Pressor Responsiveness, Hemodynamics and Plasma Renin Activity
In Essential Hypertension

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It is known that vascular reactivity to angiotensin or catecholamines is influenced by many factors such as hemodynamics, sodium homeostasis, sympathetic activity, humoral agents and thickening of arterial wall.1-6 The role of vascular reactivity in the pathophysiology of essential hypertension is still complex.

The present study was undertaken to relate the pressor responses to angiotensin, norepinephrine and tyramine with hemodynamics, sodium balance and plasma renin activity in patients with essential hypertension. In addition, by repeating the examinations, the effects of "bed-rest" on blood pressure and other parameters were investigated in order to scrutinize factors concerning elevation of blood pressure in patients with essential hypertension.

MATERIALS AND METHODS

Twenty-one hospitalized patients with benign essential hypertension (14 male and 7 female) and 15 hospitalized patients with renal diseases or hypertension of other causes (7 male and 8 female) were studied. Their ages ranged from 16 to 53 years with an average of 34 years. Essential hypertension was diagnosed after thorough examinations including pyelography and arteriography were performed. In the patients with essential hypertension, hematological and biochemical tests and renal clearance tests were within normal limits, and only mild retinal changes (KW I or II) were noted. None gave a history or any signs suggestive of cardiac failure or of malignant hypertension. All the patients were placed on a diet containing sodium chloride of 8 to 13 gm a day, and had been without any antihypertensive drugs for at least a week before the examinations.

Examinations for hemodynamics and pressor responses were done in patients who were lying on a table comfortably. Heart rate, blood pressure and cardiac output were measured. Cardiac output was measured by the dye-dilution technique using indocyanine green. Cardiac index and total peripheral resistance were calculated. A short Teflon tubing was inserted percutaneously in a femoral artery, being connected to an electronic manometer, which recorded mean blood pressure. A butterfly needle was inserted percutaneously in an antecubital vein and was jointed to a small plastic cannula through which vasoactive drugs were injected and otherwise 0.9% saline was infused slowly to keep the cannula patent. Venous blood was collected for measuring plasma renin activity and serum electrolytes immediately before starting the

Key Words:
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Hemodynamics
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<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A</th>
<th></th>
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<th></th>
<th>Group B</th>
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</thead>
<tbody>
<tr>
<td>Mean Blood Pressure (mmHg)</td>
<td>123.3 ± 3.8</td>
<td>111.0 ± 2.5</td>
<td>-12.3 ± 2.7</td>
<td>&lt; 0.05</td>
<td>118.4 ± 6.0</td>
<td>106.2 ± 5.2</td>
<td>-12.2 ± 2.6</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Response to 0.01 μg/kg of Angiotensin II (mmHg)</td>
<td>22.7 ± 1.5</td>
<td>17.2 ± 1.4</td>
<td>-5.5 ± 1.0</td>
<td>&lt; 0.01</td>
<td>18.9 ± 3.0</td>
<td>21.5 ± 3.8</td>
<td>+2.6 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Response to 0.05 μg/kg of Norepinephrine (mmHg)</td>
<td>16.1 ± 1.3</td>
<td>14.3 ± 2.8</td>
<td>-1.8 ± 2.0</td>
<td>NS</td>
<td>15.1 ± 0.3</td>
<td>19.5 ± 1.6</td>
<td>+4.4 ± 1.7</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Response to 0.025 mg/kg of Tyramine (mmHg)</td>
<td>10.6 ± 1.7</td>
<td>12.7 ± 1.4</td>
<td>+2.1 ± 1.3</td>
<td>NS</td>
<td>9.7 ± 1.1</td>
<td>17.4 ± 3.6</td>
<td>+7.7 ± 4.3</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma Renin Activity (ng/ml)</td>
<td>4.0 ± 1.8</td>
<td>17.4 ± 5.1</td>
<td>+13.4 ± 4.5</td>
<td>&lt; 0.05</td>
<td>8.8 ± 1.0</td>
<td>4.0 ± 1.3</td>
<td>-4.8 ± 1.2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Urinary Sodium Excretion (mEq/day)</td>
<td>121 ± 20</td>
<td>86 ± 15</td>
<td>-35 ± 23</td>
<td>NS</td>
<td>116 ± 19</td>
<td>141 ± 33</td>
<td>+24 ± 28</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma Volume (ml/M²)</td>
<td>1603 ± 40</td>
<td>1553 ± 18</td>
<td>-48 ± 25</td>
<td>NS</td>
<td>1377 ± 65</td>
<td>1542 ± 74</td>
<td>+165 ± 68</td>
<td>NS</td>
</tr>
<tr>
<td>Total Peripheral Resistance (dyn. sec/cm²M²)</td>
<td>2537 ± 206</td>
<td>2022 ± 212</td>
<td>-515 ± 210</td>
<td>0.05</td>
<td>2800 ± 282</td>
<td>2268 ± 409</td>
<td>-532 ± 154</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Cardiac Index (l/min. M²)</td>
<td>3.9 ± 0.2</td>
<td>4.5 ± 0.6</td>
<td>+0.6 ± 0.5</td>
<td>NS</td>
<td>3.4 ± 0.3</td>
<td>4.1 ± 0.7</td>
<td>+0.7 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Heart Rate (/min)</td>
<td>70 ± 4</td>
<td>75 ± 5</td>
<td>+5 ± 3</td>
<td>NS</td>
<td>69 ± 3</td>
<td>65 ± 2</td>
<td>-6 ± 3</td>
<td>NS</td>
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(Values are represented in mean ± SE.)
pressor response tests. The doses of the injected drugs were following: angiotensin II (AT, Hypertensin, Ciba): 0.01 µg/kg and 0.02 µg/kg; norepinephrine (NE): 0.05 µg/kg and 0.1 µg/kg; and tyramine hydrochloride (Tyr): 0.025 mg/kg and 0.05 mg/kg. After 30 minutes’ rest, each of the drugs dissolved in 0.5 to 1 ml of saline was injected rapidly through the venous cannula after blood pressure was ascertained to be on the basal level, being followed by rapid flushing with 2 ml of saline. Pressor responses were expressed in terms of absolute increments in mean blood pressure or percent increments in mean blood pressure from the basal level. Plasma volume was measured by use of 131 I-RISA or Evans blue on the following day. Urinary sodium and potassium excretion was measured for the 3 consecutive days before and after the examination. Plasma renin activity (PRA) was measured by the bioassay method.

