

Comparisons of Body Fluid Volumes, Plasma Renin Activity, Hemodynamics and Pressor Responsiveness between Juvenile and Aged Patients with Essential Hypertension

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ESSENTIAL hypertension is known to emerge in the middle of the thirties in many instances.¹ Although blood pressure elevation is often mild or labile in juvenile hypertensive patients, cardiovascular and renal complications are less frequent and less severe in these juvenile patients than in aged ones. Thus, juvenile hypertensive patients may well be considered to be more suitable subjects for the exploration of the causes of essential hypertension. In this study, body fluid volumes, plasma renin activity, hemodynamics, and pressor responsiveness were compared between patients with essential hypertension aged younger than 35 and those aged older than 36 years.

SUBJECTS AND METHODS

The subjects in the present study consisted of 52 inpatients with essential hypertension. Twenty-two of the 52 patients were younger than 35 year-old (EH-I; 20 male and 2 female, with an averaged age of 27.5 years), and the other 30 patients were older than 36 (EH-II; 17 male and 13 female, with an averaged age of 44.6

years). Their blood pressure prior to or at the time of the admission were higher than 160 mmHg systolic and 90 mmHg diastolic. Secondary hypertension was excluded with thorough examinations including aortography, and measurements of plasma aldosterone concentration and urinary catecholamine excretion. All the patients except one EH-II patient who showed a retinal change of KW III had mild retinal changes (KW I or II). Renal function did not differ significantly between the EH-I and EH-II groups, but the severity score of hypertension based on the criteria, collaborated by the Hypertension Committee from the 3 Departments of Internal Medicine, University of Tokyo², was significantly higher in the latter than the former (Table I). Sixty-seven age-matched control subjects (39 male and 28 female) were selected from normotensive inpatients who had chronic glomerulonephritis with normal renal function and those who were in the convalescent stage of acute hepatitis. In addition, 21 hypertensive patients with renal insufficiency due to chronic parenchymal renal diseases and 4 patients with primary aldosteronism were studied as to body fluid volumes for reference. All the patients were placed on a diet containing 8 to 10 gm of sodium chloride a day and had been without any anti-hypertensive drugs for at least a week before the examination.

Total body water (TBW), extracellular fluid volume (ECFV) and plasma volume were measured with about 300 μ Ci of H^3 OH, 30 μ Ci of $Na^{35}SO_4$ and 10 μ Ci of ^{131}I -RISA or Evans blue, respectively. Each of the measurements,

Key Words:

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Blood volume
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TABLE I COMPARISONS OF RENAL FUNCTION AND SCORES FOR THE SEVERITY OF HYPERTENSION BETWEEN JUVENILE AND AGED PATIENTS WITH ESSENTIAL HYPERTENSION

	<i>Patients aged younger than 35 year-old (EH-I)</i>	<i>Patients aged older than 36 year-old (EH-II)</i>
Number of patients	22 (20 male and 2 female)	30 (17 male and 13 female)
Averaged Age (year-old)	27.5	44.6
Glomerular Filtration Rate (ml/min)	93 ± 4 (SE)	84 ± 6
Renal Plasma Flow (ml/min)	525 ± 32	450 ± 44
Scores for the Severity of Hypertension*	3.9 ± 0.4	5.3 ± 0.5
p < 0.05		

* Based on the criteria collaborated by the 3 Departments of Internal Medicine, University of Tokyo.

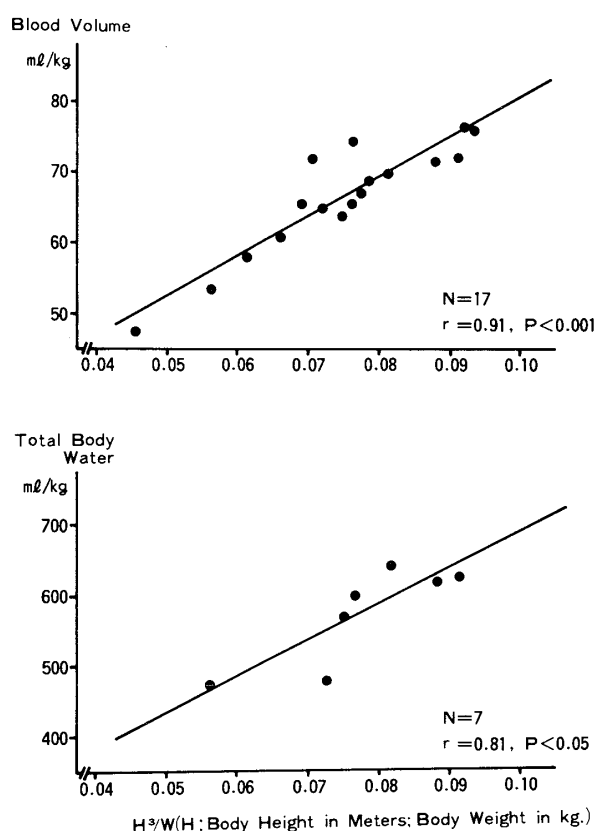


Fig.1. Relationships of leaness index (H^3/W) to blood volume and to total body water in normotensive control subjects.

