Converting-Enzyme Inhibition Corrects the Altered Adrenal Response to Angiotensin II in Essential Hypertension

TERRY TAYLOR, M.D., THOMAS J. MOORE, M.D., NORMAN K. HOLLENBERG, M.D., PH.D., AND GORDON H. WILLIAMS, M.D.

SUMMARY Of patients with essential hypertension, 30% to 50% do not modulate adrenal and renovascular responsiveness to angiotensin II (All) with changes in sodium intake. To define the role of All in mediating these altered responses, the adrenal and renal vascular responses to All infusion (0.3, 1.0, 3.0 ng/kg/min) were assessed on a sodium-restricted intake in 31 patients with essential hypertension and 13 normotensive controls before and after 72 hours of converting-enzyme inhibition. Forty percent of the hypertensive patients had a subnormal adrenal response to All. There were no differences between the normal and abnormal responding hypertensive patients in a number of clinical and biochemical factors except that the "abnormal responders" had a significantly (p < 0.03) greater control All level (37 ± 3 vs 29 ± 3 pg/ml) and lower control plasma aldosterone level (14 ± 2 vs 22 ± 3 ng/dl) than the "normal responders."

When a converting-enzyme inhibitor was administered, no change in adrenal responsiveness to All occurred in the normotensive controls or the hypertensive normal responders. In the hypertensive abnormal responders, both the threshold sensitivity and the entire dose response curve was significantly (p < 0.01) enhanced following short-term converting-enzyme inhibition. This increased sensitivity could not be explained by differences in All increment with All infusions, in basal aldosterone levels, or in blood pressure or basal All response to converting-enzyme inhibition. Since they occurred whether captopril or enalapril (MK 421) were used, this phenomenon is likely to be a specific effect of converting-enzyme inhibition. In contrast to adrenal responses, converting-enzyme inhibition enhanced renovascular responses to All equally in the two hypertensive subgroups. Thus, in 40% of patients with essential hypertension, short-term converting-enzyme inhibition partially corrected abnormalities in sodium-mediated modulation of adrenal responsiveness to All, confirming and extending the concept that this abnormality reflects an alteration in the interaction of angiotensin II and its receptor. (Hypertension 6: 92–99, 1984)

KEY WORDS • hypertension • converting-enzyme inhibitors • renal blood flow • aldosterone secretion

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N normal subjects, sodium intake has a reciprocal influence on vascular and adrenal responsiveness to angiotensin II (All), with sodium restriction enhancing the adrenal and reducing the vascular responses.1,2 In vitro studies would suggest that the change in vascular responsiveness is secondary to a change in the number of All receptors, while sodium's effect on adrenal responses to All is more complex.

Recently, it has been documented that between 30% and 50% of patients with essential hypertension lack this sodium-mediated change in tissue responsiveness to All.3-5

Studies with angiotensin antagonists and converting-enzyme inhibitors (CEI) have made it clear that All itself plays a dominant role in the normal response of both aldosterone release and renal blood flow with sodium restriction.6-7 Additionally, since CEI given to normal subjects on a low sodium intake changed vascular but not adrenal responses compared to subjects on a high sodium intake, the circulating All level itself is the probable mediator of the reduced vascular but not the enhanced adrenal responses to All with sodium restriction.8

When CEI was administered to hypertensive subjects, the responses were more complex. In a preliminary report, captopril appeared to enhance the adrenal response to All when given to a small group of patients...
with essential hypertension on a low sodium intake. It was unclear from that study whether this was a phenomenon present in all patients with essential hypertension or whether it occurred only in those individuals who had abnormalities in target tissue responsiveness to AII prior to administration of the converting-enzyme inhibitor. The present study was designed to answer this question by examining the influence of two converting-enzyme inhibitors in a sufficient number of patients to allow subclassification into normal responders (NR) and abnormal responders (AbR).

