Pressor Factors and Cardiovascular Pressor Responsiveness in Borderline Hypertension

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SUMMARY The role of various pressor factors and cardiovascular responsiveness to norepinephrine or angiotensin II in the pathogenesis of borderline hypertension was evaluated. Exchangeable body sodium, blood volume, plasma renin activity, norepinephrine or dopamine levels, and norepinephrine or epinephrine excretion rates were similar between 24 patients with borderline hypertension (mean age 34 ± 4 (SEM) years) and 22 normal subjects matched for age; the patients had a slight increase in supine plasma epinephrine. Pressor doses of norepinephrine or angiotensin II were significantly lower (p < 0.01 and 0.001, respectively) in the borderline hypertensive group. These findings suggest that borderline hypertension may be maintained by inappropriately increased cardiovascular response to norepinephrine and angiotensin II in the presence of normal sympathetic and renin activity and a normal body sodium-volume state. (Hypertension 3: 367-372, 1981)

KEY WORDS • borderline hypertension • pressor response • norepinephrine • angiotensin II • plasma catecholamines • renin • body sodium-volume state

BORDERLINE hypertension signifies the gray zone between normal blood pressure (BP) and established hypertension. At least 10% of the general adult population may have borderline hypertension. However, since this mixed group includes persons with a normal circulation, those with only a transient tendency for elevated BP, as well as those in the early stage of essential hypertension, it has been difficult to delineate distinct clinical and functional characteristics.

Several different patterns of hemodynamic function have been reported. Whether and to what extent borderline BP elevations may depend on abnormalities in major endocrine pressor factors, such as the sympathetic and/or renin-angiotensin systems, are still controversial. In borderline hypertensive patients who were grouped according to BP and age, blood levels and urinary excretion of norepinephrine as an approximate index of adrenergic activity were reported to be normal or mildly increased; plasma renin activity (PRA) was found to be either low, normal, or high. The pressor effect of any vasoactive factor depends not only on its concentration but also on cardiovascular response. Digital vascular reactivity to norepinephrine was previously noted to be high in some patients with labile hypertension. Others described a decreased norepinephrine pressor response and a normal angiotensin II response. Simultaneous evaluation of both blood levels and cardiovascular effects of the pressor factors that would allow an integrated interpretation has not been performed.

This study was undertaken to systematically investigate the interrelationships among BP, plasma catecholamines, PRA, and pressor response to norepinephrine or angiotensin II in patients with borderline hypertension as compared to age-matched normal subjects. Since body sodium and fluid volumes may per se influence these factors, exchangeable body sodium and plasma volume were also measured simultaneously.
Materials and Methods

Subjects

Twenty-four patients (18 men and six women) with borderline hypertension (H) and 22 normal (N) subjects (17 men and five women) were studied. Mean age was 35 ± 3 (mean ± SEM) years in the H patients and 37 ± 4 years in the N subjects. Borderline hypertension was defined by BP values ranging from 141 to 159 mm Hg systolic and/or from 91 to 94 mm Hg diastolic, with intermittent values below but only rare values above this range. All H patients were referred to our outpatient clinic for diagnostic evaluation of their BP. Routine physical and laboratory examinations, including hematologic screening, serum electrolyte, creatinine, BUN, thyroxin (T4), urinalysis, intravenous pyelography, ECG, and urinary vanillic mandelic acid excretion, revealed no abnormalities other than the borderline hypertension.

In all H patients, normotensive and borderline hypertensive periods were documented on several occasions in our outpatient clinic as well as in our laboratory. The BP measurements were made by a physician in the morning, after H and N had rested for 10 minutes in the supine position. The known duration of a tendency for borderline BP ranged from 2 weeks to 72 months (mean, 21 ± 6 months). Twelve H patients were being treated with a diuretic or a beta blocker; these medications were discontinued 4 weeks before the study. Since inhospital conditions are known to lower the BP to normal levels in many patients with mild hypertension, studies were performed on an outpatient basis, all persons being instructed in a diet without added salt starting 4 weeks before the study. Since inhospital conditions are known to lower the BP to normal levels in many patients with mild hypertension, studies were performed on an outpatient basis, all persons being instructed in a diet without added salt starting 4 weeks before the tests. All were informed about the purpose and investigative character of the study, and gave their consent.

