The Mechanism of Low-renin Hypertension:  
Aldosterone Response to Sodium Restriction and Upright Posture,  
Angiotensin II, ACTH and Potassium in Patients with Hypertension

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JIRO MISUMI, KAZUOKI KONDO, AND SHUN MATSUKI

Plasma renin activity and aldosterone were measured simultaneously in 67 out-patients with essential hypertension. High aldosterone was more often in patients with high renin, and low levels of aldosterone were usual in those with low or normal renin.

In order to study the mechanism by which aldosterone and renin activity are suppressed in low-renin hypertension, 25 patients (13 normal-renin hypertensives, 10 low-renin patients including 4 non-responders and two DOC excess hypertensives) were investigated as inpatients. Plasma renin activity, aldosterone and cortisol were determined by the following stimulations with 3 days of sodium restriction and 2 hours of upright posture, angiotensin II infusion (at a dose which increased 20mmHg of diastolic blood pressure), ACTH administration (rapid i.m. injection of 0.25mg of alpha 1–24 preparation) and potassium infusion (30meq of potassium i.v.).

Responses of aldosterone in normal-renin hypertensives to all stimulations were 3–5 fold increases from base line values. Low-renin hypertensives except two of four non-responders showed the responses similar to those in normal-renin patients. The responses of two of the non-responders were similar to those in DOC excess hypertensives who showed reduced responses of aldosterone to some of these stimulations. Thus, it seems that low-renin hypertension is a clinical entity caused by a variety of mechanisms, and the mechanism by which low-renin hypertension is induced is not explained by one factor such as an unknown mineralocorticoid.

It is now widely recognized that some patients with essential hypertension have low and suppressed plasma renin activity. Although a few investigators have suggested that some mineralocorticoids such as 11-deoxycorticosterone, 18-hydroxy-11-deoxycorticosterone, or 16-beta-hydroxy-dehydroepiandrosterone may be related to the development of low-renin hypertension, the cause of its abnormality is still controversial.

In the present study, we have observed the mechanism of low-renin hypertension from the findings of changes in plasma renin activity and aldosterone determined in a variety of situations, and we discussed a possibility whether some mineralocorticoids are related to the development of low-renin hypertension or not.

Materials and Methods

Key Words:  
Aldosterone  
Essential hypertension  
Mineralocorticoid  
Plasma renin activity

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This paper was presented at the V Conference on the Pathogenesis of Hypertension, December 7, 1975, Osaka.

Japanese Circulation Journal  Vol. 40, August 1976  911
TABLE I DISTRIBUTION NORMAL SUBJECTS AND PATIENTS WITH HYPERTENSION INCLUDED IN INPATIENTS STUDY BY AGE, SEX AND PLASMA RENIN ACTIVITY.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal-renin</td>
<td>Low-renin</td>
</tr>
<tr>
<td>Age</td>
<td>20-29</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>30-39</td>
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<td></td>
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<td>50-59</td>
<td>3</td>
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<td></td>
<td>70-79</td>
<td></td>
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<tr>
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<tr>
<td></td>
<td>Female</td>
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</tr>
<tr>
<td>Total</td>
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</tbody>
</table>

TABLE II DISTRIBUTION OF 67 PATIENTS WITH ESSENTIAL HYPERTENSION BY-PLASMA RENIN ACTIVITY AND ALDOSTERONE.

<table>
<thead>
<tr>
<th>Plasma Aldosterone ng/100ml</th>
<th>&lt;4</th>
<th>4-10</th>
<th>10 &lt;</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Plasma renin activity &lt;1.0</td>
<td>11</td>
<td>9</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>1.0-2.0</td>
<td>12</td>
<td>15</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>2.0 &lt;</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>28</td>
<td>14</td>
<td>67</td>
</tr>
</tbody>
</table>

Control subjects:
Control subjects used in this study were 4 women and one man ranging the age of 20-68 and were admitted in the department of internal medicine.

