Modification of Exercise Performance by Sharp Reduction of Blood Pressure

A Study in Patients With Uncomplicated Hypertension

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We evaluated exercise performance in 14 patients with uncomplicated essential hypertension 1 h after the administration of a single dose of placebo, nifedipine (20 mg), captopril (50 mg), and propranolol (80 mg). Drugs were administered at the same time of day following a randomized, double-blind protocol. Mean resting blood pressure (±SE) was 135±3 mm Hg with placebo administration, 118±4 with captopril, 110±4 with nifedipine, and 115±5 with propranolol and increased with exercise to 163±4, 148±3, 136±4, 136±4, respectively. Oxygen consumption at peak exercise and at ventilatory anaerobic threshold (VAT) was 25.2±1.1 and 18.1±1.0 ml/min/kg with placebo. Only propranolol (−2.3 ml/min/kg) decreased peak exercise oxygen consumption. Oxygen consumption at VAT was reduced by nifedipine and propranolol but unaffected by captopril. The effects on exercise capacity of blood pressure reduction in hypertensive patients are dependent on the drug utilized and are not related to the amount of blood pressure reduction. The lowered oxygen consumption at VAT observed with nifedipine and propranolol, and not with captopril, might be due to an excessive downward shift of the muscle perfusion pressure–oxygen consumption relationship which might take place during exercise.

We recently showed that in patients with uncomplicated essential hypertension acute reduction of blood pressure toward normal values obtained by administration of nifedipine lowered the ventilatory anaerobic threshold (VAT).1 While we1 and others2,3 have measured an unchanged exercise tolerance after nifedipine administration, the earlier occurrence of VAT might explain the complaints of weakness frequently reported by hypertensive patients after acute reduction of blood pressure. It is unknown whether this effect on exercise is peculiar to nifedipine or it is shared by other antihypertensive drugs. The present study was therefore undertaken to compare, in hypertensive subjects, the effects on exercise of nifedipine administration with those of other classes of antihypertensive drugs, namely propranolol and captopril.

Materials and Methods

Fourteen patients (8 male and 6 female; age, 51.7±2.6 [mean±SE]) with uncomplicated essential hypertension who were referred to the Istituto di Cardiologia, Università degli Studi di Milano, Milan, Italy, between January 1, 1991, and August 31, 1992, were requested to participate in the study. The diagnosis of hypertension was made if diastolic blood pressure was 100 mm Hg or greater at three 5-min intervals in both supine and resting positions. Patients had not received medications for at least 10 days prior to enrollment. As in our previous studies,4 all patients underwent our hypertension screening evaluation which includes a medical examination, blood sampling for measurements of resting norepinephrine, epinephrine, aldosterone, plasma renin activity, creatinine, blood nitrogen urea, and glucose. We excluded athletes, patients with fasting venous plasma glucose level 120 mg/dl or greater, serum creatinine level of 1.5 mg/dl or more, and obesity (mass index, 35 or more). We also excluded patients with symptoms or objective evidence of peripheral vascular, coronary, valvular, or myocardial diseases (regional hypokinesis, left ventricular diastolic diameter 55 mm or more, or fiber fractional shortening of 28 percent or less). The left ventricular mass was calculated by echocardiography.4 The protocol was approved by the institutional review board and subjects gave written informed consent to the study.

The protocol consisted of five cardiopulmonary exercise tests (CPXs) performed in five consecutive days between 10 and 11 AM. Patients had a light, caffeine-free breakfast, and smoking was not allowed during the 3 h preceding the CPX.

The first test was used to familiarize the patients with the exercise procedure and the laboratory; data obtained from these CPXs were therefore, discarded. Afterwards, patients received in a double-blind randomized fashion a single dose of placebo, nifedipine (20 mg), captopril (50 mg), and propranolol (80 mg). The CPXs were done 1 h after drug administration following a previously described protocol.4 In brief, the CPXs were performed on an electromagnetically braked cycloergometer with continuous ECG monitoring (Siemens Elema Sirdag 440S) and with blood pressure measured every minute (cuff manometer, left arm kept motionless). The exercise protocol consisted of 180 s of rest on the cycloergometer (sitting position), followed by 60 s of unloaded pedaling, and increments of 25 W every 180 s. The test was symptom-limited and self-interrupted by the patients. Exhaled gases were collected breath by breath (Sensor Medics MMC 4400). The carbon dioxide output-oxygen consumption relationship was utilized to calculate the VAT.4 To do so, the lower and upper limits of the two major portions of the carbon dioxide output-oxygen consumption relationship (excluding therefore data recorded at the beginning and at the end of exercise) were identified by three independent experts who were blinded to the protocol, blood pressure, and heart rate measurements. The VAT was then automatically calculated. In each

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Manuscript received January 6; revision accepted May 11, 1993.

