Hemodynamic Responses to Tilt and Beta-Adrenergic Blockade in Young Patients with Borderline Hypertension

By Rune Sannerstedt, M.D., Ph.D., Stevo Julius, M.D., Sc.D., and James Conway, M.D., Ph.D.

SUMMARY

Seventeen young patients with borderline hypertension (one female) and 18 normotensive paid volunteers (two females) were studied at rest and in the tilted position after 10 min of 45° head-up tilt. Cardiac output, heart rate, and intra-arterial pressure were recorded. The measurements at rest and during the tilt were repeated after beta-adrenergic blockade with propranolol.

By comparison with the normotensives, cardiac output and heart rate in those with borderline hypertension were elevated initially, after 50 min of rest, and during tilt. The change of the cardiac output and heart rate to tilt was of the same magnitude in patients and control subjects. Consequently, regulation of the rate and flow in borderline hypertensives appears to be normal but starts from a higher base line level.

After blockade with propranolol, cardiac output in patients with borderline hypertension was still slightly elevated, but the difference from controls was not significant. The heart rate, however, remained significantly elevated at rest and during tilt. Elevation of the heart rate in borderline hypertensives is not mediated through the beta-adrenergic system and may result from decreased parasympathetic inhibition or from different intrinsic myocardial pacing.

Additional Indexing Words:
Cardiac output  Intra-arterial pressure  Tilt  Propranolol

The evidence in the medical literature strongly indicates that a certain percentage of patients with mild early arterial hypertension of the labile borderline type (borderline hypertension) have hyperkinetic circulation at rest with increased cardiac output and systemic vascular resistance apparently within the normal range.\textsuperscript{1,8} Increased myocardial contractility,\textsuperscript{4} hyperactivity of the beta-adrenergic system,\textsuperscript{8,9} enhanced alpha-adrenergic receptor activity,\textsuperscript{10} increased venous tone,\textsuperscript{4} emotional hyperactivity,\textsuperscript{11} and increased adrenomedullary secretion\textsuperscript{12} have been discussed as possible underlying mechanisms for this hemodynamic pattern. So far, however, none of these theories can be applied to the majority of cases of borderline hypertension.

It has been shown that the hyperkinetic circulation in cases of borderline hypertension may later lead to development of the hemodynamic pattern of established hypertension with normal cardiac output and increased systemic vascular resistance.\textsuperscript{9,11} A better knowledge of the pathophysiologic mechanisms responsible for the hemodynamic alterations in arterial hypertension should provide
the rationale for a more specific preventive treatment.

The present investigation aims at further exploration of some of these pathophysiological factors. The first aim was to confirm the presence of a hyperkinetic circulation at rest in young patients with borderline hypertension, and then to study whether the circulatory responses to a nonemotional stimulus such as tilt are abnormal. Finally, this study was designed to investigate whether the increase of the cardiac output is mediated by the beta-adrenergic system, using propranolol to abolish sympathetic activity in the heart.

Methods

A total of 35 subjects were studied at rest in recumbency (table 1). Seventeen (16 males and one female) were patients aged 19 to 35 years (mean age, 23.7 ± 1.2 years) with borderline hypertension. The 18 controls (16 males and two females) between the ages of 16 and 35 (mean age, 25.3 ± 1.3 years) were healthy paid volunteers without any clinical evidence of cardiovascular disease. All patients completed the whole procedure including administration of propranolol. Among the 18 controls, 15 completed the whole procedure, one subject was not given propranolol, and two others did not have the tilt after administration of propranolol. All experimental subjects read a statement explaining the experiment and indicated their consent to participate.

Patients with borderline hypertension were defined as having, out of five auscultatory blood pressure readings within the last year, at least one with a diastolic value of 90 mm Hg or more, and at least one below 90 mm Hg.

Every patient underwent a thorough clinical examination, and only those without signs indicating secondary hypertension were accepted for the study. All of them had normal urinary analysis, plasma creatinine, and intravenous pyelogram. None presented signs of overt cardiac disease or dysfunction besides palpitations in a couple of cases, and there were no electrocardiographic changes consistent with left ventricular hypertrophy in any case. Vascular retinopathy or cerebral symptoms were not observed in any of the patients.

