Plasma Aldosterone in Essential Hypertension with Low Renin Activity

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Most patients with essential hypertension show normal plasma renin activity. An unexpected but repeatedly confirmed finding, however, has shown that there is persistently low plasma renin activity in about 20% of patients with essential hypertension. The explanation for the low plasma renin activity in these hypertensive patients is not clear, as in most cases they have normal or low secretion of aldosterone or other known mineralocorticoids. There has been speculation that these patients may be making another, as yet unidentified, mineralocorticoid. Such a compound has not yet been fully characterized, but it remains, nonetheless, the only currently acceptable physiologic explanation for persistently low plasma renin activity. On the basis of careful studies on relatively unselected hypertensive patients, the incidence of primary aldosteronism is now thought to be about 1% of the hypertensive population. Many theories have been put forward to account for renin suppression in essential hypertension. At present, however, they are inadequate to explain the mechanism.

The present study was designed to explore further the possibility that the hypertensive process of patients with suppressed renin activity might be related to mineralocorticoid excess. First, the relationship between plasma renin activity and plasma aldosterone measured by radioimmunoassay was studied in essential hypertension. Next, another mineralocorticoid, deoxycorticosterone found in the plasma of the peripheral circulation, was also estimated in essential hypertension with low renin activity.

In a condition of mineralocorticoid excess and low plasma renin activity, namely primary aldosteronism, it has been shown that high doses of spironolactone, a known mineralocorticoid antagonist, produce normotension in patients! In view of this, we have set out to assess the comparative effects of mineralocorticoid blockade with high doses of spironolactone in hypertensive patients with normal and low plasma renin activity.

Materials and Methods

Fifty-eight patients with essential hypertension admitted to Tohoku University Hospital for 2 years from April 1971 to March 1973 were studied. Although some patients were known to have had hypopotassemia previously during diuretic therapy, none had marked hypokalemia before admission. Patients with primary aldosteronism, pheochromocytoma, Cushing’s syndrome, or renal arterial stenosis were excluded. Routine investigations were performed which included determinations of urinary catecholamine, and 17-hydroxycorticosteroid levels, intravenous pyelography, renal arteriography, and in some cases, assessment of differential renal function by means of bilateral ureteral catheterization. Patients with severe renal disease, as judged by results of casts in the urine and blood urea nitrogen and serum creatinine values, were excluded, as were patients with retinal hemor-
TABLE I  PATIENTS WITH ESSENTIAL HYPERTENSION WERE CLASSIFIED INTO 9 GROUPS FROM THE LEVELS OF PRA AND PALD FOUND

<table>
<thead>
<tr>
<th>Plasma renin activity (ng/ml/h)</th>
<th>0–0.3</th>
<th>0.3–2.0</th>
<th>2.0–∞</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>6 cases</td>
<td>10 cases</td>
<td>4 cases</td>
</tr>
<tr>
<td>0–3.0</td>
<td>5</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>3.0–15.0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>15.0–∞</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Plasma renin activity in various kinds of hypertension.

rhages or exudates, papilledema, congestive heart failure, or edema. All of the patients studied, therefore, were thought to have 'essential' hypertension and to be free of severe cardiac or renal disease.

The 58 hypertensive patients were studied under metabolic ward conditions on a 250-mEq sodium and 70-mEq potassium diet. Either the patients had never been treated for hypertension before or, if they had been treated, they were off all medications for at least three weeks before starting the study.

Blood was taken for plasma renin activity (PRA) and plasma aldosterone (Pald) at 8 a.m. after 8 hours in the recumbent state and after 2 hours of quiet ambulation with 40 mg of furosemide administration. Both PRA² and Pald³ were measured by the radioimmunoassay previously described. Sodium intake was reduced to 30 mEq/day until equilibrium was reached, then patients were given 75 mg hydrochlorothiazide and 400 mg spironolactone per day for 3 days. Both PRA and Pald were measured before and after the sodium deprivation test. Serum electrolytes were measured daily. The relationship between serum potassium and PRA was investigated in essential hypertension. Plasma deoxycorticosterone levels were determined by radioimmunoassay⁴ in hypertensive patients with low levels of PRA.

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RESULTS

The number of secondary hypertension observed during the period of the experiment was as follows: 25 renovascular hypertension, 15 primary aldosteronism, 10 Cushing's syndrome, 2 17α-hydroxylase deficiency, 2 pheochromocytoma, 8 malignant hypertension and 20 chronic renal insufficiency.