together with the measurement of plasma renin activity (PRA), was done after 12 hours' fasting in the morning. Total blood volume was calculated from plasma volume and hematocrit. In this study, blood volume (BV) and TBW were expressed as percent of "normal value" in terms of ml per kg of body weight, which was obtained in the normotensive control subjects (NT),

because in normotensive subjects, BV and TBW, both in terms of ml per kg of body weight, demonstrated linear relationships with H^3/W , where H was the height, and W the weight³ (Fig. 1). ECFV was measured only in male patients and expressed in terms of ml per kg of body weight, because of the paucity of the number of control subjects for obtaining a significant correlation between ECFV and H^3/W .

Plasma renin activity (PRA) was measured by the bioassay method. In some of the hypertensive patients and of normotensive subjects, PRA was measured after 1 hour's standing or in 20 minutes after the intravenous administration of furosemide (0.5 mg/kg), in addition to PRA at rest.

Cardiac output was measured by the dye-dilution technique using indocyanine green.

Pressor responses to intravenous bolus injections of angiotensin II (AT; Hypertensin, Ciba, 0.01 and 0.02 $\mu\text{g/kg}$) and norepinephrine (NE; 0.05 and 0.1 $\mu\text{g/kg}$) were examined by directly recording the changes in mean arterial pressure of the femoral artery with an electric manometer. Pressore responses to the vasoactive drugs were indicated with the maximal elevation of mean blood pressure or the percent increment of it from the basal level. Some of the patients with essential hypertension received repeat examinations for pressor response, BV, hemodynamics, and PRA in 11 to 30 days after the initial study, being on the same diet without any antihypertensive agents.

RESULTS

I. Body Fluid Volumes in Hypertensive and Normotensive Subjects.

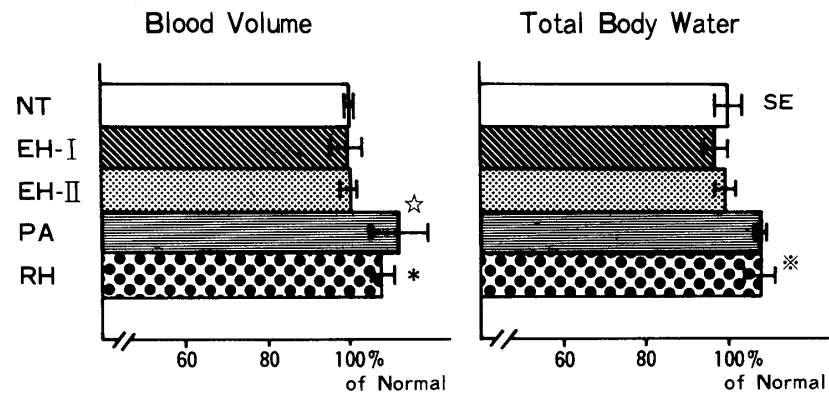


Fig.2. Blood volume and total body water in hypertensive patients and normotensive subjects. NT denotes normotensive subjects (17 patients, with ages ranging from 18 to 57 year-old), EH-I essential hypertensive patients aged younger than 35 (12 patients), EH-II essential hypertensive patients aged older than 36 (14 patients), PA patients with primary aldosteronism (4 patients) and RH hypertensive patients with renal insufficiency due to chronic renal parenchymal diseases (21 patients). Asterisks represent significance levels: ☆ $p < 0.01$ for the difference from NT, * $p < 0.02$ for the difference from NT, and X $p < 0.02$ for the difference from NT, EH-I and EH-II in combination.

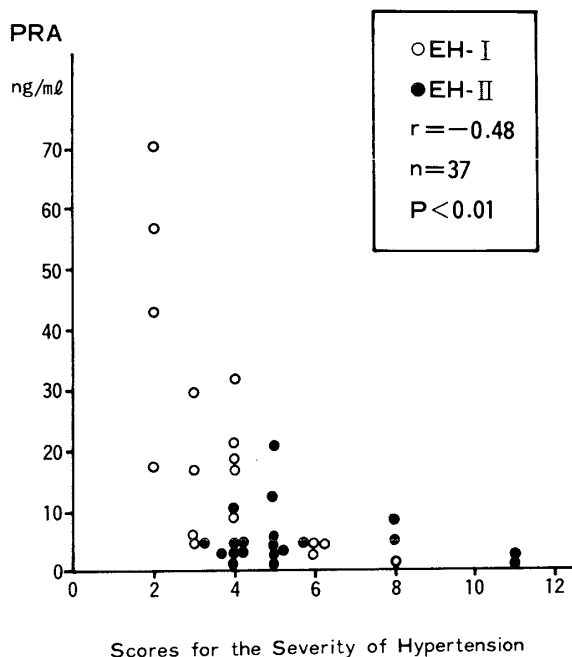


Fig.3. Relationship between plasma renin activity (PRA) and scores for the severity of hypertension in 17 EH-I and 20 EH-II patients. The scores were based on the criteria collaborated by the 3 Departments of Internal Medicine, University of Tokyo.

