Salt Intake and Hypertension

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To confirm our previous study and to observe the effect of long-term antihypertensive therapy, we studied 89 patients with essential hypertension under the following three different dietary salt balance conditions: Phase I (control diet); daily dietary salt ingestion of 10 g for more than 10 days, Phase II (low-salt diet); 2 g of salt for 4 days plus oral administration of 120 mg of furosemide on the morning of the first day and Phase III (high-salt diet); 22 g of salt for 4 days. The patients were divided into three groups according to blood pressure response to sodium: Group I (salt-sensitive); mean blood pressure (MBP) in Phase II decreased more than 10% of that in Phase I or that in Phase III exceeded by 10% or more than that in phase II, Group II (paradoxically salt-sensitive); MBP in Phase II increased more than that in Phase I, and the remaining Group III (non-salt-sensitive). Thirty-four, 18 and 37 patients could be classed into Groups I, II and III, respectively. Cardiovascular profiles of the patients on admission did not differ among the three groups except for hematocrit. As compared with MBP on admission, the fall of MBP in Phase I was greater in Group II than in Group I. Percent changes of pulse rate, body weight and hematocrit showed a tendency toward a greater fluctuation in Group I than in Group II, in all three phases. Plasma renin activity and plasma aldosterone concentration among the three groups did not differ significantly in any phase. However, pressure-renin index showed a significant difference between Groups I and II. Antihypertensive drugs given to Group I were all diuretics alone or diuretics plus other(s), whereas in Group II there were no patients taking diuretics alone. These results indicate that volume factor(s) contribute to high blood pressure in Group I and vasoconstrictive factor(s) such as renin-angiotensin and sympathetic nervous systems in Group II.

Key Words:
Essential hypertension
Salt-sensitive hypertension
Paradoxically salt-sensitive hypertension
Non-salt-sensitive hypertension
Pressure-renin index
Plasma renin activity
Plasma aldosterone concentration

We have already reported several clinical studies with regard to blood pressure and its related variables such as sodium, the renin-angiotensin-aldosterone (R-A-A) system and so on in normotensive and hypertensive subjects. Firstly, in the chronopediologic collaborative study made on the healthy young women in Japan and the United States according to the same protocol other than the contents of...
both high-salt diet and severe depletion of sodium following oral administration of 120 mg of furosemide for 3 days as compared with the period of control diet and 3) individual renin-aldosterone axis in response to changes in dietary sodium and posture varied from subject to subject. The increase in blood pressure induced by severe sodium depletion was considered to be related to the stimulation of both the renin-angiotensin system and the sympathetic nervous activity.

Recently, we reported that the patients with idiopathic hypertension could be classified as "salt-sensitive" or "non-salt-sensitive" by means of the percent changes in blood pressure with changes from low to high-sodium intake.

To confirm our previous study and to observe the effect of long-term antihypertensive therapy, we studied a large number of patients with essential hypertension.

MATERIALS AND METHODS

Eighty-nine Japanese patients with essential hypertension (61 males and 28 females, aged 17–65 years) were studied in the Second Department of Internal Medicine, Kyushu University Hospital. All antihypertensive medications were discontinued at least 2 weeks prior to the study. Blood pressure measured several times at our or other outpatient clinic was over 140 systolic and 90 mmHg diastolic and their blood pressure on admission was over 140/90 mmHg. All patients underwent a thorough inpatient evaluation which included complete history, physical examination, urinalysis, urine culture, chest X-ray, electrocardiogram, rapid sequence intravenous pyelogram, blood studies for electrolytes, plasma renin activity (PRA) and plasma aldosterone concentration (PAC) and measurements of urinary 17-ketosteroids, 17-hydroxy-corticosteroids, aldosterone and catecholamines. Aortography and blood sampling from renal vein were performed as required to rule out renovascular hypertension. In no patient was the cause of hypertension defined. All had normal renal function as evaluated from serum levels of urea nitrogen and creatinine and the value of PSP and creatinine clearance. Hypertension in all patients was benign in nature with no evidence of cardiac failure or liver damage.

Protocol

The patients were studied under 3 different
dietary conditions as illustrated in Fig. 1. Phase I (control diet): Daily dietary salt of 10 g was given for more than 10 days and most clinical and laboratory studies were made during this phase to rule out secondary hypertension. Phase II (low-salt diet): A salt-poor diet which still contained 2 g of salt per day was given for 4 days. On the morning of the first day of this phase, 120 mg of furosemide was given orally to initiate a negative sodium balance. Phase III (high-salt diet): A diet of 15 g per day of salt was given for 4 days with 4 salt capsules each containing 10 mEq of sodium, with the 3 meals each day.

Potassium intake was maintained at 50 to 60 mEq per day throughout the study.