PRA and Pald in essential hypertension showed a lower level of 0.2-1.0 (normal 1.07 ± 0.90) ng/ml/h and a relatively high level of 0.29.0 (8.3 ± 5.7) ng/dl, respectively (Figs. 1 & 2). The Pald levels were paralleled with PRA in patients with essential hypertension with PRA above 0.50 ng/ml/h, but not correlated with PRA in cases with PRA below 0.50 ng/ml/hr.

As a result of our study, the 58 cases of essential hypertension could be classified into 9 groups from the levels of PRA and Pald found. The levels of 0.30 ng/ml/h in PRA and of 15.0 ng/dl in Pald were used as limits of low renin and high aldosterone, respectively, because these values in primary aldosteronism are low in PRA (below 0.30 mg/ml/h) and high in Pald (above 15.0 mg/dl). The results were as shown in Table 1: low renin hypertensive, 20 cases (34.5%), normal renin, 37 cases (64.0%), and high renin, only one case. Of 20 patients with low-renin essential hypertension, 6 cases had low aldosterone values and 10 had normal aldosterone. It is to be noted that four patients in the subgroup of patients with benign essential hypertension and suppressed PRA, had aldosterone levels above the upper normal limit. In these four patients the Pald was below 20 ng/dl, indicating that their high plasma levels were not caused by excessive aldosterone production.

No correlation between serum potassium and PRA was observed. Pald levels in 3 cases in which low levels of serum potassium were found, were 2.1, 10.7 and 15.2 mg/dl, respectively, which is within normal limits. Therefore, excess of mineralocorticoid other than aldosterone was suspected as a cause of hypokalemia. However, in these 3 patients, PRA levels were markedly elevated after upright posture for 2 hours following furosemide administration or the administration of hydrochlorothiazide and spironolactone with sodium deprivation. This would suggest that hypertension does not depend on mineralocorticoid excess.

With upright posture and furosemide administration, PRA rose from 1.45 ± 1.70 ng/ml/h (0.01 < p < 0.025) in 8 normal subjects. In 9 cases of primary aldosteronism, PRA increased slightly from 0.11 ± 0.09 to 0.25 ± 0.16 ng/ml/h on upright posture after furosemide administration (0.025 < p < 0.05). Pald, however, increased slightly from 65.3 ± 35.8 to
161.1 ± 145.1 ng/dl (0.05 < p < 0.10). After the removal of an adrenal adenoma in 4 cases, the combined stimulus of upright posture with furosemide administration increased PRA from $0.66 \pm 0.71$ to $1.25 \pm 0.93$ ng/ml/h (0.025 < p < 0.05). Pald rose from 0 to $18.6 \pm 12.4$ ng/dl after removal of adenoma in 3 cases with primary aldosteronism. In 3 cases of Cushing's syndrome, the change in PRA was very little, ranging from $0.34 \pm 0.21$ to $0.40 \pm 0.26$ ng/ml/h (p > 0.01), and in 10 cases of essential hypertension, PRA and Pald increased from $1.04 \pm 1.27$ to $2.34 \pm 2.08$ ng/ml/h (0.01 < p < 0.025) and from $32.3 \pm 25.4$ to $59.0 \pm 39.5$ ng/dl (p < 0.05), respectively, after furosemide administration and maintenance of upright posture. A positive correlation ($r = 0.762$) was found between PRA and Pald after the upright position and the sodium deprivation (Fig. 3).

The other mineralocorticoid, deoxycorticosterone, in plasma showed a relatively high value, 26.0 ng/dl, in a case of low-renin essential hypertension. No significant difference in plasma deoxycorticosterone concentration was observed between low and normal renin groups of essential hypertension (Fig. 4).

After treatment with spironolactone, all of the patients with low PRA became normotensive. The mean postspironolactone blood pressure for this group was 136/86 mmHg. Twelve of the fifteen patients with normal PRA had only minimal changes in blood pressure on the high dose of spironolactone. Three of the patients in this group became normotensive on 400 mg of spironolactone daily. The mean postspironolactone blood pressure for the entire group was 168/110 mmHg.

In the hydrochlorothiazide treatment group the patients with suppressed and low-normal PRA showed approximately the same response as those treated with spironolactone, while those with higher PRA had a smaller response.

