(^10\)\(^21\)\(^-\)\(^25\) Thus, intra-adrenal tissue concentrations of Ang II or changes in the adrenal receptor have been offered as alternative hypotheses. In the kidney, the subnormal renal blood flow in non-modulating subjects on a high sodium diet and correction after CEI is consistent with the hypothesis that intrarenal concentrations of Ang II are inappropriately elevated in non-modulators.\(^16\) The present study on a sodium-restricted intake is consistent with this hypothesis; basal PAH clearance progressively increased after CEI in hypertensive subjects, but a significant increment above control was only observed in non-modulators at 6 weeks (Table 2). An alternative explanation could be that, in addition to lowering tissue Ang II levels, CEI may also alter tissue or circulating prostaglandin and bradykinin levels. However, the role of tissue adrenal Ang II and plasma renin activity levels and their effects on glomerulosa steroidogenesis remain controversial. The present study supports previous work\(^10\) indicating that, in normal subjects and modulating hypertensive subjects, factors other than changes in circulating Ang II levels are responsible for the enhanced responsiveness to Ang II seen on a sodium-restricted diet since responsiveness is unaffected by either short-term or, as in the present study, longer-term CEI. However, what appears to be clear is that Ang II-mediated aldosterone secretion is not regulated in the same way in non-modulating hypertensive subjects as in normotensive subjects. We have speculated that the failure to shift renal and adrenal sensitivity to Ang II as sodium changes in the diet is the fundamental abnormality in non-modulating subjects. The present study, showing full correction of the adrenal abnormality without demonstrable changes in circulating Ang II levels would support a tissue defect in the renin–angiotensin II system in non-modulating hypertensive subjects.
References


KEY WORDS • non-modulating hypertension • aldosterone • converting enzyme inhibition • renin-angiotensin system • angiotensin II
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