Response of Aldosterone and 18-Hydroxycorticosterone to Angiotensin II in Normal Subjects and Patients with Essential Hypertension, Conn’s Syndrome, and Nontumorous Hyperaldosteronism


SUMMARY Dose-response curves relating plasma angiotensin II (All) concentration during All infusion to blood pressure (BP), to plasma aldosterone, and to plasma 18-hydroxycorticosterone were compared in normal subjects and in patients with essential hypertension, Conn’s syndrome, and nontumorous hyperaldosteronism. The BP response was steeper than normal in patients with Conn’s syndrome and essential hypertension. Before infusion, mean plasma aldosterone concentration was approximately four-fold higher in Conn’s syndrome than in the normal group, while that of 18-hydroxycorticosterone was ninefold higher. Neither increased significantly during All infusion. In essential hypertension, both corticosteroids were within the normal range, but their responses to All infusion were greater than normal. In the three subjects with nontumorous hyperaldosteronism, plasma aldosterone and 18-hydroxycorticosterone concentrations were raised, and their responses to All infusion resembled those found in essential hypertension and were different from those found in Conn’s syndrome. This suggests that nontumorous hyperaldosteronism is not a variant of Conn’s syndrome. In the response to All and in other ways, it is indistinguishable from essential hypertension.

(Hypertension 3 (supp I): I-87-I-92, 1981)

KEY WORDS • aldosterone • angiotensin II • 18-hydroxycorticosterone • essential hypertension • normal subjects • Conn’s syndrome • nontumorous hyperaldosteronism

ALTHOUGH many interacting factors, notably ACTH, sodium, and potassium, determine the secretion rate and plasma concentration of aldosterone in humans, angiotensin II (All) is probably the most important. Angiotensin II also raises the plasma concentrations of 18-hydroxycorticosterone, the probable immediate precursor of aldosterone, but is unimportant in controlling the plasma levels of other corticosteroids. In normal subjects, the relationship between plasma All and aldosterone levels can be altered, for example, by sodium depletion or loading: the effect on plasma 18-hydroxycorticosterone concentration is less clear but may also change in this way (see review 1).

The All: aldosterone relationship may differ from normal in some types of hypertension, including essential hypertension, primary hyperaldosteronism due to a benign adrenocortical adenoma (Conn’s syndrome), and hyperaldosteronism associated with bilateral micronodular hyperplasia of the adrenal cortex (nontumorous hyperaldosteronism). Data on the behavior of 18-hydroxycorticosterone in plasma in these categories are sparse. The present study compares the effect of All infusion on plasma concentrations of aldosterone and 18-hydroxycorticosterone in groups of subjects with these forms of hypertension to its effect in normal subjects.

Methods

All subjects were studied under identical conditions in a metabolic ward. For 5 to 6 days before the study, they ate a fixed diet containing between 145 and 155 mEq sodium and between 50 and 80 mEq potassium daily. Angiotensin II (Hypertensin, Ciba) was infused according to techniques already published, in 5% dextrose (5 ml hr⁻¹) at successive rates of 0.5, 1.0, 2.0, 4.0, and 8.0 ng • kg⁻¹ min⁻¹, each rate being continued for 1 hour. Each subject received only three rates depending on the basal BP. Blood samples were taken at the end of each period, and BP was measured auto-
matically (Bosomat) at 10-minute intervals. Plasma concentrations of AI\textsuperscript{1} and aldosterone\textsuperscript{2} were measured by radioimmunoassay and 18-hydroxycorticosterone\textsuperscript{3} and cortisol\textsuperscript{4} by gas-liquid chromatography. Total body clearance of infused AI\textsuperscript{1} was calculated by dividing the infused dose $\text{min}^{-1}$ by the associated change in plasma concentration and using the mean for the three infusion rates.

Details of patients and controls are given in table 1. Those with essential hypertension had a diastolic BP consistently above 100 mm Hg in the outpatient department, a normal intravenous pyelogram, normal plasma concentrations of aldosterone and electrolytes, and normal urinary vanilmandelic acid (VMA) excretion. Of the 10 patients, seven had normal plasma renin concentrations; three had low renin essential hypertension.\textsuperscript{5} The diagnosis of Conn's syndrome was based on the demonstration of an adrenal lesion by computed tomography and adrenal venography and of a gradient in the adrenal vein blood levels of aldosterone; in five of eight patients, this was confirmed by surgery followed by histological examination of the tumor. Nontumorous hyperaldosteronism was diagnosed in three patients with high plasma aldosterone in whom no tumor was demonstrable by computed tomography and adrenal venography and in whom adrenal vein aldosterone levels did not indicate a unilateral lesion. All hypertensive subjects were untreated at the time of study or had had treatment withdrawn for at least one month (bethanidine for at least 2 days). Control subjects had an arterial pressure consistently below 140/90 mm Hg before the study.

