The Pressor Response to Angiotensin II in Patients with Low Renin Essential Hypertension

ALLAN D. MARKS, DAWN B. MARKS, YOUNG N. KIM, JESUS MOCTEZUMA, E. VICTOR ADLIN, AND BERTHAM J. CHANNICK

SUMMARY The etiology of low renin essential hypertension (LREH) has not been established with certainty, but mineralocorticoid excess has been implicated frequently in its pathogenesis. The finding of several investigators of a normal exchangeable sodium space and extracellular fluid volume, however, does not support this hypothesis. To evaluate the possible role of sodium and water retention in LREH, the pressor response to infused angiotensin II (A II) was determined and compared to that of normal subjects and that of subjects with normal renin essential hypertension (NREH). This approach was based on the known supersensitivity of vascular receptors to A II in situations in which sodium and water compartments are expanded as they are, for example, in proven hypermineralocorticoid states such as primary aldosteronism. In this study, we found that subjects with LREH demonstrated no increased pressor response to graded doses of A II; this suggests that LREH is not primarily mediated by sodium and water retention.

A SIGNIFICANT percentage of patients with essential hypertension have normal aldosterone excretion rates but unresponsive or low plasma renin activity (PRA), a condition referred to as low renin essential hypertension (LREH). Because sodium retention with expansion of the body fluid and sodium compartments can suppress renin and raise blood pressure, it has been suggested that LREH is mediated by sodium- and volume-dependent forms of hypertension. A number of investigators have presented evidence, for example, that this disorder is the result of adrenal hypersecretion of a mineralocorticoid, other than aldosterone, which might be deoxycorticosterone (DOC), 18-hydroxydeoxycorticosterone, or 16-hydroxydehydroepiandrosterone.

Further evidence in support of a mineralocorticoid-mediated increase in pressure in LREH is that the reduction in blood pressure noted when these patients are given an inhibitor of adrenal steroidogenesis or high doses of spironolactone, a competitive inhibitor of mineralocorticoid action. In addition, the improvement seen in the degree of hypertension after partial adrenalectomy in patients with LREH and the low sodium-to-potassium ratio reported in the saliva of these patients have also been interpreted as evidence supporting increased mineralocorticoid activity in this subset of essential hypertension.

On the other hand, although it has clearly been shown that patients with primary aldosteronism, a well-documented form of mineralocorticoid hypertension, have increased plasma and extracellular fluid (ECF) volumes as well as an expanded exchangeable sodium space (NaE), measurement of these parameters in LREH have given conflicting results; some investigators demonstrated slight to moderate increases, whereas others reported normal values in patients with LREH.

Although the precise mechanism responsible for the development of LREH has not yet been determined, it is well established that when hypertension is caused by mineralocorticoid hypersecretion with resultant sodium retention, such as occurs in primary aldosteronism or DOC excess, there is a greater sensitivity to the pressor effect of angiotensin II (A II) than is found in normal subjects or in patients with hypertension due to other causes.

If LREH is, in fact, mediated by sodium and water retention, as has been frequently suggested, a similar sensitivity would be expected in these patients. In this study the pressor responsiveness to A II (Hypertensin; Ciba) was measured in patients with LREH and compared to that of normal subjects, patients with normal renin essential hypertension (NREH), and one patient with primary aldosteronism.

Methods

A total of 21 patients with essential hypertension, one with surgically proven primary aldosteronism, and six control subjects were studied on the 4th day of a diet containing 150 mEq of sodium and 70 mEq of potassium in the Clinical Research Center of Temple University Hospital.

The hypertensive subjects underwent a complete physical examination and laboratory and radiological studies designed to rule out all known causes of secondary hypertension. In all instances, renal function was normal as assessed by blood urea nitrogen (BUN), serum creatinine, creatinine clearance, and intravenous pyelography. No subject showed evidence of any serious complication of hypertension such as congestive heart failure or advanced
hypertensive retinopathy. All had an arterial blood pressure of 145/95 mm Hg or greater on at least three different occasions prior to study. All hypertensive medications were discontinued at least 2 weeks prior to admission to the general clinical research center.

