Relationship Between Cardiac Output and Peripheral Resistance in Borderline Hypertension

By Stevo Julius, M.D., Sc.D., Arturo V. Pascual, M.D., Rune Sannerstedt, M.D., Ph.D., and Charles Mitchell, B.Sc.

SUMMARY
Eighty-eight observations on 77 patients with borderline hypertension and 82 single observations in healthy control subjects are reported. Hemodynamic effects of assumption of the sitting position, mild exercise, infusion of dextran, blockade with propranolol and with a combination of propranolol and atropine are evaluated. In the recumbent position, patients with borderline hypertension have increased cardiac output and "normal" peripheral resistance. Under all other experimental conditions, the peripheral resistance in patients with borderline hypertension was elevated. Increased resistance was accompanied by a decrease of the cardiac output. After administration of the atropine and propranolol combination, cardiac output in patients with borderline hypertension was significantly below the normal. Nevertheless, whether cardiac output was high or low and resistance normal or elevated, patients with borderline hypertension maintained mild elevations of the blood pressure. Consequently, borderline hypertension is not caused solely by elevations of cardiac output.

Additional Indexing Words: Volume expansion Exercise Dextran Propranolol Atropine

It has frequently been reported that patients with borderline hypertension have an elevated resting cardiac output.1-7 Calculated peripheral resistance in these patients widely overlaps values observed in normal subjects. It was, therefore, suggested that in borderline hypertension, a normal peripheral resistance prevails and the blood pressure is elevated by increases in the cardiac output.6, 8, 9 Such a concept of normalcy is dubious since the usual adjustment to increased output is a lowering of the resistance and maintenance of normal blood pressure.10 particularly if the increase in output is mild. Therefore, to show that the resistance is entirely normal in borderline hypertension, one has to observe the blood pressure of subjects who are normotensive by history but who, during the testing, exhibited higher cardiac outputs. This was done in a previous paper,7 and when compared at similar levels of cardiac output, patients with borderline hypertension always had higher blood pressures and, consequently, a higher peripheral resistance than normal subjects. In this study, we are presenting further experimental evidence of an abnormal relationship between cardiac output and peripheral resistance in a large group of patients with borderline hypertension.

Materials and Methods
Eighty-eight observations on 77 patients with borderline hypertension and 82 observations on 82 healthy paid volunteers are presented. All were males. Sixty-two patients and 71 control

From the Department of Internal Medicine (Hypertension Unit), University of Michigan Medical School, Ann Arbor, Michigan 48104.

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Peripheral resistance and the relationship of the peripheral resistance to cardiac index. Recumbent measurements taken 10 min after the arterial and venous catheters were placed. Triangle indicates a patient with borderline hypertension; circle, a normotensive control subject. The scale for peripheral resistance given to the left of the columns also applies to the plot on the right side of the figure.

$$\text{Resistance index} = \frac{\text{mean blood pressure}}{\text{cardiac index}}$$

Subjects were between the ages of 18 and 34 years; the remainder were between the ages of 35 and 54. The age composition of each experimental group will be presented later in this report. In none of the different experimental procedures was the average age of the control and patient groups statistically different.

If a patient had at least one of three casual diastolic readings above, and one below 90 within the last year, he was said to have borderline hypertension. A thorough physical examination was given and a thorough history was taken, and whenever indicated, a further work-up for secondary causes of hypertension was completed. None of the patients had history or signs of heart failure; all had normal results upon funduscopic examination and urine analysis. In 52 patients intravenous pyelography was performed.

**Table 1**

**Observations in the Resting Recumbent Position**

<table>
<thead>
<tr>
<th></th>
<th>Cardiac index (liters/min/m²)</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Vascular resistance index* (arbitrary units)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>3.31 ± 0.08</td>
<td>83 ± 1.10</td>
<td>26.1 ± 0.7</td>
<td>67 ± 1.10</td>
</tr>
<tr>
<td>Borderline hypertension</td>
<td>3.79 ± 0.10</td>
<td>100 ± 1.50</td>
<td>27.7 ± 0.8</td>
<td>76 ± 0.67</td>
</tr>
<tr>
<td>Significance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$P &lt; 0.001$</td>
<td>$&lt; 0.001$</td>
<td>NS</td>
<td>$&lt; 0.001$</td>
</tr>
</tbody>
</table>

Mean and standard error of hemodynamic measurements at rest, 10 min after all catheters have been placed.

*Resistance index = $\frac{\text{mean blood pressure}}{\text{cardiac index}}$

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formed, and in all cases the results were normal. In 56 patients, blood sugars after fasting were documented as normal.