Study Plan

At the beginning, both H and N participants received placebo tablets for 4 weeks. At the end of the placebo phase, 24-hour urinary sodium, potassium, norepinephrine, and epinephrine excretion rates, plasma sodium and potassium, plasma and blood volumes, and exchangeable body sodium were obtained; and PRA, aldosterone, norepinephrine (NE), epinephrine, and dopamine levels, BP, and pulse rate were determined following overnight fast between 8 am and 11 am after 1 hour of recumbency and after 1 hour of ambulation, according to our standard procedure. An indwelling intravenous catheter was placed at least 30 minutes before initial blood sampling was begun. On a separate day, responses of BP and pulse rate to intravenously infused NE and angiotensin II were determined between 8 and 12 am; basal plasma NE levels were obtained immediately before starting the NE infusion, while basal PRA was obtained immediately before starting the angiotensin II infusion. An intravenous catheter for blood sampling was placed 60 minutes before cardiovascular response testing was begun. In two normal subjects, testing of cardiovascular responsiveness to NE could not be completed because of the development of extrasystoles during the procedure.

Techniques

Blood pressure was measured using a standard cuff and sphygmomanometer; each BP recorded was the mean of three measurements. To determine the cardiovascular pressor response, BP was registered with the Physiometrics SR 2 automatic recorder. Mean BP was calculated as the sum of the diastolic (disappearance of sounds) and one-third of the pulse pressure. Plasma and urinary sodium and potassium concentrations were determined by flame photometer, and plasma and blood volumes and exchangeable body sodium by standard isotope dilution methods using 131I-human serum albumin and 24Na respectively. PRA and plasma aldosterone were measured by radioimmunoassay, urinary catecholamines by fluorometric assay, and the plasma catecholamines (NE, epinephrine, dopamine) by a radioenzymatic method. All endocrine measurements were made in duplicate, and the mean value was used.

Mean coefficients of intrassay and interassay variations in 65 to 210 unselected consecutive determinations obtained with these methods were: PRA 6.5% and 7.6%, respectively; plasma aldosterone 7.5% and 15.8%; urinary NE 12.4% and 16.7%; urinary epinephrine 6.0% and 9.1%; plasma NE 9.8% and 10.1%; plasma epinephrine 12.2% and 15.6%; plasma dopamine 12.2% and 15%. Coefficients of interassay variation of catecholamine levels in control plasma were 2.0% for NE, 2.5% for epinephrine, and 5.2% for dopamine.

Pressor response testing was performed while the participants were supine. Following 60 minutes of a slow intravenous infusion of 5% glucose (6-12 ml/hr by constant-infusion pump), at least five basal BP values and pulse rates were obtained; the dextrose infusion was then replaced by a solution of NE (1-norepinephrine-tartrate in 5% glucose). By varying the pump speed and utilizing several standard solutions with NE concentrations of 15 to 30 µg/ml, the rate of infused NE was increased stepwise every 5 to 15 minutes until the BP had stabilized for at least 10 minutes on several different levels between two target points, namely, 10-15 and 25-35 mm Hg above the basal mean BP. After an interval of 30 minutes with infusion of only 5% glucose, an infusion of angiotensin II (1-angiotensin-amide [Hypertensin, Ciba] in 5% glucose) was begun. By varying the pump speeds and using angiotensin II solutions with concentrations ranging from 1.5 to 3 µg/ml, the angiotensin dose was titrated to reach several different pressure levels between two target points of 5-15 and 20-30 mm Hg above the basal diastolic BP. Pulse rate was always measured simultaneously with BP during NE or angiotensin II infusion. Individual dose-BP response curves were plotted on semilogarithmic paper. Since log NE or log angiotensin II dose-BP response curves char-
acteristically have sigmoid form, we used only the two to three consecutive data points from the part of the curve with the steepest slope to construct a regression line, assuming that these points represent best the rectilinear central portion of the log dose-BP response curve. The pressor dose was defined as the dose necessary to increase the mean (NE) or diastolic (angiotensin II) BP by 20 mm Hg.