The change in body weight that occurred during the first week of treatment with the active drug has been compared with the fall in mean blood pressure. The patients treated with spironolactone lost 0.9 kg and the patients treated with hydrochlorothiazide lost 1.3 kg. In the spironolactone group, there was a significant correlation between weight loss and blood pressure response ($r = 0.507$), but there was no statistically significant correlation in the hydrochlorothiazide group ($r = 0.362$).

**DISCUSSION**

Several laboratories have now reported that approximately 20 per cent of all patients with a
Plasma DOC In Hypertension

<table>
<thead>
<tr>
<th>Normal subjects</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30 ng/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low renin hypertension</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Normal renin hypertension</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>17α-hydroxylase deficiency</td>
<td>0</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig.4. Plasma DOC in essential hypertension and 17α-hydroxylase deficiency.

syndrome otherwise indistinguishable from essential hypertension have hyporesponsive plasma renin activity. These observations coincide with Conn's description of normokalemic primary aldosteronism. It would be reasonable to expect, therefore, that these 20 per cent of patients with essential hypertension and hyporesponsive plasma renin activity would turn out to have primary aldosteronism.

However, our results show that most of the patients with essential hypertension and hyporesponsive plasma renin activity had normal or low aldosterone secretory rates. Hypertensives with hyporesponsive plasma renin activity who had normal or low aldosterone secretory rates showed a close association between renin and aldosterone secretion, but this does not exclude the operation of other factors in this close hormonal interaction. The renin-aldosterone relationship might be slightly deflected at the low range of hormone activities so that decreases in plasma renin activity were not associated with fully commensurate decrease in aldosterone secretion. Accordingly, the results suggest that there may be a basal rate of aldosterone secretion which is sustained in the absence of effective renin stimulation. It also might be interpreted to mean that other hormonal factors are involved in supporting aldosterone secretion at these low levels of renin activity.

To explain these phenomena, one can postulate that the renin-angiotensin-aldosterone system can be 'short-circuited' by another mineralocorticoid. Increased secretion of an ACTH-dependent mineralocorticoid could directly act upon the distal tubule to bring about increased sodium retention in exchange for potassium and hydrogen ions. This, in turn, could result in an increased effective plasma volume which, through the system outlined above, would suppress plasma renin activity and, as a consequence, aldosterone secretion would remain at a low level.

In an attempt to determine the cause of suppressed plasma renin activity in patients with essential hypertension, levels of an other known mineralocorticoid, 11-deoxycorticosterone, were measured but were found to be normal. Recently, Melby and associates have found high levels of 18-hydroxy-deoxycorticosterone in a few such patients, but the contribution of this mineralocorticoid to the hypertensive process remains unknown. Thus there has been no consistent evidence that any one of the known mineralocorticoids is excessively secreted by patients with the syndrome of essential hypertension and suppressed renin activity.

In the hypertensive patients in our present series, plasma aldosterone concentration increased after sodium deprivation and after chlorothiazide. Plasma aldosterone concentration was strongly correlated with plasma renin activity, but not with other factors which stimulate secretion of aldosterone. These findings support the current view that increased release of renin and the generation of angiotensin in plasma, play
a part in the increased secretion of aldosterone during sodium depletion.

If mineralocorticoid excess is the cause, or a contributing factor in the blood pressure elevation in low-renin hypertension, one would expect these patients to respond particularly well to treatment with spironolactone, an inhibitor of the effect of mineralocorticoids on the renal tubule. It is well known that patients with mineralocorticoid excess due to primary aldosteronism do respond well to spironolactone, and, indeed, this drug had been used in the diagnosis as well as in the therapy of aldosterone-producing adenomas.

Our studies tend to confirm these observations by showing that high doses of spironolactone result in significant weight loss and normotension in hypertensive patients with low plasma renin activity. It should be noted however that patients with hypertension and normal plasma renin activity do not generally respond to high doses of spironolactone with either weight loss or appreciable decrease in blood pressure. On the other hand, inadequate mineralocorticoid blockade with conventional doses of spironolactone results in weight gain and a return of hypertension. These findings are consistent with the hypothesis that excessive production of an as yet unidentified mineralocorticoid may be responsible for the hypertension and hyporesponsive plasma renin activity observed in selected patients with essential hypertension.

The possibility exists that the changes observed in plasma renin activity and the differing response to high doses of spironolactone may be independent of any mineralocorticoid excess. It may be that, for some unexplained reason, patients with hypertension and low plasma renin activity have expanded plasma volumes, as has recently been suggested by Dustan and Tarazi. In such cases one might conclude that the favorable response of these patients to high doses of spironolactone depends on a nonspecific diuretic effect rather than on a specific antimineralocorticoid effect.