Patients with essential hypertension:
Of the 67 patients, 23 were studied as inpatients and 44 were studied in the outpatient department.
At least two weeks before the study, all patients had been taken off antihypertensive drugs and were taking a diet containing normal amount of sodium (150-250 meq/day).
Either before or on admission routine examinations were performed, including electrolyte determination, measurement of various hormones such as plasma renin activity, aldosterone, cortisol and urinary VMA, intravenous pyelography and sometimes renal arteriography to exclude any known cause of hypertension.
Low-renin essential hypertension was diagnosed if plasma renin activity was less than 1.0 ng/ml/hour at rest on normal diet. Non-responder in low-renin hypertension was diagnosed if plasma renin activity failed to exceed 1.0 ng/ml/hour following 3 days of sodium restriction and 2 hours of upright posture.
Distribution of 23 inpatients by age and sex was shown in Table I.
A patient with deficiency of 17-alpha hydroxylase:
This patient was a 20 year-old man. He had a history of three years of hypertension. Two years before admission a diagnosis of "testicular
Fig. 1. Response of plasma renin activity to 3 days of sodium restriction and 2 hours of upright posture.

Fig. 2. Response of plasma aldosterone to 3 days of sodium restriction and 2 hours of upright posture.

feminization" was made at the department of gynecology of this hospital, where low serum potassium was found and referred to the department of internal medicine. On examination, serum potassium was 3.2 meq/l, plasma renin activity was 0.8 ng/ml/hour, aldosterone was 2.5 ng/100ml, DOC was 110 ng/100ml, cortisol was 56 ng/ml and ACTH was 140 pg/ml. Bilateral adrenal hyperplasia was indicated by the adrenal venography. Blood pressure was reduced by the administration of adrenal corticosteroid.

A patient with DOC producing tumor:

This patient was a 35 year-old woman. She was well 6 years previously, when she was pregnant, examinations revealed hypertension and proteinuria, and three month before admission, examination at another hospital revealed that blood pressure was 226/146 mm Hg and serum potassium was 2.4 meq/l.

On examination at this hospital, serum potassium was 2.4 meq/l, plasma renin activity was 0.4 ng/ml/hour, aldosterone was 2.8 ng/100ml, DOC was 121 ng/100ml and cortisol was 66 ng/ml. Abdominal examination disclosed an abdominal tumor, that accumulated $^{131}$I-19iodocholesterol.
Fig.3. Response of plasma aldosterone to angiotensin II at a dose which increased 20mmHg of the diastolic blood pressure above base line, for one hour.

Fig.4. Response of plasma aldosterone one hour after the administration of ACTH (0.25mg of Cortrosyn).

Operation was performed to excise the tumor and after the operation blood pressure was reduced.

Procedures of aldosterone stimulation:
Following studies were performed on 23 inpatients with essential hypertension, a patient with deficiency of 17 alpha hydroxylase and that with DOC producing tumor. Written informed consent was obtained from all the patients.

Investigations were carried out on a regular sodium diet (150–250 meq/day) and after 8 hours of recumbency.
1. Stimulation by sodium restriction and 2 hours of upright posture
On the fourth day of a diet containing below 40 meq/day of sodim, after assumption of upright posture for two hours, blood was sampled.

*Japanese Circulation Journal  Vol. 40, August 1976*
2. Stimulation by angiotensin II
   Angiotensin II (Hypertensin, Ciba) was infused at a dose which increased 20 mmHg of the diastolic blood pressure above base line, for one hour.
3. Stimulation by ACTH
   0.25 mg of a synthetic alpha 1-24 preparation (Cortrosyn) was given by intramuscular administration. Blood samples were drawn before and one hour after the administration.
4. Stimulation by potassium
   500 ml of 5% glucose solution containing 30 meq of potassium chloride was infused beginning at 9.00 am at the rate of 150–200 ml/hour. Analytical method

   Plasma renin activity was determined by the method of Skinner. Plasma aldosterone was measured by the method of Bayard et al using the radioimmunoassay after methylenechloride extraction and paper chromatography. Plasma cortisol was determined by a competitive protein binding assay after methylenechloride extraction.