**Methods**

Thirty-one patients with normal- or high-renin essential hypertension (age range, 24–65 years) and 13 normotensive subjects (age range, 21–63 years) were studied in the Clinical Research Center at the Brigham and Women’s Hospital. Some results in some of these patients and normal subjects have been reported.\(^8\)\(^9\) Patients with low-renin essential hypertension, defined as a plasma renin activity (PRA) response to upright posture on a 10 mEq sodium diet of less than 2.4 ng/ml/hr, were excluded. Each patient had had outpatient diastolic blood pressure measurements in excess of 90 mm Hg on at least three occasions and documented evidence of hypertension for at least 6 months prior to the study. Patients with secondary forms of hypertension were excluded by urinalysis, serum creatinine, plasma aldosterone, plasma norepinephrine and epinephrine, and 24-hour urine vanillylmandelic acid, norepinephrine, epinephrine, and \(^{131}\)I-hippuran renograms in 12 patients. Seven subjects also underwent renal arteriography to eliminate this possibility definitively. Fifteen patients who did not undergo arteriography also had a saralasin infusion test with a normal blood pressure response.

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

**Paraaminohippurate Infusion**

Renal plasma flow was assessed after metabolic balance had been achieved on the sodium-restricted intake, as previously described.\(^8\) In brief, an intravenous catheter was placed in each of the subject’s arms, one for infusion and the other for blood sampling. A control blood sample was obtained and then an 8 mg/kg loading dose of paraaminohippurate (PAH) was given. A constant infusion of PAH was immediately begun at a rate of 12 mg/min using an IMED pump (IMED Corporation, San Diego, California). 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, when corrected for individual body surface area, represents about 90% of the effective renal plasma flow. PAH clearance was calculated from the plasma concentration and the infusion rate.\(^8\) Plasma samples were obtained 45 and 60 minutes after the start of the constant infusion and steady state was achieved. The mean values were used for calculations.

**Angiotensin II Infusion**

After assessment of the basal PAH clearance, the 31 hypertensive subjects received an infusion of angiotensin II amide (Hypertensin, Ciba-Geigy Corporation, Pharmaceuticals Division, Summit, New Jersey) at successive doses of 0.3, 1.0, and 3.0 ng/kg/min for 45 minutes each, using a Harvard infusion pump. The constant infusion of AII continued throughout the AII infusion to assess the changes in PAH clearance with increasing AII 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 positioned 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 AII and analyzed for PAH, aldosterone, AII, PRA, cortisol, sodium, and potassium.

The 13 normal subjects completed a similar protocol. We have previously defined a normal aldosterone response under these circumstances as an increment greater than 15 ng/dl in response to a 3 ng/kg/min infusion of AII.\(^5\)\(^6\) The hypertensive subjects were, therefore, divided into normal (NR) and abnormal (AbR) responders according to this definition.

**Converting-Enzyme Inhibition**

On the afternoon after the control AII infusions were completed, the 31 patients and 13 normal controls were given their first dose of converting-enzyme inhibitor. Ten patients and four normal subjects received captopril, 25 mg by mouth every 6 hours for 72 hours. Twenty-one patients and nine normals received enalapril (MK 421) in escalating daily doses of 2.5, 5, 10, and 20 mg at 8 a.m. on consecutive mornings for a total of 72 hours. At 8:00 a.m., 72 hours after the control AII infusion, the last dose of converting-enzyme inhibitor was administered. Two and one half hours later, the AII dose-response relationship was defined as above.

**Laboratory Procedures**

All blood samples were collected on ice, 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. All, aldosterone, PRA, and cortisol were assayed by ra-

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dioimmunoassay techniques that have been previously described. Cross-reactivity of the All antibody with AI was 0.2%. All AI levels were corrected for AI content in the sample (maximum correction was 5 pg/ml). All levels in charcoal stripped plasma were less than the sensitivity of the assay (7 pg/ml).

Plasma PAH concentration was measured by a Technicon autoanalyzer spectrophotometric technique. The absolute average difference in paired PAH measurements on a single sample on the Technicon autoanalyzer on the same run was less than 1%. The internal standards varied by 1% or less on different days. In nine normal subjects in whom duplicate determinations of PAH clearance were obtained by this method on two different days while they were ingesting the same diet, the mean PAH clearance was 638 ± 10 ml/min. The absolute day-to-day variation was 30 ± 39 ml/min/1.73 m², an average of 4.7% ± 3%. The absolute average difference in paired PAH clearances was less than the sensitivity of the assay (7 pg/ml).

