STUDIES ON ESSENTIAL HYPERTENSION WITH SUPPRESSED PLASMA RENIN ACTIVITY: SODIUM EXCRETION PATTERN ON SALT RESTRICTION AND EFFECTS OF SPIRONOLACTONE ON BLOOD PRESSURE AND PLASMA RENIN ACTIVITY

KENZO UCHIDA, SHINPEI MORIMOTO, RYÖYU TAKEDA, AND MOTOTAKA MURAKAMI

It has been generally accepted that suppressed plasma renin activity (PRA) is one of the critical findings in diagnosing primary aldosteronism, as well as the existence of hypertension with increased levels of aldosterone and normal levels of 17-OHCS in urine. When the patients with essential hypertension in the general population are screened through the PRA assay alone, 12 to 53 per cent of the patients have been found to show a suppressed PRA; however, the majority of them have had normal or rather low aldosterone levels. In fact, the incidence of normokalemic primary aldosteronism among essential hypertension has been extremely low. Against the early proposition by Conn et al. who assumed that it accounts for about 20 per cent of the population of essential hypertension. Thus the pathogenesis of suppressed PRA without hyperaldosteronism still remains not fully explained, though several investigators have suggested indirect evidence that such patients might be producing an as yet unidentified mineralocorticoid.

In order to investigate the pathogenesis of suppressed PRA without hyperaldosteronism, the present study was carried out to characterize the patients with suppressed PRA by the pattern of electrolyte homeostasis during four-days' salt restriction, and the effect of spironolactone on the blood pressure and PRA. The results were compared with that obtained by the identical studies performed in the patients with proven primary aldosteronism.

MATERIALS AND METHODS

Fifty-three inpatients were studied, including 38 patients with benign essential hypertension (26 males and 12 females), 5 patients with primary aldosteronism (1 male and 4 females), and 10 patients with normotension (6 males and 4 females). The diagnosis of benign hypertension was established by detailed history, urinalysis, intravenous pyelography, radio-isotope renography, renal function studies, ophthalmoscopic examination of the optic fundi and renal angiography in most cases. The age of these patients ranged from 16 to 69 and the mean was 44 years. All of them had no evidence of severe renal or cardiovascular complications and had a blood pressure higher than 150/90 mmHg on repeated determinations at rest. Normotensive controls consisted of patients in convalescent states with other diseases than renal, cardiovascular and endocrine. The clinical evaluations of their original diseases were negative and a supine blood pressure never exceeded 140/90 mmHg throughout the experimental period. The mean age of normotensive patients was 31 years. All five patients with primary aldosteronism had typical clinical symptoms and signs, and the diagnosis was proved by removal of the unilateral adrenal adenoma with a resultant normalization of blood pressure. The mean age of these patients was 37 years. Prior to the experiment, all

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Fig. 1. Effects of furosemide administration on PRA, 4-hour urine volume, and serum and urinary electrolytes in patients with normotension, essential hypertension, and primary aldosteronism.

Antihypertensive and diuretic drugs were discontinued for at least two weeks and a diet was prepared to contain 200 mEq of sodium a day during this period. The furosemide test was carried out according to the method previously reported elsewhere. After furosemide test PRA was again determined while the patients were in the recumbent position on a diet containing 200

mEq of sodium a day and in the upright posture after they had been on a diet containing 25 mEq of sodium a day for 4 days. The spironolactone (Aldactone A\(^9\)) was given to the patients with primary aldosteronism in doses of 300 to 400 mg a day and to the patients with a suppressed PRA in a dose of 200 mg a day. Blood pressure, PRA in the recumbent position, and serum levels of electrolytes were determined weekly for more than 7 weeks during spironolactone therapy. The determination of PRA was performed according to the method of Skinner\(^2\). The urinary levels of

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<table>
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<th>Control</th>
<th>1st day</th>
<th>2nd day</th>
<th>3rd day</th>
<th>4th day</th>
</tr>
</thead>
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<td>Urinary K (mEq/day)</td>
<td>100</td>
<td>50</td>
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Fig. 2. Urinary excretion patterns of sodium and potassium during salt restriction in patients with normotension, suppressed PRA (group A and B), and primary aldosteronism.
aldosterone were determined by the method\textsuperscript{2,3} using Mattox's paper chromatography in combination with two dimensional thin layer chromatography by Cavina et al.\textsuperscript{4} Serum and urinary electrolytes and creatinine values were determined by a Technicon autoanalyzer.

