Sympathetic Nervous System Response to Graded Exercise: Effect of Beta-Blockade

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SUMMARY This study compares the sympathetic nervous system response to graded exercise in normotensive and essential hypertensive subjects with and without beta-adrenergic blockade. Blood pressure (BP), heart rate, and plasma norepinephrine (NE), epinephrine (E), and dopamine (DA) were measured just before starting the exercise (Pre-Ex), in the submaximal exercise (Sub-max), and after 8 minutes rest (Post-Ex). On placebo, Sub-max induced in both normotensives and hypertensives a similar increase in NE and E plasma levels. Plasma DA remained unchanged. Propranolol in controls and propranolol or mepindolol in hypertensives didn't modify significantly: 1) Pre-Ex plasma levels of E, NE, and DA; 2) response at Sub-max in controls; 3) plasma E and DA in hypertensive patients. In hypertensives on beta-blockade, submaximal exercise elicited a greater increase in plasma NE. Values for plasma NE in patients on propranolol were 1135 ± 229 pg/ml higher than those obtained in the same patients on placebo (p < 0.001). On mepindolol, the plasma NE increment was higher than that on placebo (p < 0.05), but lower than that on propranolol (p < 0.01). In controls, propranolol did not significantly modify BP at Pre-Ex or its response to exercise, whereas systolic and diastolic BP were significantly lower at Pre-Ex, Sub-max, and Post-Ex in hypertensives. On beta-blockade, heart rate decrease in Pre-Ex, Sub-max, and Post-Ex were not different in controls and hypertensives. The differences found on beta blockade would indicate that the effects of beta blockers are not identical in normotensive and hypertensive subjects. (Hypertension 3 (suppl II): 11-155—11-159, 1981)

KEY WORDS • plasma catecholamines • essential hypertension • beta-blockade • sympathetic nervous system • exercise

It has been supposed that blockers of beta-adrenoreceptors affect either directly or indirectly the production of sympathetic amines. In fact, it has been reported that acute infusion of propranolol to hypertensive patients induces a rise in circulating plasma NE and E. Demonstration that beta-adrenergic receptor blockade alters the extent of the sympathetic response in a stress situation would be of considerable importance.

The present study is concerned with the sympathetic response to graded physical exercise in normotensive and hypertensive subjects both with and without prolonged beta-blockade.

Material and Methods

Subjects

Thirteen normal subjects (6 men and 7 women; mean age 37 ± 4 years SEM) with basal BP below 140/90 mm Hg on three occasions and 36 patients
with essential hypertension of World Health Organization (WHO) stages I and II (24 men and 12 women; mean age 49 ± 2 years SEM) were studied after at least 2 weeks without any medication. Secondary forms of hypertension were ruled out by appropriate methods in all cases. All patients were free from associated diseases, such as heart failure, valvular or myocardial lesions, coronary disease, renal disease, or diabetes. The diastolic pressure of the patients was ≥ 100 mm Hg. Normal, and hypertensive subjects were on a constant sodium intake (8 g salt/day) for 1 week prior to the study. Placebos were administered for 2 weeks. After placebos, hypertensive patients were selected at random for propranolol or mepindolol administration. Nine normal subjects received propranolol. The beta-blockers were administered by mouth at increasing doses reaching a maximum mean dose of propranolol of 140 ± 18 SEM mg/day to the normotensives and 190 ± 32 SEM mg/day to the hypertensives. Mepindolol mean dose was 20 ± 2 SEM mg/day. These doses resulted in a satisfactory reduction of the heart rate in all subjects at rest, and this condition remained unchanged after a brisk 50-meter walk. No significant differences were found between the doses of propranolol administered to each group.

Methods

Subjects on placebo and beta-blockers were studied under identical conditions and techniques. Subjects had a light breakfast without coffee at 8:00 a.m. and were told not to smoke for 2 hours before the test. They exercised between 9:00 and 12:00 a.m. The exercise was performed in a sitting position on a bicycle ergometer according to the graded multistage procedure. The cycling rate was 20 km/hour. After sitting for 30 minutes, subjects performed the exercise on the bicycle starting at 25 W (150 kg/min) with a 25 W increment every 3 minutes until submaximal heart rate (85% of Robinson's13 maximal target heart rate) was attained. The workload attained did not differ between normal and hypertensive subjects; normotensives 96 W (588 ± 12.8 kg/min); hypertensives 92 W (562 ± 10.0 kg/min). On beta-blockers the exercise was performed at identical work load levels as in the placebo test. Exercise was followed by an 8 minute rest period in sitting position. Blood pressure and heart rate were recorded: 1) just before starting exercise (Pre-Ex); 2) when reaching the submaximal heart rate (Sub-max); and 3) at the end of the rest period (Post-Ex). Blood was drawn through an indwelling cannula previously inserted in an antecubital vein for catecholamine determination. Plasma catecholamines were determined in 13 normotensives and 32 hypertensives on placebo, 8 normotensives and 6 hypertensives on propranolol, and 10 hypertensives on mepindolol.

