Effect of Acute Volume Depletion on Blood Pressure, Plasma Renin Activity and Plasma Aldosterone Concentration in Hypertensive Subjects

Kenshi Kumamoto, Yoshitaka Yamamoto, Terukazu Kawasaki, Teruo Omae and Kenjiro Tanaka

RECENTLY much attention has been paid to "low-renin essential hypertension". There have been several studies suggesting that volume expansion is a major factor maintaining high blood pressure in this type of hypertension. However, no consistent findings were reported concerning plasma or blood volume, ECF-volume and exchangeable sodium (1).

The purpose of this study is to observe the effect of acute volume depletion on blood pressure, plasma renin activity (PRA) and plasma aldosterone concentration (PAC) in patients with benign essential hypertension of different PRA values. Acute volume depletion was elicited by diuretic agent (furosemide) under mild dietary Na-restriction. The same observation was also made in patients with primary aldosteronism.

MATERIALS AND METHODS

Twenty three patients with essential hypertension and 7 with primary aldosteronism were studied. Of the patients with essential hypertension, 17 were men and 6 were women aged between 18 and 63 (mean age 33 years old). Seven patients with primary aldosteronism were 24 to 57 years old; 4 were women. Of all the patients with primary aldosteronism, the diagnosis was confirmed by surgical finding of adrenocortical tumor and normalization of blood pressure after extirpation of the tumor. All of the patients were on benign stage of hypertension and had no evidence of congestive heart failure.

Any medication was discontinued at least 10 days before the study. Control period with regular diet (Na 170 to 200 mEq/day, K 50 to 75 mEq/day) for at least 7 days was followed by per oral administration of furosemide (120 mg/day) for 3 days. During furosemide administration, sodium in the diet was restricted to 100 mEq/day and potassium intake was increased to 100 to 130 mEq/day.

Urinary electrolytes excretion was measured daily in 24 hour urine aliquots. The averaged urinary electrolytes and body weight in the last three days during control period were compared with those in three consecutive days during furosemide administration. Blood pressure was taken daily in early morning and was analyzed in the same manner as urinary electrolytes and body weight. Reduction in blood pressure was judged as significant when mean blood pressure (diastolic blood pressure +1/3 pulse pressure) following furosemide administration reduced more than 10% of the control value.

Blood samples were drawn for determination of PRA, PAC, serum electrolytes and hematocrit (Ht) immediately after the day of both control period and furosemide administration. Blood sampling was done after quiet ambulation for one hour before breakfast. PRA and PAC were determined by radio-immunoassay.

Normal values for PRA and PAC were

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TABLE I  RELATIONSHIP BETWEEN PRA, PAC AND BLOOD PRESSURE RESPONDING TO FUROSEMIDE IN PATIENTS WITH ESSENTIAL HYPERTENSION

<table>
<thead>
<tr>
<th>PAC response</th>
<th>Hyporesponsive</th>
<th>Normal response</th>
<th>Hyperresponsive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyporesponse</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Normal response</td>
<td>7 (6)</td>
<td>10 (2)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Hyperresponse</td>
<td>0</td>
<td>4 (0)</td>
<td>0</td>
</tr>
</tbody>
</table>

( ): Number of cases with a significant fall of blood pressure after furosemide. Responsiveness of PRA and PAC in hypertensive patients was determined from the range of response to furosemide in normotensive control subjects.

TABLE II  CHANGES IN PARAMETERS IN PATIENTS WITH ESSENTIAL HYPERTENSION AND IN PATIENTS WITH PRIMARY ALDOSTERONISM FOLLOWING FUROSEMIDE ADMINISTRATION

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Percent changes following furosemide (Mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BW</td>
</tr>
<tr>
<td>Essential HT</td>
<td></td>
</tr>
<tr>
<td>Group 1 §</td>
<td>7</td>
</tr>
<tr>
<td>Group 2 §</td>
<td>10</td>
</tr>
<tr>
<td>Primary ald.</td>
<td>7</td>
</tr>
</tbody>
</table>

Difference between

| Group 1 & 2  | NS      | NS      | <0.001     | NS      | NS      |
| Group 2 & Primary a. | NS | <0.02  | <0.02     | <0.05  | —       |
| Group 1 & Primary a. | NS | <0.02  | NS        | NS      | —       |

§ Group 1 = patients with hyporesponsive PRA and normally responsive PAC.
§ Group 2 = patients with normally responsive PRA and PAC.

BW = body weight, Ht = hematocrit, BP = mean blood pressure (diastolic pressure + 1/3 pulse pressure).

*p < 0.05, **p < 0.02, ***p < 0.01, ****p < 0.005, *****p < 0.001, NS = not significant.

determined during control period from 13 normotensive subjects without any evidence of cardiovascular, renal or hepatic disease, aged between 20 and 57 years old (mean age 37). Of 13 control subjects, 5 were also studied after furosemide administration. Normal values of PRA during control period and after furosemide administration were ranged 1.70 to 3.00 ng/ml/hr (mean 2.44), 3.07 to 12.00 (mean 5.52), respectively. Those of PAC were 6.7 to 28.5 ng/100 ml (mean 14.8), 13.0 to 42.8 (mean 28.3), respectively.

