THE HEMODYNAMICS IN YOUNG PATIENTS WITH
BORDERLINE HYPERTENSION

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Hemodynamics in supine position were studied echocardiographically in 56 young patients with borderline hypertension and 56 age-matched normotensive subjects. In hypertensive patients, the cardiac index (CI) did not increase, but the total peripheral resistance (TPR) increased significantly (p < 0.005). The hypertensive patients were classified into 2 groups, according to the level of the CI. In patients in group A ("normal" CI), the CI, heart rate and the mean circumferential fiber shortening velocity (mVCF) were normal, but the TPR was increased significantly. In patients in group B ("high" CI), the CI, heart rate and the mVCF increased significantly (hyperkinetic state), but the TPR was normal. Plasma renin activity (PRA) was significantly higher in patients in group B than the normal subjects, but the level of PRA in patients in group A was normal. These findings support the hypothesis that sympathetic nervous activity increases in patients in group B, but not in those in group A. Therefore, this study provides evidence that the TPR is abnormal in patients with borderline hypertension, and an impaired neurogenic activity seems to be important in the early stage of hypertension, as in borderline hypertension associated with a hyperkinetic circulatory state (group B).

BORDERLINE hypertension is commonly characterized by an increased cardiac output with a normal or low total peripheral resistance. Animal experiments and computer analysis support the hypothesis that this hemodynamic pattern may represent the initial stage in the development of fixed hypertension with a normal or decreased cardiac output. Moreover, Safar et al. have indicated the significance of the increased cardiac output in borderline hypertension, suggesting that "hyperkinetic" circulatory state may play an important role in the early stage of hypertension. Recently, the mean velocity of the circumferential fiber shortening (mVCF) is used as a reliable index of myocardial contractility. In the present study, therefore, in order to determine the role of the increased cardiac output in borderline hypertension, we carried out hemodynamic studies including the measurement of the mVCF in 56 young patients who were classified into 2 groups according to the level of cardiac output.

SUBJECTS AND METHODS

Fifty-six normotensive subjects (20 ± 1 years old, mean ± SEM) and 56 patients with untreated borderline hypertension (20 ± 1 years old) were studied (Table I). Borderline hypertension was defined as the state of patients who had at least one measurement of 90 mmHg or more and at

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Japanese Circulation Journal Vol. 47, July 1983 795
TABLE I  CLINICAL CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Borderline hypertension</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>56</td>
<td></td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>Male / Female</td>
<td>56/1</td>
<td></td>
<td>31/1 ns</td>
<td>25/1 ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20 ± 1</td>
<td></td>
<td>20 ± 1 ns</td>
<td>20 ± 1 ns</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.75 ± 0.02</td>
<td></td>
<td>1.82 ± 0.02 × 1.83 ± 0.02 ×</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as mean ± 1 SEM.
*p < 0.01 (as compared with a matched group with normotension); ns = not significant

TABLE II  HEMODYNAMIC FINDINGS, PLASMA RENIN ACTIVITY AND URINARY ELECTROLYTES IN NORMAL SUBJECTS AND PATIENTS WITH BORDERLINE HYPERTENSION

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Borderline hypertension</th>
<th>Group A</th>
<th>Group B</th>
<th>(2) vs (1)</th>
<th>(3) vs (1)</th>
<th>(4) vs (1)</th>
<th>(4) vs (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>121 ± 2</td>
<td>149 ± 2</td>
<td>147 ± 2</td>
<td>152 ± 3</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>ns</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72 ± 1</td>
<td>86 ± 2</td>
<td>87 ± 2</td>
<td>85 ± 2</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>ns</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>88 ± 1</td>
<td>107 ± 1</td>
<td>107 ± 2</td>
<td>108 ± 3</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>ns</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>63 ± 1</td>
<td>69 ± 2</td>
<td>62 ± 2</td>
<td>77 ± 3</td>
<td>0.01</td>
<td>ns</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>3.46 ± 0.10</td>
<td>3.68 ± 0.10</td>
<td>3.20 ± 0.06</td>
<td>4.31 ± 0.13</td>
<td>ns</td>
<td>ns</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>SI (ml/min)</td>
<td>55.3 ± 1.0</td>
<td>54.5 ± 1.1</td>
<td>52.3 ± 1.3</td>
<td>57.2 ± 1.9</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>0.05</td>
</tr>
<tr>
<td>TPR (dyne·sec·cm⁻¹·m⁻²)</td>
<td>2098 ± 61</td>
<td>2380 ± 63</td>
<td>2677 ± 64</td>
<td>2011 ± 63</td>
<td>0.005</td>
<td>0.001</td>
<td>ns</td>
<td>0.001</td>
</tr>
<tr>
<td>mVCF</td>
<td>1.34 ± 0.03</td>
<td>1.39 ± 0.03</td>
<td>1.34 ± 0.03</td>
<td>1.46 ± 0.05</td>
<td>ns</td>
<td>ns</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>PRA (ng/ml/hour)</td>
<td>2.29 ± 0.11</td>
<td>2.72 ± 0.18</td>
<td>2.38 ± 0.17</td>
<td>3.03 ± 0.22</td>
<td>0.05</td>
<td>ns</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Urinary Na (mEq/day)</td>
<td>249 ± 15</td>
<td>233 ± 10</td>
<td>241 ± 14</td>
<td>223 ± 15</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Urinary K (mEq/day)</td>
<td>43 ± 3</td>
<td>44 ± 2</td>
<td>46 ± 3</td>
<td>41 ± 3</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