A radioenzymatic method14 modification of the one described by Da Prada and Zürcher15 was used for the determination of plasma catecholamines (CA): E, NE, and DA. Sensitivity was 3.2 pg for E, 3.8 pg for NE, and 11.3 pg for DA. The assay was found to be linear up to 1 ng per tube of each of the three amines. The interassay variation coefficients were 15%, 16%, and 12% for E, NE, and DA respectively.

Data in the text are expressed as mean ± standard error (SEM). Statistical significance was assessed with Student's t test for paired and nonpaired data.

Results

Plasma Catecholamines: Studies on Placebo

Table 1 shows the Pre-Ex plasma levels of E, NE, and DA in normotensives, and in hypertensives. No significant differences were found between the groups in any of the three amines. In normal subjects, Sub-max exercise produced a marked increase in plasma concentrations of E and NE, but there was no change in plasma DA. Plasma NE showed an increment of 320 ± 91 pg/ml (p < 0.005) over Pre-Ex levels. In Post-Ex, values decreased again, but still remained 88 ± 37 pg/ml above the Pre-Ex levels (p < 0.05). Plasma E also showed an increase at Sub-max: 67 ± 24 pg/ml over Pre-Ex (p < 0.01) while Post-Ex levels did not differ from the initial values. A similar pattern of response was found in hypertensive patients: the Sub-max increment in plasma NE was 380 ± 59 pg/ml while in Post-Ex it was 59 ± 20 pg/ml. Plasma E increased 53 ± 10 pg/ml in Sub-max and in Post-Ex reverted to the Pre-Ex levels. All of these values are not statistically different from those observed in controls.

Plasma Catecholamines: Studies on Beta-Adrenoreceptor Blockade

Beta-adrenergic blockade with propranolol in controls and with propranolol or mepindolol in hypertensive patients did not cause significant changes in the Pre-Ex plasma levels of E, NE, and DA (table 1). In controls on propranolol the plasma CA response to graded exercise was similar to that observed on placebo (fig. 1). In hypertensive patients (fig. 1) on

<table>
<thead>
<tr>
<th>Conditions of subjects</th>
<th>Plasma levels</th>
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<tbody>
<tr>
<td></td>
<td>E (pg/ml)</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>placebo (n = 13)</td>
<td>84 ± 13</td>
</tr>
<tr>
<td>propranolol (n = 8)</td>
<td>76 ± 12</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td></td>
</tr>
<tr>
<td>placebo (n = 32)</td>
<td>75 ± 5</td>
</tr>
<tr>
<td>propranolol (n = 6)</td>
<td>56 ± 9</td>
</tr>
<tr>
<td>mepindolol (n = 10)</td>
<td>57 ± 6</td>
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Data are mean values ± SEM. No significant differences were found among the groups.
propranolol, Sub-max exercise elicited a greater increase in plasma NE than in those on placebo. The increment in plasma NE was 1135 ± 229 pg/ml on propranolol, i.e., significantly different \((p < 0.001)\) from the increase observed in the same subjects on placebo \((371 ± 69 \text{ pg/ml})\). In hypertensive patients on mepindolol (fig. 1) the increment of plasma NE in response to Sub-max was 571 ± 136 pg/ml. The increment was higher than that observed in the same patients on placebo \((p < 0.05)\), but significantly lower than that obtained in the group on propranolol \((p < 0.01)\). Plasma E and DA responses in hypertensive patients on propranolol or mepindolol were not statistically different from those obtained on placebo.