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Table 1—Mean Systemic Blood Pressure at Rest and During Exercise With Placebo, Nifedipine, Captopril and Propranolol*

<table>
<thead>
<tr>
<th>Mean BP (mm Hg)</th>
<th>Placebo</th>
<th>Captopril</th>
<th>Nifedipine</th>
<th>Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>135 ± 3</td>
<td>118 ± 4†</td>
<td>110 ± 4†</td>
<td>115 ± 5</td>
</tr>
<tr>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
</tr>
<tr>
<td>25 W</td>
<td>143 ± 3</td>
<td>125 ± 3†</td>
<td>116 ± 3†</td>
<td>116 ± 4†</td>
</tr>
<tr>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
</tr>
<tr>
<td>50 W</td>
<td>150 ± 4</td>
<td>131 ± 3†</td>
<td>123 ± 3†</td>
<td>122 ± 5†</td>
</tr>
<tr>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
</tr>
<tr>
<td>75 W</td>
<td>158 ± 4</td>
<td>141 ± 3†</td>
<td>136 ± 3†</td>
<td>130 ± 5†</td>
</tr>
<tr>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 13)</td>
<td>(n = 14)</td>
</tr>
<tr>
<td>100 W</td>
<td>167 ± 6</td>
<td>147 ± 5†</td>
<td>139 ± 6†</td>
<td>140 ± 6†</td>
</tr>
<tr>
<td>(n = 7)</td>
<td>(n = 8)</td>
<td>(n = 7)</td>
<td>(n = 6)</td>
<td>(n = 6)</td>
</tr>
<tr>
<td>VAT</td>
<td>151 ± 4</td>
<td>132 ± 2†</td>
<td>123 ± 3†</td>
<td>121 ± 4†</td>
</tr>
<tr>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
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<tr>
<td>Peak exercise</td>
<td>163 ± 4</td>
<td>146 ± 3†</td>
<td>136 ± 4†</td>
<td>136 ± 4†</td>
</tr>
<tr>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 14)</td>
</tr>
</tbody>
</table>

*Data are means ± SE. Mean blood pressure was calculated as diastolic pressure + 1/3 (systolic-diastolic pressure).
†p<0.001 vs placebo.
‡p<0.02 vs nifedipine and propranolol.

CPX, we plotted the heart rate versus the oxygen consumption between 40 and 80 percent of exercise and calculated the slope of the relationship. The mean slope for each group (placebo, nifedipine, captopril, and propranolol) were then calculated. The oxygen consumption, heart rate, and ventilation measurements reported are means over 30 s. The predicted maximal oxygen consumption was calculated as 0.9 x observed weight (in kilograms) x (50.75 – 0.572 age).*

RESULTS

All patients completed the study and no significant side effects were reported. The left ventricular mass index of the patients was 141 ± 12 g/m² (normal values for our laboratory 97 ± 19 g/m², mean ± 1 SD). Compared to placebo, a single dose of nifedipine, captopril, and propranolol reduced blood pressure at rest, VAT, peak exercise, and at all steps of exercise (Table 1). The greatest blood pressure reduction was observed with nifedipine and propranolol (Table 1). All patients gave a good effort; indeed the gas exchange ratios (carbon dioxide output-oxygen consumption ratios) reached at peak exercise were 1.26 ± 0.02, 1.28 ± 0.03, 1.27 ± 0.03, 1.27 ± 0.04 with placebo, captopril, nifedipine, and propranolol, respectively. Exercise performance was in the normal range while patients received placebo (maximal oxygen consumption at peak exercise observed, 94 ± 5 percent of predicted).
a lower oxygen consumption with propranolol and nifedipine, but not with captopril.

The left ventricular mass was elevated in our patients, suggesting that they were chronically hypertensive. We recorded blood pressure with a noninvasive technique which might not provide precise measurements during exercise. However, blood pressure was measured by personnel blinded to the study protocol; furthermore, the blood pressure changes recorded during exercise with both placebo or active drugs were in agreement with previous observations done with \(^2\) and without \(^{10-12}\) intravascular devices.