The hemodynamic functions analyzed were: intra-arterial blood pressure, cardiac output, and heart rate, measured by methods described in detail elsewhere.13 A short Teflon tube was percutaneously inserted in the brachial artery, and from an antecubital vein a polyethylene catheter was advanced up to the level of subclavian vein. The arterial catheter was connected to a Statham strain gauge and a Gilson polygraph. Special care was paid in keeping the strain gauge in relatively the same position both in recumbency and during tilt, the zero reference level being at the sternal angle. The cardiac output was measured by dye dilution with indocyanine green and inscription of the curve in the Gilson recorder after being read in a Gilford densitometer. The heart rate was calculated from the arterial curves immediately preceding administration of the dye. The stroke volume index has been expressed in ml per m² of body surface area, and the systemic vascular resistance in arbitrary units calculated by dividing the cardiac output into the mean blood pressure.

The subjects rested comfortably on a tilt table placed in a horizontal position. An average of 6 min after the arterial catheter was introduced, the first measurement of cardiac output was performed. This was followed by a subsequent determination 10 min after the insertion of the catheters. The subjects were then tilted to 45° head-up position and cardiac output was determined after 10 min in this position. In the majority of cases this was also preceded by one determination after 8 min of tilt. Twenty-five minutes after the return to horizontal position another resting determination of the cardiac output was made.

Table 1

<table>
<thead>
<tr>
<th>Age and Body Characteristics: Mean Values, Standard Errors, and Probability (P) of Differences between Patients and Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>No. of subjects</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>BSA (m²)</td>
</tr>
</tbody>
</table>

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Propranolol* 0.12 mg/kg of body weight was then injected slowly intravenously. New sets of recumbent determinations were obtained 15 min after the injection. Finally, the subjects were again tilted and measurements taken after 8 and 10 min. For the tilt test, the average of the two determinations, when available, has always been used for calculations.

Student's t-test was used to analyze the significance of difference under various circumstances and between the two groups.

*Propranolol (Inderal) was kindly provided by the Ayerst Company.

Results

Before Propranolol
At Rest Recumbent

The averages of the two determinations after 6 and 10 min are given in table 2. Patients with borderline hypertension had significantly higher cardiac index, higher mean brachial artery pressure, and higher heart rate. The figures for the stroke index and systemic vascular resistance were, on the other hand, not different for the two groups.

The repeated determinations at rest in recumbency before and after the tilt (fig. 1, I

Figure 1

Presentation of cardiac index and heart rate during different stages of the experiment. Vertical lines with bars indicate standard error. Probability values are those between patients and controls.
and II) allowed an analysis of the variability of the systemic hemodynamics immediately after introduction of the catheters compared to a later period of reasonable comfort and apparent relaxation. In both groups of subjects there were no significant changes in heart rate and cardiac index, and the initial differences were on the whole maintained throughout the procedure. This was true also for the blood pressure.

**During Tilt**

Results are given in table 3. All subjects completed the 10-min tilt period without difficulties. Both patients and controls showed significant reductions in cardiac index and in stroke volume index, while a significant drop in mean brachial artery pressure was seen only in the control group. At the same time, the heart rate rose significantly in both groups. A significant increase in the systemic vascular resistance was observed only in patients with borderline hypertension.

With the exception of blood pressure, the magnitude of the changes induced by the tilt was of the same order in both categories of subjects, and the initial differences were kept. Thus, the cardiac index and heart rate during the tilt were still significantly higher among the patients with borderline hypertension (fig. 1, I), while the levels of stroke volume index and systemic vascular resistance remained not significantly different.

**After Propranolol**

**At Rest Recumbent**

Results are given in table 4. Propranolol induced a significant drop in cardiac index in patients and control subjects (fig. 1, III). The decrease was somewhat larger in patients than

| Table 2 |

**Hemodynamic Data at Rest in Recumbency: Averages of Two Measurements 6 and 10 Minutes after Insertion of Catheters**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 18)</th>
<th>Borderline hypertensives (n = 17)</th>
<th>Borderline hypertensives vs. controls (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \bar{x} \pm s )</td>
<td>( \bar{x} \pm s )</td>
<td></td>
</tr>
<tr>
<td>( P_{BA} ) (mm Hg)</td>
<td>83.8 ± 2.2</td>
<td>100.6 ± 3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>3.18 ± 0.15</td>
<td>3.72 ± 0.16</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>64.7 ± 1.9</td>
<td>76.9 ± 2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVR (units)</td>
<td>14.17 ± 0.78</td>
<td>14.22 ± 0.72</td>
<td></td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>50.3 ± 1.9</td>
<td>48.8 ± 2.5</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: \( P_{BA} \) = mean brachial artery pressure; CI = cardiac index; HR = heart rate; SVR = systemic vascular resistance; SI = stroke index; \( n \) = number of subjects; \( \bar{x} \) = mean value; \( s \) = standard error; \( P \) = probability of difference.

