Altered Renin-Angiotensin-Aldosterone Relationships in Normal Renin Essential Hypertension

Thomas J. Moore, Gordon H. Williams, Robert G. Dluhy, Samuel Z. Bavli, Thep Himathongkam, and Martin Greenfield

SUMMARY Aldosterone responsiveness to angiotensin II (AII) was evaluated in 64 subjects with “normal renin” hypertension. Plasma aldosterone (PA) and plasma renin activity (PRA) levels were determined with the subjects supine and after 2½ hours in the upright position while they were in metabolic balance on a 10 mEq of sodium/100 mEq of potassium diet. The increment in PA between supine and upright postures divided by the increment in PRA (ΔPA/ΔPRA) was used as an estimate of adrenal sensitivity to AII. Under identical conditions, the ΔPA/ΔPRA ratio in 11 normal controls was 3.8. Although 52 of the hypertensive subjects had normal ΔPA/ΔPRA, 12 had low ΔPA/ΔPRA. Supine PA and PRA were similar in both groups, but the upright PA was lower (41 vs. 69 ng/dl) and the upright PRA higher (11.1 vs. 7 ng/ml per hr) in the group with the subnormal ΔPA/ΔPRA. The low ΔPA/ΔPRA ratios indirectly suggest subnormal aldosterone responsiveness to AII. To test this hypothesis directly, AII was infused into 19 of the 64 subjects (0.1, 0.3, 1.0, and 3.0 ng/kg per min). PA and AII levels were measured before and 20 and 30 min after each dose was begun. Blood pressure was monitored at 2-min intervals. In 14 hypertensives with normal ΔPA/ΔPRA, PA rose significantly during the 0.3, 1.0, and 3.0 ng/kg per min doses. In five subjects with low ΔPA/ΔPRA, PA did not rise significantly at any dose of AII. Plasma AII levels and blood pressure rose comparably in both groups. These data demonstrate that, in the sodium-depleted state, some “normal renin” hypertensive subjects have decreased aldosterone but normal pressor responsiveness to angiotensin II.

SUBJECTS WITH “normal renin” hypertension were originally thought to be a homogenous group with normal renin-angiotensin-aldosterone (RAA) interrelationships.1-4 There is now, however, a growing body of data suggesting that the RAA axis is abnormal even in “normal renin” subjects.5-11 Recently, Kisch et al.12 reported that normal renin hypertensives on high sodium intakes had greater aldosterone responsiveness to infused angiotensin II than did normotensive controls on similar diets. Since it has been shown that sodium depletion increases adrenal glomerulosa responsiveness to angiotensin II,13-16 it could be hypothesized that sodium depletion the hypertensive subjects before infusing angiotensin might magnify the adrenal hyperresponsiveness described by Kisch et al.12 Thus, it could be demonstrated whether increased adrenal responsiveness to angiotensin II was common to all or just a subgroup of normal renin hypertensives.

The present study was performed to characterize the adrenal’s response to angiotensin II in sodium-depleted normal renin hypertensive subjects. Two methods of assessing adrenal responsiveness were employed: (1) the adrenal response to endogenous angiotensin stimulation was determined by relating the incremental response of plasma aldosterone to upright posture to the increment in plasma renin activity; (2) exogenous angiotensin II was infused intravenously in graded doses. Rather than finding an enhanced adrenal response, many of the hypertensive subjects demonstrated subnormal adrenal responsiveness to angiotensin II.

Methods

Sixty-four patients with normal renin essential hypertension (47 males, 17 females) were studied at the Clinical Research Center of the Peter Bent Brigham Hospital and their responses compared with 11 normotensive controls (six males, five females) studied under identical conditions. The age range of the normal subjects was 20-39 (mean of 28 years). Responses in some of these normal subjects have been reported previously.14 The criteria for inclusion of hypertensive subjects in the study were as follows: outpatient supine diastolic blood pressure greater than 90 mm mercury determined on three different occasions and documented evidence of hypertension for at least 6 months before the study. All antihypertensive medications were discontinued at least 2 weeks prior to admission. The subjects were fed an isocaloric diet of 10 mEq of sodium/100 mEq of potassium. Daily 24-hour urine samples were analyzed for sodium, potassium, and creatinine. Subjects with primary aldosteronism, pheochromocytoma, renal vascular disease, and Cushing’s syndrome were ex-
cluded by rapid sequence intravenous pyelogram, urinalysis, serum creatinine, serum electrolytes, 24-hour urinary vanillylmandelic acid (VMA), metanephrines, 17-OH, and aldosterone levels, and, where clinically indicated, renal arteriogram and bilateral renal vein renin determinations. Thirty-nine per cent of the 64 subjects reported herein did have a renal angiogram which in all cases was normal. Subjects with high and low renin essential hypertension also were excluded. The normal PRA in our laboratory is 2.4-15 ng/ml per hour (upright posture, 10 mEq of sodium diet). The protocol was approved by the Human Subjects Committee of the Peter Bent Brigham Hospital and written informed consent was obtained in all cases.