Results

Plasma Angiotensin II

Basal plasma AI\textsubscript{1} concentration was similar in normal subjects and patients with essential hypertension or nontumorous hyperaldosteronism (table 2). It was slightly, but not significantly, lower in patients with Conn's syndrome. Total body AI\textsubscript{1} clearance was also similar in normal subjects ($5.6 \pm 0.4 \text{ SEM} \text{ l} \cdot \text{min}^{-1}$), in patients with essential hypertension ($6.2 \pm 0.6 \text{ l} \cdot \text{min}^{-1}$) and nontumorous hyperaldosteronism ($5.2 \pm 1.1 \text{ l} \cdot \text{min}^{-1}$), but slightly lower ($3.7 \pm 0.9 \text{ l} \cdot \text{min}^{-1}$, $p < 0.05$) in Conn's syndrome compared with essential hypertension.

Blood Pressure

Blood pressure was highest in Conn's syndrome (table 2, fig. 1). The largest increase of arterial pressure for a given rise in plasma AI\textsubscript{1} was seen in Conn's syndrome, and the response in essential hypertension was also greater than normal. The enhanced pressor response in essential hypertension was not a consequence of lower AI\textsubscript{1} levels before infusion, since these were similar to those found in normal subjects. Too few data were obtained to compare the pressor response to AI\textsubscript{1} in the nontumorous hyperaldosteronism group.

Plasma Aldosterone and Cortisol

Basal plasma aldosterone concentration (table 2) was slightly but insignificantly higher in patients with essential hypertension than in normal subjects. It was significantly raised in both nontumorous hyperaldosteronism ($p < 0.05$) and in Conn's syndrome ($p < 0.02$).

Infusion of AI\textsubscript{1} (table 2, figs. 2 and 3) increased plasma aldosterone concentration in all groups except in Conn's syndrome. The dose-response curve was steeper than normal in patients with essential hypertension (fig. 2). For example, at the 4 ng $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$ infusion rate, plasma aldosterone concentration increased by a mean of 23 ng 100 ml$^{-1}$ in essential hypertension as compared with 15 ng 100 ml$^{-1}$ in normal subjects. This increased responsiveness can also be illustrated by expressing the changes in plasma aldosterone and AI\textsubscript{1} as a ratio that was significantly higher ($p < 0.05$) in essential hypertensive patients ($0.62 \pm 0.12$) than in normal subjects ($0.32 \pm 0.06$). In the three cases of nontumorous hyperaldosteronism, (fig. 2) a positive response of aldosterone to AI\textsubscript{1} infusion compared to normal was obtained that resembled that seen in essential hypertension.

Basal plasma cortisol levels were not significantly different in the four groups (normal, $7.9 \pm 0.9 \mu g$ 100 ml$^{-1}$; Conn's syndrome, $7.0 \pm 1.3 \mu g$ 100 ml$^{-1}$; nontumorous hyperaldosteronism, $3.1 \pm 2.3 \mu g$ 100 ml$^{-1}$) and were not significantly altered by AI\textsubscript{1} infusion.
Plasma 18-Hydroxycorticosterone

Basal plasma 18-hydroxycorticosterone concentrations were slightly but insignificantly raised in essential hypertension and nontumorous hyperaldosteronism (table 2). However, concentrations in patients with Conn's syndrome were markedly (p < 0.01) higher than normal. The proportionate increase was greater for 18-hydroxycorticosterone (ninefold) than for aldosterone (fourfold).

As with aldosterone, plasma 18-hydroxycorticosterone increased in response to AII infusion in normal subjects. In patients with essential hypertension and nontumorous hyperaldosteronism, the response was enhanced (figs. 4 and 5) while in Conn's syndrome

