Neurohumoral Factors in Borderline Hypertension

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Role of neurohumoral factors in borderline hypertension was evaluated in comparison to those in established hypertension. Although there was no significant difference in urinary noradrenaline between the 2 groups, urinary adrenaline was significantly higher in borderline hypertension than in established hypertension. During head-up tilt and Schellong's test a significant increase of diastolic blood pressure was demonstrated in borderline hypertension, whereas a significant decrease of systolic blood pressure was observed without any significant change of diastolic pressure in established hypertension. There was no significant difference in blood pressure response to cold pressor test, plasma volume, total body potassium and plasma renin activity (PRA) between the 2 groups. Blood pressure did not change after administration of captopril in normal subjects but it decreased significantly after captopril in patients with borderline hypertension even when blood pressure became normotensive during hospitalization. Blood pressure decreased significantly after captopril in patients with established hypertension. However, no significant relationship between the pretreatment PRA and the reduction of mean blood pressure was observed in both groups.

It can be concluded from the present study that borderline hypertension is intermediate between normal subjects and established hypertension and that both the renin-angiotensin system and the kinin-prostaglandin system play some role in the maintenance of blood pressure in borderline hypertension.

Since the risk of future established hypertension is higher in patients with borderline hypertension than in normotensive subjects, the mechanism of borderline hypertension may be connected with the pathogenesis of essential hypertension. The studies of neurohumoral mechanism in borderline hypertension are very important in order to clarify whether or not borderline hypertension may be an early stage of established hypertension. The purpose of the present investigation is to evaluate the following items in patients with borderline hypertension as compared to those in established hypertension: 1) blood pressure reduction after admission to the hospital; 2) urinary excretion of catecholamines; 3) blood pressure response during head-up tilting, Schellong's test and cold pressor test; 4) determination of plasma volume and total body potassium; 5) determination of plasma renin activity; 6) blood pressure response to captopril.

MATERIALS AND METHODS

Subjects
Sixteen patients with borderline hypertension,
aged 28 to 64 years (mean 41.6), and 23 patients with established hypertension, aged 26 to 58 years (mean 44.5), were the subjects of this investigation. Borderline hypertension was defined when more than half of the blood pressure readings obtained at an outpatient clinic, once or twice a year for the past 3 to 5 years, was between 160/95 and 140/90 mmHg and the remaining blood pressure readings were below 140/90 mmHg. Established hypertension was defined when the blood pressure was constantly above 160/95 mmHg, obtained at an outpatient clinic at least twice a year for 3 to 5 years, and the level of hypertension was maintained after hospitalization.

Eight normal subjects, aged 27 to 37 years, were used as controls for a tilting study. The other 10 normal subjects, aged 15 to 36 years, were used as controls for a captopril study.

Secondary hypertension was excluded by thorough clinical examinations and laboratory investigations such as creatinine clearance rate, serum and urinary electrolytes, plasma renin activity, plasma aldosterone concentration, plasma cortisol, urinary catecholamine determination and rapid intravenous pyelography.

For the present investigation the patients were hospitalized and kept on a normal sodium diet (NaCl 12 g/day) at least one week. None of the borderline hypertensive patients received any medications prior to admission to our hospital. Although most patients with established hypertension had never been treated previously, all antihypertensive drugs were discontinued at least 2 weeks before the study.

**Test Procedures**

**Changes of Blood Pressure after Admission:**
The blood pressure was measured at 10:00 a.m. in the recumbent position on the day of admission and one week after admission.

**Tilting Test:** After assuming the supine position for 30 min the patient was tilted abruptly to a 65 degree head-up position for 15 min on a tilt table. Blood pressure was measured during the test using a standard mercury sphygmomanometer.

**Schellong's Test:** After assuming the supine position for 30 min the patient was asked to stand erect for 10 min. Blood pressure was measured using a sphygmomanometer.

**Cold Pressor Test:** After assuming the supine position for 30 min prior to the test the hand was immersed to the wrist level in a container of

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half ice and half water for one min. Blood pressure was measured before and at one minute intervals during procedure.