\textbf{RESULTS}

1) \textbf{Response to furosemide administration (Fig. 1)}

In 10 normotensive patients the mean PRA prior to furosemide administration while recumbent was 1.4±0.4 ng/ml/h. Four hours after furosemide administration there was a significant increase (p<0.01) in the mean to 5.2±1.6 ng/ml/h, ranging from 3.3 to 8.3 ng/ml/h. The mean values of urine volume, sodium and potassium excretions during 4-hour period were 1567±304 ml, 196±48 mEq and 24±6 mEq, respectively. Serum levels of sodium and potassium were unchanged after ingestion of the drug. The criterion for a suppressed PRA was employed in patients showing a PRA increment less than 1.8 ng/ml/h (standard deviation of the mean value of PRA in 52 normal controls on recumbent position) following hypovolemic maneuvers. Among 38 patients with benign essential hypertension, 13 patients (34 per cent) failed to respond at all with an increased PRA to the furosemide administration, while the remaining 25 patients had normal response of PRA. The mean 4-hour urine volume after furosemide administration was 1383±193 ml in the group of suppressed PRA and 1481±337 ml in the group of normal PRA response. The mean sodium and potassium excretions during 4-hours after furosemide administration were 168±25 and 25±11 mEq in the former group, and 180±42 and 21±6 mEq in the latter, respectively. In 5 patients with primary aldosteronism the mean values of 4-hour urine volume, sodium and potassium excretions were 1408±152, 171±42 and 28±15 mEq, respectively. No statistically significant difference between the three groups were found with regard to any of these values in urine volume, sodium and potassium excretions.

2) \textbf{Response to salt restriction (Fig. 2)}

As depicted in figure 2, in the normotensive patients, sodium excretion during 4-days' salt restriction was gradually decreased from 185±17 mEq/day at the control period to 135±33 mEq/day in the lst day, 83±20 mEq/day in the second day, 57±15 mEq/day in the third day and 31±9 mEq/day in the fourth day, without any significant change in the potassium excretion. PRA significantly increased from 1.2±0.5 ng/ml/h at the control period to 4.6±1.4 ng/ml/h after salt restriction (p<0.01). On the other hand, in the patients with primary aldosteronism the sodium excretion following salt restriction was abruptly decreased from 175±17 mEq/day to 51±20 mEq/day in the first day, 30±18 mEq/day in the second day, 20±11 mEq/day in the third day and 19±6 mEq/day in the fourth day with a significant reduction in the potassium excretion (p<0.05).

Of 13 hypertensive patients with a suppressed PRA to furosemide administration, 12 patients failed to respond with a significant increase of PRA also to the salt restriction; and only one patient showed a normal PRA response to salt restriction. As shown in Figure, in 5 of 12 patients with a suppressed PRA to both furosemide and salt restriction tests, the pattern of sodium excretion following salt restriction was similar to that of the patients with primary aldosteronism (group A); that is, there was an abrupt decrease of sodium excretion with a significant decrease of potassium excretion (p<0.05). On the other hand, the remaining 7 patients showed the same sodium excretion pattern after salt restriction as that of normotensive patients (group B). In an exceptional patient (SN) who had a suppressed PRA response to furosemide but responded normally to the salt restriction, the pattern of sodium and potassium excretions was similar to that of the normotensive patients.

3) \textbf{Effects of spironolactone on hypertension, serum potassium and PRA (Table I)}

Within two weeks after spironolactone, all the patients of group A became normotensive with significant increase in the serum levels of potassium and PRA (p<0.05) (Fig.3); while 7 patients of group B had an insignificant reduction of blood pressure without any changes in the serum levels of potassium and PRA for 7 weeks after spironolactone therapy (Fig. 4).