   All results are means ± SE, and statistical comparisons were made using Student’s t-test.

RESULTS
Outpatients study (Table II)
67 hypertensive patients were distributed by plasma renin activity and aldosterone in nine subgroups. Plasma renin activity and aldosterone
were correlated \( r=0.32, P < 0.05 \). In the patients with elevated plasma renin activity, there was a tendency for high plasma aldosterone. In low-renin patients plasma aldosterone was either normal or correspondingly low.

Inpatients study (Figure 1,2,3,4,5 and 6)

Normal subjects:

In normal subjects, plasma aldosterone increased 3-4 folds after each stimulation. Plasma renin activity rose above twice in all subjects after sodium restriction and 2 hours of upright posture. Other stimuli did not change the plasma renin activity. After ACTH administration, plasma cortisol showed above twice increase, but other stimuli did not affect the plasma cortisol.

There was an increase in diastolic blood pressure of more than 20 mmHg while angiotensin II was infused at a rate of 5.8 ± 0.8 ng/Kg body weight/min. Increase in serum potassium was 0.4 ± 0.1 meq/l after the infusion of potassium.

Patients with essential hypertension:

1. Sodium restriction and 2 hours of upright posture

In normal- and low-renin patients, plasma aldosterone and renin activity were increased significantly. But four non-responders of low-renin hypertension showed a tendency for lesser degree of rise in plasma aldosterone.

Positive correlation between the percent increase in plasma aldosterone and that in plasma renin activity was present \( r=0.67, P < 0.05 \) in normal-renin patients but not present in those with low-renin \( r=0.03, \text{N.S.} \).

2. Angiotensin II

Angiotensin II dose required to evoke pressor response was 6.0 ± 0.8 and 6.0 ± 0.7 ng/Kg body weight/min. in normal- and low-renin patients, respectively.

Rise in plasma aldosterone in normal-renin hypertension was similar to that in low-renin patients including non-responder. Plasma renin activity in normal-renin hypertension was 1.8 ± 0.2 ng/ml/hour and 1.2 ± 0.2 ng/ml/hour, before and after the infusion of angiotensin II, respectively. Plasma renin activity in low-renin patients was 0.9 ± 0.2 ng/ml/hour and 0.6 ± 0.2 ng/ml/hour, before and after the infusion of angiotensin II, respectively.

Plasma cortisol was not changed.

3. ACTH

Plasma aldosterone and cortisol were increased in normal and low-renin patients simi-

larly. Plasma renin activity was not affected by ACTH.

4. Potassium

Serum potassium was increased from 4.3 meq/l (range 3.6–5.6 meq/l) to 4.8 meq/l (range 4.0–6.1 meq/l) in normal-renin patients. In low-renin patients serum potassium was 4.0 meq/l (range 3.3–4.4 meq/l) and 4.4 meq/l (range 4.0–4.8 meq/l) before and after the infusion of potassium, respectively.

A rise in plasma aldosterone in non-responders of low-renin hypertension was smaller than that in normal- and low-renin patients as a whole.

Plasma renin activity and cortisol were not significantly changed in response to potassium infusion.

Patient with deficiency of 17 alpha hydroxylase:

Plasma aldosterone was increased from 2.8 ng/100ml to 6.0, 4.3 to 7.5, 3.8 to 14.5 and 5.5 to 20.0 in response to sodium restriction and 2 hours of upright posture, angiotensin II, ACTH and potassium, respectively.

Angiotensin II dose required to evoke pressor response was 3.8 ng/Kg body weight/min. In plasma renin activity was low and was not changed in response to all stimulations. Plasma cortisol rose from 56 to 100 ng/ml after the administration of ACTH.

Patient with DOC producing tumor:

In this patient, stimulation with angiotensin II was not applied because of severe hypertension.