<table>
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<tr>
<th>Characteristics</th>
<th>Normal subjects</th>
<th>Essential hypertension</th>
<th>Primary hyperaldosteronism</th>
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<td>Number</td>
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<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>9/3</td>
<td>9/1</td>
<td>2/6</td>
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<tr>
<td>Age (yrs)</td>
<td>36 ± 3</td>
<td>42 ± 3</td>
<td>39 ± 3</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>71.3 ± 4.7</td>
<td>79.7 ± 3.2</td>
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<tr>
<td>Blood pressure (mm Hg)</td>
<td>121/77 ± 4/2</td>
<td>152/97 ± 5/3</td>
<td>170/109 ± 11/7</td>
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<td>Plasma sodium (mmole/liter)</td>
<td>140 ± 1</td>
<td>139 ± 1</td>
<td>142 ± 1</td>
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<td>Plasma potassium (mmole/liter)</td>
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<td>4.2 ± 0.1</td>
<td>3.0 ± 0.2</td>
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<td>Plasma urea (mmole/liter)</td>
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<td>5.4 ± 0.2</td>
<td>4.3 ± 0.5</td>
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<td>Plasma renin concentration (active, µU/ml)</td>
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<td>16 ± 4</td>
<td>8 ± 2</td>
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<tr>
<td>Plasma angiotensin II (pg/ml)</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>NS</td>
<td>17.5 ± 2.5</td>
<td>—</td>
<td>—</td>
<td>38.2 ± 5.3</td>
<td>77.5 ± 6.7</td>
</tr>
<tr>
<td>EH</td>
<td>17.0 ± 1.8</td>
<td>—</td>
<td>29.8 ± 2.7</td>
<td>50.4 ± 5.2</td>
<td>73.0 ± 4.2</td>
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<tr>
<td>Conn</td>
<td>13.2 ± 2.8</td>
<td>23.9 ± 4.0</td>
<td>35.1 ± 6.9</td>
<td>58.2 ± 10.4</td>
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<td>NTPA</td>
<td>17.7 ± 2.4*</td>
<td>25.5 ± 6.6†</td>
<td>34.5 ± 5.6†</td>
<td>41.3 ± 9.3*</td>
<td>124‡</td>
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<td>NS</td>
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<td>91 ± 3</td>
<td>98 ± 7</td>
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<tr>
<td>EH</td>
<td>95 ± 3 (&lt;0.05)</td>
<td>—</td>
<td>100 ± 3</td>
<td>107 ± 3 (&lt;0.01)</td>
<td>115 ± 3 (&lt;0.01)</td>
</tr>
<tr>
<td>Conn</td>
<td>119 ± 6 (&lt;0.001)</td>
<td>124 ± 6</td>
<td>130 ± 8</td>
<td>138 ± 6 (&lt;0.001)</td>
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<tr>
<td>NTPA</td>
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<td>108 ± 1†</td>
<td>105 ± 1</td>
<td>120 ± 8*</td>
<td>155‡</td>
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<td>Plasma aldosterone (ng/100 ml)</td>
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<td>—</td>
<td>—</td>
<td>17.2 ± 2.0</td>
<td>23.9 ± 2.5</td>
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<tr>
<td>EH</td>
<td>11.2 ± 1.0</td>
<td>—</td>
<td>16.5 ± 1.7</td>
<td>26.5 ± 2.3 (&lt;0.01)</td>
<td>34.1 ± 2.9 (&lt;0.02)</td>
</tr>
<tr>
<td>Conn</td>
<td>27.9 ± 8.8 (&lt;0.02)</td>
<td>29.6 ± 6.7</td>
<td>27.0 ± 5.3</td>
<td>25.5 ± 3.3 (0.05)</td>
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<tr>
<td>NTPA</td>
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<td>28.5 ± 5.6†</td>
<td>37.0 ± 9.1†</td>
<td>39.3 ± 6.3*</td>
<td>34‡</td>
</tr>
<tr>
<td>Plasma 18-hydroxycorticosterone (ng/100 ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>7.4 ± 1.2</td>
<td>—</td>
<td>—</td>
<td>13.9 ± 2.1</td>
<td>22.1 ± 2.3</td>
</tr>
<tr>
<td>EH</td>
<td>13.5 ± 2.6</td>
<td>—</td>
<td>20.1 ± 2.6</td>
<td>30.3 ± 5.5 (&lt;0.01)</td>
<td>36.9 ± 5.6 (0.02)</td>
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<tr>
<td>Conn</td>
<td>64.4 ± 13.8 (&lt;0.01)</td>
<td>60.7 ± 19.2</td>
<td>70.7 ± 25.6</td>
<td>66.4 ± 20.4 (&lt;0.01)</td>
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</tr>
<tr>
<td>NTPA</td>
<td>15.8 ± 3.8*</td>
<td>37.0 ± 27.8†</td>
<td>43.5 ± 13.6†</td>
<td>51.0 ± 17.9*</td>
<td>44‡</td>
</tr>
</tbody>
</table>

NS = normal subjects; EH = essential hypertension; Conn = Conn's syndrome; NTPA = nontumorous primary aldosteronism. Figures in parenthesis are probability values from comparison with the normal group by Student's t. Where no value is given, p > 0.05.

* n = 3.
† n = 2.
‡ n = 1.
FIGURE 2. Response of plasma aldosterone to angiotensin II infusion in normal subjects and patients with essential hypertension and nontumorous hyperaldosteronism.