Blood volume (BV) and total body water (TBW), both of which were expressed as percent of the predicted normal value, were 100.1 ± 1.2 (SE) %, and $100.0 \pm 2.9\%$ in 17 normotensive control subjects, respectively, while BV was $106.0 \pm 2.3\%$ and TBW $98.8 \pm 2.4\%$ in 26 patients with essential hypertension. There were

no significant differences of these volumes between the two groups. Furthermore, there were no definite differences of BV and TBW between 12 EH-I and 14 EH-II patients (Fig. 2). However, the BV had a significantly larger distribution in the essential hypertensive patients, particularly in the EH-I patients, than in the normotensive subjects ($p < 0.05$), BV being reduced in some of the essential hypertensive patients and enlarged in others. Extracellular fluid volume (ECFV), which was measured only in male subjects, was slightly but not significantly smaller in the essential hypertensive patients ($19.3 \pm 1.3\%$ of body weight in the NT, 17.5 ± 0.6 in the EH-I and 17.9 ± 1.2 in the EH-II). There was no significant difference of ECFV between the EH-I and EH-II patients either.

When BV was related to mean blood pressure, there was a rough but not significant positive correlation between the two parameters in the normotensive subjects and the essential hypertensive patients in combination ($r = 0.25$, $p = 0.1$). In addition, a significant inverse correlation was found between BV and PRA ($r = -0.57$, $p < 0.01$).

In patients with primary aldosteronism, BV and TBW were increased, with a significant difference of BV from that in the normotensive subjects (Fig. 2). In 21 hypertensive patients with renal insufficiency due to chronic renal parenchymal diseases, each of BV, TBW and ECFV was significantly increased as compared to

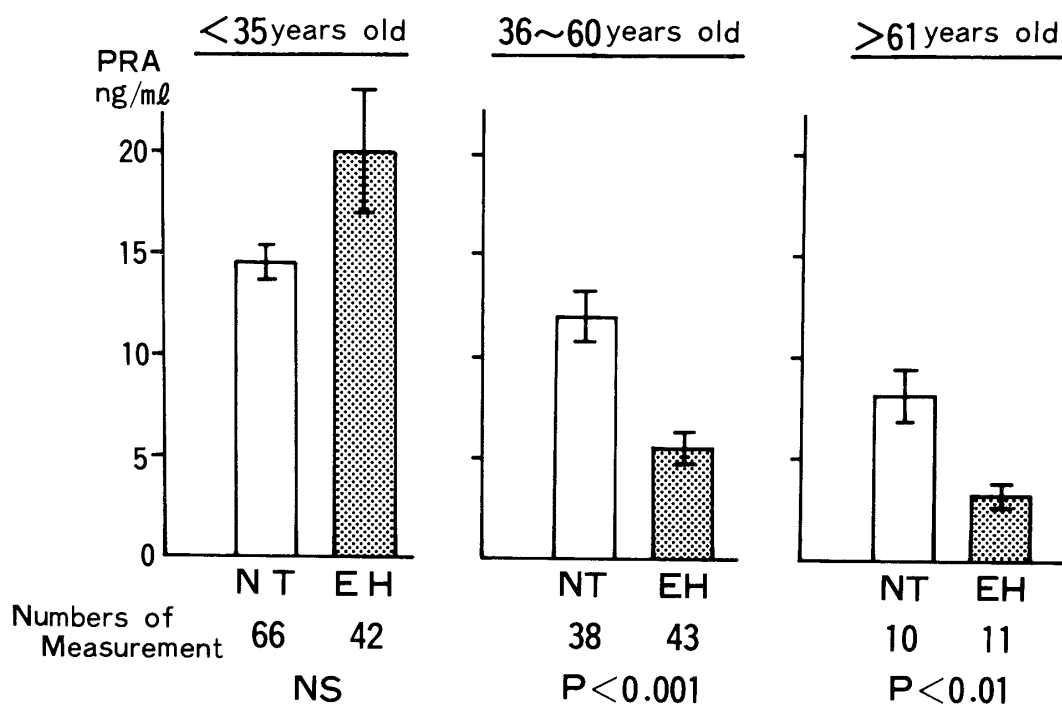


Fig.4. Plasma renin activity (PRA) at rest was compared between normotensive subjects (NT) and patients with essential hypertension (EH) in each generation. A small bar represents SE.