The cardiac output and arterial pressure were measured under the following conditions:
(a) resting recumbent 10 min after the placement of catheters;
(b) sitting, after 4 min;
(c) during the fourth minute of mild exercise;
(d) after plasma volume expansion with dextran;
(e) ten minutes after intravenous injection of propranolol;
(f) five minutes after injection of atropine, in addition to propranolol.

All measurements of cardiac output were performed by dye dilution with indocyanine green. The blood pressure was measured intraarterially. Details of method and equipment are described elsewhere.\textsuperscript{11}

The significance of differences between group means was determined by Student's t-test.

Results

Observations in the Resting Recumbent Position

Data on 77 patients with borderline hypertension and 82 normotensive subjects are presented. Only one determination per person is considered, and if a patient participated in more than one experiment the result of the first test is taken. Fifteen patients with borderline hypertension and 11 control subjects were between the ages of 35 and 54 years; the remainder were between the ages of 18 and 34.

Results are given in table 1. Cardiac index, heart rate, and mean blood pressure in patients with borderline hypertension were significantly elevated. The peripheral resistance, however, did not differ significantly from that of the control subjects. This is
illustrated in figure 1, where a wide overlap of individual values of peripheral resistance in the two groups is seen on the left side of the figure. On the right side the peripheral resistance is plotted against the cardiac index, and patients with borderline hypertension are shown to have a higher resistance than the control subjects at comparable levels of cardiac index. The relationship of cardiac index and the peripheral resistance index is a log/log function, and if the logarithms of both values are plotted, a straight line results. The equation for this line is:

in patients: \( \log TPR = 4.43 - 0.87 \log Q \)
in controls: \( \log TPR = 4.11 - 0.75 \log Q \)
where TPR is the peripheral resistance index and Q is the cardiac index. Analysis of variance shows that these lines are different \( (P = 0.05) \).

Observations in the Sitting Position

The results for blood pressure, cardiac index, and peripheral resistance during the fourth minute after changing from the recumbent to the sitting position are presented in figure 2 and table 2. In this experiment, 11 patients with borderline hypertension and 15 control subjects were between the ages of 35 and 54 years. Twenty patients and 19 control subjects were from 18 to 34 years of age.

In the initial recumbent position, cardiac index and blood pressure in patients with borderline hypertension were elevated, but the peripheral resistance of both groups was similar. After assuming the sitting position, patients with borderline hypertension developed a higher peripheral resistance than normotensive controls. This larger increase of resistance in borderline hypertensive patients was paralleled by a larger fall of cardiac output, whereas the increase of mean blood pressure was similar for both groups.

Observations with Mild Exercise

The same group of subjects for whom data were collected in the sitting position proceeded, after 4 min of sitting, to exercise on an ergometer bicycle at a load of 300 kg-m/min.

Figure 3

Cardiac index, mean blood pressure, and peripheral resistance at rest, after exercise, and after plasma volume expansion. (Left panel) results during exercise; (right panel) results after plasma volume expansion.

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Table 2

**Stimuli that Increase Peripheral Resistance in Borderline Hypertensive Patients and Control Subjects**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Resting</th>
<th>New levels</th>
<th>Change from resting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>86.8 ± 1.9</td>
<td>108.6 ± 1.8***</td>
<td>95.3 ± 2.2</td>
</tr>
<tr>
<td>Cardiac index (liters/min/m²)</td>
<td>3.4 ± 0.1</td>
<td>4.2 ± 0.1***</td>
<td>3.0 ± 0.1</td>
</tr>
<tr>
<td>Resistance index</td>
<td>25.8 ± 0.8</td>
<td>27.3 ± 1.4</td>
<td>32.7 ± 1.2</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>82.0 ± 1.4</td>
<td>98.6 ± 1.9***</td>
<td>82.7 ± 2.0</td>
</tr>
<tr>
<td>Cardiac index (liters/min/m²)</td>
<td>3.3 ± 0.1</td>
<td>3.8 ± 0.1*</td>
<td>2.6 ± 0.8</td>
</tr>
<tr>
<td>Resistance index</td>
<td>26.2 ± 1.1</td>
<td>27.7 ± 1.1</td>
<td>33.3 ± 1.3</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>79.7 ± 1.4</td>
<td>93.1 ± 1.7***</td>
<td>84.4 ± 2.0</td>
</tr>
<tr>
<td>Cardiac index (liters/min/m²)</td>
<td>3.1 ± 0.1</td>
<td>3.6 ± 0.2</td>
<td>3.4 ± 0.1</td>
</tr>
<tr>
<td>Resistance index</td>
<td>26.1 ± 1.2</td>
<td>27.9 ± 1.8</td>
<td>25.6 ± 1.0</td>
</tr>
</tbody>
</table>

Mean and standard error of hemodynamic measurements. All resting values are in recumbency.