An exceptional patient (SN) with paradoxical response of PRA to furosemide and salt restriction had a minimal reduction of blood pressure with a marked increase of PRA (Table I). Serum level of potassium in this patient did not change.

After spironolactone therapy with high doses of 300 to 400 mg a day for more than 8 weeks, the patients with primary aldosteronism became normotensive with a prompt elevation of serum potassium and gradual restoration of PRA (Fig. 5).

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4) Urinary excretion of aldosterone in the hypertensive patients with a suppressed PRA and the patients with primary aldosteronism (Table 1).

In the hypertensive patients with suppressed PRA, the mean value of urinary aldosterone on a diet containing 200 mEq of sodium a day was 4.9±1.6 μg/day, ranging from 3.5 to 6.8 μg/day.
Fig. 4: Effects of spironolactone therapy on blood pressure, serum concentrations of sodium and potassium, and PRA in hypertensive patients with suppressed PRA (group B).

On the other hand, in the hypertensive patients with a normal response of PRA, the mean value was 4.1±1.0 µg/day, ranging from 2.4 to 6.2 µg/day. In 5 patients with primary aldosteronism, the mean value was 16.8±8.8 µg/day, ranging from 12.0 to 30.0 µg/day. (normal range 3.0–9.0 µg/day, n=18).

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Fig. 5. Effects of spironolactone therapy on blood pressure, serum concentrations of sodium and potassium, and PRA in patients with primary aldosteronism.

**Discussion**

The incidence of suppressed PRA in the patients with essential hypertension varies widely according to the utilized maneuvers for screening of suppressed PRA such as upright posture,
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<th>Blood pressure (mmHg)</th>
<th>Serum Na &amp; K (mEq/L)</th>
<th>PRA (ng/ml/h)</th>
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<td>140/98</td>
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<td>148/90</td>
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<td>16.8 ± 8.8</td>
<td>192.0 ± 11.7/</td>
<td>134.5 ± 12.2/</td>
<td>145.3 ± 0.5</td>
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<td>4.9 ± 1.6</td>
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<td>4.6 ± 1.0</td>
<td>174.0 ± 18.2/</td>
<td>160.9 ± 18.6/</td>
<td>143.0 ± 2.2</td>
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<td>4.5</td>
<td>172/104</td>
<td>154/96*</td>
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* after 3 weeks
diuretics, salt restriction and acute blood pressure reduction. For instance, Creditor et al. found an incidence of 53 percent of suppressed PRA among the patients with essential hypertension following upright posture alone; however, 45 per cent of these patients showed a normal response of PRA to salt restriction. McGuinnes et al. found that 8 of 15 patients with normal response of PRA to salt restriction plus diuretic showed a suppression of PRA after intravenous administration of chlorothiazide.

