Role of Autonomic and Non-Autonomic Circulatory Components in Borderline Hypertension in Young Men

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SUMMARY

The role of autonomic nervous system and non-autonomic components in hemodynamic abnormalities of young patients with borderline hypertension was examined by comparing the effects of sequential pharmacological autonomic blockade on hemodynamics between 8 patients with borderline hypertension (mean age 20.0 ± 0.2) and 10 normotensive subjects (mean age 19.3 ± 0.2). Propranolol (0.2 mg/Kg), atropine (0.04 mg/Kg), and phentolamine (10 or 15 mg) were given intravenously in that order to produce "total" autonomic blockade. Increased cardiac index, heart rate, and mean arterial blood pressure with normal peripheral vascular resistance were noted at rest in patients with borderline hypertension. Cardiac index and heart rate in patients with borderline hypertension were normalized by propranolol, but after "total" autonomic blockade mean arterial blood pressure and peripheral vascular resistance were higher in patients with borderline hypertension as compared to those in normotensive subjects. These results suggest that, although autonomic nervous system control of circulation is abnormal, non-autonomic components play an important role in maintaining increased peripheral vascular resistance in borderline hypertension in young men.

Additional Indexing Words:
Pharmacological blockade "Total" autonomic blockade Propranolol Atropine Phentolamine Heart rate Cardiac index Peripheral resistance index

PATIENTS with borderline hypertension display 2 hemodynamic patterns.1) The first pattern is characterized by elevated heart rate and cardiac index with normal or even low peripheral vascular resistance at rest. The second pattern consists of elevated or normal heart rate, normal cardiac index and moderately elevated peripheral resistance. The latter pattern may be considered to represent a somewhat later stage of hypertensive process.3)
In the first group, although peripheral vascular resistance at rest remains within normal range, vascular resistance at any given level of cardiac output is higher than in normotensive subjects so that normal vascular resistance in a state of elevated cardiac output is considered inappropriately normal.\textsuperscript{4,5} Previously we demonstrated impaired baroreflex function in these patients and speculated that impaired baroreflex function may conceivably account for the abnormal adjustment of peripheral resistance to elevated cardiac output.\textsuperscript{6} However, this abnormality may be due to non-autonomic components such as structural changes since previous studies suggest that non-autonomic components play an important role in hemodynamic abnormalities in the second group of borderline hypertension\textsuperscript{7} as well as in established hypertension.\textsuperscript{8}

In the present study we examined the role of non-autonomic components in hemodynamic abnormalities in patients with borderline hypertension of 20 years old or less who had increased cardiac output and normal peripheral vascular resistance at rest.

\textbf{Methods}

Eight patients with borderline hypertension and 10 control subjects of comparable age were studied. All subjects were 20 years old or less. The mean age of patients with borderline hypertension was 20.0±0.2 years old (mean±SE) and that of control subjects was 19.3±0.2 years old.

Patients with borderline hypertension were selected on the basis of arterial blood pressure readings higher than 150 mmHg systolic or 90 mmHg diastolic at least 3 times out of 5 recordings in the outpatient clinic. All patients were asymptomatic. Every patient had a thorough clinical examination and none provided evidence that hypertension was secondary. The studies undertaken on these patients included complete blood counts, urinalysis, urine culture, serum and urine electrolytes, intravenous pyelography, creatinine clearance, plasma renin activity at rest and after 1 hour of upright posture, 24 hours urine for VMA, 17KS and 17OHCS, T\textsubscript{3} and T\textsubscript{4}, chest X-ray and electrocardiogram. No patient had evidence of the end-organ disease of hypertension on physical examinations, chest X-ray, ECG or on renal function studies. No patient was on any antihypertensive medication. Plasma renin activity in these patients were normal except for 1 patient.

The control group consists of 10 normal volunteers.