PRA in the peripheral blood was determined on the morning of the A II infusions to ascertain that there was a significant difference in PRA between the subjects with LREH and NREH on that specific day. PRA was determined again on the morning of the 7th day of the hospitalization after the subject had been on a 10 mEq sodium diet for 3 days and had been in the upright posture for 4 hours to classify subjects as having low or normal renin essential hypertension. Subjects were defined as having LREH if their PRA value following the latter stimulus was less than 3.5 ng/ml per hr and NREH if their PRA exceeded this level as previously reported.1 PRA was measured by the method of Sealey et al.20 Urinary aldosterone excretion rate was determined on the 3rd day of the 150 mEq sodium diet, by a method previously reported.21 The urinary sodium excretion rate was determined on the same 24-hour specimen. On the morning of the 4th hospital day, after an overnight fast and with the subject supine, blood pressure was measured at 2-minute intervals for 20 minutes prior to the infusion of A II, using a cuff sphygmomanometer to establish the basal pressure level. A II then was infused with a Braun variable speed infusion pump at a rate of 0.5, 2.0, and 5.0 ng/kg per min. A 30-minute interval was allowed between infusions in order to avoid possible tachyphylaxis.22 During each 30-minute infusion, blood pressure was recorded every 2 minutes.

Because the values for each subject were correlated with each dose of A II, it was not valid to use classical regression methods. However, it is valid to compute a slope for each subject and then do an analysis of variance comparing the variability of the slopes among the three groups with the pooled estimate of variance obtained from using the data of the three groups.23

For the purpose of this study, the threshold of the pressor response or the sensitivity to A II was defined as the rate of A II infusion required to produce a 5 mm Hg rise in mean systolic and diastolic blood pressure and was derived from the linear regressions based on the samples used. The true threshold to A II is the rate of infusion necessary to cause an infinitely small increment in pressure. This point is impossible to determine because the lower end of a typical dose-response curve is not linear, and rises in pressure due to A II are not distinguishable from spontaneous fluctuations in pressure in this range. Although the arbitrary threshold determined in this study exceeds the true threshold, the difference is small and the arbitrary threshold can be used as a measure of the sensitivity of the vascular receptors to threshold doses of A II. The slope of the linear regression, on the other hand, reflects the pressor responsiveness to doses of A II exceeding threshold levels. To distinguish between a change in threshold and a change in slope, a dose-response relationship as used in this study must be determined. A single rate of infusion of A II, as used in the critical dose method of Kaplan and Silah,29 may produce the same rise in systolic or diastolic pressure when the threshold and slope are actually different.27

The protocol was approved by the Human Research Committee of Temple University Hospital, and informed written consent was obtained from each participant prior to the start of the study.

Results

The clinical and metabolic characteristics of the normal subjects and the subjects with hypertension are shown in Table 1. Thirteen of the essential hypertensive subjects had normal PRA responses (NREH) following provocation with sodium restriction and upright posture on the 7th day; in eight, the response was low or suppressed (LREH). The difference in PRA values determined in this way between these two groups was significant (P < 0.001). The difference in PRA values for the two groups determined on the 3rd day while on a normal sodium intake in the supine position was also significant (P < 0.01).

The BUN, serum sodium, and serum potassium after 3 days on a normal sodium diet were not significantly different between the normal subjects and the subjects with LREH or NREH. The subject with primary aldosteronism had hypokalemia, slight hypernatremia, an elevated aldosterone excretion rate, and suppressed PRA.

The urinary sodium and aldosterone excretion rates on the 3rd day of the 150 mEq sodium diet were also not different between the low and normal renin essential hypertension groups. No correlation existed between urinary sodium excretion rates and blood pressure responses to A II infusions in any group studied.

Mean blood pressure was significantly higher in both essential hypertension groups than in normal subjects (P < 0.001 in both instances), but there was no difference between LREH and NREH subjects.

The normal subjects were younger than the hypertensives, but there was considerable overlap in age between the groups.

The observed mean increments in systolic and diastolic pressure with each dose of A II are shown in Table 2. These increments were plotted against the logarithm of the rate of A II infusion in ng/kg per min and are shown in Figures 1 and 2, respectively. It was noted that the dose-response curve was linear with the log dose.

There was no significant difference in either the pressor threshold dose of A II (sensitivity) or the slope of the linear regression for systolic pressure increments for the low and normal renin essential hypertensives (Fig. 1). The pressor threshold and the slope for systolic pressure increments were significantly lower (P < 0.05) in the normal subjects, and significantly higher (P < 0.001) in the subject with primary aldosteronism, than in either group of essential hypertensives.