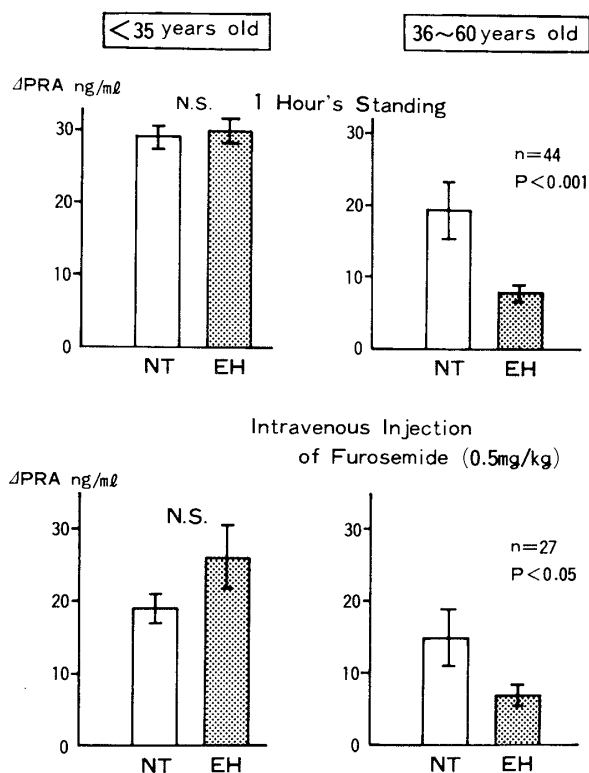


Fig.5. Comparisons of the increases in PRA in response to 1 hour's standing (upper half of the figure) and to intravenously injected furosemide (lower half of the figure) between normotensive subjects (NT) and patients with essential hypertension (EH).

the normotensive subjects or the normotensive subjects and the patients with essential hypertension in combination (Fig. 2). The ECFV in these patients was 23.6 ± 1.9 (SE) % of body weight.

II. Plasma Renin Activity in Patients with Essential Hypertension.

In 37 patients with essential hypertension, PRA at rest showed a significant inverse correlation with mean blood pressure ($r = -0.33$, $p < 0.01$, 72 measurements), and with the severity scores for hypertension ($r = -0.48$, $p < 0.01$; Fig. 3). Since PRA is known to be influenced by aging, comparisons of PRA between essential hypertensive patients and normotensive subjects were done in each of the generations of younger than 35, 36 to 60, and older than 61 year-old. In the generation of younger than 35 years, mean PRA was slightly higher in 15 hypertensive patients than in 22 normotensive subjects, but the difference was not significant (Fig. 4). On the other hand, in both of the generations of 36 to 60 years (21 hypertensives and 30 normotensives) and of older than 61 years (5 hypertensives and 11 normotensives), PRA was markedly lower in the hypertensive patients than in the age-matched control subjects (Fig. 4). Furthermore, increases in PRA in response to 1 hour's standing or to intravenous administration of furosemide

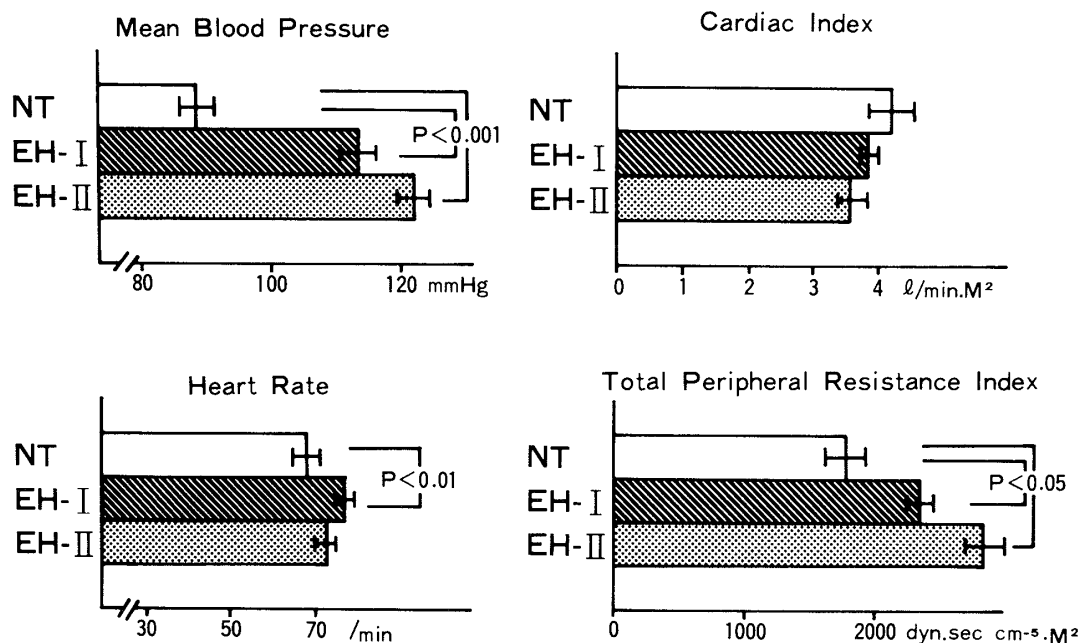


Fig. 6. Comparisons of the hemodynamic parameters at rest between 11 normotensive subjects (NT; ages ranging from 15 to 37 year-old), and patients with essential hypertension (41 measurements in 16 EH-I and 17 EH-II patients). A small bar represents SE.