The studies were done in supine position without sedation. An intra-arterial cannula was inserted in a branchial artery and was connected to a Stetham transducer. Arterial blood pressure and ECG were recorded simultaneously on a multichannel oscillographic recorder. A venous cannula was inserted in an antecubital vein, through which intravenous injections of drugs were given. Cardiac output was measured by the dye-dilution technique, in which 2 ml of Cardiogreen dye was injected into the antecubital vein and was immediately flushed with a bolus injection of normal saline, 10 ml. Dye-dilution curves were recorded through a densitometer put at a ear lobe. The reproducibility of measurements was checked.
by repeating measurements twice. Total vascular resistance index was calculated from cardiac index and mean arterial blood pressure.

Propranolol, atropine, and phentolamine were given intravenously to block the effects of β-adrenergic, parasympathetic, and α-adrenergic activities, respectively. Drugs were given in that order. Measurements of arterial blood pressure, heart rate, and cardiac output were done 1) at control state, 2) 5 min after an intravenous injection of propranolol, 0.2 mg per Kg of body weight, 3) 2 min after an intravenous injection of atropine, 0.04 mg per Kg of body weight, and 4) lastly, during maximum hypotension produced by intravenous phentolamine, 10 or 15 mg. Measurements at the control states were done after 10 min of rest following insertions of all catheters.

RESULTS

Heart rate, mean arterial blood pressure, and cardiac index at the control state, after propranolol (0.2 mg/Kg IV), after propranolol and atropine (0.04 mg/Kg IV), and after propranolol, atropine, and phentolamine (10 or 15 mg IV) are summarized in Table I.

At the control state, heart rate and arterial blood pressure were significantly higher in patients with borderline hypertension than those in control subjects (p<0.01). Cardiac index tended to be greater in patients with borderline hypertension (0.05<p<0.1). Total vascular resistance index was not different between 2 groups.

Propranolol reduced heart rate in both groups (p<0.01) but reduction was significantly greater in patients with borderline hypertension (p<0.01) (Table I and Fig. 1). Heart rate after propranolol was slightly higher in

![Graph 1](image1.png)  
**Fig. 1.** Effects of propranolol and atropine on heart rate and cardiac index. C, P, and A represent control, propranolol and atropine, respectively. Solid circles and lines indicate data on patients with borderline hypertension. Open circles and broken lines indicate data in normotensive subjects. **indicates p<0.01 and # represents 0.05<p<0.01. Heart rate was higher and cardiac index tended to be higher in patients with borderline hypertension at control, but these changes were normalized after propranolol.
## Table I