In 16 of the 21 patients with essential hypertension, the examinations were repeated 11 to 30 days thereafter. During the period between the first and the second examinations, the patients were kept hospitalized with no changes in daily salt intake and without any anti-hypertensive drugs.

RESULTS

When the pressor responses to each of the drugs were related to blood pressure in 37 measurements in the 21 patients with essential hypertension, the response to AT significantly correlated with the pre-injection levels of mean blood pressure ($r = 0.43$, $p < 0.01$ for 0.01 µg/kg of AT, Fig. 1). However, the responses to NE or Tyr had no significant relationship with the mean blood pressure levels. The response to AT showed a similar relationship with the mean blood pressure levels also in all the patients in this study.

Daily sodium excretion in the urine ranged from 34 mEq to 262 mEq. When the responsiveness to the vasoactive drugs were related to the urinary sodium excretion in the essential hypertensive patients, the percent increments in mean blood pressure after the injection of each of AT, NE, and Tyr were observed to be correlated with the daily urinary sodium excretion ($r = 0.43$, $p < 0.01$ for 0.01 µg/kg of AT; $r = 0.54$, $p < 0.001$ for 0.1 µg/kg of NE; and $r = 0.39$, $p < 0.02$ for 0.025 mg/kg of Tyr, Fig. 2). Similar relationships of the pressor responsiveness to the drugs with the urinary sodium excretion were found in 52 measurements in the whole patients as well.

While the AT-responsiveness showed a significant negative correlation with PRA in all the patients studied ($r = -0.48$, $p < 0.01$), such a relationship was not observed in the essential hypertensive patients. In the entire study, the AT-responsiveness had no significant relation to total peripheral resistance, plasma volume or cardiac output.

Twelve of the 16 patients with essential hypertension, in whom the examinations were repeated in 11 to 30 days (21 days in average) after the initial study, showed a decline in blood pressure at the time of the second study. In these 12 patients, the reduction in blood pressure was accompanied by a marked decrease in total peripheral resistance ($p < 0.05$) and by insignificant increases in cardiac output and PRA. The 12 patients who responded to “bed-rest” with a reduction in blood pressure could be divided into 2 groups, depending on the alterations in the responsiveness to AT. Seven out of the 12 patients had a concomitant decrease in the AT-responsiveness (group A), and the others showed invariable or rather increased responsiveness to AT (group B). The data for each of

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the studies in the groups A and B are summarized in Table I. When each of the parameters was compared between the first and the second studies, a marked elevation of PRA and insignificant decreases in urinary sodium excretion and plasma volume were seen to accompany the reduced response to AT in the group A (Table I). On the other hand, a significant decrease in PRA and an enhancement in the response to NE were seen together with insignificant increases in plasma volume and urinary sodium excretion in the group B (Table I). Total peripheral resistance was noted to be decreased in both groups. The plasma volume at the first study was significantly larger in the group A than in the group B.