To exclude the possibility of suppressed PRA probably due to an inadequate stimulus to renin release, 12 patients with essential hypertension who failed to show a normal response of PRA to both furosemide test and salt restriction plus upright posture, were selected in the present study. Since none of these 12 patients were found to have hypokalemia or an increased level of aldosterone in urine, it was unlikely to assume that a suppressed PRA in the patients was due to hyperaldosteronism. Therefore, factor(s) other than aldosterone must be involved in the mechanism of suppressed PRA in our 12 patients. As an approach to study these factors, the authors attempted to first analyze how the pattern of electrolyte excretion in these patients on salt restriction resembled that of the patients with primary aldosteronism and then to evaluate the effects of spironolactone on blood pressure, and PRA. If some mechanism relating to other mineralocorticoid excess than aldosterone is responsible for a suppressed PRA, the withdrawal of dietary sodium will induce a prompt fall in urinary sodium with reduction of potassium excretion as observed in our patients with primary aldosteronism. In this study only 5 out of 12 patients demonstrated the "primary aldosteronism-pattern" in the electrolyte excretion (group A); 7 of them showed a gradual decrease of sodium excretion without a significant change in potassium excretion as shown in normotensive subjects (group B). However, it was an interesting finding that in 4 patients of group A, the therapy with a high dose of spironolactone resulted in normotension with an increase of serum level of potassium and PRA. Furthermore, patient KM had a normal response of PRA to furosemide administration after spironolactone therapy for four weeks. These effects of spironolactone as well as the above-mentioned findings, that the dietary sodium restriction led to sodium and potassium retention indirectly, suggest that there were at least two types of hypertension with a suppressed PRA, one was mineralocorticoid-dependent and other one was not. Concerning the effects of high dose of spironolactone therapy in hypertensive patients with a suppressed PRA, Spark et al. and Crane et al. have reported similar results to ours. A question might arise as to whether the hypotensive effect of spironolactone in these patients is due to the specific action of mineralocorticoid inhibition or to the non-specific antihypertensive property of the drug; because it has been reported that 8 of 24 hypertensive patients with normal PRA response became normotensive on spironolactone therapy. Spark et al. noted that the patients who became normotensive with high-dose spironolactone therapy experienced a significant weight loss but became again hypertensive when the dose of spironolactone was reduced; the finding observed during high dose spironolactone therapy could be considered as a proof of elimination of mineralocorticoid activity. In our experience and that of others, however, smaller doses of spironolactone could control the blood pressure even in the patients with primary aldosteronism after high blood pressure was once normalized by high doses of spironolactone.

In the patients of group A an apparently indicative finding for a state of mineralocorticoid excess was suggested when the administration of large doses of spironolactone produced a rapid increase of serum potassium with a concomitant restoration of PRA and lowering of blood pressure. It should be pointed out that compared with the patients with primary aldosteronism, the patients in group A could be readily controlled by lesser doses of spironolactone. Such a difference in the required dose of spironolactone for lowering the blood pressure between group A and primary aldosteronism appears to depend upon the activity or the amounts of mineralocorticoid acting at the distal tubule. It has been reported that in adrenalectomized rats the sodium-retaining and potassium-excreting activities of exogenous mineralocorticoid could be progressively inhibited by increasing doses of spironolactone, and large amounts of mineralocorticoid could overcome the effects of spironolactone.

It is difficult to explain the mechanism(s) of suppressed PRA in group B. From the results obtained by observations of electrolyte handling on salt restriction and the effects of spironolactone on blood pressure, serum potassium and PRA, the mechanism of PRA suppression appears...
to be mineralocorticoid independent. Possible mechanisms of PRA suppression include an expanded extracellular fluid volume probably due to prolonged intake of excessive sodium\textsuperscript{12,37,38} or altered activity of renal sympathetic nerve\textsuperscript{9} or increased intravascular pressure at the level of the juxtaglomerular cells\textsuperscript{39} but at the present time no proof for any of these possibilities has been demonstrated.

**Summary**

Based on the evaluation of plasma renin activity (PRA) responses to the two different maneuvers designed to produce hypovolemia; furosemide administration and dietary salt restriction, 12 hypertensive patients with a suppressed PRA were screened from 38 patients with benign essential hypertension. Urinary levels of aldosterone in these 12 patients were within normal limits. In five (group A) of 12 patients with a suppressed PRA the pattern of sodium excretion following salt restriction resembled that of five patients with primary aldosteronism. On the other hand, the remaining 7 patients (group B) showed the same pattern of sodium excretion following salt restriction as that of normotensive patients. All the patients of group A became normotensive within two weeks with spironolactone therapy with significant increases in the serum levels of potassium and PRA, while the patients of group B had an insignificant reduction of blood pressure without any changes in the serum levels of potassium and PRA for 7 weeks after spironolactone therapy.

From these results it was suggested that there were at least two types of hypertension with a suppressed PRA, one was mineralocorticoid (other than aldosterone)-dependent (group A) and other one was not (group B).

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**REFERENCES**