<table>
<thead>
<tr>
<th></th>
<th>Control (C)</th>
<th>After Propranolol (P)</th>
<th>Δ P-C</th>
<th>After Propranolol and Atropine (A)</th>
<th>Δ A-P</th>
<th>After Propranolol, Atropine, and Phentolamine (ph)</th>
<th>Δ ph-A</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Borderline Hypertensive (n=8)</strong></td>
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<tr>
<td>HR</td>
<td>74.4±4.0**</td>
<td>57.6±2.3**</td>
<td>(-16.7±2.6)**</td>
<td>103.7±3.1**</td>
<td>(46.1±2.6)</td>
<td>114.1±5.4#</td>
<td>(10.4±4.4)*</td>
</tr>
<tr>
<td>MAP</td>
<td>105.7±4.3**</td>
<td>107.6±2.9**</td>
<td>(1.7±2.4)</td>
<td>137.5±5.5**</td>
<td>(29.9±6.5)</td>
<td>109.5±6.2**</td>
<td>(-28.0±3.8)</td>
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<tr>
<td>CI</td>
<td>3.2±0.1#</td>
<td>2.5±0.1**</td>
<td>(-0.7±0.1)#</td>
<td>4.0±0.3**</td>
<td>(1.5±0.2)</td>
<td>4.3±0.4</td>
<td>(0.2±0.5)</td>
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<tr>
<td>TVRI</td>
<td>31.1±2.1</td>
<td>45.0±3.1**</td>
<td>(13.8±2.8)*</td>
<td>36.0±2.6#</td>
<td>(-8.7±2.8)</td>
<td>26.8±2.2**</td>
<td>(-9.2±2.4)</td>
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<td><strong>Normotensive (n=10)</strong></td>
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<tr>
<td>HR</td>
<td>62.5±2.1</td>
<td>54.5±1.5**</td>
<td>(-8.0±1.5)</td>
<td>103.6±4.5**</td>
<td>(48.1±5.8)</td>
<td>102.9±3.6</td>
<td>(-0.7±1.5)</td>
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<tr>
<td>MAP</td>
<td>88.7±3.5</td>
<td>89.0±3.6**</td>
<td>(0.2±1.3)</td>
<td>113.1±2.8**</td>
<td>(24.1±3.5)</td>
<td>83.1±3.7**</td>
<td>(-30.0±3.2)</td>
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<tr>
<td>CI</td>
<td>2.8±0.2</td>
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<td>(-0.1±0.3)</td>
<td>4.1±0.5**</td>
<td>(1.4±0.4)</td>
<td>4.4±0.4</td>
<td>(0.4±0.3)</td>
</tr>
<tr>
<td>TVRI</td>
<td>34.7±2.6</td>
<td>38.8±3.2</td>
<td>(4.0±4.0)</td>
<td>30.3±2.4**</td>
<td>(-8.5±2.7)</td>
<td>21.1±1.7**</td>
<td>(-9.1±1.3)</td>
</tr>
</tbody>
</table>

HR=heart rate; MAP=mean arterial pressure; CI=cardiac index; TVRI=total vascular resistance index; *=borderline hypertensive vs normotensive (p<0.05); **=borderline hypertensive vs normotensive (p<0.01); # =borderline hypertensive vs normotensive (0.05<p<0.1); **=comparison with values before intervention (p<0.01).
patients with borderline hypertension but this difference was not significant. Propranolol did not alter mean arterial blood pressure in either group (Table I). Cardiac index was reduced by propranolol in patients with borderline hypertension (p<0.01) to the level compatible with those of normotensive subjects similarly treated (Table I and Fig. 1). Total vascular resistance index was increased by propranolol in patients with borderline hypertension (p<0.01). As shown in Fig. 2, total vascular resistance after propranolol tended to be higher in patients with borderline hypertension (0.05<p<0.1).

An administration of atropine after propranolol increased heart rate, mean arterial blood pressure, and cardiac index in both groups (p<0.01). Increases in these measurements produced by atropine were similar between 2 groups. Total vascular resistance index after atropine remained higher in patients with borderline hypertension.

An administration of phentolamine after propranolol and atropine increased heart rate slightly in patients with borderline hypertension but not in control subjects. Although these results suggest that parasympathetic blockade was not complete in patients with borderline hypertension, the increase in heart rate was small, suggesting that blockade was near complete. Cardiac index was unaltered in either group. Reduction of mean arterial blood pressure and total vascular resistance index produced by phentolamine were similar between 2 groups, but mean arterial blood pressure and total vascular resistance index remained higher after phentolamine in patients with borderline hypertension than control subjects (p<0.01).
The role of autonomic nervous system as non-autonomic components in hemodynamic abnormalities of patients with borderline hypertension was examined by comparing the effects of sequential pharmacological autonomic blockade on hemodynamics between patients with borderline hypertension and age-matched normotensive subjects. All subjects were 20 years old or less and many of our patients with borderline hypertension were studied shortly after the first discovery of their borderline hypertension. Although abnormalities in cardiovascular regulation of autonomic nervous system were noted in these patients, the results suggest that non-autonomic component is an important factor for increased peripheral vascular resistance even in the early stage of borderline hypertension.