UPRIGHT POSTURE STUDY

When subjects had achieved metabolic balance, usually on the 5th or 6th day of sodium restriction, after an overnight fast and maintenance of a supine position for at least 12 hours, two supine control samples were drawn at least 30 minutes apart and the subjects were told to walk for 21/2 hours. Additional blood samples were obtained after 120 and 150 minutes of upright posture. All samples were analyzed for plasma renin activity, aldosterone and cortisol, serum sodium and potassium, and, in a subpopulation of 16 subjects, angiotensin II levels. Eleven normal controls were studied in an identical fashion.

ANGIOTENSIN II INFUSION

On a different day, during the same hospital stay when the subjects were still in balance on a sodium-restricted intake, 19 of the previously studied hypertensive subjects were infused with angiotensin II. Adrenal and vascular responses to angiotensin II were compared to those of six normotensive controls studied under identical conditions. After an overnight fast, with the subjects in the supine position, an intravenous line was placed in each of the subject's arms (one for infusion and one for blood sampling). Control blood samples were obtained and a graded infusion of angiotensin II (Hypertensin, Ciba) was begun with a Harvard infusion pump at rates of 0.1, 0.3, 1.0, and 3.0 ng/kg per min as previously described. Each dose was infused for 30 minutes and blood samples were obtained at 20 and 30 minutes at each level. All samples were analyzed for angiotensin II, aldosterone, cortisol, sodium, and potassium. Blood pressure was monitored using an indirect recording sphygmomanometer (Arteriosonde, Hoffmann-La Roche) at 2-minute intervals for a 30-minute control period and throughout the angiotensin infusion.

LABORATORY PROCEDURES

All blood samples were immediately centrifuged and the plasma separated and frozen until time for assay. Samples for PRA and A II levels were drawn with ethylenediaminetetraacetic acid (EDTA) as the anticoagulant; heparin was used as the anticoagulant in the samples for cortisol and aldosterone. Serum and urine sodium and potassium levels were measured by flame photometry with lithium as an internal standard. Plasma aldosterone, renin activity, and angiotensin II values were measured by radioimmunoassay techniques as previously described. The values for renin activity and angiotensin II were reported in reference to the World Health Organization Standards 71-328 and 70-302, respectively. Therefore, the absolute values may differ somewhat from those reported previously from this laboratory. The results are expressed as mean ± standard error of the mean. Threshold dose during angiotensin infusion is defined as the lowest dose of angiotensin II required to produce a response significantly different from control using two way analysis of variance and P values were obtained in Dunnett's tables. For other statistical analyses for parametric data Student's t-test and for nonparametric data, Fisher Exact Test (FET) were used. Differences are considered significant for P < 0.05 unless otherwise indicated.

Results

UPRIGHT POSTURE STUDY

Release of endogenous renin and generation of angiotensin II were increased by upright posture. The increment in plasma renin activity between supine and upright positions (ΔPRA) was used as an estimate of the degree of acute stimulation of the adrenal gland by angiotensin II. The plasma aldosterone increment (ΔPA) (supine → upright) was used as a measure of the adrenal response. Thus, the ratio ΔPA/ΔPRA reflects the response of plasma aldosterone relative to changes in plasma renin.

