Pathogenesis of Essential Hypertension
with a Suppressed Plasma Renin Activity

KENZO UCHIDA, M.D., ISAMU MIYAMORI, M.D.,
KENKO HASATANI, M.D., SHINPEI MORIMOTO, M.D.,
AND RYOYU TAKEDA, M.D.

The pathogenesis of essential hypertension with a suppressed plasma renin activity (PRA) remains obscure.

In the present study, the pattern of electrolyte homeostasis during four-days' salt restriction, and the effects of spironolactone on the blood pressure and PRA in patients with essential hypertension with a suppressed PRA were compared with that obtained by identical studies on the patients with proven primary aldosteronism and on the normal controls. Fifty-three patients were studied, including 38 patients with benign essential hypertension, 5 patients with primary aldosteronism, and 10 patients with normotension.

After a furosemide test, PRA was 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 was given to the patients with a suppressed PRA in a dose of 200 mg a day and to the patients with primary aldosteronism in a dose of 300 to 400 mg a day.

The results were as follows:
1) 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 PRA response.

2) Of 13 hypertensive patients showing a suppressed PRA response to the 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 the salt restriction.

3) In five of 12 patients with a suppressed PRA to both tests (Group A), the pattern of sodium excretion following salt restriction resembled that of patients with primary aldosteronism; that is, there was an abrupt decrease of sodium excretion with a significant decrease of potassium excretion. The remaining seven patients (Group B) showed the same sodium excretion pattern after salt restriction as that of normotensive patients.

4) All the patients of group A became normotensive within 2 weeks after spironolactone therapy with significant increases in the serum levels of potassium and PRA; 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.

5) All patients with a suppressed PRA showed normal levels of aldosterone in urine.

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).

Discussion:

Chairman: SOITSU FUKUCHI, Tohoku Univ.

Chairman: Thank you for your nice presentation about the pathogenesis of essential hyperten-

---

Key Words:
Essential hypertension
Primary aldosteronism
Suppressed plasma renin activity (PRA)
Spironolactone
Salt restriction
Furosemide administration

2nd Department of Internal Medicine, School of Medicine, University of Kanazawa, Kanazawa, Japan

* This paper was presented on the II Conference of Pathogenesis of Hypertension, November 20, 1972, Fukuoka

Japanese Circulation Journal Vol. 37, October 1973 1261
sion with suppressed plasma renin activity. Any comments and discussion?
Dr. TAKEDA (Tokyo Univ.): Did you find any differences in exaggerated natriuresis on saline loading between your A- and B-groups of essential hypertension?
Dr. UCHIDA (Kanazawa Univ.): Saline loading was performed in a few cases with essential hypertension. Exaggerated natriuresis was observed upon 1.0% saline loading in a case of A-group.
Dr. MOTOMURA (Utano Hosp.): (1) How do you explain a simultaneous decrease in potassium excretion with a decrease in sodium excretion upon sodium deprivation?
(2) How much is the potassium intake in your experiment?
(3) I think that you need to describe the exact amount of potassium intake in such a experiment.
(4) In the experiment estimating sodium and potassium excretion, it is necessary to make the potassium intake stable.
Dr. UCHIDA: (1) I supposed that the decrease in potassium excretion was caused by the decrease in sodium content in distal tubule on mineralocorticoid excess.
Regarding the questions (2)–(4), I agree with your opinion that a definite control of potassium intake is important, however, it was not so strict because of cooking problem.
Dr. ISHII (Tokyo Univ.): (1) It is impossible to presume the condition of mineralocorticoid excess from the decrease in urinary potassium excretion upon sodium restriction.
(2) We observed the increase of plasma renin activity upon sodium deprivation and furosemide administration in renin-suppressed essential hypertension. This is different from your results.
(3) How was the blood pressure changed upon spironolactone and thiazide administration in essential hypertension with suppressed renin?
Dr. UCHIDA: (1) Bartter and Biglieri have reported that a decrease in both sodium and potassium excretion upon sodium deprivation was due to mineralocorticoid excess and that the fact is useful for the diagnosis of primary aldosteronism. In our A-group, a decrease in sodium and potassium excretion was observed on the first day of sodium deprivation and spironolactone induced lowering of blood pressure with a rise in plasma renin activity and in serum potassium. Therefore the suppression of plasma renin activity in the group was supposed to be depending upon mineralocorticoid excess.
(2) In one of 13 cases which had no response of plasma renin activity to furosemide administration, plasma renin activity increased normally to sodium deprivation.
(3) We did not study the effect of spironolactone and thiazide on the blood pressure in renin-suppressed essential hypertension. However, in a case of B-group, no change in the blood pressure, serum potassium and plasma renin activity was observed on thiazide administration similar to the result on spironolactone.
Dr. ODA (Nihon Univ.): (1) Are there the two groups of mineralocorticoid-dependent and -independent in renin-suppressed essential hypertension?
(2) Which symptom or laboratory findings were first improved with spironolactone in renin-suppressed essential hypertension?
(3) When the blood pressure was lowered to normal level with the long term administration of spironolactone, has plasma renin activity been responded quite normally or still suppressed?
Dr. UCHIDA: (1) Yes, there are.
(2) The effect of spironolactone was occurred first on serum potassium, second on the blood pressure and lastly on the plasma renin activity. The effect was similar to that observed in primary aldosteronism.
(3) The administered dose of spironolactone was 200 mg/day. The effect of smaller amount (75–100 mg/day) on plasma renin activity has not been tested. However, in primary aldosteronism, even if the administered dose of spironolactone was reduced to 75–100 mg/day after lowering of blood pressure to normal level with the large dose of 300–400 mg/day, plasma renin activity had no response to furosemide administration.
Dr. KISHIMOTO (Osaka Municipal Univ.): (1) Is plasma renin activity correlated to renin content in kidney?
(2) Does no increase in plasma renin activity mean a block of passway to stimulus or low renin content in kidney?
Dr. UCHIDA: (1) We did not estimate the renin content in kidney.
(2) We suppose that the suppressed renin activity means depression in renin release from juxtaglomerular apparatus of kidney.
CHAIRMAN: We observed in primary aldosteronism that the suppression of plasma renin activity existed after the short-term administration of spironolactone, however, an increase in plasma renin activity to normal range was obtained after the long-term administration of spironolactone. How long does it take to increase to normal levels?
of plasma renin activity with spironolactone administration?
Dr. MORIMOTO (Kanazawa Univ.): In primary aldosteronism about 2 month administration of spironolactone restored plasma renin activity to respond normally to various stimuli. The details of results were presented in J. Clin. Endocr. 1970.

Dr. KAWASAKI (Kyushu Univ.): (1) On sodium deprivation the potassium intake also declines to decrease because of a decrease of appetite, so it needs to check the exact amount of sodium and potassium intake.

(2) Have you experienced gynecomastia or gastrointestinal disturbances with long-term administration of spironolactone?

(3) Have you estimated aldosterone secretion in hypertension on spironolactone administration?

Dr. UCHIDA: (1) Gynecomastia was observed in 2 male subjects with spironolactone administration, but its cessation induced a disappearance of the symptom.

(2) We have not measured aldosterone secretion.