Adrenal responsiveness to All over the entire dose response curve in the AbR was significantly greater than in the NR (p < 0.001 chi-squared). In neither group nor the other according to a number of clinical parameters, i.e., age, sex, duration of hypertension, evidence of secondary effects of hypertension, admission blood pressure (Table 1). Furthermore, there were no significant differences on the day of study, prior to administration of converting enzyme inhibitors (CEI), in either PRA, cortisol, sodium, potassium, systolic or diastolic blood pressure, PAH clearance, or 24-hour urine sodium and potassium levels (Table 2). There were, however, significant differences in the pre-CEI aldosterone and All concentrations in the two groups. The abnormal responders (AbR) had significantly greater All levels (p < 0.029) and significantly lower plasma aldosterone levels (0.023, Fisher Exact Test [FET]).

**Results**

**Baseline Comparison**

The normal and abnormal hypertensives 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 study, prior to administration of converting enzyme inhibitors (CEI), in either PRA, cortisol, sodium, potassium, systolic or diastolic blood pressure, PAH clearance, or 24-hour urine sodium and potassium levels (Table 2). There were, however, significant differences in the pre-CEI aldosterone and All concentrations in the two groups. The abnormal responders (AbR) had significantly greater All levels (p < 0.029) and significantly lower plasma aldosterone levels (0.023, Fisher Exact Test [FET]).

**Control Response to All**

Aldosterone responses to All infusion in the two subgroups of hypertensive patients before the administration of the converting enzyme inhibitor are shown in Figure 1, left. Adrenal responsiveness to All over the entire dose response curve in the AbR was significantly less than in the NR (p < 0.001chi-squared). Separate analysis of the threshold sensitivity revealed a significant difference (p < 0.01): the threshold sensitivity in the AbR was 3 ng/ml/min, while in the NR it was 0.3 ng/ml/min. The NR fell within the range of normotensive subjects (Figure 1, left). In neither group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal responders</th>
<th>Abnormal responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>39 ± 4</td>
<td>48 ± 4</td>
</tr>
<tr>
<td>Subjects (no.)</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Men (no.)</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Duration of hypertension (yrs)</td>
<td>7 ± 2</td>
<td>8 ± 4</td>
</tr>
<tr>
<td>Admission systolic BP (mm Hg)</td>
<td>147 ± 4</td>
<td>145 ± 11.0</td>
</tr>
<tr>
<td>Admission diastolic BP (mm Hg)</td>
<td>99 ± 2</td>
<td>100 ± 2</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.1</td>
</tr>
</tbody>
</table>

**Table 2. Control Data Prior to All Infusion in Hypertensive Subjects (Means ± SEM)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal responders</th>
<th>Abnormal responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>2.8 ± 0.3</td>
<td>16.6 ± 3.1</td>
</tr>
<tr>
<td>Plasma All (pg/ml)</td>
<td>29 ± 3</td>
<td>20 ± 2</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>22 ± 3</td>
<td>11 ± 2</td>
</tr>
<tr>
<td>Plasma cortisol (µg/dl)</td>
<td>12 ± 1</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>Serum sodium (mEq/liter)</td>
<td>137 ± 1</td>
<td>136 ± 1</td>
</tr>
<tr>
<td>Serum potassium (mEq/liter)</td>
<td>4.1 ± 0.1</td>
<td>4.0 ± 0.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85.9 ± 9.9</td>
<td>85.3 ± 3.9</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>128 ± 3</td>
<td>112 ± 3</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>84 ± 2</td>
<td>71 ± 2</td>
</tr>
<tr>
<td>PAH clearance (cc/min/1.73 m²)</td>
<td>567 ± 20</td>
<td>649 ± 35</td>
</tr>
<tr>
<td>24-hour urine sodium (mEq)</td>
<td>16 ± 2</td>
<td>20 ± 1</td>
</tr>
<tr>
<td>24-hour urine potassium (mEq)</td>
<td>74 ± 3</td>
<td>77 ± 5</td>
</tr>
</tbody>
</table>
was there a significant difference in the increment in All achieved during the course of the angiotensin infusion, which also fell within the range observed in normotensive subjects (Figure 1, right).