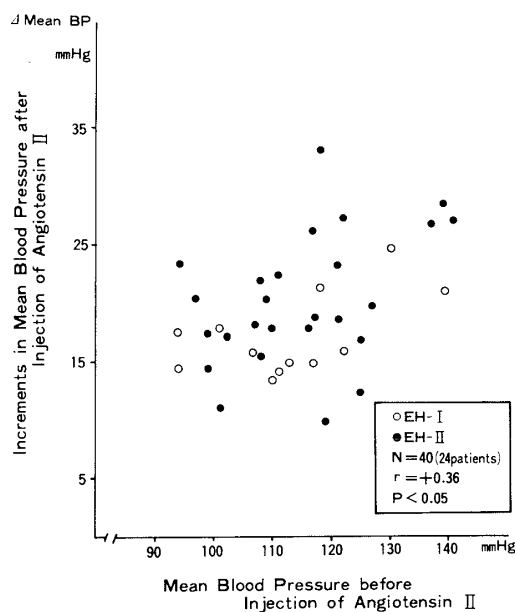


Fig. 7. Relationship between pressor response to angiotensin II (0.01 μ g/kg) and mean blood pressure before injection in EH-I and EH-II patients.

were normal in the EH-I patients, while the responses of PRA were significantly suppressed in the EH-II patients as compared to those in the age-matched control subjects (Fig. 5).

III. Hemodynamics and Pressor Responses to Angiotensin and Norepinephrine in Essential Hypertension and Their Changes following

“Bed-rest”.

Heart rate, cardiac index (CI), and calculated total peripheral resistance index (TPRI) in 16 EH-I patients and 17 EH-II patients, whose blood pressure was higher than 160/90 at the time of the study, were compared with those in 11 normotensive subjects, whose ages ranged from 15 to 37 year-old. Heart rate was slightly but significantly increased in the EH-I groups as compared to the normotensive group. Mean CI was 4.2 ± 0.3 (SE) l/min.M² in the normotensive group, 3.9 ± 0.1 in the EH-I, and 3.6 ± 0.2 in the EH-II groups. The differences in CI among the three groups were not significant. Thus, TPRI was elevated in both of the EH-I and EH-II groups (Fig. 6). The correlation between mean blood pressure and TPRI was significant ($r = 0.67$, $p < 0.001$).

Pressor responses to AT and NE were related to various parameters in 24 patients with essential hypertension. It was noted that the pressor response to AT had a significant positive correlation with the mean blood pressure before injection ($r = 0.36$, $p < 0.05$; AT in a dose of 0.01 μ g/kg), without any significant relationship with 24 hours' urinary sodium excretion ($U_{Na}V$) or PRA (Fig. 7). On the other hand, the pressor response to NE significantly correlated with $U_{Na}V$ ($r = 0.58$, $p < 0.001$; NE in a dose of 0.05 μ g/kg:

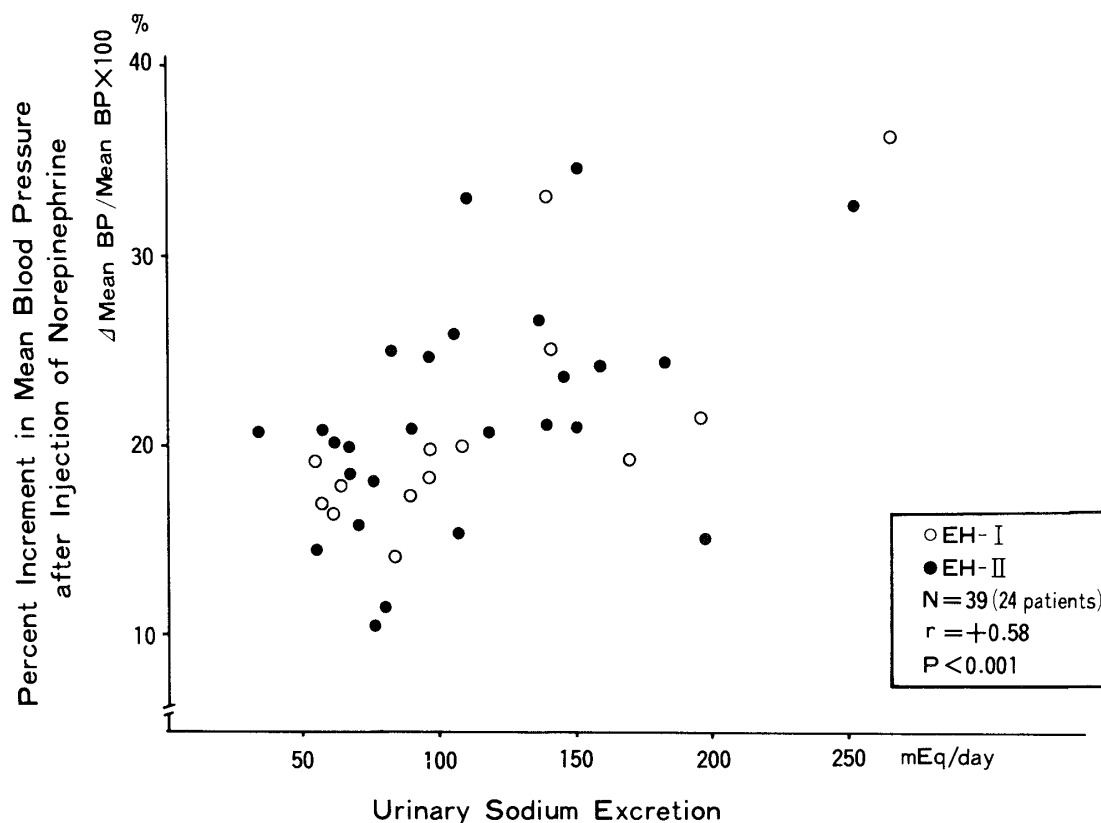


Fig.8. Relationship between pressor response to norepinephrine ($0.05 \mu\text{g/kg}$) and 24 hours' urinary sodium excretion in EH-I and EH-II patients.

Fig. 8). However, it did not demonstrate a definite relationship with blood pressure or PRA. The correlation of AT-pressor response to mean blood pressure did not reach significance level, when they were analyzed in 10 EH-I and 14 EH-I patients separately. The correlation between NE-pressor response and $U_{\text{Na}}V$ was still significant in each of the EH-I and EH-II groups as well as in the entire patients.

Sixteen patients with essential hypertension whose ages ranged from 16 to 48 year-old (36.4 in an average) received repeat examinations for hemodynamics, pressor responsiveness, PRA and BV in 11 to 30 days (21 days in an average) after the initial study. Twelve of the 16 patients showed a reduction in mean blood pressure by 12.3 mmHg in an average at the second study ($p < 0.01$). The TPRI also decreased by 17% ($p < 0.05$), but the CI increased slightly but not significantly in these 12 patients. The 12 patients who responded to "bed-rest" could be divided into two groups, depending on the alterations in the AT-pressor response. Seven out of the 12 patients showed enhanced pressor responses to AT, a significant increase in PRA and a significant decrease in BV (group A, Fig. 9). The other

5 patients had an equivocal increase in the pressor response to AT, a significant decrease in PRA, and enhanced response to NE (group B, Fig. 9). The BV at the initial study was 108.6 ± 2.1 (SE) % in the group A and $96.5 \pm 4.6\%$ in the group B, with a significant difference between the two groups ($p < 0.05$). In the 4 patients whose blood pressure remained stable during hospitalization, there were seen no definite changes in the pressor responses to AT and NE, PRA, BV and cardiac output (group C Fig. 9). Mean age was 34.3 in the group A, 42.0 in the group B and 33.2 years in the group C. The differences in age were not significant among the three groups.

DISCUSSION

In the present study, mean BV, TBW and ECFV of untreated patients with essential hypertension were not different from those of normotensive subjects. In addition, these fluid volumes were not significantly different between EH-I and EH-II patients. However, the distribution of BV was larger in the essential hypertensive patients, BV being contracted in some and enlarged in others. When BV was related to blood