| Table 3 |

**Hemodynamic Data during Tilt: Averages of Two Measurements after 8 and 10 Minutes of Tilt Together with Mean Changes from Values in Recumbency; Probability of Differences between Tilt Values for Patients and Controls**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 18)</th>
<th>Borderline hypertensives (n = 17)</th>
<th>Borderline hypertensives vs. controls (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \bar{x} \pm s )</td>
<td>( \Delta )</td>
<td></td>
</tr>
<tr>
<td>( P_{BA} ) (mm Hg)</td>
<td>73.6 ± 2.4</td>
<td>-10.2***</td>
<td></td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.47 ± 0.14</td>
<td>-0.71***</td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>77.2 ± 2.9</td>
<td>+12.5***</td>
<td></td>
</tr>
<tr>
<td>SVR (units)</td>
<td>16.09 ± 0.89</td>
<td>+1.92</td>
<td></td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>32.7 ± 1.9</td>
<td>-17.6***</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: \( \Delta \) = mean changes from recumbency to tilt position; *, **, and *** denote significant changes from values in recumbency, \( P \) being <0.05, <0.01, and <0.001 respectively. For other symbols see table 2.
Table 4

Hemodynamic Data after Beta-Adrenergic Blockade with Propranolol, Together with Mean Changes from Basal State; Probability of Differences between Propranolol Values for Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 17)</th>
<th>Borderline hypertensives (n = 17)</th>
<th>Borderline hypertensives vs. controls (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>±± sE</td>
<td>±± sE</td>
<td>±± sE</td>
</tr>
<tr>
<td><strong>P</strong>&lt;sub&gt;BA&lt;/sub&gt; (mm Hg)</td>
<td>83.4 ± 2.2</td>
<td>+1.2</td>
<td>102.9 ± 3.2</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.55 ± 0.14</td>
<td>-0.43*</td>
<td>2.82 ± 0.13</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>56.0 ± 1.7</td>
<td>-8.0*</td>
<td>66.2 ± 2.1</td>
</tr>
<tr>
<td>SVR (units)</td>
<td>18.08 ± 1.18</td>
<td>+3.20*</td>
<td>19.22 ± 1.18</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>46.1 ± 2.7</td>
<td>-1.1</td>
<td>42.9 ± 2.0</td>
</tr>
</tbody>
</table>

For abbreviations see tables 2 and 3.

in controls. Consequently, the initial significant difference in cardiac index between the two groups was lost and the cardiac index in borderline hypertensives remained only slightly elevated. The heart rate, too, dropped significantly in both groups of subjects. At the new level the heart rate remained significantly higher among patients with borderline hypertension than in the controls.

The responses of the stroke indices to propranolol were variable in both groups of subjects, the mean changes being insignificant reductions. The mean brachial arterial pressure did not change after propranolol, so that the initial significant difference between the groups was maintained.

The combination of a marked reduction in the cardiac output with unchanged blood pressure resulted in significantly increased systemic vascular resistances in both groups of subjects. The new levels of the systemic vascular resistance of patients and controls remained statistically not different.

**During Tilt**

The responses to tilt after propranolol were qualitatively and quantitatively not different from those during the control period (table 5). The fall in cardiac index on tilt after propranolol was thus on an average not significantly greater than during the control tilt period for either patients or controls (fig. 1, IV). The new levels of cardiac index did not significantly differ in either group. Dizziness was, however, noted in five subjects (two patients and three controls) who also presented more marked reductions in cardiac output and blood pressure than the average changes for the groups.