In the two hypertensive subgroups, there was no significant difference in the renal vascular responses to All (Figure 1, center). In both groups, All at a dose of 1.0 ng/kg/min significantly reduced PAH clearance ($p < 0.01$). Additionally, the responses in both hypertensive subgroups fell within the normal range.

### Hormonal and Vascular Responses to Converting-Enzyme Inhibition

In response to administration of a converting-enzyme inhibitor, both the AbR and NR had a significant ($p < 0.01$) increase in plasma renin activity and PAH clearance, with a significant ($p < 0.01$) reduction in plasma All and aldosterone and blood pressure (Table 2). Furthermore, the magnitude of the response was similar in the two hypertensive subgroups. Several indices showed no significant change after administration of CEI or between the two subgroups including plasma cortisol, serum sodium and potassium, weight, and sodium and potassium excretion (Table 2). The response of both subgroups of hypertensive patients was similar to the normotensive subjects, where the mean decrement in All was $15 \pm 4$ pg/ml and in aldosterone, $17 \pm 4$ ng/dl, and the increment in PAH clearance was $130 \pm 38$ cc/min/1.73 m$^2$.

Figure 2 depicts the responses of the individual hypertensive patient's basal aldosterone and All levels and PAH clearance to converting-enzyme inhibition. The subjects are divided into those who received captopril and those who received enalapril as well as to whether they are NR or AbR. There was no significant difference in the effectiveness of captopril vs enalapril in reducing All or aldosterone levels or increasing PAH clearance. Furthermore, in the two subgroups of hypertensive patients there was no significant difference in the efficacy of converting-enzyme inhibition in reducing All levels or increasing renal blood flow. There was a significant correlation ($p < 0.02$) between the pre- and post-All and PAH clearance levels in both the NR and AbR. On the other hand, there was a significant correlation between the pre- and post-aldosterone levels only in the NR and normotensive subjects ($p < 0.01$). There was no significant correlation between the pre- and post-aldosterone levels in the AbR. Indeed, in over half of the AbR, converting-enzyme inhibition had little, if any, effect on the basal aldosterone concentration (Figure 2).

### Responses to All after CEI

After CEI administration there was no change in the aldosterone response curve or threshold sensitivity in the NR (Figure 3, left), similar to what had been described previously in normotensive subjects. In contrast, the AbR showed a significant increase in responsiveness over the entire dose response curve ($p < 0.01$ chi-squared). Threshold sensitivity fell from 3 to 1 ng/kg/min (Figure 3, left).

In neither group was there a significant difference in the increment in All achieved during the course of the All infusion or a difference before or after administration of the converting-enzyme inhibitor (Figure 3 right).

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**Figure 1.** Dose response relationships between dose of All infused and increment in plasma aldosterone (left) and plasma All (right) and decrement in PAH clearance (center). The hypertensive subjects were divided into normal and abnormal responders (means ± SEM). Responses (means ± 2 SEM) of normotensive subjects are depicted as the shaded area (aldosterone and All, $n = 37$; PAH, $n = 13$).
Figure 2. Regression relationships between control levels of plasma aldosterone (left), renal blood flow (PAH clearance) (center), and plasma angiotensin II (right) before and after CEI in 31 hypertensive subjects. Abnormal responders are denoted by (○) and normal responders by (△). If captopril was used, the symbols are closed; if enalapril, they are open. The line represents the line of equality ($x = y$). Points below the line denote a reduction while points above represent an increase in level after CEI.