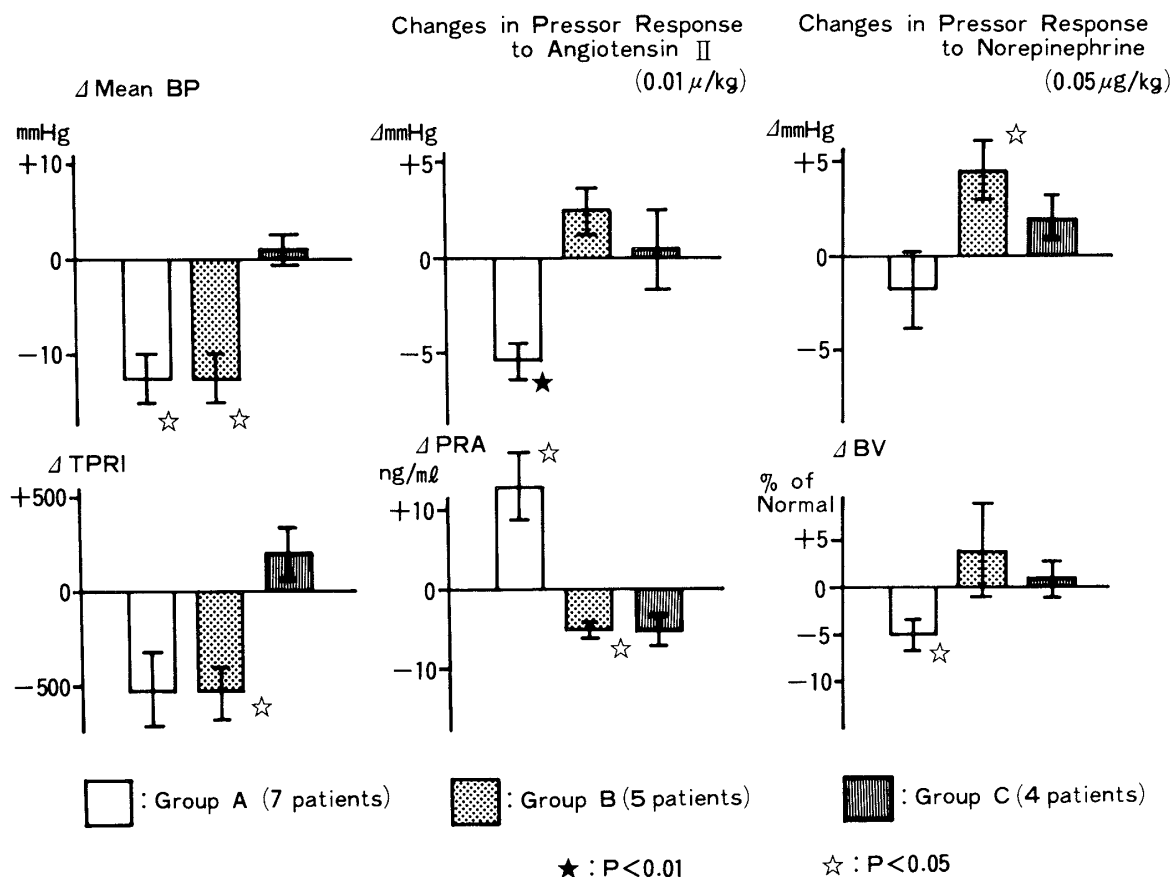


Fig.9. Each bar represents the difference of a parameter between the initial and the second studies. The group A consists of 7 essential hypertensive patients in whom the blood pressure reduction was accompanied by a decrease in AT-pressor response, the group B 5 patients in whom the blood pressure reduction and an equivocal increase in AT-pressor response were seen, and the group C 4 patients whose blood pressure did not change following "bed-rest". Vertical lines represent standard errors. The change in TPRI in the group A is significantly larger than that in the group C ($p < 0.05$).

pressure, there was a rough but not significant positive correlation between the two parameters. These findings are in contrast to other studies in which BV or plasma volume is decreased with an inverse correlation with blood pressure in essential hypertension.⁴⁻⁶ It seems likely that the changes in body fluid volumes are not homogenous in essential hypertension and that expanded BV may be related to the development of hypertension in some patients.

Although BV or ECFV is known to be one of the factors influencing PRA, it is still under controversy whether or not low-renin essential hypertension is accompanied by expansion of BV or ECFV.^{7,8} The significant inverse correlation, demonstrated in the present study, between BV and PRA in the essential hypertensive patients and the normotensive subjects as a whole supports an opinion that essential hypertension with low renin should have an increase in BV.^{9,10}

Low PRA at rest and its blunt responses to various stimuli have been noticed in about 20 to 30% of patients with essential hypertension in many reports.^{11,18} Deranged metabolism of mineral corticoid hormones such as aldosterone,^{12,15} 18-OH-DOC,^{14,15} or other unknown hormones,¹³ nephrosclerosis,¹⁶ and increased renal vascular resistance¹⁷ have been incriminated as the causes of the low renin in essential hypertension. In the present study, PRA showed significant inverse correlations with mean blood pressure and with the scores of the severity of hypertension in patients with essential hypertension. Furthermore, while PRA at rest and renin responses to standing or furosemide were normal in the EH-I patients, they were much lower in the EH-II than in the age-matched normotensive subjects. These findings suggest that the low renin in essential hypertension is secondary to hypertension: long-lasting hypertension sup-

presses renin release and renin synthesis in corollary to the feed-back mechanism functioning between blood pressure and renin-angiotensin system. They are consistent with other studies that demonstrated significant inverse correlations between blood pressure and PRA in adult spontaneous hypertensive rats¹⁹ or in patients with benign essential hypertension.¹⁷ It also has been reported that the mean age of essential hypertensive patients with low renin is higher than that of those with normal renin.¹⁸

The cause of the high renin in relation to blood pressure in the EH-I patients remains to be determined, while a possibility exists that the disturbed relationship of PRA to blood pressure may have been concerned with the development of hypertension in the younger patients.²⁰

Although "increased total peripheral resistance and normal or reduced cardiac output" has been considered to be a hall mark of essential hypertension, many recent studies are putting important implications on "increased cardiac output and low or normal vascular resistance" in the early stage of essential hypertension, because patients with borderline or labile hypertension are frequently hyperdynamic.^{21,22} In our study, mean cardiac output at rest was slightly but not significantly less in the EH-I and EH-II patients than in the normotensive subjects. As shown in the later part of the study, the blood pressure decline following "bed-rest" was associated with a decrease in TPRI. Thus, the increased peripheral vascular resistance is considered to be responsible for the hypertension even in the younger patients. More evidences are needed to confirm the exact incidence of established essential hypertension in the advancing ages in patients with borderline or labile hypertension.