The heart rate rose significantly in both groups of subjects and to about the same degree as during the control tilt. Thus, the

Table 5

Hemodynamic Data During Tilt after Beta-Adrenergic Blockade with Propranolol: Averages of Two Measurements after 8 and 10 Minutes of Tilt, Together with Mean Changes from Values in Recumbency Immediately before the Tilt; Probability of Differences between Tilt Values for Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 15)</th>
<th>Borderline hypertensives (n = 17)</th>
<th>Borderline hypertensives vs. controls (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>±± sE</td>
<td>±± sE</td>
<td>±± sE</td>
</tr>
<tr>
<td><strong>P</strong>&lt;sub&gt;BA&lt;/sub&gt; (mm Hg)</td>
<td>72.4 ± 2.7</td>
<td>-11.0**</td>
<td>94.5 ± 4.0</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.12 ± 0.10</td>
<td>-0.43*</td>
<td>2.26 ± 0.14</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>66.5 ± 2.3</td>
<td>+10.5**</td>
<td>75.7 ± 2.4</td>
</tr>
<tr>
<td>SVR (units)</td>
<td>18.93 ± 1.23</td>
<td>+0.85</td>
<td>22.04 ± 1.73</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>32.1 ± 1.5</td>
<td>-14.0***</td>
<td>30.7 ± 2.2</td>
</tr>
</tbody>
</table>

For abbreviations see tables 2 and 3.
patients with borderline hypertension were still characterized by having a significantly higher heart rate. The stroke indices decreased significantly to the same extent as during the control tilt. As before, there was no difference in the stroke indices between the two groups after the tilt.

The mean brachial artery pressure on tilt after propranolol did not on an average decrease more in either group than on tilt without the drug. As on the control tilt, the blood pressure decreased significantly in the controls but not among the patients. The difference in blood pressure between the two groups was maintained and remained significant. As during the control tilt, the systemic vascular resistance increased, but not significantly more so after the administration of propranolol. The average resistance in patients remained not different from that for the controls.

Discussion

With the exception of one paper,14 many reports indicate that the salient hemodynamic feature in borderline hypertension is the elevation of the cardiac output.1–8,12 Our study again confirms previous reports. Some controversy has developed as to the mechanism by which the cardiac output is elevated. In our material, the increase was mainly caused by higher heart rates so that the stroke volume remained within normal limits. This is in agreement with several studies,6,7,12 but not with others.1–4 Two of the studies finding increased stroke volume,3,4 however, include older subjects, and this may in part be responsible for the divergence in findings.

Whereas it is reasonably simple to evaluate the respective roles of the heart rate and stroke volume, little has been previously done to elucidate the physiologic mechanism by which the cardiac output is elevated. Such mechanisms alone or in various combinations, as expanded intravascular volume, increased venous tone, increased myocardial contractility, and increased adrenergic activity, are all theoretically possible. Our data are relevant for the evaluation of the role of the sympathetic nervous system in borderline hypertension.

Excess sympathetic stimulation appeared to be a highly likely mechanism for the elevation of the cardiac output since this elevation is maintained by an increased heart rate and normal stroke volume. This theory was further strengthened by the apparent similarity between borderline hypertension and the hyperdynamic beta-adrenergic syndrome described by Frohlich and co-workers.15 Moreover, it has been reported that, among the 20% of hypertensive patients who occasionally excreted raised amounts of catecholamines, many had the labile form of the disease,16 and such patients have also been reported to respond to mental stress with an exaggerated catecholamine excretion.17

Our data, however, do not indicate an excessive beta-adrenergic drive at rest if the heart rate is considered, since after propranolol, patients with borderline hypertension maintained significant elevations of the heart rate at rest and during the tilt. This is contingent on acceptance that intravenous administration of 0.12 mg/kg of body weight of propranolol indeed produces a substantial beta-adrenergic blockade. Jose and Taylor18 provided extensive data on animal response to propranolol. Stimulation of the stellate ganglion in dogs 20 min after injection of 0.2 mg/kg of propranolol increased the heart rate for only 2% of the response before beta blockade. Similarly, the elevation of the heart rate after 0.4 µg/kg of isoproterenol amounted to only 5% of the base-line response. In humans, Jose and Taylor asserted the need for the dose by measurement of the resting heart rate after increasing doses of propranolol in 36 subjects. Whereas there were still some additional decreases of the rate when the dose was increased from 0.1 mg/kg to 0.15 mg/kg, no further decrease was observed with 0.2 mg/kg. Human data from other studies indicate that lower doses of propranolol than the one applied by us are capable of abolishing very potent beta stimulation. Bender's group19 gave a continuous infusion of isoproterenol sufficient to increase the heart.
rate to 120/min (average 0.07 µg/min). Additive doses of 0.1 mg of propranolol produced a continuous decrease of the heart rate until finally 1.1 mg totally abolished the effect of the continuous infusion of isoproterenol. Forsberg and Johnsson\textsuperscript{20} gave 10 mg of propranolol to their subjects and even 45 min after the injection of propranolol observed an increase of only 13 beats/min to 0.09 µg/kg/min. Before the beta blockade, the heart rate increased for 36 beats though only 0.03 µg/kg of isoproterenol was infused.