**Statistical Analysis**

Since natural logarithmic transformation rather than absolute values followed a Gaussian distribution, the natural logarithmic transformation of PRA, plasma aldosterone, plasma and urinary catecholamines, and pressor doses was used for unpaired t test, linear regression analysis, or analysis of covariance. The approach of Olkin and Pratt was applied for the calculation of the correlation coefficients from linear regression analysis. The null hypothesis was rejected when a p value was less than 0.05 (two-tailed test).

**Results**

At the end of the 4-week placebo period, mean pulse rate, body weight, plasma and blood volumes, exchangeable body sodium, PRA, plasma aldosterone, NE, dopamine, sodium and potassium levels, and urinary NE, sodium, and potassium excretion rates did not differ significantly between the H and N groups (tables 1 and 2). In the H group, when compared to our age-related normal ranges, individual upright PRA was normal in 21, high in two, and low in one, while upright plasma NE was normal in 20 and mildly elevated in four. Supine plasma epinephrine was slightly higher in the H group (p < 0.01), but upright plasma epinephrine and epinephrine excretion rates were similar between H and N groups.

Mean pressor dose of NE was significantly lower in the H than in the 20 N subjects in whom this procedure could be completed (87 ± 7 vs 146 ± 17 ng/kg/min, p < 0.01) (fig. 1). Basal (pre-NE infusion) plasma NE (21.8 ± 1.8 vs 21.9 ± 2.0 ng/100 ml), the slopes of the NE dose-BP response curves (16.0 ± 1.5 vs 18.6 ± 1.6), and the maximal changes of mean arterial pressure (+29 ± 2 vs +30 ± 2 mm Hg) or pulse rate (−10 ± 2 vs −11 ± 2 beats/min) during NE infusion were similar in the two groups. The NE pressor dose correlated positively with preinfusion plasma NE levels in H and N subjects (fig. 2); while the slopes of the two regression lines were similar, their intercepts differed significantly (p < 0.001). Thus, for any given preinfusion NE level, the NE pressor dose was about 35% lower in H than in N subjects.

Mean angiotensin II pressor dose was also significantly lower in H than in N subjects (8.1 ± 0.7 vs 16.0 ± 2.0 ng/kg/min, p < 0.001) (fig. 1). Again, the two groups did not differ significantly in the mean slopes of the angiotensin II dose-BP response curves (12.1 ± 0.9 vs 10.7 ± 1.0), the maximal changes in mean arterial pressure (+25 ± 1 vs +23 ± 1 mm Hg), or pulse rate (−3 ± 1 vs −4 ± 1 beats/min) during angiotensin II infusion, or basal (pre-angiotensin II infusion) PRA (1.8 ± 0.3 vs 2.2 ± 0.3). In both groups, the relationship between angiotensin II pressor dose and basal PRA was not statistically significant (r = 0.14 and 0.31, respectively). This relationship became statistically significant when all subjects were analyzed jointly (r = 0.38, p < 0.02). Since basal PRA tended to be mildly (not significantly) lower in the H patients, analysis of covariance was applied to eliminate a possible influence of PRA on the difference in angiotensin II pressor dose between the two groups. This analysis confirmed the presence of a significant (p < 0.001) renin-independent decrease in mean angiotensin II pressor dose in H as compared to N subjects.

### Table 1. Blood Pressure and Body Sodium-Volume State in Normal Subjects and Patients with Borderline Hypertension (Mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Borderline hypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>37 ± 4</td>
<td>35 ± 3</td>
</tr>
<tr>
<td><strong>Blood pressure (mm Hg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>supine</td>
<td>119/73 ± 3/3</td>
<td>141/89 ± 6/3</td>
</tr>
<tr>
<td>upright</td>
<td>101/72 ± 3/4</td>
<td>123/84 ± 5/2*</td>
</tr>
<tr>
<td><strong>Pulse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>supine</td>
<td>63 ± 3</td>
<td>65 ± 2</td>
</tr>
<tr>
<td>upright</td>
<td>94 ± 4</td>
<td>90 ± 4</td>
</tr>
<tr>
<td><strong>Body weight (kg)</strong></td>
<td>69.0 ± 2.8</td>
<td>76.0 ± 3.1</td>
</tr>
<tr>
<td><strong>Exchangeable sodium (mEq/kg LBM)</strong></td>
<td>45.0 ± 0.6</td>
<td>44.3 ± 0.6</td>
</tr>
<tr>
<td><strong>Blood volume (ml/kg LBM)</strong></td>
<td>70.2 ± 3.2</td>
<td>71.2 ± 3.1</td>
</tr>
<tr>
<td><strong>Plasma volume (ml/kg LBM)</strong></td>
<td>40.0 ± 1.7</td>
<td>39.5 ± 1.8</td>
</tr>
<tr>
<td><strong>Urinary sodium (mEq/24 hr)</strong></td>
<td>131 ± 14</td>
<td>120 ± 14</td>
</tr>
</tbody>
</table>