Changes in diastolic pressure are shown in Figure 2. Again, neither the pressor threshold dose of A II nor the slope of the regression was statistically different for diastolic pressure increases in the low and normal renin essential hypertensives. The differences between normal subjects and both essential hypertensive groups also were not significant. On the other hand, both the diastolic
pressor threshold dose of A II and the slope of the linear regression were significantly greater in the subject with primary aldosteronism than in the subjects with LREH or NREH \( (P < 0.001) \).

**Discussion**

In 1964 Kaplan and Silah\(^{20}\) reported a relative insensitivity to the pressor effect of A II in patients with renovascular hypertension when compared to the response in patients with elevations in blood pressure of other etiologies. These authors proposed that this blunted pressor response was related to the high levels of endogenous A II already present in renovascular hypertension when exogenous A II was infused. Although some studies have supported this view,\(^{21,27,28}\) others have not confirmed these observations.\(^{29,31}\)

The conflicting data suggest that when the circulating level of A II is either normal or elevated, the pressor response to infused A II does not reliably reflect the concentration of A II in the circulation. On the other hand, the pressor threshold dose of A II and the slope of the linear regression were significantly greater in the subject with primary aldosteronism than in the subjects with LREH or NREH \( (P < 0.001) \).

### Table 1: Characteristics of Normal and Hypertensive Subjects

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Subjects with NREH*</th>
<th>Subjects with LREH†</th>
<th>Subject with aldosteronism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>6</td>
<td>13</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31 (23-40)</td>
<td>36 (18-51)</td>
<td>42 (26-53)</td>
<td>49</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67 (48-84)</td>
<td>69 (51-87)</td>
<td>68 (54-82)</td>
<td>64</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>14 ± 1.4</td>
<td>15 ± 1.9</td>
<td>15 ± 2.4</td>
<td>16</td>
</tr>
<tr>
<td>Serum sodium (mEq/liter)</td>
<td>141 ± 3.8</td>
<td>141 ± 3.7</td>
<td>140 ± 3.7</td>
<td>147</td>
</tr>
<tr>
<td>Serum potassium (mEq/liter)</td>
<td>4.1 ± 0.24</td>
<td>4.1 ± 0.29</td>
<td>4.0 ± 0.38</td>
<td>2.9</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml per hr)§</td>
<td>-</td>
<td>1.7 ± 0.72</td>
<td>1.0 ± 0.27</td>
<td>0.8</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml per hr)∥</td>
<td>-</td>
<td>11.1 ± 5.7</td>
<td>1.6 ± 0.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Aldosterone excretion rate (µg/day)</td>
<td>-</td>
<td>8.2 ± 2.4</td>
<td>10.1 ± 3.2</td>
<td>34</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>85 ± 8</td>
<td>119 ± 5</td>
<td>116 ± 4</td>
<td>135</td>
</tr>
<tr>
<td>Urinary sodium (mEq/24 hr)</td>
<td>-</td>
<td>152 ± 20</td>
<td>154 ± 16</td>
<td>142</td>
</tr>
</tbody>
</table>

Subjects were on a 150 mEq sodium, 70 mEq potassium diet for 4 days, except where otherwise stated.

* NREH = normal renin essential hypertension.
† LREH = low renin essential hypertension.
§ Standard deviation.
∥ Measured on 3rd day of a 150 mEq sodium, 70 mEq potassium diet and 8 hours of supine posture.

### Table 2: Blood Pressure Responses to Angiotensin II in Normal and Hypertensive Subjects

<table>
<thead>
<tr>
<th>Angiotensin II dose (ng/kg per min)</th>
<th>Observed means (predicted values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1.90 (0.65) 3.40 (6.53) 12.32 (10.42) 3.87</td>
</tr>
<tr>
<td>2.0</td>
<td>0.68 (2.66) 9.97 (11.02) 18.75 (18.12) 1.29</td>
</tr>
<tr>
<td>5.0</td>
<td>2.67 (1.83) 11.42 (13.53) 22.52 (21.25) 2.60</td>
</tr>
</tbody>
</table>