Blood Pressure Response to an Administration of Captopril: Each patient was asked to fast overnight. Early on the following morning, after assuming recumbent position for 60 min, a single oral dose (25 mg) of captopril was given. Blood pressure was measured and plasma was obtained before, and 60 and 120 min after an oral administration of captopril.

**Determination of Urinary Catecholamines, Plasma Volume, Total Body Potassium and Plasma Renin Activity**

Urinary Excretion of Catecholamines: The urinary noradrenaline and adrenaline were determined using high performance liquid chromatography for 3 successive days and were expressed as the averages per 24-hour.

Plasma Volume: The plasma volume was measured by the dilution method with RISA.

Total body Potassium: The total body potassium (TBK) was estimated by measuring the potassium 40 (K40), natural isotope of potassium, using the whole body counter. The total body potassium was expressed as the ratio of actual value to the age-matched control value. Since values of plasma volume and total body potassium were influenced by body weight, the ratio of total body potassium to plasma volume (TBK/PV) was obtained.

Plasma Renin Activity: The plasma for renin assay was obtained from an antecubital vein 1) in the early morning after the overnight recumbent position (supine) and 2) after 4-hour ambulation following a restricted sodium intake of below 3 g/day of NaCl for 3 days. The plasma renin activity was determined by radioimmunoassay of angiotensin I released during incubation at pH 7.4.

Statistical analysis of data was performed using Student's t-test and the results were expressed as mean ± standard deviation.

**RESULTS**

**Changes of Blood Pressure after Admission**

Figure 1 demonstrates the changes of mean blood pressure after admission in patients with borderline and established hypertension. In patients with borderline hypertension a significant decrease of mean blood pressure was observed one week after admission as compared to that on the day of admission (p < 0.02). On the other hand, no significant decrease of mean blood pressure in established hypertension was observed. In 8 of 15 cases with established
Fig. 4. Blood pressure responses during Schellong’s test.
DBP = diastolic blood pressure, SBP = systolic blood pressure, BHT = borderline hypertension, EHT = established hypertension, B = during recumbent position, max. change = maximum change in blood pressure from the control value during Schellong’s test.

Fig. 5. Changes of blood pressure during cold pressor test. Vertical bars represent mean ± 1SD. Abbreviations are the same as in Fig. 3.

Urinary Excretion of Catecholamines
Figure 2 shows the urinary excretion of catecholamines in patients with borderline and established hypertension. There was no significant difference in urinary noradrenaline between 2 groups. On the other hand, urinary adrenaline was significantly higher in the patients with borderline hypertension than in patients with established hypertension (p < 0.02).

Blood Pressure Response during Tilting Test, Schellong’s Test and Cold Pressor Test
Figure 3 shows the changes in systolic and diastolic blood pressure during the tilting test in normal subjects and patients with borderline and established hypertension. In 8 normal subjects, a significant increase of systolic and diastolic blood pressure was observed 5 and 15 min after the head-up tilting (p < 0.05). On the other hand, in patients with borderline hypertension, the initially elevated systolic blood pressure returned...
to the basal level after 15 min of tilting but a significant increase of diastolic blood pressure was demonstrated both 5 and 15 min after the head-up tilting (p < 0.05). In patients with established hypertension, a significant decrease of systolic blood pressure (p < 0.02) and no significant change of diastolic blood pressure were observed after 5 and 15 min of tilting.

Figure 4 demonstrates the blood pressure response during Schellong's test in patients with borderline and established hypertension, expressed as the maximum changes in systolic and diastolic blood pressure as compared to the control levels. In patients with borderline hypertension, diastolic blood pressure increased in all cases but systolic blood pressure varied from −34 to +32 mmHg. On the other hand, in patients with established hypertension, systolic blood pressure decreased significantly (p < 0.02), whereas diastolic blood pressure did not change.

Figure 5 shows the changes of blood pressure during the cold pressor test. The cold pressor test resulted in a systolic blood pressure increase of 32 ± 20 mmHg in patients with borderline hypertension and that of 34 ± 18 mmHg in patients with established hypertension, showing no significant difference between the 2 groups. During this test, diastolic blood pressure increased to 28 ± 20 mmHg in patients with borderline hypertension and to 23 ± 15 mmHg in patients with established hypertension.

**Plasma Volume**

Figure 6 shows plasma volume in patients with borderline and established hypertension. There was no significant difference in plasma volume between 2 groups.