All evidence from the literature indicates that 0.12 mg/kg of body weight of propranolol induces substantial inhibition of the beta receptor's responsiveness. This dose should certainly be sufficient to abolish physiologic variations of sympathetic tone in the resting state. One could postulate that patients with borderline hypertension are tolerant to propranolol, but this is hardly likely since patients indeed responded with a decrease of heart rate in much the same fashion as normotensive controls (fig. 1). It must, therefore, be accepted that the elevation of the heart rate in borderline hypertension is maintained by a mechanism relatively independent from the beta-adrenergic system. This could be explained either by a difference in the intrinsic pacemaker\textsuperscript{18} or by a lesser level of parasympathetic inhibition in patients with borderline hypertension. Further research for the differentiation among these is necessary.

The different response of cardiac output and heart rate to propranolol poses some additional questions. Whereas the heart rate remained elevated, the cardiac output after blockade with propranolol decreased more in borderline hypertension and the mean was no longer significantly higher than in control subjects. This could be explained as a differentiated sensitivity to the chronotropic and inotropic effects of propranolol. It is hard to accept such an explanation involving only patients with borderline hypertension, particularly since the responses of the heart rate and the stroke index to propranolol were qualitatively and quantitatively similar in patients and controls. The other possibility is that propranolol possesses some nonspecific myocardial depressing properties and that this minimizes the group difference in cardiac output.\textsuperscript{21}

The qualitative and directional responses of the cardiac output and heart rate to tilt before the application of propranolol were the same in patients with borderline hypertension and normotensive controls. This indicates that the central regulation of the heart rate and systemic flow in borderline hypertension, while starting from a higher base-line level, is not abnormal. However, when the blood pressure response is considered the picture changes, since patients with borderline hypertension failed to reduce the blood pressure to the same degree as controls. They responded with a significant increase of the systemic vascular resistance not observed in the control group. The same tendencies were detectable after beta-adrenergic blockade with propranolol. The head-up tilt is considered a potent stimulus for increased sympathetic activity. Nicotero and co-workers\textsuperscript{10} have shown that peripheral vasoconstrictive mechanisms are intact and capable of greater responsiveness after beta-adrenergic blockade with propranolol. Frohlich and co-workers,\textsuperscript{22} describing increased pressor response to tilt among some patients with mild hypertension, believed this to be a sign of neurogenic hyperreactivity. In the light of such findings, the failure of our patients with borderline hypertension to decrease the blood pressure on tilt could be taken as evidence of increased peripheral alpha-sympathetic stimulation or increased alpha-sympathetic responsiveness. However, this has not been experimentally tested in our study and an alternative explanation could justifiably be forwarded. Lack of decrease of blood pressure to tilt could be related to structural changes in blood vessels, or to unusually finely tuned baroreceptor reflex in borderline hypertension.

Conclusions

1. Recumbent cardiac index and heart rate are significantly elevated in young patients with borderline hypertension.
2. The elevated heart rate and cardiac index are still present after prolonged rest and after 10 min of 45° head-up tilt.

3. The changes of the heart rate and cardiac output to the stimulus of tilt are of the same magnitude in patients with borderline hypertension as in normal subjects. It is, therefore, concluded that the regulation of the heart rate and cardiac output in borderline hypertension appears normal, but starts from a higher level of base-line values.

4. The systemic vascular resistance, on the other hand, reacts to tilt with a significant increase in the patients, but not among the controls.

5. After large doses of propranolol the difference of cardiac output between patients with borderline hypertension and normotensive controls decreases. However, the increased heart rate in borderline hypertension is still maintained.

References


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