Abbreviations: C = control subjects; B = patients with borderline hypertension; * = significance of difference at 5% level between patients and control subjects; ** = at 1% level; *** = at 0.1% level.

Table 3

**Stimuli to Reduce Peripheral Resistance in Borderline Hypertensive Patients and Control Subjects**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Resting</th>
<th>New levels</th>
<th>Change from resting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>95.3 ± 2.2</td>
<td>114.0 ± 1.7***</td>
<td>106.5 ± 2.1</td>
</tr>
<tr>
<td>Cardiac index (liters/min/m²)</td>
<td>3.0 ± 0.1</td>
<td>3.3 ± 0.2</td>
<td>5.6 ± 0.2</td>
</tr>
<tr>
<td>Resistance index</td>
<td>32.7 ± 1.2</td>
<td>38.1 ± 2.1*</td>
<td>19.8 ± 0.7</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>72.9 ± 1.8</td>
<td>92.5 ± 2.8***</td>
<td>81.7 ± 1.2</td>
</tr>
<tr>
<td>Cardiac index (liters/min/m²)</td>
<td>2.8 ± 0.1</td>
<td>3.5 ± 0.2***</td>
<td>3.8 ± 0.2</td>
</tr>
<tr>
<td>Resistance index</td>
<td>26.6 ± 1.0</td>
<td>27.0 ± 1.2</td>
<td>22.4 ± 1.5</td>
</tr>
</tbody>
</table>

Mean and standard error of hemodynamic measurements. Note that resting values for exercise are in sitting position and for plasma volume expansion, in recumbent position.

Abbreviations: See table 2.
During the fourth minute of such exercise, measurements of cardiac output were performed. The results are given in figure 3 and table 3. As mentioned earlier, the peripheral resistance in the sitting position was higher in patients with borderline hypertension than in normal subjects. This difference became even greater during the mild exercise. Patients with borderline hypertension failed to increase the cardiac output to the same level as normotensive controls. Again, the increment of blood pressure was similar in both groups.

Expansion of the Plasma Volume with Dextran

After hemodynamic measurement in the resting recumbent position, 13 ml/kg of 5% dextran in saline (average molecular weight 70,000) was infused in 45 min. Immediately after the infusion, a measurement of cardiac output was taken. There were 18 patients and 11 control subjects; two of the 18 patients had participated earlier in the exercise testing. All subjects were from 18 to 34 years of age. The results are given in figure 3 and table 3. In recumbency, patients with borderline hypertension had significant elevation of cardiac index and blood pressure, but the peripheral resistance of both groups was practically identical. After the infusion, patients with borderline hypertension had higher levels of peripheral resistance than the control subjects, but the difference was not statistically significant. However, if changes are considered, the decrease of the peripheral resistance was significantly less in patients with borderline hypertension. Again, as in exercise, failure to decrease the resistance was accompanied by smaller increases in cardiac output, whereas blood pressure changes in both groups were comparable.

Blockade with Propranolol

In this experiment subjects were recumbent, and 0.2 mg/kg of propranolol was injected intravenously. Measurements of cardiac output were taken at rest and 10 min after the injection. Results are presented in figure 2 and table 2. There were 39 patients and 34 control subjects, all between the ages of 18 and 34 years. Nine patients had participated in earlier tests.

Before administration of propranolol, patients with borderline hypertension had elevated cardiac index and blood pressure, whereas the peripheral resistance was similar to values in normotensive controls. After propranolol was given, the peripheral resistance had increased to a value which was now significantly higher than that in normotensive controls. There was practically no change in the blood pressure in both groups, and the new levels of peripheral resistance were accompanied by a slightly larger decrease of cardiac index in patients with borderline hypertension.

“Intrinsic” Cardiac Output

These experimental subjects are a subgroup of those who had received propranolol.

Cardiac index, mean blood pressure, and peripheral resistance before and after the injection of 0.2 mg propranolol and 0.04 mg atropine/kg of body weight. The resting value is measured in recumbency 10 min after the catheters were inserted. Symbols as in figure 2.
Seventeen control subjects and 18 patients were given 0.04 mg/kg of atropine i.v. after the previous injection of propranolol. Measurements were performed 5 min after the injections of atropine. Results are presented in figure 4 and table 2.

As in the preceding studies reported here, the resting cardiac index in the patients was elevated (although, in this instance, the difference from that of normal controls did not achieve statistical significance). In spite of the higher mean blood pressure, the resting peripheral resistance in patients with borderline hypertension was not elevated.