The individual ratios for the 64 hypertensives and 11 normotensive controls are shown in Figure 1. All of the normal subjects had APA/APRA ratios greater than 3.8. In contrast, 12 of the 64 subjects with normal renin essential hypertension (20%) had ratios lower than those of any of the normotensive controls. There were no significant differences in a number of metabolic or biochemical parameters between the normotensive and hypertensive subjects (Table 1). Specifically, there was no diff-

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**Figure 1**: Comparison of normotensive and hypertensive subjects classified according to their ΔPA/ΔPRA ratios which represent the increment in plasma aldosterone (ΔPA) divided by the increment in plasma renin activity (ΔPRA) when the subjects change from the supine to the upright position (10 mEq Na diet).
sive controls, the plasma renin activity and angiotensin II subgroups of hypertensive subjects and in the normoten-sive hypertensive subjects \((y = 7.1x + 15)\). In both the normal controls \((y = 8.1x + 1.7)\) and the low APA/APRA, angiotensin II and renin activity was not significantly different between seven with low APA/APRA and all of the normal sub-
groups. The regression relationship between angiotensin II could be a decrease in the generation of angiotensin II per unit of renin activity, angiotensin II levels were measured in 16 of 64 hypertensive subjects (nine with normal and seven with low APA/APRA) and all of the normal sub-
jects. The regression relationship between angiotensin II and renin activity was not significantly different between the normal controls \((y = 8.1x + 1.7)\) and the low APA/APRA hypertensive subjects \((y = 7.1x + 15)\). In both subgroups of hypertensive subjects and in the normoten-sive controls, the plasma renin activity and angiotensin II values correlated significantly \((P < 0.001)\).

**ANGIOTENSIN II INFUSION**

To assess more directly the adrenal responsiveness to angiotensin II and to compare adrenal and vascular responses, angiotensin II was administered intravenously to 19 (30%) of the 64 hypertensive subjects and to six normoten-sive controls. Fourteen hypertensive subjects had normal and five had low \(\Delta PA/\Delta PRA\) ratios. There were no significant biochemical or metabolic differences be-tween the two subgroups (Table 2). Figure 3 shows the mean increment in blood pressure, angiotensin II, and aldosterone levels in response to graded infusions of angiotensin II in the two subgroups of hypertensive subjects compared to the normotensive controls. There were no significant differences in the plasma aldosterone or angiotensin II levels obtained at 20 and 30 minutes after the initiation of a particular dose of angiotensin II; therefore, the 20- and 30-minute values have been pooled.

Angiotensin II levels rose similarly in all three groups. The only difference was at the highest angiotensin II infusion rate for which the increment in angiotensin II in the low \(\Delta PA/\Delta PRA\) hypertensive group was significantly greater \((P < 0.005; \text{FET})\) than in either the normal \(\Delta PA/\Delta PRA\) group or the normotensive controls. The latter two were not significantly different from each other.

The threshold dose for blood pressure response was 0.3 ng/kg per min in the normal \(\Delta PA/\Delta PRA\) hypertensives and 1.0 ng/kg per min in the low \(\Delta PA/\Delta PRA\) hypertensives and normotensive controls. However, the blood pressure increments at each dose of angiotensin II were not significantly different in the three groups.

A significant increment \((P < 0.01)\) in plasma aldosterone occurred at an infusion rate of 0.3 ng/kg per min in hypertensive subjects with normal \(\Delta PA/\Delta PRA\) and at 1 ng/kg per min in the normotensive controls. On the other

![Figure 2](http://circres.ahajournals.org/)

**Figure 2** Supine and upright plasma aldosterone and plasma renin activity in normal \((n = 52)\) and low \((n = 12)\) \(\Delta PA/\Delta PRA\) hypertensives \((10 \text{ mEq Na diet}; \text{mean } \pm \text{ SEM})\).
TABLE 2 Characteristics of Hypertensive Subjects Who Were Infused with Angiotensin II (Divided into Two Groups According to Their $\Delta$PA/$\Delta$PRA Upright Posture Responses)

<table>
<thead>
<tr>
<th>Normal $\Delta$PA/APRA</th>
<th>Low $\Delta$PA/APRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>14</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>35 ± 3</td>
</tr>
<tr>
<td>Low salt Na$_{\text{c}}$ (mEq/24 hr)*</td>
<td>12 ± 4</td>
</tr>
<tr>
<td>Low salt K$_{\text{c}}$ (mEq/24 hr)*</td>
<td>87 ± 5</td>
</tr>
<tr>
<td>Control serum Na (mEq/liter)</td>
<td>142 ± 1</td>
</tr>
<tr>
<td>Control serum K (mEq/liter)</td>
<td>4.1 ± 0.1</td>
</tr>
<tr>
<td>Control mean BP (mm Hg)</td>
<td>103 ± 3</td>
</tr>
<tr>
<td>Control angiotensin II (pg/ml)</td>
<td>35 ± 4</td>
</tr>
<tr>
<td>Control aldosterone (ng/dl)</td>
<td>25 ± 4</td>
</tr>
<tr>
<td>Control cortisol (µg/dl)</td>
<td>13 ± 2</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM. BP = blood pressure.
* Values on the day of angiotensin infusion.