**Equation of least square line**

<table>
<thead>
<tr>
<th>Normal subjects</th>
<th>Equation of least square line</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n = 6 )</td>
<td>( y = 3.59 + 9.78x )</td>
</tr>
<tr>
<td>Normal renin, essential hypertension</td>
<td>( n = 13 ) ( y = 5.64 + 17.85x )</td>
</tr>
<tr>
<td>Low renin essential hypertension</td>
<td>( n = 8 ) ( y = 7.70 + 19.42x )</td>
</tr>
<tr>
<td>Subject with primary aldosteronism</td>
<td>( n = 1 ) ( y = 24.14 + 60.92x )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Normal subjects</th>
<th>Equation of least square line</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n = 6 )</td>
<td>( y = 3.16 + 8.82x )</td>
</tr>
<tr>
<td>Normal renin essential hypertension</td>
<td>( y = 4.21 + 14.17x )</td>
</tr>
<tr>
<td>Low renin essential hypertension</td>
<td>( y = 4.44 + 13.26x )</td>
</tr>
<tr>
<td>Subject with primary aldosteronism</td>
<td>( y = 9.77 + 35.16x )</td>
</tr>
</tbody>
</table>

**Increments in systolic pressure**

<table>
<thead>
<tr>
<th>Increments in systolic pressure</th>
<th>Equation of least square line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>( y = 3.59 + 9.78x )</td>
</tr>
<tr>
<td>Normal renin, essential hypertension</td>
<td>( y = 5.64 + 17.85x )</td>
</tr>
<tr>
<td>Low renin essential hypertension</td>
<td>( y = 7.70 + 19.42x )</td>
</tr>
<tr>
<td>Subject with primary aldosteronism</td>
<td>( y = 24.14 + 60.92x )</td>
</tr>
</tbody>
</table>

**Increments in diastolic pressure**

<table>
<thead>
<tr>
<th>Increments in diastolic pressure</th>
<th>Equation of least square line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>( y = 3.16 + 8.82x )</td>
</tr>
<tr>
<td>Normal renin essential hypertension</td>
<td>( y = 4.21 + 14.17x )</td>
</tr>
<tr>
<td>Low renin essential hypertension</td>
<td>( y = 4.44 + 13.26x )</td>
</tr>
<tr>
<td>Subject with primary aldosteronism</td>
<td>( y = 9.77 + 35.16x )</td>
</tr>
</tbody>
</table>
hand, under experimental or clinical conditions in which body water and sodium compartments are expanded and endogenous A II levels, as a result, are suppressed, the pressor response to infused A II has been shown repeatedly to be enhanced. 14-15

In studies on rats, for example, Brunner et al. 32 showed that the affinity of A II for its vascular receptors in normal animals varied directly with sodium intake, being 8-fold greater in those fed a high rather than low sodium diet. These authors demonstrated the same sodium dependence of A II receptors in DOC-treated rats. The affinity of the vascular receptors for A II was inversely related to endogenous A II levels in these studies. More recently, Thurston and Laragh,33 using a specific inhibitor of angiotension I-converting enzyme, confirmed these findings in rats fed diets varying in sodium content. They suggested that the heightened A II pressor activity seen in sodium-loaded animals is a function of diminished occupancy of A II receptor sites prior to the infusion of exogenous A II.

These studies support the concept that the pressor response to infused A II is enhanced whenever Na\textsubscript{i} is increased and the endogenous A II level suppressed either by sodium loading or by mineralocorticoid excess. In primary aldosteronism, in which expansion of body fluid and sodium compartments and the resultant suppression of endogenous A II are well-established features of the disease, increased sensitivity to the pressor effect of A II has been repeatedly demonstrated.20,22,23. The subject with surgically proven primary aldosteronism in this study also showed increased sensitivity to the pressor action of A II when compared with normal controls or subjects with essential hypertension.

It is not clear whether the increased pressor response cited in these experimental and clinical examples is related primarily to a change in the configuration of the receptor for A II induced by an increased concentration of sodium ions at the vascular membrane, as suggested by Schaechtelin et al. or to diminished occupancy of these receptors by the suppressed level of endogenous A II independent of sodium ion excess per se. If due to the former, it would be reasonable to expect that if LREH is, in fact, mediated by sodium and water retention, from whatever cause, patients with this disorder should also manifest an enhanced pressor response to infused A II. If, on the other hand, the enhanced A II pressor sensitivity of the sodium-loaded, A II-suppressed state is a function of a low A II concentration at the receptor site, the absence of an increased pressor response to infused A II in the LREH subjects of this study is not readily explained but cannot
be used as evidence against sodium excess in LREH. However, a high sodium ion concentration at the receptor is a prerequisite for an augmented pressor response, the lack of such a response found in the subject with LREH in this study does not favor sodium and water retention in the pathogenesis of this disease.