Figure 3. Dose-response relationships between dose of All infused and increment in plasma aldosterone (left) and plasma All (right) and decrement in renal blood flow (center). The hypertensive subjects were divided into normal and abnormal responders (means ± SEM). Data are presented for responses both before and after CEI administration.
In contrast to the effect of CEI on aldosterone responses to All, CEI had a similar effect on PAH clearance in the two hypertensive subgroups. In both subgroups, converting-enzyme inhibition significantly \((p < 0.001, \chi^2)\) enhanced the renal vascular response to All to the same degree (Figure 3 center). There was also a significant increase \((p < 0.01, \text{Wilcoxon Sign rank test})\) in the basal PAH level after CEI in both groups (Table 2). The responses in the hypertensive patients to CEI was similar to what has been reported previously in normotensive subjects.

Influence of Basal Plasma Aldosterone Concentration on CEI-Induced Changes in All Responsiveness

As noted above, the AbR hypertensive subgroup had significantly \((p < 0.023)\) lower basal aldosterone levels than the NR group prior to CEI. For that reason, it is important to assess whether the low basal aldosterone level, per se, could account for the change in responsiveness with CEI administration. The AbR were divided into two subgroups based on whether their control aldosterone level pre-CEI was greater or less than 13 ng/dl. The mean basal aldosterone level, as anticipated, was significantly less in those whose values were less than 13 ng/dl \((7.3 \pm 1.2 \text{ ng/dl})\) than those who had values greater than 13 ng/dl \((20.5 \pm 2.8 \text{ ng/dl})\), the latter value being indistinguishable from the basal pre-CEI aldosterone level in the NR (see Table 2). Even though the control aldosterone levels in the two subgroups of hypertensive abnormal responders were significantly different from each other, the influence of CEI on aldosterone responsiveness to All was identical (Figure 4), i.e., there was a significant enhancement \((p < 0.01)\) in aldosterone responses to All in both subgroups after CEI administration.

Discussion

Several studies over the past decade have suggested that a substantial fraction, perhaps 30% to 50%, of patients with essential hypertension have a blunted adrenal response to volume challenge and/or All infusion. \(^3\)\(^-\)\(^3\)\(^13\) This abnormality has been reported to be secondary to the absence of a sodium-intake-mediated change in adrenal sensitivity to All in these individuals. Thus, these patients cannot modulate their adrenal response to All above a basal level regardless of the level of sodium intake. The results of this study suggest that the level of All, itself, may play a role in producing these altered responses. In contrast to what occurred in the NR hypertensive patients and in normotensive subjects, converting-enzyme inhibition significantly enhanced the adrenal response to All in the AbR.

What could account for the differences in adrenal responsiveness to All between the two groups of hypertensives and the effect of converting-enzyme inhibitors on that responsiveness? Judged by clinical criteria, the subjects were similar. Other factors that might account for the blunted aldosterone response are differences in serum potassium or ACTH. However, in both groups of hypertensive patients, serum potassium levels were comparable and unchanged during All in-

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**Figure 4.** Dose-response relationship between dose of All and aldosterone increment in hypertensive abnormal responders. Subjects were divided into two groups according to whether the control plasma aldosterone level was less than \((n = 6)\) or greater than \((n = 6)\) 13 ng/dl. The mean basal aldosterone levels in the two groups were 7.3 \(\pm\) 1.2 and 20.5 \(\pm\) 2.8 ng/dl, respectively. The aldosterone response to All and the influence of CEI was not different between the two groups (means \(\pm\) SEM).
fusion, and plasma cortisol levels declined in the normal diurnal fashion.

What potential mechanisms could produce these abnormalities? Abnormalities in the tissue concentration of All or the All receptor are obvious candidates. Restriction of sodium intake enhances the adrenal response to All in normal subjects. The mechanisms responsible for these abnormalities at each step are still controversial; however, several lines of evidence would suggest that these changes could reflect differences in receptor effects produced by sodium intake. For example, anephric patients, despite low and fixed endogenous All levels, increase adrenal responses to infused All with sodium depletion. In vitro studies have produced conflicting results. In some studies in which ligand binding was assessed directly, All appears to upregulate its receptors. In other reports in which pharmacologic probes were used, downregulation seems to have occurred. In normal subjects studied under conditions identical to those used in the present study with hypertensive patients, adrenal responses to All were not modified by converting-enzyme inhibitors. The present study, as well as others, suggest that in normal subjects, factors other than changes in endogenous All levels are primarily responsible for the enhanced adrenal response to All with sodium restriction, since the responsiveness was unaffected by CEI. In a preliminary report, in 10 patients with essential hypertension who were given captopril there was an enhanced adrenal response to All. The present study suggests that this finding is not universal in patients with essential hypertension, but is isolated to those individuals who have a decreased adrenal response to All with sodium restriction.