Plasma aldosterone rose from 4.4 ng/100ml to 14.7, 6.1 to 34.0 and 2.8 to 5.6 in response to sodium restriction and two hours of upright posture, ACTH and potassium, respectively.

Plasma renin activity was suppressed and not affected by each stimulus. Plasma cortisol was increased from 93 ng/ml to 122 in response to ACTH.

**Discussion**

In the patients with essential hypertension studied herein, plasma levels of aldosterone were various. However, it seemed that high levels of plasma aldosterone were more often in the patients with high renin and low levels of plasma aldosterone were more often in the patients with low or normal renin. Especially in the patients with low renin, only two of 22 patients showed high levels of plasma aldosterone, in whom primary aldosteronism was excluded by adrenal venography and determination of plasma aldosterone in the adrenal vein samples. As the renin-angiotensin system is the important factor

to control the aldosterone secretion, high levels of plasma aldosterone in the patients with high renin may be dependent upon increased renin levels. However, in the patients with low renin, it is difficult to say whether low aldosterone is mediated by the renin deficiency itself and/or due to other mechanisms such as the suppression by other mineralocorticoids as seen in the experiment of DOC hypertension.

In order to make clear this problem, a variety of aldosterone stimulation tests were performed in the patients with essential hypertension and those with DOC excess hypertension. As four humoral factors, angiotensin II, ACTH, potassium and sodium are known to be related to the secretion of aldosterone and seem to control aldosterone production in the different mechanisms, these four factors were employed to stimulate aldosterone secretion.

Effects of sodium restriction and two hours of upright posture, angiotensin II infusion to increase 20 mmHg of diastolic blood pressure, 0.25 mg of Cortrosin and 30 meq of potassium infusion upon plasma aldosterone were almost similar in normal subjects and patients with normal-renin hypertension. Plasma aldosterone increased 3–4 times of pre-treatment levels. In the patients with DOC excess hypertension, plasma renin activity was low and responses of plasma aldosterone to some of these stimulations were reduced. It is suggested that the reduction of plasma aldosterone in DOC excess hypertension is induced by the suppression of plasma renin activity by DOC and/or resultant fluid retention, although intra-adrenalin inhibition of aldosterone production is not excluded.

Some of the patients with low-renin hypertension also showed poor responses of aldosterone upon a variety of stimulations, especially most of patients with nonresponsive low-renin, but not all, seemed to respond poorly to the aldosterone stimulations.

From these results of aldosterone stimulation tests in the patients with DOC excess hypertension and low-renin essential hypertension, it was also suggested that some patients with low-renin essential hypertension were in the situation similar to DOC excess hypertension. Therefore, we cannot exclude the possibility that some mineralocorticoids may play a role in a few patients with non-responsive low-renin hypertension.

However, in the patients who have low level of plasma renin activity but normal response of aldosterone to four stimulations, it should be considered that the mechanism other than mineralocorticoid, such as disturbance of neurological control of renin. Furthermore, in the aged patients with essential hypertension, in whom plasma renin activity and aldosterone seem to decrease gradually with age, the effects of aging upon juxta-glomerular cell and adrenal cortex should be considered.

Ultimately, low-renin essential hypertension doesn't seem to be induced by one factor. It is a clinical entity developed by a variety of mechanisms, and if present, the mineralocorticoid will be no more than one cause of low renin hypertension.

Acknowledgments

We are indebted to Prof. Soitsu Fukuchi of Fukushima medical college and Dr. Sumie Kidokoro of Hiraizuka city hospital for assistance in this investigation.

This study was supported by a grant from Keio university.

REFERENCES

CHAIRMAN: Thank you for your nice presentation on the renin-angiotensin-aldosterone system in low-renin essential hypertension.

Now we would like going to discussion on the mechanism of suppressed plasma renin activity in essential hypertension.

Dr. Y. KANEKO (Yokohama City Univ.): It seems that there are some problems in evaluating the plasma renin activity and aldosterone measured in the outpatients, since plasma renin activity is influenced by sodium intake.