**Total Body Potassium and TBK/PV**

Figure 7 demonstrates total body potassium and TBK/PV in patients with borderline and established hypertension. There was no significant difference in total body potassium between 2 groups. TBK/PV in patients with borderline hypertension was higher than that in patients with established hypertension, but this difference was statistically not significant.

**Plasma Renin Activity**

Figure 8 shows plasma renin activity in patients with borderline and established hypertension. In both groups plasma renin activity increased significantly after 4 hours of ambulation on the third day of low sodium diet as
compared to that on the recumbent position (p < 0.05). However, there was no significant
difference in plasma renin activity after 4 hours
of ambulation on the third day of low sodium
diet between 2 groups.

Blood Pressure Response to Administration of Captopril

Figure 9 demonstrates the blood pressure
response to a single oral dose of captopril and the
relationship between the changes of blood
pressure and the pretreatment plasma renin
activity (PRA). In 10 normal subjects, blood
pressure did not change significantly even if
plasma renin activity was high. In 11 of 13
patients with borderline hypertension, mean
blood pressure decreased significantly after an
administration of captopril, although the blood
pressure of all patients was normal on the day of
the captopril study. There was no significant
relationship between the changes in mean blood
pressure and the pretreatment PRA. In 13 of 19
patients with established hypertension, mean
blood pressure decreased markedly, but there
was also no significant relationship between the
changes in mean blood pressure and the pretreat-
ment PRA.

DISCUSSION

It has been reported that borderline hyperten-
sion carries a higher risk for future established
hypertension\textsuperscript{1,9,10} and that borderline hyperten-
sion has at least double mortality as compared to
the general population\textsuperscript{11,12}. Linss et al.\textsuperscript{13} have
demonstrated that 33% of the patients who had
borderline hypertension (blood pressure more
than 140/90 mmHg but less than 159/95) in
1968, developed into hypertensives (blood pres-
sure $\geq$ 160/96) in 1970, and only 44% of the
patients, who were judged hypertensive in 1970, were still hypertensive in 1972.

Changes of sympathetic nervous system activity, such as decreased baroreceptor function, increased vasoconstrictor response to norepinephrine and decreased endogenous β-receptor sensitivity have been observed in essential hypertension. Determination of plasma catecholamines and plasma renin activity and blood pressure response during a head-up tilt Schellong's test, the cold pressor test and mental arithmetic have been used for evaluating the sympathetic nerve activity in normal and hypertensive subjects. Borderline hypertension presents an opportunity for further elucidation of the pathophysiology of established hypertension. Therefore, urinary catecholamines, plasma volume, total body potassium, plasma renin activity, and blood pressure responses during tilting, Schellong's test, cold pressor test and captopril administration were utilized for evaluating neurohumoral factors in the present study.

Several investigators have defined borderline hypertension as a state found in relatively young patients who had at least one casual diastolic blood pressure reading above 90 mmHg and at least one reading below 90 among more than 3 most recent pressure measurements. However, Linss et al have reported that 20% of patients who had borderline hypertension in 1968 but were judged to be normotensive in 1970, developed hypertension (blood pressure ≥ 160/95) in 1972. Therefore, it is very important to select the patients with borderline hypertension from the individuals followed up for 3 or 5 years as in the present study. In most investigations, the age of the patients with borderline hypertension was below 35 years, while it ranged from 28 to 64 in our study.

Plasma and urinary catecholamines have been studied extensively as an indicator of sympathetic overactivity in established essential hypertension and borderline hypertension. Increases in plasma catecholamines and urinary noradrenaline were observed in some patients with essential hypertension. Furthermore, Nestel and Doyle and Kuschle have reported increased urinary catecholaminas in patients with borderline hypertension as compared to that in healthy subjects. On the other hand, Esler and Nestel have found normal urinary adrenaline and noradrenaline in all patients with borderline hypertension. Furthermore, DeQuattro and Chan have demonstrated elevated plasma catecholamine levels in a small number of patients with borderline hypertension. In our study an increased urinary excretion of noradrenaline was observed in some patients with borderline hypertension, but as a whole there was no significant difference between borderline and established hypertensive patients. Robertson et al have reported that the plasma adrenaline level was higher in patients with borderline hypertension than in normal subjects. In the present study urinary excretion of adrenaline was significantly higher in borderline hypertension than in established hypertension, though it was within normal range in both groups.