Statistical analysis was done by Student's test.

RESULTS

Control Study

PRA was lower than normal in 11 of 23 patients with essential hypertension (low PRA group). Of 12 remainders, 10 showed normal PRA (normal PRA group) and 2 high PRA (high PRA group). Since patients with high PRA were only two, statistical analysis was not done. Of all the patients with primary aldosteronism PRA was much lower than normal.

PRA of 0.21 ± 0.12 ng/ml/hr (Mean ±SE) in patients with primary aldosteronism was significantly lower than that of 0.81 ± 0.14 in low PRA.
group of essential hypertension (p < 0.005). The latter was significantly lower than PRA of normal PRA group of 2.09 ± 0.12 (p < 0.001). Mean PAC was not different between low and normal PRA group (14.2, 16.0, respectively). It was 14.8 for normotensive control group and 74.4 for primary aldosteronism.

Mean blood pressure in each group of low PRA, normal PRA and primary aldosteronism was 119 ± 4 mmHg (Mean ±SE), 115 ± 4, 129 ± 8, respectively. The difference among the three groups was not statistically significant. Blood urea nitrogen and serum creatinine were all within normal range.

Effects of Furosemide Administration

Following furosemide administration, 8 of 11 patients in low PRA group (73%) and 4 of 7 patients with primary aldosteronism showed a significant reduction in blood pressure. On the contrary, only one of 10 patients in normal PRA group and none of 2 in high PRA group were significantly reduced of their blood pressure. Reduction in blood pressure in low PRA group, 12.3 ± 1.6% (Mean ±SE), and in primary aldosteronism, 11.9 ± 2.5, was greater than that in normal PRA group, 2.7 ± 1.3 (p < 0.001, for both relations). The difference was not statistically significant between the former two groups.

After furosemide administration, PRA in 8 of 11 patients in low PRA group was even lower than the lowest PRA in normotensive control subjects. PRA of 3 remainders in low PRA group and all in normal PRA group responded normally to furosemide with increasing PRA. Response of one in high PRA group was normal and that of another one was more marked than normal. Response of PRA to furosemide was much smaller in patients with primary aldosteronism than the lower limit of normotensive control subjects. PRA in patients with primary aldosteronism was significantly lower than in low PRA group (p < 0.001), and the latter was lower than that in normal PRA group (p < 0.001).

Blood pressure response to furosemide showed a direct correlation with PRA both during control period and after furosemide administration (r = 0.62, p < 0.005, r = 0.68, p < 0.001, respectively). No such a correlation was found between blood pressure response and PAC.

All of the patients with essential hypertension except one in low PRA group responded to furosemide with increasing PAC. Response of PAC was excessive in 2 patients in each group of low and normal PRA, whose PRA responded normally to furosemide.

Relationship between the response of PRA, PAC and blood pressure to furosemide in essential hypertension was summarized in Table I. Seven patients showed hyporesponsive PRA with normally responsive PAC; 6 of whom showed a significant reduction in blood pressure following furosemide (Group 1). Responsiveness of both PRA and PAC were normal in 10 patients, only 2 of whom was significantly reduced of blood pressure following furosemide (Group 2).

Comparison of Various Parameters between Group 1, 2 and Primary Aldosteronism

During control study, serum sodium in primary aldosteronism was higher than that in Group 1 or 2 (p < 0.001, p < 0.005, respectively) and serum potassium was lower than the latter two groups (p < 0.001, for both relations). Including these parameters, there were no differences in urinary sodium and potassium excretion and urinary Na/K ratio between Group 1 and 2 during control study.

Percent change of various parameters in each group following furosemide was shown in Table II. Of all three groups, their body weight reduced significantly to the same extent. Nevertheless, Ht remained unchanged in primary aldosteronism, whereas it increased significantly in both Group 1 and 2. A significant reduction in blood pressure was observed in all these 3 groups (p < 0.001 for Group 1, p < 0.05 for Group 2, p < 0.01 for primary aldosteronism), but the degree of it was the smallest in Group 2.

PRA and PAC increased significantly and to the same extent both in Group 1 and 2, although increase in PRA was insignificant in primary aldosteronism. Since PAC was measured in only two of 7 patients with primary aldosteronism after furosemide, no statistical analysis was done.

Serum sodium concentration was unchanged in Group 1 and primary aldosteronism, while it was reduced significantly in Group 2. The difference of change in serum sodium was significant between primary aldosteronism and Group 2 (p < 0.05). Change in urinary sodium and potassium excretion were not significantly different among the three groups.

DISCUSSION

It has been reported that hypertensives with low PRA show a greater decrease in blood
pressure responding to long-term administration of diuretics. The present study also shows that the same effect can be observed in a short-term administration of diuretics.

In the present study, furosemide administration combined with mild restriction of dietary sodium produced negative sodium balance, decrease in body weight and increase in Ht in the majority of the subjects. This indicate that volume contraction occurred. Most of the patients with low PRA decreased their blood pressure significantly responding to the maneuver, while the same effect could not be observed in most of the patients with normal PRA.