Dr. I. SAITO: We are aware of that problem. The purpose of the study on outpatient was only to explore the relation of plasma renin activity to aldosterone in many cases under unrestricted salt intake. We found that there were some patients with both low renin and low aldosterone from this preliminary study. Then we proceeded to the inpatient study.

Dr. Y. KANEKO: How many patients having high plasma aldosterone with low renin were there?

Dr. I. SAITO: Two of 67 patients, in whom adrenal adenoma was excluded by adrenal venography and scintigram, were suspected to have idiopathic hyperaldosteronism.

Dr. K. KUMAMOTO (Kyushu Univ.): I want to ask the definition of low renin hypertension, and I wonder if it is appropriate to say that low renin hypertension is a clinical entity.

Dr. I. SAITO: The study on inpatient was carried out under a controlled diet. Low renin hypertension was defined if plasma renin activity was less than 1.0 ng/ml/hr at rest. Non-responder was defined as a patient with plasma renin activity which didn’t exceed 1.0 ng/ml/hr following 3 days of sodium restriction and 2 hours of upright posture. Therefore, non-responder is considered to be a patient with a kind of low renin hypertension. The extent of suppression of plasma renin activity was various. In a broad sense, we might say that low renin hypertension is a clinical entity which consisted of a variety of pathophysiological mechanisms.

Dr. S. FUKUCHI (Fukushima Med. College): Did the suppression of plasma renin activity comparable to that found in primary aldosteronism exist in low renin hypertension?

Dr. Y. SARUTA (Keio Univ.): In some patients with low renin, in whom the degree of suppression of plasma renin activity was similar to that of primary aldosteronism, primary aldosteronism was ruled out by the simultaneous measurement of aldosterone and other various diagnostic ex-
amination.

Dr. S. FUKUCHI: On the occasion of the evaluation of the pathophysiological significance of low plasma renin activity, plasma renin activity should be suppressed to the same extent that found in primary aldosteronism.

Dr. Y. MIURA (Tohoku Univ.): Since a variety of maneuvers for renin stimulation are employed by each investigator in this country, it may be desirable to decide the standard method of stimulation of renin release in order to avoid the confusion.

Dr. S. FUKUCHI: I agree to your comment.

Dr. SAITO: I should like to emphasize that not only the measurement of plasma renin activity but that of aldosterone and DOC will offer the further information about the mechanism of hypertension.

Dr. T. TAKEDA (Tokyo Univ.): You defined the infused dosage of angiotensin II for stimulation of aldosterone secretion as a rate at which an increase of arterial pressure by 20 mmHg was attained. I am afraid, then, that requirements of angiotensin may vary according to low or high plasma renin levels. I feel that the dosage should be preferably determined on the basis of the patient's body weight in order to compare the response for aldosterone stimulation.

Dr. I. SAITO: As a matter of fact, the average dose of angiotensin II infused was 6.0 ng/kg/min in both normal and low renin patients. In non-responder, the scatter on the dose of angiotensin II was large.

Dr. T. TAKEDA: Was there no difference in the pressor responsiveness between the patients with normal renin and low renin?

Dr. I. SAITO: No, there wasn't, except some patients of non-responder.

Dr. S. FUKUCHI: As it is suggested that the vascular smooth muscle receptor and adrenal receptor differ, it will be better to administer fixed dose than pressor dose of antihypertensin II.

Dr. Y. SARUTA: With regard to the dose of angiotensin II, fixed dose was not employed in the human study of this kind to avoid the danger of unexpected exaggerated response of blood pressure to antihypertensin II.

Dr. S. FUKUCHI: You presented the data the response of DOC excess hypertension was poor to the aldosterone stimulation. How do you explain the mechanism of suppression of the response?

Dr. I. SAITO: I cannot answer your question from the present study. Two mechanisms will be possible; the first one is mediated through the increased plasma volume, the second is the direct suppression on the level of adrenal glands.