Discussion

The present study demonstrates that some subjects with normal renin essential hypertension do not have a normal relationship between the various components of the RAA axis when studied in the sodium-depleted state. However, in contrast to the enhanced adrenal responsiveness found by Kisch et al.22 in sodium-loaded hypertensives, in 12 of the 64 hypertensives in this study (20%) aldosterone responsiveness was diminished as determined by the ratio of the increment in plasma aldosterone to renin activity in the upright position. The altered adrenal responsiveness in these subjects was directly confirmed by infusing angiotensin II, with the low $\Delta$PA/APRA group responding subnormally both in terms of threshold dose and absolute aldosterone increments. It is important to note that while adrenal responses to angiotensin II were significantly different in the two hypertensive subgroups, blood pressure responses were similar.

Although the state of sodium and potassium balance can influence adrenal responsiveness to angiotensin II,15-16 no differences in electrolyte balance were found between the hypertensive groups. In addition, because cortisol levels were similar, it is unlikely that the aldosterone levels reflect differences in adrenocorticotropin (ACTH) secretion in the two groups. Another explanation for the difference in aldosterone levels could be an increase in the metabolic clearance rate of aldosterone in the low $\Delta$PA/APRA group. This is unlikely because only decreases in aldosterone metabolic clearance rates have been reported in essential hypertensives.23 However, because aldosterone one metabolic clearance in our subjects was not assessed, such a possibility cannot be definitely excluded.

It has been reported that subjects with high circulating angiotensin II levels are less sensitive to both the pressor and aldosterone-stimulating effects of infused angiotensin II. Kaplan24 found that higher doses of angiotensin II were needed to achieve a rise in blood pressure in subjects with malignant hypertension or cirrhosis and ascites. Ames et al.25 reported diminished blood pressure and aldosterone responses to angiotensin II in subjects with cirrhosis. These findings suggest that high angiotensin II levels per se may cause relative unresponsiveness to infused angiotensin II. It is unlikely that this phenomenon accounts for the differences found in the hypertensive population in this report for two reasons. First, the angiotensin II levels were within the normal range and identical in both hypertensive subgroups at the start of the angiotensin II infusion (35 pg/ml). Second, in the previous reports, high circulating angiotensin II levels were associated with both pressor and aldosterone hyporesponsiveness to infused angiotensin II. In the present study, the hypertensive subjects with subnormal adrenal responsiveness had normal pressor responsiveness; this suggests a more specific defect in the interaction of angiotensin II with the glomerulosa cell.

It is possible that sodium depletion uncovers a subgroup...
of normal renin hypertensive subjects with a specific defect in angiotensin-aldosterone interaction. This is unlikely because the distribution of ΔPA/ΔPRA ratios in Figure 1 suggests that there are no distinct subgroups among the hypertensive subjects but rather this group constitutes a single population with a wider range of adrenal responsiveness than in the normotensive subjects. A more likely hypothesis to explain the subjects with subnormal adrenal responsiveness is that dietary sodium content does not alter adrenal sensitivity to angiotensin II as consistently in hypertensive as in normotensive subjects. Therefore, the hypertensives' adrenal responsiveness would increase less in the sodium-depleted state and reveal those individuals with low ΔPA/ΔPRA ratios (subnormal adrenal responsiveness). Conversely, sodium loading would suppress adrenal responsiveness less in the hypertensive than in the normotensive subjects and reveal the adrenal hyperresponsiveness to angiotensin II reported by Kisch in his hypertensive patients. If this is the case, the present study and Kisch's findings, although seemingly contradictory, could be demonstrating the same phenomenon.

In conclusion, it could be speculated that hypertensive subjects with subnormal adrenal responsiveness, in order to close their renin-angiotensin-aldosterone volume feedback loop, generate more angiotensin II even though the plasma levels are still within the normal range. Since blood pressure response to angiotensin II is normal, the net effect could be an elevated blood pressure. In support of this hypothesis is a preliminary communication which reports that some but not all patients with normal renin essential hypertension show a reduction in blood pressure when given an angiotensin I converting enzyme inhibitor; this suggests that these individuals have an angiotensin- mediated component to their hypertension.

References

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