It is concluded that plasma concentration and urinary excretion of catecholamine probably increased in some patients with borderline hypertension.

It has been demonstrated that some patients with borderline hypertension have a greater response of blood pressure to stimuli such as tilt Schellong's test, cold pressor test and mental stress. Frohlich et al have reported that hypertensive patients without medication were divided into the orthostatic hypertension group, the orthostatic hypotensive group and the normal responder group (within ±10 mmHg change of mean arterial pressure) according to the diastolic blood pressure change during 50 head-up tilt for 5 min, and that the orthostatic hypertensive group had the least severe vascular disease; the orthostatic hypotensive group was the opposite extreme and the normal responder group was intermediate. In the present study, in patients with borderline hypertension, the initially elevated systolic blood pressure returned to the basal level after 15 min of tilting, while a significant increase of diastolic blood pressure was demonstrated throughout the period of tilting. In patients with established hypertension, however, a significant decrease of systolic blood pressure was observed during tilting without a significant change of diastolic blood pressure. These findings suggest that according to their blood pressure response to tilt borderline hypertensives were intermediate between normal subjects and established hypertensive patients.

Smith et al have found notably similar cardiovascular responses to 70-degree tilt and standing in healthy young men. Hull et al have reported a significant rise in diastolic blood pressure in response to 5-min standing and to 70-degree tilt in both normotensive subjects and

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patients with borderline hypertension. In the present studies diastolic blood pressure increased in all patients with borderline hypertension whereas it did not change in patients with established hypertension, and it is suggested that cardiovascular responses to tilt and Schellong's test are closely similar both in patients with borderline and established hypertension.

Greene et al.29 have studied the hemodynamic changes during the cold pressor test in patients with essential hypertension and stated that the cold pressor test is not reliable for separating hypertensive patients from normotensive subjects. It has been shown that blood pressure response during cold pressor test is neither characteristic for patients with borderline hypertension30 nor useful as a predictor of future established hypertension.31 The present study suggests that the blood pressure response during cold pressor test may not separate borderline hypertension from established hypertension.

Decreased plasma volume has been reported in borderline hypertension,32 Safar al33 have reported that plasma volume was normal in borderline hypertensive patients with normal cardiac index and decreased in those with high cardiac index.

Total body potassium in essential hypertension has rarely been studied34, 35 Ellis et al.34 have reported that hypertensive patients had TBK values entirely within ± 2 standard deviations of the normal mean value. However, we have demonstrated that TBK decreased in some patients with low renin essential hypertension.35 In the present study there were no significant differences in TBK and TBK/PV between patients with borderline and established hypertension, because both groups included hypertensive patients with low, normal and high plasma renin activity, as demonstrated in Fig. 8.

An elevation of plasma renin activity on the recumbent position has been reported in some patients with borderline hypertension.36, 37 Kuchel et al.38 have reported a significantly greater orthostatic increase in plasma renin activity in subjects with borderline hypertension than in normotensive subjects. In the present study, there was no significant difference in plasma renin activity between the borderline and established hypertensive patients during the recumbent position and after a 4-hour ambulation on the third day of low sodium diet, because both groups included hypertensive patients with low, normal and high plasma renin activity, and there was no significant difference in 24-hour urinary catecholamines between 2 groups.

Captopril has been found to decrease blood pressure in human hypertension with either low, normal or high plasma renin activity.39, 40 We have reported that blood pressure was decreased further after an administration of captopril in patients with essential hypertension whose blood pressure became normotensive during hospitalization.40 As shown in Fig. 9, the blood pressure decreased after captopril in patients with borderline hypertension even when blood pressure was normal on the day of captopril study. In the patients with established hypertension blood pressure was decreased significantly. However, no significant correlation between the pretreatment PRA and a reduction of the mean blood pressure was observed both in patients with borderline and established hypertension.

The present study may suggest that both renin-angiotensin system and kinin-prostaglandin system play some role in the maintenance of blood pressure in patients with borderline hypertension.

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