At each determination, the group with hypertension is compared to a matched group with normotension. SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; HR = heart rate; CI = cardiac index; SI = stroke index; TPR = total peripheral resistance; mVCF = mean circumferential velocity; PRA = plasma renin activity

least one below 90 mmHg in 3 casual diastolic blood pressure determinations during the previous year. Every patient underwent a thorough clinical examination and was considered not to have any signs of secondary hypertension. The examination involved taking medical histories related to renal disease, pheochromocytoma and primary aldosteronism. All patients had a normal urine, serum creatinine and serum potassium.

Cardiac output was measured echocardiographically, and blood pressure was measured using a sphygmomanometer, at the Hypertensive Clinic of Tsukuba University. All patients were

Japanese Circulation Journal  Vol. 47, July 1983
made to rest comfortably on an examination table at least 30 min before the hemodynamic study.

Echocardiographic Analysis

Echocardiograms were recorded with ALOKA SSD 110 using a 2.25 MHZ, 1 cm in diameter and nonfocused transducer. The ultrasonic beams were introduced from the 3rd or the 4th intercostal space to the left ventricle, where the endocardial echoes of the interventricular septum and the posterior wall were clearly identified, and the tips of both leaflets of the mitral valve were recorded between them, as described by Feigenbaum. Photographic recordings were obtained at a paper speed of 100 mm/sec with simultaneous recording of an electrocardiogram, a phonocardiogram, and the pericardial echo was identified at the end of each recording with the use of damping procedure. The results obtained from 5 consecutive beats were averaged. The end-diastolic left ventricular diameter (LVDD) was measured at the peak of the R wave of the simultaneously recorded electrocardiogram. The end-systolic left ventricular diameter (LVDs) was taken at the onset of the second heart sound of the phonocardiogram. The stroke index (SI) was calculated as follows: SI = (LVDd³ - LVDs³)/body surface area. The cardiac index (CI) was obtained by the formula: CI = SI x heart rate. The cardiac index was expressed in L/min/m² by correcting for body surface area. The total peripheral resistance index (TPRI) was calculated from the following formula: TPRI (dynes·sec·cm⁻⁵·m²) = mean blood pressure/cardiac index x 79.32. The ejection time (ET) was measured by the simultaneous recording of an indirect carotid artery pulse tracing and an electrocardiogram at a paper speed of 100 mm/sec. The mean velocity of the circumferential fiber shortening (mV_C) was calculated from the formula: mV_C = (LVDd - LVDs)/LVDD·ET. mV_C was used as an index of myocardial contractility.

In other experiments we examined the reproducibility of our method. We studied 12 subjects with normal ventricles after 30 min of rest in the supine position on 2 separate days of
ad libitum diet. At the same time each day, duplicate measurements were made over a 20-min period. The average variation of cardiac output obtained by this method was 3.6%. The reliability of left ventricular volume has been also assessed. There is a good correlation between the echocardiographic and the thermodilutional volume measurement in 11 patients who had no left ventricular asynegry. The correlation coefficient for cardiac output by these 2 methods was $r = 0.786$ ($p < 0.005$).

All echocardiograms were recorded by the same doctor and were evaluated by 2 independent observers.

Before the hemodynamic study, blood for the determination of plasma renin activity was taken from each patient in the sitting position. Plasma renin activity was measured by angiotensin I radioimmunoassay.\[^1\] Twenty-four hour urine for the measurements of sodium and potassium concentrations was collected on the day before the hemodynamic and endocrine studies. Numerical results are expressed as mean ± 1 SEM. For statistical study, the significance of the difference in mean values and in paired averages between groups was determined by Student's $t$-test.

**RESULTS**

There was no significant difference in sex or age between normotensives and hypertensives, but body surface area was significantly larger in hypertensives than normotensives (Table I). Borderline hypertensive subjects had a significant increase in blood pressure ($p < 0.001$), heart rate ($p < 0.01$) and total peripheral resistance ($p < 0.005$), but it showed an insignificant increase in the cardiac index (Table II, Figs. 1 and 2). The cardiac index of normal subjects was $3.46 ± 0.10$ L/min/m² (Fig. 2). As reported by Safar et al.,\[^5\] it is possible to classify patients with borderline hypertension into 2 groups according to the level of the cardiac index (Fig. 3): group A with a higher cardiac index than 3.66 L/min/m² (mean value of the cardiac index in normal subjects) and group B with a cardiac index of 3.66 L/min/m² or less.