After the “chemical denervation” of the heart by atropine and propranolol, a highly significant elevation of the peripheral resistance occurred in patients with borderline hypertension. The peripheral resistance of normotensive controls remained practically unchanged. Again, the blood pressure changes in both groups were similar. The behavior of the cardiac output, however, was quite different. In the healthy volunteers, the cardiac output rose slightly, whereas in the patients with borderline hypertension, there was a substantial decrease of the cardiac output.

**Discussion**

A series of experiments is presented to illustrate the unusual relationship between systemic flow and resistance in borderline hypertension. Resting in recumbency, a high cardiac output prevails, and the peripheral resistance overlaps that of the control group. However, the resistance is not decreased below the normal level, as would be expected with an elevated output, and, consequently, the blood pressure is increased. In these borderline hypertensive patients, whenever the unusual balance between peripheral resistance and the increased cardiac output at rest is disturbed, an almost stereotyped response occurs. If the stimulus is such as to require a decrease of peripheral resistance (exercise, plasma volume expansion), patients with borderline hypertension fail to show a decrease in their peripheral resistance to the same degree as normotensive controls, and a higher resistance results. Conversely, if the stimulus is such as to call for an increase in the resistance (sitting, injection of propranolol), there occurs a larger rise, again resulting in significantly higher peripheral resistance among patients with borderline hypertension.

Finally, after administration of propranolol and atropine, no change in peripheral resistance occurs among normotensive controls, whereas the patients with borderline hypertension responded with a precipitate rise in peripheral resistance. The described abnormal changes of peripheral resistance in borderline hypertension are not reflected by an excessive rise of the blood pressure. On the contrary, these changes are consistently paralleled by an inadequate adjustment of the cardiac output to the new physiologic state.

Our results contradict the widely held notion that patients with borderline hypertension are a clinical example of a “high output normal resistance” hypertension, a condition which was theoretically described by Wezler and Böger. Under resting conditions, the cardiac output in patients with borderline hypertension is elevated. However, after “chemical denervation of the heart,” our patients experienced a reduction in cardiac output but, nevertheless, maintained elevated blood pressure. In the latter condition, the average cardiac output in patients with borderline hypertension was significantly below the control group’s values and, therefore, “high output” could not be responsible for the maintenance of higher blood pressure.

In view of our data, borderline hypertension appears to be a condition of an abnormal relationship between cardiac output and peripheral resistance, resulting in elevation of the blood pressure. Cardiac output may vary from elevated to decreased, and the peripheral resistance from normal to grossly increased, but the blood pressure remains consistently elevated. It appears as if the hemodynamic homeostasis is so regulated as to maintain a mild increase of the blood pressure, regardless of which component prevails.

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In addition to not confirming the prime importance of elevated cardiac output in borderline hypertension, our data also contradict the view accepted by many workers\textsuperscript{14, 15} that patients with borderline hypertension are vascular hyperreactors. If vascular hyperreactivity is defined as increased rise in blood pressure to certain stimuli, the figures shown here indicate that changes of the blood pressure in these borderline hypertensive patients, under all experimental conditions studied here, are practically identical in direction and magnitude to the changes in normotensive controls. It, therefore, appears that in borderline hypertension the blood pressure is maintained on a higher level, but the regulation of pressure response to acute hemodynamic changes is normal.

Finally it is important to stress that a group of subjects selected for a casual elevation of the diastolic blood pressure, which was later followed by normal readings, already exhibited profound hemodynamic changes. We can not find support for the idea that this is a "benign" and "only nervous" blood pressure elevation. These subjects were evaluated in our laboratory weeks and months after the original diagnosis of "labile" hypertension was established. In the laboratory, the average blood pressure of the group with borderline hypertension was $136/81 \pm 10/7$, which falls into the normotensive range. Nevertheless, as a group, borderline hypertensive patients maintained clearly and statistically significantly higher readings than normotensive controls. The consistency of this elevation under different experimental procedures is impressive. The so-called normalization of the blood pressure after the rest is misleading. Merely because the blood pressure declined below the arbitrary limit of 140/90, subjects with borderline hypertension did not revert to a normal hemodynamic pattern; they maintained elevated pressure readings and exhibited abnormalities of vascular peripheral resistance.

Conclusions

1. Elevated cardiac output is not essential for the maintenance of increased blood pressure in borderline hypertension.

2. Under various experimental conditions, significant elevation of the peripheral resistance in borderline hypertension can also be demonstrated.

3. Regardless of which component prevails, cardiac output or peripheral resistance, patients with borderline hypertension maintain a greater blood pressure level under the various experimental conditions than control subjects.

4. Among patients with borderline hypertension, there is no evidence of a hyperreactive pressure response to different stimuli. The blood pressure is maintained on a higher level, but acute pressure changes are regulated in a fashion closely resembling that in normotensive subjects.

References


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