*p < 0.005.

p < 0.001.

LBM = lean body mass.
TABLE 2. Plasma Renin, Aldosterone, and Catecholamines, and Catecholamine Excretion Rates in Normal Subjects and Patients with Borderline Hypertension (Mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Borderline hypertensives</th>
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<tbody>
<tr>
<td><strong>Plasma</strong></td>
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<tr>
<td>Renin activity (ng/ml/hr)</td>
<td></td>
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<tr>
<td>supine</td>
<td>1.6 ± 0.2</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td>upright</td>
<td>6.0 ± 1.0</td>
<td>6.4 ± 1.4</td>
</tr>
<tr>
<td>Aldosterone (ng/100 ml)</td>
<td></td>
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<tr>
<td>supine</td>
<td>4.2 ± 1.1</td>
<td>5.1 ± 0.9</td>
</tr>
<tr>
<td>upright</td>
<td>16.2 ± 2.6</td>
<td>17.6 ± 3.3</td>
</tr>
<tr>
<td>Norepinephrine (ng/100 ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>supine</td>
<td>21.2 ± 1.8</td>
<td>20.1 ± 1.7</td>
</tr>
<tr>
<td>upright</td>
<td>56.3 ± 5.2</td>
<td>54.3 ± 5.1</td>
</tr>
<tr>
<td>Epinephrine (ng/100 ml)</td>
<td></td>
<td></td>
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<tr>
<td>supine</td>
<td>2.9 ± 0.4</td>
<td>4.3 ± 0.4*</td>
</tr>
<tr>
<td>upright</td>
<td>5.8 ± 1.1</td>
<td>7.6 ± 1.0</td>
</tr>
<tr>
<td>Dopamine (ng/100 ml)</td>
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<tr>
<td>supine</td>
<td>6.5 ± 0.9</td>
<td>7.8 ± 1.0</td>
</tr>
<tr>
<td>upright</td>
<td>8.8 ± 1.0</td>
<td>9.4 ± 1.3</td>
</tr>
<tr>
<td><strong>Urinary</strong></td>
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<tr>
<td>Norepinephrine (µg/g creatinine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22.5 ± 2.6</td>
<td>24.8 ± 2.8</td>
</tr>
<tr>
<td>Epinephrine (µg/g creatinine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.6 ± 0.5</td>
<td>4.2 ± 0.6</td>
</tr>
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</table>

*p < 0.01, vs normal subjects.

**Discussion**

Major pressor factors such as the body sodium-volume state, the renin-angiotensin-aldosterone system, and the activity of the peripheral sympathetic nervous system appeared to be normal in our H patients. Thus, mean exchangeable body sodium, urinary sodium excretion, plasma and blood volumes, and supine or upright blood levels of renin, aldosterone, NE, and dopamine, as well as NE excretion rates, did not differ significantly between these H patients and age-matched N subjects. The rare occurrence of abnormal PRA and NE values in H patients contrasts somewhat with certain previous reports. Differences in renin interpretation could possibly be related to patient selection and the lack of age-related normal ranges in other studies; however, except for the use of different methodology, we have no explanation for isolated observations of a distinct increase in circulating NE in borderline hypertension. Nevertheless, it is conceivable that plasma renin or norepinephrine levels could vary with the duration of borderline BP elevations. Known duration in our patients ranged from 2 weeks to 72 months (mean, 21 ± 6 months), but no information on this factor has been provided in the previous reports of frequently altered plasma renin or norepinephrine levels in borderline hypertension.