Four of the 16 patients with essential hypertension did not show a reduction in blood pressure during hospitalization. In these patients, no consistent alterations were observed in the other parameters either.

**DISCUSSION**

While many factors are considered to be concerned with vascular responsiveness to vasoactive substances, important implications have been put on the relationship between sodium balance and vascular responsiveness in regard to the pathophysiology of hypertension. The close relationships between the pressor responses to each of the drugs and the urinary sodium excretion, observed in the present study, are considered to imply that sodium plays an important role in the cardiovascular response to AT and catecholamines. Although the pressor response to AT negatively correlated with PRA in the patients of the entire study, it had no definite relationship with PRA within the patients with essential hypertension. The vascular responsiveness to AT would be influenced more effectively by some other factor(s) than circulating angiotensin II in essential hypertension.

In 16 patients with essential hypertension, the examinations for pressor responsiveness and hemodynamics were repeated without changing daily salt intake and without giving antihypertensive agents. Twelve out of the 16 patients showed a decline in blood pressure at the time of the second study. When each of the parameters was compared between the first and the second studies in those 12 patients, total peripheral resistance was found to be significantly decreased with the reduction of blood pressure, while there were slight increases in cardiac output and in PRA as a whole. The results suggest that the blood pressure reduction following "bed-rest" during the hospitalization was due to the decrease in total peripheral resistance.

In spite of the reduction in blood pressure in
the 12 patients, alterations in the responsiveness to AT or NE at the second study were not consistent; 7 patients showed a decrease in the response to AT (group A), and 5 patients showed invariable or rather augmented response to AT (group B). In the group A, a marked increase in PRA and insignificant decreases in urinary sodium excretion and plasma volume were found besides the reduction in AT-responsiveness (Table I). In the group B, there were a significant decrease in PRA and enhanced pressor response to NE, and urinary sodium excretion and plasma volume were rather increased (Table I). A chain of the events observed in the group A seems to have been related to a loss of sodium during the hospitalization, since the increase in PRA and the decreases in the response to AT and in plasma volume could be explained by sodium loss. On the other hand, in the group B, a chain of the events may have been associated with sodium excess or with a decrease in sympathetic activity during the hospitalization. If sodium excess had been responsible for the chain of the events, the peripheral resistance and blood pressure should have been raised further. Accordingly, it appears that a decrease in sympathetic activity was possibly responsible for the reduction in blood pressure in the group B; the decrease in PRA and the increases in the responses to AT and NE and in plasma volume could be explained by decreased sympathetic activity. It has been described that patients with essential hypertension fall into two groups as regard to total exchangeable sodium: "variable-sodium" patients, whose plasma volume varies with diet sodium, and "low-sodium" patients, whose plasma volume remains constant regardless of diet. In the patients of the group A, hypertension appears to be more dependent on sodium; sodium excess seems to have been associated with the elevation of blood pressure at the first study with subsequent sodium loss leading to the reduction in blood pressure at the second study. On the other hand, in the patients of the group B, hypertension appears not to be dependent on sodium, but to be associated with increased sympathetic activity.

**SUMMARY**

In 21 hospitalized patients with benign essential hypertension, pressor responses to angiotensin were significantly correlated with levels of mean blood pressure, and pressor responses to each of angiotensin, norepinephrine and tyramine were correlated significantly with urinary sodium excretion. Sixteen of the 21 patients were studied twice with an averaged interval of 21 days without changes in daily salt intake during the hospitalization. Twelve of the 16 patients exhibited a decline in blood pressure at the second study, and the blood pressure reduction was due to a decrease in total peripheral resistance. At the same time, in 7 of the 12 patients (group A), there were a significant decrease in response to angiotensin, a marked increase in plasma renin activity and insignificant decreases in urinary sodium excretion and plasma volume. The other 5 patients (group B) showed a decrease in plasma renin activity, an enhanced response to norepinephrine, insignificant increases in urinary sodium excretion and plasma volume, and invariable or rather increased responses to angiotensin, when blood pressure was declined at the time of the second study. It is suggested that the hypertension in the group A may have been related to sodium excess, while that in the group B may have been associated with an increased sympathetic activity.