Pharmacological autonomic blockade by sequential administrations of propranolol, atropine, and phentolamine has been used to evaluate roles of autonomic and non-autonomic components in hemodynamic abnormalities of patients with hypertension.7)-9) The doses of drugs used in this study were similar to those used in previous studies. The doses of propranolol and atropine, 0.2 mg/Kg and 0.04 mg/Kg, respectively, are the standard doses to block adrenergic and parasympathetic effects initially shown by Jose and Taylor.10) To block \(\alpha\)-adrenergic effects, phentolamine, 10 or 15 mg, was given by a bolus intravenous injection. Ten mg of phentolamine was given to 4 patients with borderline hypertension and to 6 normotensive subjects, 15 mg to 4 hypertensive and 4 normotensive subjects. These doses of phentolamine were sufficient to block hypertensive effects of intravenous injection of 100 mcg of phenylephrine.

Using the method of pharmacological autonomic blockade, it has been shown that non-autonomic components play a major role in maintaining increased peripheral vascular resistance in established hypertension8) as well as in a group of borderline hypertension7) whose hemodynamic changes were characterized by normal cardiac output with moderately increased peripheral vascular resistance. However, Esler et al recently demonstrated that autonomic blockade reduced blood pressure to normal level in a subgroup of borderline hypertension who exhibited increased cardiac output, low peripheral vascular resistance and high plasma renin activity.9) Our patients were different from Esler's patients by plasma renin activity being normal except for 1 patient. The different results between these 2 studies may suggest that patients with borderline hypertension showing increased cardiac output and normal or low peripheral vascular resistance at rest are heterogenous and that plasma renin activity may be a clue to know a subgroup of neurogenic
hypertension.

Although the present study suggests that non-autonomic components are important in maintaining increased peripheral vascular resistance, the results of the present study indicate the abnormality of autonomic nervous function. Increased cardiac index and heart rate at rest were normalized by propranolol, suggesting that increased $\beta$-adrenergic activity is responsible for these changes. Julius et al previously reported that increased cardiac output and heart rate in these patients were not only due to increased $\beta$-adrenergic activity but also reduced parasympathetic activity.\footnote{Julius et al previously reported that increased cardiac output and heart rate in these patients were not only due to increased $\beta$-adrenergic activity but also reduced parasympathetic activity.\footnote{11}) In our patients, changes of cardiac index and heart rate in response to atropine were similar between patients with borderline hypertension and normotensive subjects. The reason for failure to demonstrate reduced parasympathetic activity in our patients is not clear, but this may be due to the difference in age of patients. The reduction of blood pressure and peripheral vascular resistance produced by phentolamine was similar between patients with borderline hypertension and normotensive subjects. This may suggest that $\alpha$-adrenergic activity is not different between the 2 groups.

The exact nature of non-autonomic components is not known. This may be structural changes of vascular walls as seen in established hypertension.\footnote{The exact nature of non-autonomic components is not known. This may be structural changes of vascular walls as seen in established hypertension.\footnote{12}) However, we are not aware of any study which has shown the presence of significant structural changes in young patients with borderline hypertension such as those examined in the present study. This question, whether structural changes are present in young patients with borderline hypertension, appears important to be studied since the importance of structural changes in the development of established hypertension has been stressed.\footnote{Other possible mechanisms as non-autonomic components include increased myogenic tone of vascular smooth muscle in response to sustained high cardiac output.\footnote{14}) The recent study by Mark et al may also relevant to the results of the present study. Mark et al demonstrated that high sodium intake increased vascular resistance in patients with borderline hypertension but not in normotensive subjects.\footnote{Since sodium contents in average Japanese diets are high, increased peripheral vascular resistance observed in our patients may be partly due to high sodium intake.}} Other possible mechanisms as non-autonomic components include increased myogenic tone of vascular smooth muscle in response to sustained high cardiac output.\footnote{Mark et al demonstrated that high sodium intake increased vascular resistance in patients with borderline hypertension but not in normotensive subjects.\footnote{15}) Since sodium contents in average Japanese diets are high, increased peripheral vascular resistance observed in our patients may be partly due to high sodium intake.}

### References