Gwinnup and Steinberg found that four patients with primary aldosteronism had favorable blood pressure responses to spironolactone, but not to hydrochlorothiazide. If response to spironolactone, but not to thiazide, is characteristic of other forms of mineralocorticoid excess, then our finding that hydrochlorothiazide, as well as spironolactone is effective in hypertensive patients with low renin might suggest that mineralocorticoid excess is not the explanation for their response to treatment. On the other hand, although it is not clear to what extent the antihypertensive effect of thiazide diuretics is due to their natriuretic properties, it is reasonable to expect that patients who are hypertensive because of the action of sodium-retaining steroids might respond to drugs with a direct natriuretic effect, as well as to drugs that inhibit the effect of the steroid. There is evidence that patients with low renin have increased extracellular fluid volume and exchangeable sodium compared to other hypertensive patients and this may be the reason for their responsiveness to diuretic drugs, whether aldosterone-antagonist or thiazide.

CONCLUSION

The study was designed to explore the possibility that the hypertensive process of patients with suppressed renin activity might be related to mineralocorticoid excess.

1) Plasma renin activity (PRA) and plasma aldosterone (Pald) in essential hypertension showed a lower level of 0-2.10 ng/ml/h and a relatively high level of 0-29.0 ng/dl, respectively. The Pald was paralleled with PRA in patients with essential hypertension with PRA above 0.50 ng/ml/h, but not correlated with PRA in cases with PRA below 0.50 ng/ml/h.

2) Low PRA was found in 20 of 58 cases with essential hypertension, of which 6 cases had low aldosterone and 10 had normal aldosterone values.

3) After upright posture and sodium deprivation, a positive correlation was found between changes in PRA and in Pald.

4) No significant difference in plasma deoxycorticosterone was observed between low and normal renin groups of essential hypertension.

5) After treatment with spironolactone, all patients with low PRA became normotensive.

It is concluded, from these results, that there is no consistent evidence that any of the known mineralocorticoids are secreted in excess by patients with low-renin essential hypertension.

REFERENCES

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Discussion:


CHAIRMAN: I think that the patients with low renin level have three different types of plasma aldosterone level (namely high, normal or low). So would you tell me what do you say about the differentiation between essential hypertension with low renin activity and primary aldosteronism?

Dr. SOITSU FUKUCHI (Tohoku University): 20 cases, 34.5% in 58 cases with essential hypertension showed low plasma renin level (below 0.30 ng/ml/h). In these cases 6 showed low plasma aldosterone level (p.a.l.), 10 normal p.a.l. and 4 high p.a.l. that is, the p.a.l. of most of patients with low renin level showed normal and low values.

CHAIRMAN: I don't believe 100% of cases with primary aldosteronism who have very long duration since onset of the disease (such as several to ten years until diagnosis) will come to levels of normal blood pressure by means of large dose of spironolactone. What do you think about this point?

Dr. S. FUKUCHI: It was very difficult that we make sure when the accurate time of onset of the disease is. However I have an idea which the blood pressure is difficult to fall in cases of over than 50 years old with primary aldosteronism by means of spironolactone, than younger patients.

Dr. S. MOTOMURA. (udano Hospital): I heard you have experienced in the last case the fall of blood pressure without the variation of electrolytes by spironolactone. So I have one question to you that in this case you saw the increase of urine volume and sodium excretion or not.

Dr. S. FUKUCHI: I have experienced the increase of urinary sodium excretion and the decrease of potassium excretion even in the cases which were not observed lowering blood pressure by spironolactone. I couldn't show an apparent increasing effect to urinary volume in contrast.

Dr. H. KURIHARA (Tokyo University): Would you tell me what the conditions for diagnosis of hyporeninaemia are? What is the reproductivity of hypo, normo-and hyperreninaemia respectively in cases with essential hypertension?

Dr. S. FUKUCHI: Blood sampling were performed in the condition of 250 mEq Na and 75 mEq K diet uptake per day, moreover in fasting time and recumbent position. Blood sampling were especially repeated in the cases with abnormal plasma renin activity and plasma aldosterone level. We obtained almost always subnormal renin level in the cases with hyporeninaemia, but big variations (often normal values) in the cases with hyperreninaemia. Namely we observed a good reproductivity in cases with hyporeninaemia.