Heart Rate and Blood Pressure

The response of systolic and diastolic BP and heart rate produced by Sub-max in controls and hypertensive subjects is shown in figure 2. Submaximal work increased both systolic and diastolic BP to the same extent in controls and in hypertensives on placebo treatment. Propranolol did not modify significantly the BP response to exercise in controls. The systolic and diastolic BP of hypertensive patients treated with propranolol showed significant minor levels in Pre-Ex, Sub-max, and Post-Ex when compared with values of the same patients on placebo. In Pre-Ex, heart rate showed no difference between controls and hypertensives on placebo. Nevertheless, in hypertensives on placebo the increase induced by Sub-max exercise was smaller than that observed in controls \((p < 0.01)\). In Post-Ex, heart rate remained higher than in Pre-Ex in both groups. Beta-blockade induced a reduction of Pre-Ex, Sub-max, and Post-Ex heart rate values in both groups (fig. 2).

Discussion

This study shows that Pre-Ex plasma E, NE, and DA levels of normotensives and patients with essential hypertension (not supine, but seated for 30 minutes) are not statistically different. In a previous study,\(^{18}\) supine normotensive subjects showed lower values of plasma NE \((235 ± 24 \text{ pg/ml})\) than our seated controls \((379 ± 37 \text{ pg/ml}, p < 0.01)\). This would indicate an activation of the sympathetic nervous system when subjects are seated, which could mask the possible differences in plasma NE levels between normotensive and hypertensive patients described by other authors.\(^{14, 18}\) Nevertheless, Lake et al.\(^{14}\) found that age-adjusted NE plasma levels in essential hypertensive patients
Figure 2. Blood pressure and heart rate response to exercise in controls and hypertensive patients on placebo, propranolol ---, and mepindolol -..-.. Significance of differences between placebo and beta-blockade is indicated by *p < 0.05-0.02, +p < 0.01; tp < 0.001.

were not different from those of normotensive subjects. A positive correlation between plasma NE and age was also reported in normotensives and hypertensives, but other authors failed to observe it in hypertensive patients under basal conditions. No correlation between age and Pre-Ex levels of E, NE, or DA was found in our normotensive or hypertensive subjects, neither was it found between plasma NE concentration and systolic or diastolic blood pressure. The present study also shows that in normotensives as well as in hypertensive patients. Sub-max exercise causes an increase in plasma levels of both E and NE. These findings are in agreement with previous reports. At the end of the rest period E returned to Pre-Ex values but plasma NE still remained high. Plasma DA remained unchanged during Sub-max exercise either in normotensive or in hypertensive subjects. An increase in plasma DA has been reported in response to exercise in normal subjects, whereas this increase was not observed in hypertensives. Beta-blockade lowered Pre-Ex values of systolic and diastolic blood pressure and heart rate in hypertensive patients. The fact that Pre-Ex plasma NE levels were not modified by beta-blockade suggests that the mechanism of the antihypertensive effect of beta-blockers is independent of circulating NE levels. Beta-blockers did not modify plasma E and DA responses to exercise in normotensives and hypertensives. In hypertensive patients, treatment with beta-blockers enhanced the increase in plasma NE induced by Sub-max exercise. Propranolol had a greater effect than mepindolol. This effect was absent in normotensives. It has been reported that exercise-induced increases in plasma NE and E tended to be higher after treatment with beta-blockers. An increase in plasma DA was only seen after a 15 month treatment. It has also been shown that acute treatment with propranolol increases an increase in circulating plasma NE in hypertensive patients.

The absence in our study of an effect on the basal values which could be ascribed to beta-blockade in either normotensives or hypertensives, suggests that the dosage of beta-blockers used did not cause any release of CA. It is clear; however, that the treatment modified the NE response to Sub-max exercise in hypertensive patients, but not in normotensives.

There is no clear explanation for this finding. In this study there were no significant differences either in the doses of propranolol administered, or in the decrease in heart rate produced by propranolol in Pre-Ex in normotensives and hypertensives, indicating a similar degree of beta-blockade. Besides, in spite of the fact that the hypertensive patients studied were older than the normotensive controls, and that their heart rate increase in Sub-max was lower, the work load attained during submaximal exercise was similar in both groups.

Therefore, the higher increase in plasma NE levels seems not to be related to a difference in the degree of beta-blockade or in the physical work performed. Since the increase in plasma NE in response to physical exercise has been attributed to a compensatory adrenergic activity in nonmuscular beds designed to counteract the effects of the vasodilatation induced by exercise in the muscle beds, beta-blockade seems not to affect this mechanism in normotensive subjects. However, it seems that it enhances the response in hypertensive patients. This would indicate that the effects of beta-blockers, as reported in spontaneously hypertensive rats and in normotensive Kyoto-Wister rats, are not identical in hypertensive and normotensive subjects.

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