Clinical implications of pressor responses to vasoactive substances are still moot, since they are influenced by many factors such as vascular responsiveness,²³ blood pressure,²⁴ sodium balance,^{25,28} endogenous vasoactive substances,^{26,27} and baroreceptor functions of the cardiovascular system. In our study, the pressor responses to AT significantly correlated with the pre-injection levels of mean blood pressure, but not with $U_{Na}V$ or PRA in the entire patients with essential hypertension. On the other hand, the pressor responses to NE significantly correlated with $U_{Na}V$, but not with blood pressure or PRA. Thus, it seems likely that pressor response to AT and that to NE are modified by different factors. Comparisons of the relationship between

AT-pressor response and mean blood pressure and that between NE-pressor response and $U_{Na}V$ did not reveal any significant differences between the EH-I and the EH-II patients, suggesting that the influences of aging on the pressor responses are equivocal.

Not only patients with borderline or labile hypertension but also those with established essential hypertension are frequently noticed to show a reduction in blood pressure without any hypotensive drugs during hospitalization. It may be helpful for understanding the mechanisms of essential hypertension to analyze the physiological and biochemical changes accompanying the reduction of blood pressure following "bed-rest". Sixteen patients with essential hypertension received repeat examinations in 21 days in an averages after the initial study. Twelve of the 16 patients showed a reduction in blood pressure during hospitalization. The associated changes in these 12 patients were a decrease in TPRI, and slight but not significant increases in cardiac output and PRA. No definite changes in the pressor responses to AT and NE were observed as a whole. Thus, the reduction in blood pressure could be attributed to the decrease in peripheral vascular resistance, but not to changes in cardiac output. Seven of the 12 "bed-rest" responsive patients had a weakened pressor response to AT, a significant increase in PRA and a significant decrease in BV (group A). The other 5 patients had an equivocal increase in AT-pressor response, a significant decrease in PRA and an enhanced pressor response to NE (group B). In addition, the BV at the initial study was significantly larger in the group A than in the group B. Accordingly, it is suggested that the mechanisms through which the reduction in blood pressure was induced following "bed-rest" might be different between those two groups. In the group A, the reduction in blood pressure could be explained by loss of BV, probably as a result of mild salt restriction during hospitalization. The loss of BV seems to have elevated PRA, leading to the decreased pressor response to AT. In the group B, a chain of events could be attributed to a sympathetic activity; the decrease in PRA and the enhanced pressor response to NE are possibly explained by a decreased activity of the sympathoadrenal system.^{27,29} In other words, the hypertension in the group A was likely related to excess sodium intake prior to the admission, and to increased sympathetic activity in the group B.

In 4 patients of the 16 patients, who were put

on the repeat study, no definite changes were observed regarding blood pressure, PRA, cardiac output, and BV (group C). Another way of approach will be needed to gain access to the hypertension in these patients.

SUMMARY

Body fluid volumes, cardiac output, PRA and pressor responses to angiotensin II (AT) and norepinephrine (NE) were compared between untreated patients with essential hypertension aged younger than 35 (EH-I) and those aged older than 36 years (EH-II). Mean blood volume, total body water and extracellular volume were not significantly different between the patients with essential hypertension and normotensive subjects. There were no definite differences in each volume between the EH-I and EH-II patients either. However, the distribution of blood volume was significantly larger in the essential hypertensive patients than in the normotensive subjects, suggesting that the changes in blood volume might not be homogenous in essential hypertension. In addition, blood volume was noted to have a significant inverse correlation with PRA.

Cardiac output at rest was slightly but not significantly less in the EH-I and EH-II groups than in the normotensive group. A decline in blood pressure following "bed-rest" was accompanied by a decrease in total peripheral resistance index (TPRI). Thus, elevated peripheral vascular resistance seems to be responsible for the mild to moderate hypertension even in the younger patients.

PRA and its increases in response to standing or furosemide were normal in the EH-I patients, while they were markedly suppressed in the EH-II patients as compared to the age-matched normotensive subjects. In addition, PRA had a significant inverse correlation with the blood pressure and the scores of the severity of hypertension in the patients with essential hypertension. Thus, it seems likely that low renin in essential hypertension is secondary to long-lasting hypertension.

Pressor response to AT significantly correlated with mean blood pressure and that to NE did so with 24 hours' urinary sodium excretion in essential hypertensive patients. The influence of aging on the pressor responses were obscure: the relationships of the pressor responses to blood pressure or to urinary sodium excretion were not different between the EH-I and EH-II groups.

The examinations were repeated in 16 pa-

tients with essential hypertension (16 to 48 year-old) in 11 to 30 days after the initial study. Twelve of the 16 patients had declines in blood pressure and TPRI at the second study. In 7 of the patients whose blood pressure declined following "bed-rest", there were significant decreases in pressor response to AT and in blood volume and a significant increase in PRA (group A). The other 5 patients showed a significant decrease in PRA and an enhanced pressor response to NE (group B). The blood volume in the group A was significantly larger than that in the group B at the initial study. It is suggested that the cause of essential hypertension is not homogeneous in that the increased vascular resistance may have been attributed to sodium excess in some patients and to an increased sympathetic activity in others. Some additional factors remain to be taken into account to clarify the complicated aspects of essential hypertension.

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