The latter is supported by the report of Schalekamp et al.\textsuperscript{18} in which normal rather than increased plasma and ECF volumes were found in patients with LREH. Lebel and his coworkers\textsuperscript{19} have also found that, in patients with primary aldosteronism, the Na\textsubscript{+} was found to be normal in spite of the finding that in many instances their PRA and AII levels expanded in relation to the degree of suppression of their plasma renin and A II levels, whereas in patients with LREH, the Na\textsubscript{+} was found to be normal in spite of the finding that in many instances their PRA and A II levels were suppressed to the same degree as in those patients with primary aldosteronism.

Although we\textsuperscript{13,38} and others\textsuperscript{4-10} have presented evidence suggesting mineralocorticoid excess as an etiological factor in LREH, the present study does not support this hypothesis.

References
20. Kaplan NM, Silah JG: The effect of angiotensin II on the blood
30. Higashi Y, Kawasaki T, Tanaka K, Omae T, Katsuki S: A study of angiotensin, the peptides angiotensin and bradykinin, certain biogenic amines such as 5-hydroxytryptamine and norepinephrine, the peptides angiotensin and bradykinin, certain

---

**Metabolism and Uptake of Adenosine**

**Triphosphate and Adenosine by Porcine Aortic and Pulmonary Endothelial Cells and Fibroblasts in Culture**

**YVONNE DIETERLE, CHRISTIANE ODY, ALICE EHRENSBERGER, HANS STALDER, AND ALAIN F. JUNOD**

SUMMARY Incubation of cultured porcine aortic and pulmonary endothelial cells and mediastinal fibroblasts in the presence of H-ATP resulted in the hydrolysis of the nucleotide and the appearance of adenosine, while, simultaneously, a saturable, temperature-dependent uptake of radioactivity was taking place. The same pattern was observed in the three cell types. Adenosine uptake was studied in the same cell populations and also found to be a saturable, temperature-dependent process. The presence of two components for the transport, a high affinity system (Km of 3 μM) and low affinity system (Km of 0.3-1.1 μM), was established in both types of endothelial cells, as well as in fibroblasts (Km of 8.3 μM and 0.8 μM). Endothelial cells, however, could be easily differentiated from fibroblasts on the basis of several kinetic features. In the three cell types, adenosine, once taken up, was rapidly phosphorylated under the action of adenosine kinase. No evidence of adenosine deaminase activity was found in intact cells, whereas conversion of adenosine to inosine was observed in a subcellular fraction of sonicated cells. The effect of low temperatures was more marked on adenosine kinase activity than on the uptake process itself. Inosine and adenosine had no effect on the transport of adenosine, whereas diprymidolamine, at 10^-5 M, had a very strong inhibitory action. The role of ATP and adenosine in the control of smooth muscle tone could be reexamined in view of their handling by endothelial cells of systemic and pulmonary origins.

IN THE PAST 10 years, several groups of investigators have shown that the lung is capable of degrading and/or taking up various types of substances, among which are biogenic amines such as 5-hydroxytryptamine and norepinephrine, the peptides angiotensin and bradykinin, certain prostaglandins, and adenosine nucleotides. Binet and Burststein were the first ones to report on the disappearance of ATP in the pulmonary circulation. More recently, Ryan and his group investigated this phenomenon, using isolated perfused rat lungs. They found that 5-AMP and ATP were hydrolyzed to yield adenosine and, possibly, deaminated to give rise to inosine, whereas the question of a cellular uptake of these products or of their metabolites was left open. They also took advantage of the presence of 5’-nucleotidase at the level of the plasma membranes of pulmonary endothelial cells to design a
The pressor response to angiotensin II in patients with low renin essential hypertension.
A D Marks, D B Marks, Y N Kim, J Moctezuma, E V Adlin and B J Channick

Circ Res. 1978;42:864-869
doi: 10.1161/01.RES.42.6.864

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/42/6/864

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/