Body weight (BW) was measured each morning after the patients had voided at 8:00 a.m. Blood pressure was determined with a sphygmanometer and pulse rate (PR) was counted from the radial pulse.

At the end of each phase, venous blood samples were taken in the recumbent position at 8:00 a.m. after an overnight fast to determine hematocrit (Hct), serum Na, K and creatinine,
Fig. 3. Percent changes of mean blood pressure (MBP) (a), pulse rate (PR) (b), body weight (BW) (c) and hematocrit (Hct) (d) between the values on admission and Phase-I value (Admission → Phase I), between Phase-I and II values (Phase I → Phase II) and between Phase II and III values (Phase II → Phase III) in Groups I, II and III. * p < 0.05, *** p < 0.01

PRA and PAC. The patients were then kept in an upright position for one hour and blood samples were obtained at 9:00 a.m.

The blood samples for PRA and PAC were drawn into chilled vacutainer tubes containing EDTA and heparin, respectively, and immediate-
ly centrifuged at 4°C, 3,000 rpm for 15 min. The plasma was separated and kept frozen at -20°C until use.

PRA was determined by radioimmunoassay with the kit from CEA-IRE-SORIN (CIS) and based on a slight modification of the assay system of Haber et al. PRA in logarithm formation (log-PRA) was also used for analysis.

Pressure-renin index defined as a product of supine log-PRA and mean blood pressure just before blood sampling for PRA in Phase II was compared with each group.

PAC was determined by radioimmunoassay with the kit from CIS.

Hct measurements were performed by a micromethod after centrifugation of the capillary tubes at 11,000 rpm for exactly 5 min. A mean of 3 tubes was used for each analysis.

Both blood pressure and PR of the patients were measured in the recumbent position, and the values obtained on admission and just before the blood sampling at the end of each phase were used for analysis.

Mean blood pressure (MBP) was calculated as diastolic pressure plus one third of pulse pressure. Patients whose MBP value in Phase II decreased more than 10% of that in Phase I or those whose MBP value in Phase III exceeded by 10% or more than that in Phase II were classified as Group I (salt-sensitive), those whose MBP in Phase II increased more than that in Phase I, as Group II (paradoxically salt-sensitive) and the rest, as Group III (non-salt-sensitive).

Percent changes in MBP, PR, BW and Hct were used to compare the influence of dietary sodium ingestion of the three groups.

The blood pressure value and antihypertensive effects of the drugs were checked in 44 patients followed in our outpatient clinic at about 6 months after discharge.

All data were expressed as mean ± standard error of the mean (SEM), and Student's t-test or paired t-test was used for statistical analysis.

RESULTS

Thirty-four, 18 and 37 patients could be classed into Groups I, II and III, respectively. Cardiovascular profiles and laboratory findings on admission are shown in Table I. Significant differences in distribution by age and sex or in clinical findings were nil, except for Hct on admission, which was significantly higher in Group II than in Groups I and III.

MBP, PR, BW and Hct in Phase I (control diet) in each group are shown in Table II. The average MBP for the three groups on admission did not differ, whereas MBP for Group II in Phase I showed a significant decrement with an average of 109 ± 3.2 mmHg as compared with that for Group I (118 ± 2.0 mmHg) as illustrated in Fig. 2. A significant difference of PR in Phase I was found in Groups I and II although there was no difference of PR on admission among the three groups. In contrast, no difference of BW on admission and in Phase I was found among the three groups. Hct in Phase I showed no significant differences.

Percent changes of MBP, PR, BW and Hct between the value on admission and that in Phase I, between the value in Phases I and II and between the value in Phases II and III of each group are illustrated in Figs. 3-a, b, c and d. Percent change of MBP between the value on admission and that in Phase I differed significantly between Groups I and II (Fig. 3-a). Percent change of PR between the value in Phases II and III in Group I and that in Group II differed significantly (Fig. 3-b). On the other hand, percent changes of BW and Hct did not differ.
TABLE III  LONG-TERM* EFFECTS OF ANTITHYPERTENSIVE TREATMENT IN 
THE THREE GROUPS

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of cases</th>
<th>Blood Pressure (mmHg, Mean ± SEM)</th>
<th>Diuretics</th>
<th>Nondiuretics</th>
<th>Combined**</th>
<th>No drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>18</td>
<td>137 ± 3/90 ± 2</td>
<td>11</td>
<td>0</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>11</td>
<td>143 ± 4/93 ± 2</td>
<td>0</td>
<td>4</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>15</td>
<td>139 ± 4/90 ± 2</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

* about 6 months,  ** Diuretics + Nondiuretics

among the three groups through three phases, 
as shown in Figs. 3-c and d.