The pattern of free peripheral epinephrine that originates from the adrenal gland was less clearcut in our present study. Epinephrine excretion rates and upright plasma epinephrine concentrations did not differ significantly between our H and N subjects, but circulating epinephrine measured in the supine position was slightly increased in H. Others have also noted high blood levels of epinephrine in borderline hypertensive patients. It is not clear whether this tendency may be due to increased adrenomedullary secretion or decreased plasma clearance of epinephrine in borderline hypertension.

The major finding of our present study is the demonstration of a significantly increased pressor response to both NE (p < 0.01) and angiotensin II (p < 0.001) despite normal levels of plasma NE and renin in patients with borderline hypertension. In our N subjects, the NE pressor dose correlated positively with endogenous plasma NE (p < 0.02), pointing to a physiologic regulatory mechanism. A similar relationship existed also in borderline hypertension, but it was shifted so that NE pressor response for any given basal plasma NE value was significantly (p < 0.001) increased by about 35%. Philipp et al. described a comparable disturbance of the relationship between exercise-stimulated plasma NE and NE pressor response in patients with established essential hypertension, whose diastolic BP was >100 mm Hg. Our findings indicate that this abnormality may occur...
already at the borderline stage of hypertension. It is interesting to note that an other response parameter, namely, digital vascular NE reactivity, was also increased in such patients.9

The absence of a significant relationship between angiotensin II pressor dose and basal PRA29, 32 when our normal or borderline hypertensive subjects were analyzed separately is probably due to the narrow observation range of basal PRA in the two study groups. However, based on such a correlation when both groups were considered jointly, analysis of covariance could be applied and indicated that the increased angiotensin II response in the patient group with borderline hypertension could not be explained by variations in PRA.

Several mechanisms modify pressor response. Exaggerated pressor responses could be a consequence of altered baroreflexes, which may be impaired already at the borderline stage of hypertension.24-26 Since NE as well as angiotensin II have direct cardiac action,24, 27 an exact analysis of baroreflex responses could not be made during NE or angiotensin II infusion. Nevertheless, the obvious similarity of changes in pulse rate and BP during infusion of NE or angiotensin II in our H and N subjects suggests that decreased baroreceptor sensitivity was not a major cause of the increased pressor response in borderline hypertension. This increased response also could not be related to a slightly higher body weight in the borderline hypertensive group, which exceeded the mean value in normal subjects by only 10%, while decreases in NE and angiotensin II pressor doses averaged 40% and 55%. An influence from mildly increased plasma epinephrine concentrations cannot be excluded, but such an interaction would possibly decrease rather than increase the pressor response to NE.28 Since plasma and blood volumes and exchangeable body sodium were normal in our H patients, these factors per se also did not appear to contribute.29

It is possible that the exaggerated pressor response to NE or angiotensin II observed in H patients is based on other factors not investigated in this study. High BP-induced structural changes in the blood vessel walls,31, 32 which may be a major cause of the increased vascular reactivity,33-38 or pressor response9 to NE or angiotensin II in established hypertension, could already occur at the borderline stage of hypertension.39 Moreover, increased pressor response could be an unspecific consequence of increased vasoconstriction, although elevated peripheral resistance is found only in a subgroup of patients with borderline hypertension.4 A lack in vasodressor substances also deserves consideration, since urinary excretion of prostaglandin E was found to be decreased in established essential hypertension.37, 38 On the other hand, certain patients with labile hypertension had an increased response of cardiac betareceptors40 or blood levels of cyclic AMP4 to isoproterenol. Doyle and Fraser41 described an enhanced forearm vascular response to NE in the setting of prehypertension, that is, in normotensive sons of hypertensive parents; these findings could be interpreted as evidence for a primary
defect of certain cardiovascular receptors or sensitivity in borderline hypertension.

Whatever the exact underlying cause, our observations suggest that an exaggerated pressor response to NE and angiotensin II, in the presence of normal activity of the sympathetic nervous and renin-angiotensin systems, may be an important pathogenic factor in borderline hypertension.

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References

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