How might converting-enzyme inhibitors modify aldosterone responses in the AbR? Several possibilities exist. It has been suggested that converting enzyme inhibitors may modify a variety of hormonal systems in addition to its effect on All generation. Potentially, some of these other effects may be responsible. However, none have been shown to modify aldosterone secretion directly. Thus, while a nonspecific effect of converting-enzyme inhibitors may be producing the change, the fact that the correction was produced both with captopril and enalapril makes this less likely. A second possibility could simply be the effect of a lower blood pressure per se. This seems unlikely since blood pressure was lowered to a comparable extent in both subgroups of hypertensive patients, but only in the AbR were aldosterone responses modified.

A third possibility is related to its primary effect: reduction of All and the consequential reduction in aldosterone secretion. The net result of the former should be a tendency for potassium retention, which has been reported in individuals who have taken converting-enzyme inhibitors. Since increasing potassium will enhance the ability of the adrenal to respond to All, there is a possibility that the alterations that we are seeing are secondary to a potassium effect. However, we did not see a change in serum potassium concentration in our hypertensive patients. Moreover in normal subjects, increasing potassium intake is much less potent than decreasing sodium intake in enhancing adrenal responsiveness to All.

Finally, there is the possibility that angiotensin-mediated aldosterone secretion is not regulated in the same way in the AbR as in normotensive subjects. It has been suggested that the major factor regulating the amount of aldosterone produced in the adrenal gland with changes in All concentration is not the changes in receptor number or affinity but rather a change in an event distal to that, i.e., at the late pathway of aldosterone biosynthesis. The late pathway enzymatic activity is modified so that there is an increased rate of conversion of corticosterone to aldosterone with sodium restriction and a reduced rate of conversion with sodium loading. If this mechanism were absent in the AbR, then one of the ways that the converting-enzyme inhibitors could increase adrenal responsiveness is utilizing the same mechanisms operating on the vascular smooth muscle.

There is little disagreement that the enhanced response of the renal vasculature to All administration after converting-enzyme inhibition reflects upregulation of the All receptor because of a reduced All concentration. Theoretically, this could also modify adrenal responses by upregulating adrenal All receptors, thereby increasing responsiveness of the adrenal glomerulosa cell to All. This would require two assumptions: first, the patients would have to have an inoperative late pathway modulating system and secondly, the adrenal All receptor would have to downregulate with increased All concentration, a phenomenon that has been difficult to consistently demonstrate in normal animals or humans; and indeed, in the rat the opposite appears to be true.

This study, in contrast to some previous studies of this phenomenon, clearly documents that the abnormal responsiveness is not related to the basal preinfusion aldosterone levels. As a group, the AbR had lower basal aldosterone levels. Yet, even those with normal basal aldosterone levels had a shift in the dose response curve in contrast to the NR hypertensive subjects (Figure 4). Finally, it should be pointed out that even after converting-enzyme inhibition the adrenal response to All was not the same in the AbR and NR subjects. Whether this is a reflection of a continued abnormality or that the duration of converting-enzyme inhibition was not long enough to fully restore normal responsiveness is uncertain.

In summary, 30% to 50% of patients with normal and high renin essential hypertension have decreased adrenal responsiveness to All when assessed on a sodium-restricted intake. This abnormality is partially corrected by administration of a converting-enzyme inhibitor in a remarkably short time, 72 hours. These results provide further insight into the mechanism underlying this abnormality and, perhaps more important, provide a therapeutic approach to correct it and thereby normalize blood pressure in a more specific way.
Acknowledgments

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