No difference was found in both supine and 
upright PRA in any phase among the three 
groups. Supine log-PRA in Group I in Phase I 
was lower than that in Groups II and III, but the 
difference was not significant (Group I vs. II: 
t = 1.878, p < 0.1; Group I vs. III: t = 1.851, 
p < 0.1). Similarly, both supine and upright log-
PRA in Group I showed a tendency to be lower 
than those in Groups II and III in Phases II and 
III (Fig. 4). Both supine and upright PAC among 
the three groups also did not differ in any phase 
although findings in Group I showed a tendency 
imp. lower than those in Groups II and III.

Mean pressure-renin index in Groups I, II and 
III was 48.4 ± 8.9, 87.2 ± 10.8 and 60.8 ± 10.1 
arbitrary unit, respectively, and there was a 
significant difference between Groups I and II 
t = 2.727, p < 0.01.

Long-term effect of antihypertensive treatment 
in the three groups is summarized in Table III. 
Blood pressure was fairly well controlled and 
there was no significant difference of pressure 
level among the three groups. Diuretics alone 
were given in 11 and combined treatment was 
carried out in 6 out of the 18 patients in Group I, 
and nondiuretics were given in 4 and combined in 
7 out of 11 in Group II. No patients in Group I 
received treatment of nondiuretics alone and none in Group II received diuretics alone.

DISCUSSION

Essential hypertension may well prove to be 
heterogenous. Several investigators tried to 
subdivide their cohorts of essential hypertensive 
patients according to plasma renin\cite{12} or plasma 
norepinephrine level\cite{13,14}. It is clear from 
the present results together with previous reports\cite{6,7} 
that the acute response of blood pressure to 
salt manipulations is quite different among 
the patients with essential hypertension. The patients 
were classified into 3 groups according to our 
tentative criteria and approximately 20% fell into 
Group II. These patients showed increments in 
blood pressure on a low-salt diet and/or a decre-
ment on a high-salt diet. We tentatively termed 
this group “paradoxically salt-sensitive” in con-
trast to the group termed “salt-sensitive” in our 
previous report\cite{9}. In this “paradoxically salt-
sensitive” group, significantly lower levels in 
MBP were observed in Phase I as compared to 
Group I. At the same time approximately 11.5% 
decrease in pulse rate was also observed in this 
group (Group II). Percent changes in both body 
weight and hematocrit in Phase I, however, were 
similar among the three groups. Lake\cite{5} reported 
that hospitalization significantly reduced plasma 
norepinephrine in both normotensive and hyper-
tensive subjects. Thus, the effect of the hospital-
ization may have played a considerable role in 
lowering both blood pressure and pulse rate in 
Group II. Therefore, the role of the sympathetic 
nervous system as a pressor activity may be more 
important in Group II than in Groups I and III.

The increment of percent change in MBP was 
observed in Phase II in Group II, whereas percent 
change in MBP decreased in the same phase in 
Groups I and III. This phenomenon in Group II 
seemed to be paradoxical. However, we observed 
identical paradoxical phenomenon in normal 
young subjects whose blood pressure increased 
significantly when given 120 mg of furosemide 
orally on the first day of low-salt dietary regi-
men\cite{3}. Salt-poor diet combined with oral furose-
midine administration may have acted as a stimulus 
of the sympathetic nervous system in Group II.

PRA in supine or upright position in any 
phase did not show significant difference among 
the three groups. When PRA was transformed in 
logarithm (log-PRA), however, log-PRA in Group 
II had a tendency to be the highest among the 
three groups in Phases I and II, as shown in Fig. 4.

Pressure-renin index between Groups I and II 
showed a significant difference in Phase II. We
have already proposed that the pressure-renin index is of greater value than PRA in predicting the role of the renin-angiotensin system in blood pressure regulation in patients with essential hypertension. Therefore, the renin-angiotensin system may play a more important role in Group II than in Group I. This was consistent with the finding of blood pressure control in relation to antihypertensive drugs. At about 6 months after the patients were discharged, the blood pressure was fairly well controlled with diuretics alone or a combination of drugs in Group I, whereas in Group II there were no patients on diuretics alone. These results suggest Laragh’s vasoconstriction-volume hypothesis.

Essential hypertension may be classed into two groups according to the response of blood pressure to changing salt balance. The proposition, however, was based upon the acute response of blood pressure to changing salt balance. More studies are needed to elucidate the mechanism or pathophysiology of chronic hypertension in relation to salt balance.

Acknowledgement

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ADDENDUM

Immediately after the presentation of this paper at the Symposium of 44th Scientific Session of the Japanese Circulation Society (March 26, 1980, Nagoya), a paper has appeared (Longworth et al., Clin Pharmacol Ther 27: 544, 1980) suggesting the existence of the so-called “paradoxical salt-sensitive” group in essential hypertension.

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