*Group A:* In 31 out of 56 patients, the cardiac index was normal ($3.20 ± 0.06$ L/min/
m²). Mean blood pressure increased significantly, but heart rate was normal. Total peripheral resistance was significantly greater than normal subjects (p < 0.001). The mean \( V_{\text{CF}} \) was the same as compared with the normotensive subjects (1.34 ± 0.03 vs 1.34 ± 0.02 circ/sec).

**Group B:** In 25 out of 56 patients, the cardiac index increased (4.31 ± 0.13 L/min/m², p < 0.001 as compared with the normotensive subjects). Mean blood pressure increased significantly to the same extent as the patients in group A. Heart rate increased (p < 0.001), and total peripheral resistance was normal. The m\( V_{\text{CF}} \) increased significantly (1.46 ± 0.05 circ/sec, p < 0.01) (Fig. 4).

Plasma renin activity increased significantly in the patients in group B (3.03 ± 0.22 ng/ml/hour) than the normal subjects (2.29 ± 0.11) and the patients in group A (2.38 ± 0.17), although there was no difference in urinary sodium excretion among the 3 groups (Table II).

**DISCUSSION**

In a substantial proportion of patients with borderline hypertension, cardiac output is elevated (hyperkinetic borderline hypertension)\(^{13-17}\) However, an increased cardiac output has not been found in all patients with borderline hypertension, but in some cases it was normal\(^{18,19}\). In the present study, cardiac output increased slightly, but not significantly, i.e., it increased in some patients but not in others. Although cardiac output of our patients with borderline hypertension was distributed continuously (Fig. 2), we were interested in separating patients with “normal” and “high” output, in order to study the role of this factor in increased blood pressure. In the present study, the blood pressure level was similar in the 2 subgroups of young borderline hypertensive patients. However, in group A the cardiac index and heart rate were normal, and in group B the cardiac index and heart rate increased, as observed by most other authors\(^{15,16}\). In the present study, moreover, the mean \( V_{\text{CF}} \) increased in group B, but not in group A (Fig. 4). These findings suggest that patients of group B are in the “hyperkinetic” state, since the m\( V_{\text{CF}} \) is a reliable index of left ventricular performance which reflects an ino-
accommodating state of the left ventricular myocardium.\textsuperscript{6,7} Julius et al\textsuperscript{20} have observed that the increased cardiac index and heart rate became normal after autonomic blockade of the heart. Therefore, they proposed that the elevation of the cardiac output in some patients with borderline hypertension stems from neurogenic influences on the heart. This hypothesis seems to be supported by the present study, in which the patients with "high" cardiac output, with normal subjects and the patients with "normal" cardiac output, since the importance of the renal sympathetic nerves in the control of renin release is well known.\textsuperscript{21} Mohlzan et al\textsuperscript{22} have found elevated plasma renin values at rest in patients with hyperkinetic borderline hypertension. Furthermore, several investigators have demonstrated that the clinical entity of "borderline hypertension" is associated with pathophysiological alterations in the autonomic nervous system, systemic hemodynamics and the renin-angiotensin system.\textsuperscript{23–25} In the present study, therefore, an increased sympathetic stimulation of the kidney and the heart would account for both the hyperreninemia and the most specific hemodynamic features of borderline hypertension associated with high cardiac output, increased heart rate and increased mVCF.

Abnormality of total peripheral resistance was observed at rest in patients with "normal" cardiac index, but not in patients with "high" cardiac index. However, it must be noted that under normal circumstances, when blood flow increases, there is an appropriate decrease of vascular resistance, so that blood pressure remains unchanged. Therefore, even in group B ("high" cardiac index) with normal TPR, peripheral resistance may be considered inappropriately high relative to the elevated cardiac output. When the cardiac output is taken into consideration, patients with borderline hypertension always show an increased peripheral resistance.\textsuperscript{26}

These findings suggest a high level of neurogenic activity in patients in group B ("high" cardiac output). Frohlich et al\textsuperscript{23,27} have found that neurogenic activity was greatest in mild hypertension with an increased output and least in the severe form of hypertension. Thus, it can be suggested that patients with "high" cardiac index were in an earlier phase of hypertension. According to "autoregulation" theory\textsuperscript{28} moreover, a primary increase of cardiac output later triggers an autoregulatory increase of the peripheral resistance. This increased resistance acts to restrict cardiac output, and finally a new balance with a normal cardiac output and an elevated peripheral resistance is established (group A). Our results did not confirm this suggestion because no difference of age distribution or blood pressure level existed between the patients in groups A and B. However, if it is assumed that the patients in group B were in an earlier phase of hypertension, impaired neurogenic activity appears to play a role in the initial stage of hypertension associated with a "hyperkinetic" circulatory state.

ADDENDUM

Regarding the increased TPR in borderline hypertension, we have recently indicated, in contrast to "autoregulation" theory, that the increased TPR is in some way related to the impaired membrane sodium transport in vascular smooth muscle in patients with borderline hypertension.\textsuperscript{29} Thus, it is still controversial.

REFERENCES

10. CRAWFORD MH, GRANT D, O’ROURKE RA, STARLING MR, GROVES BM: Accuracy and reproducibility of new M-mode echocardiographic recommendations for measuring left ventricular

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