**REFERENCES**


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Discussion:

Chairman: YOSHIHIRO KANEKO, Yokohama City Univ.

Dr. Sokabe (Toho Univ.): I have two questions. Are the patients in group A different in "type" or "stage" of hypertension from those in group B? Secondly, do you think that the sympathetic activity does not participate in hypertension of the group A?

Dr. Ishii: It was hard to know exact durations of hypertension in patients of both groups, but the averaged age of the patients was not significantly different between the two groups. As demonstrated, significantly larger plasma volume in group A at the first study and the alterations of PRA and sodium excretion observed during hospitalization in the two groups seem to suggest that there was a difference in "type" rather than "stage" of hypertension between the groups A and B. We do not think that the sympathetic activity is unrelated to hypertension of the group A, but it appears that expansion of fluid volume was more contributory to hypertension.

Chairman: We think these findings suggest that there may be two types in patients with essential hypertension: one type more related to sodium excess and the other type more associated with increased sympathetic nervous activity. However, we do not think that the difference is due to a different disease entity. It may be that one of the factors concerning the maintenance of hypertension is different.

Dr. Masuyama (Tokyo Univ.): (1) When did you measure the averaged sodium excretion after the patients had been placed on a constant sodium diet? (2) How close was the correlation between AT-responses and NE-responses in each patient? You emphasized a significant correlation between AT-responses and the pre-injection mean blood pressure and one between NE-responses and UNaV. Do you think of any pathophysiological difference in responsiveness between AT and NE? (3) How do you relate the enhanced responses to NE to the blood pressure reduction during hospitalization in group B?

Dr. Ishii: (1) Sodium excretion was measured from daily UNaV during 3 consecutive days before and after the pressor response study. All of the patients were placed on a constant sodium diet soon after the admission. When the study was done in a few days after admission, sodium excretion could have been influenced by sodium intake prior to the admission. (2) The correlation coefficient between AT- and NE-responses was about 0.7 in the entire study. However, in the patients with essential hypertension, only AT-responses correlated significantly with the pre-injection mean blood pressure, while AT- and NE-responses significantly correlated with UNaV. (3) It is well known that surgical or pharmacological sympathectomy causes an increase in pressor responses to NE. The enhanced responsiveness to NE and a decrease in blood pressure observed in group B may have been possibly related to a decrease in sympathetic activity.

Dr. Omae (Kyushu Univ.): UNaV of the patients in your study showed a fairly wide variation. Was there any relationship between PRA and UNaV? In addition, do you not think that PRA at the first study was influenced by sodium intake prior to the admission?

Dr. Ishii: A rough and insignificant correlation was observed between PRA and UNaV in this study. It is possible that PRA at the first study was influenced by salt intake before the admission, but we have no idea how much the influence was.

Dr. Saruta (Keio Univ.): How many patients had a family history of hypertension in groups A and B?

Dr. Ishii: We do not think that there was any difference in a family history of hypertension between both groups.

Dr. Yoshida (Hiroasaki Univ.): It should be recognized that pressor responses to NE or AT are not always parallel in regard to the vascular reactivity. We formerly observed that mecholyl caused a greater decrease in blood pressure in hypertensive patients than in normotensive subjects, but vasodilatation following mecholyl, examined with plethysmograph and under microscope, was smaller in the hypertensives. The discrepancy appears to be caused by vasoconstriction or smaller vascular lumen in hypertensive patients. Accordingly, pressor responses to NE or AT seem to be influenced by pre-injection vasoconstriction in hypertensive patients. How do you think about that?

Dr. Ishii: We are aware that pressor responses
to NE or AT are influenced by many factors other than vascular reactivity. It is obvious that pressor responses to vasoactive agents do not always represent vascular reactivity.

Dr. IKEDA (Tokyo Univ.): It is interesting to try to classify patients with essential hypertension into two groups, a sodium dependent group and a sympathetic activity dependent group, according to the alterations of PRA and plasma volume accompanied by blood pressure reduction in response to bed rest. However, we have to be careful in relating alterations of pressor responses to sympathetic activity. For example, when the sympathetic activity is supposed to be activated in the central nervous system, NE is released from the cardiac muscle, leading to a decrease in NE content in the heart. Subsequently, the cardiac muscle with less NE content becomes more sensitive to exogenous NE. Accordingly, when we relate alterations of NE-responses to sympathetic activity, we have to take into account the changes in content and turnover of NE in vascular walls. It is also known that sodium balance have some influences on NE-metabolism in vascular walls. I suggest you to consider these points in the future study.

Dr. ISHII: Thank you for your comments.