It has been demonstrated with consistency that plasma volume, ECF-volume and exchangeable sodium space are increased in patients with primary aldosteronism compared with both normal subjects and essential hypertension. Present results showed that reduction in body weight and blood pressure in patients with low or hyporesponsive PRA was similar as those in patients with primary aldosteronism.

These data, along with direct correlation between PRA and blood pressure response to furosemide, suggest that patients with low or hyporesponsive PRA have volume expansion and whose hypertension may occur in association with sodium or water excess. Thus, nonspecific volume depletion induced by diuretic may produce a reduction in effective volume and possibly lowering blood pressure.

However, present study offers some puzzling evidence against this explanation. Firstly, some patients with low PRA did not respond and some patients with normal PRA did respond to this maneuver. This lack of uniformity in blood pressure response was similar when patients with hyporesponsive PRA was compared with those with normally responsive PRA. Secondly, the degree of reduction in body weight, increase in Ht and urinary sodium excretion following furosemide were not larger in patients with hyporesponsive PRA than those with normally responsive PRA: reduction in blood pressure of the former, as a group, was significantly greater than in the latter.

Therefore, the assumption can not be supported by the present study that volume expansion of any etiology may play an important role in maintaining elevated blood pressure in patients with low or hyporesponsive PRA, although acute volume depletion caused a greater hypotensive effect in those patients.

Laragh suggested that an inability to excrete potassium normally might result in hypertension with low PRA, especially low PRA with normal aldosterone. Brunner et al. reported that low-PRA hypertensives retain more potassium than normal PRA hypertensives when placed on a low sodium diet. However, the present study showed that potassium balance, expressed as serum and urinary potassium, in patients with hyporesponsive PRA with normally responsive PAC, as a group, did not differ from that in those with normally responsive PRA and PAC.

Conclusion

Acute volume depletion induced by diuretic and mild restriction of dietary sodium produced a greater reduction in blood pressure in hypertensive patients with low or hyporesponsive PRA and in patients with primary aldosteronism than in patients with normal or normally responsive PRA. However, the present study could not support the assumption that volume expansion plays an important role in the mechanism of hypertension in patients with low or hyporesponsive PRA.

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Reference


Discussion:

Chairman: SOITSU FUKUCHI, Tohoku Univ.

Dr. SOITSU FUKUCHI (Chairman, Tohoku Univ.): Thank you for your nice presentation about the effects of acute volume depletion on blood pressure, plasma renin activity and plasma aldosterone in hypertensive subjects.

In your experiment, the incidence of low renin values in essential hypertension (11 out of 23 cases) was relatively higher than that reported by other researchers. I would like to ask you about the criteria of low renin group in your experiment.

Dr. KUMAMOTO: Normal range of plasma renin activity was the values obtained after 1-hour-upright posture before breakfast in early morning in 13 normotensive patients without any abnormalities in heart, kidney and liver functions. Low renin group was defined as the patients with lower values of plasma renin activity than that described above.

Dr. TEIZO ITO (Jieitai Central Hospital): Did you find any differences of urinary sodium and potassium excretions between in low and normal renin groups of essential hypertension?

Dr. KUMAMOTO: No significant difference between low and normal renin groups was found in urinary sodium and potassium excretion after furosemide administration.

Dr. NAGAO KAIJHARA (Nihon Univ.): 1) Did you estimate body fluid volume, circulating plasma volume and cardiac output before and after the furosemide administration?

2) Do you think that the high blood pressure in low-renin group of hypertension with normal aldosterone secretion depends on the expansion of body fluid?

Dr. KUMAMOTO: 1) I have already estimated body fluids in a part of patients reported, but have not yet done analyze these results.

2) According to the present experiment, I could not conclude that the hypertension with low-renin and normal-aldosterone secretion was caused by the expansion of body fluid.

Dr. KENJIRO KIKUCHI (Sapporo Med. College): 1) We have also studied on the depressor mechanism of sodium deprivation and the cause of hypertension from the change of plasma renin activity, total exchangeable sodium and plasma volume observed during long-term sodium deprivation in essential hypertension. The depletion of blood pressure upon sodium deprivation was larger in hypertensive patients with low-renin activity and high values of total exchangeable sodium and of plasma volume. In this group an increase of plasma renin activity upon upright posture was a little. Total exchangeable sodium and circulating plasma volume decrease upon sodium deprivation in the low-renin group. From these results it is concluded that the increase of body fluid and body sodium may be the cause of hypertension with low renin activity.

2) The pressor response to norepinephrine or angiotensin infusion was larger in low-renin hypertension than in normal- or high-renin hypertension. The pressor response to norepinephrine or angiotensin decreased upon sodium deprivation.

Dr. NOBUHIRO SUGINO (Tokyo Women’s Med. College): 1) Although furosemide caused natriuretic and depressor effects on normal and hypertensive patients, no increase in body fluid volume was observed in essential hypertension.

2) Intermittent increase in GFR and a change in fractional resorption of sodium were observed after furosemide administration. It is interested in the change of these elements during furosemide administration in the 3 groups of hypertension divided by renin values.