FIGURE 3. Response of plasma aldosterone to angiotensin II infusion in patients with Conn's syndrome.

it was subnormal (fig. 6). Angiotensin II infused at a rate of 4 ng · kg⁻¹ min⁻¹ raised plasma 18-hydroxycorticosterone concentration by a mean of 23 ng · 100 ml⁻¹ in the essential hypertension group, but only 15 ng · 100 ml⁻¹ in the normal subjects. The ratio of the changes in plasma 18-hydroxycorticosterone and All (see above) was also higher (p < 0.001) in essential hypertension (0.68 ± 0.12) than normal (0.31 ± 0.05).

Discussion

Blood Pressure Response

Angiotensin II infusion increased BP in a dose-dependent manner in all groups. The rise was greatest in Conn's syndrome, but was also greater than normal in essential hypertension. These differences are unlikely to be explained by differences in All metabolism among groups since similar infusion rates produced similar plasma concentrations and because, in contrast to one previous study,⁴ angiotensin clearance rates were also not very different from normal. A number of possible mechanisms have been suggested to account for changes in pressor sensitivity to All.⁴ Among these is the "occupancy theory," which postulates that at low plasma levels of All, such as oc-
cur for example in sodium-loaded subjects, proportionately large numbers of smooth muscle receptors are free and available for stimulation. However, this cannot account for the difference between normal and essential hypertension here where basal octapeptide levels were similar.

Aldosterone and 18-Hydroxycorticosterone

Previously reported ratios of the plasma concentrations of 18-hydroxycorticosterone and aldosterone in normal subjects lie between 1 and 2. The ratio is increased during sodium depletion. Schamberlan et al. reported higher ratios. In our current study, the ratio was approximately 1 for normal subjects and for patients with essential hypertension. In nontumorous hyperaldosteronism, the ratio was similar to that found in these groups while that in Conn's syndrome, as also reported by Biglieri and Schamberlan, was higher at 2.3.

In agreement with previous studies in normal subjects, All infusion provoked parallel dose-dependent increases in the plasma concentrations of aldosterone and 18-hydroxycorticosterone, but failed to do so in subjects with Conn's syndrome. Indeed, in some studies All infusion may even have a mildly inhibitory effect on plasma aldosterone. Explanations of this poor response, which is well documented, include the autonomous nature of the tumor secretion and a failure of exogenous All to penetrate the steroid-secreting tissue. Neither explanation seems likely, however, since infusion of ACTH causes a brisk increase in aldosterone, often greater than that obtained in normal subjects. Exogenous All inhibits ACTH in normal subjects. In a recent study, infusion of ACTH at a low, constant rate restored the response of aldosterone to simultaneously-infused All in Conn's syndrome. This suggests that the poor response to angiotensin alone may have been due to inhibition of the endogenous ACTH secretion on which aldosterone is abnormally dependent. Poor 18-hydroxycorticosterone responses probably have the same explanation. In addition, fewer All receptors may be present in the adenoma tissue.

In patients with essential hypertension, plasma aldosterone concentration was more sensitive to infused All than in normal subjects, confirming several previous studies and plasma 18-hydroxycorticosterone levels showed the same difference from normal. In both groups, however, there was a close positive correlation between steroid and octapeptide levels, suggesting that the mechanism of the effect was
similar but exaggerated in essential hypertension. In theory, increased response could be due to an increase in the number or the affinity of adrenocortical angiotensin receptors. These can change independently. There is some evidence of altered affinity in essential hypertension.

**Distinction Between Tumorous and Nontumorous Hyperaldosteronism**

Although only three cases of nontumorous hyperaldosteronism were studied, the pattern of response to angiotensin more closely resembled that seen in essential hypertension than in Conn's syndrome. Other similarities of essential hypertension and nontumorous hyperaldosteronism have been discussed elsewhere. For example, while both All and aldosterone levels remain within the normal range, in both conditions the aldosterone level associated with a given All concentration is higher than in normal subjects: that is, All is low relative to aldosterone. In this respect, the concentrations resemble those in Conn's syndrome, although the mechanism is clearly different.

Reflecting this, the correlation between basal All and aldosterone values is negative in Conn's syndrome and positive in both normal subjects and patients with essential hypertension. A positive correlation also exists between the two variables in nontumorous hyperaldosteronism, again calling into question the "primary" nature of this disease. Demonstration of adrenocortical micronodular hyperplasia in some patients with essential hypertension increases doubt as to the relevance of the pathology to hypertension.

We suggest that nontumorous hyperaldosteronism is not a variant of Conn's syndrome, but is indistinguishable from essential hypertension from which it has been wrongly separated.

**References**

Response of aldosterone and 18-hydroxycorticosterone to angiotensin II in normal subjects and patients with essential hypertension, Conn's syndrome, and nontumorous hyperaldosteronism.

R Fraser, C Beretta-Piccoli, J J Brown, A M Cumming, A F Lever, P A Mason, J J Morton and J I Robertson

Hypertension. 1981;3:I87
doi: 10.1161/01.HYP.3.3_Pt_2.I87

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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