Exercise capacity is normal in untreated patients with uncomplicated essential hypertension, if obese subjects or patients with enlarged left ventricle are excluded from the analysis.\(^3\) In the present study, oxygen consumption at peak exercise and anaerobic threshold were in the normal range for nonathletes. Similarly, the slope of the relationship between heart rate and oxygen consumption was normal (Fig 3), suggesting a normal stroke volume during exercise.\(^4,15\)

Limited information is available with regard to the effect of therapy on exercise performance in patients with hypertension. Our data confirm previous observations showing a reduced exercise performance with beta blockers in hypertensive subjects\(^16\) and hypertensive sportsmen.\(^11\) The precise mechanism of the impairment of exercise performance after beta blocker administration is not yet clear; however, hemodynamic and metabolic effects are unlikely to be involved.\(^11,17\)

Our study shows that the changes of peak exercise performance induced by propranolol are not simply due to a reduction of systemic blood pressure; indeed, nifedipine reduced peak exercise blood pressure as

**Discussion**

This study shows that the administration of a single dose of nifedipine, propranolol, and captopril reduces blood pressure at rest and during exercise in patients with uncomplicated essential hypertension. Only propranolol reduced exercise tolerance and peak exercise oxygen consumption. The VAT occurred earlier and at

**Figure 2.** Amount of blood pressure lowering and reduction of oxygen consumption at VAT. Solid circle, captopril; solid triangle, nifedipine; solid diamond, propranolol; open diamond, \(p<0.01\).

Oxygen consumption, heart rate, ventilation at peak exercise, as well as exercise tolerance time were unaffected by nifedipine and captopril but were reduced by propranolol (Fig 1). The VAT occurred at a lower oxygen consumption with nifedipine and propranolol, but not with captopril (Fig 1). A linear relationship between reduction of blood pressure and reduction of oxygen consumption at VAT was not observed (Fig 2). The heart rate-oxygen consumption relationship between 40 and 80 percent of exercise values are reported in Figure 3. Only propranolol reduced the slope of the relationship which was \(3.8 \pm 0.3\) beat/ml/kg/min with placebo (\(p<0.01\) vs propranolol), \(3.7 \pm 0.4\) with captopril (\(p<0.01\) vs propranolol), \(4.1 \pm 0.5\) with nifedipine (\(p<0.01\) vs propranolol), and \(2.5 \pm 0.2\) with propranolol, respectively.

**Figure 3.** Heart rate (HR)-oxygen consumption (VO\(_2\)) relationship between 40 and 80 percent of exercise. Slopes were \(3.8, 3.7, 4.1, \) and \(2.5\) with placebo, captopril, nifedipine and propranolol, respectively (\(p<0.01\) vs propranolol, all values except placebo). Symbols refer to data obtained in each patient during 30-s measurements at each work load included between 40 and 80 percent of exercise.

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much as propranolol, but did not influence exercise tolerance or oxygen consumption at peak exercise.

We previously showed that VAT occurred earlier and at a lower oxygen consumption in hypertensive patients after nifedipine administration. We interpreted this as due to a peripheral vascular effect of nifedipine. The data from this study confirm these previous findings. Furthermore, the observation that nifedipine does not change the slope of the heart rate-oxygen consumption relationship during exercise suggests that the stroke volume index during exercise is unchanged. This supports the hypothesis that after nifedipine administration the earlier occurrence of VAT is due to an action of the drug on the distribution of blood flow in the peripheral vessels and not on the heart.

Angiotensin-converting enzyme inhibitors frequently are used in the treatment of hypertension and do not change total exercise tolerance in normal and hypertensive subjects. In this study, we confirmed these observations and found that unlike nifedipine and propranolol, VAT was unchanged after captopril administration. The variable effect of nifedipine and captopril on VAT might be due to differences between the two drugs in either the degree of blood pressure reduction or the hemodynamic behavior. Indeed, the less pronounced arteriolar vasodilating action of captopril might impede the shifting of blood away from the exercise muscles which we propose as the main cause of the earlier occurrence of the VAT in hypertensive subjects after nifedipine administration.

The effect of blood pressure reduction in hypertensive patients on exercise capacity is dependent on the drug utilized. Indeed, oxygen consumption at peak exercise and exercise tolerance are not solely related to the amount of blood pressure reduction. On the other hand, it is possible that the earlier occurrence of VAT observed with two drugs, propranolol and nifedipine (which induced the greatest blood pressure reduction), and not with captopril, is due to an excessive downward displacement during exercise of the muscle perfusion pressure-oxygen consumption requirement relationship. This might be due to a reduction of cardiac output (propranolol, 2) or to a shift of blood flow from the exercising muscles to other tissues (nifedipine, 1). The absence of a linear relationship between the amount of blood pressure lowering and the reduction of oxygen consumption at VAT (Fig 3) suggest that a threshold level on the downward displacement on the muscle perfusion pressure-oxygen requirement relationship has to be reached before VAT is anticipated. To confirm this hypothesis, further study is needed to test the relationship between amount of blood pressure lowering-exercise performance with various drugs. At the present time, suggestions obtained from our study might be utilized when choosing the treatment for hypertension, but whether these effects on exercise performance persisted or not with long-term treatment still needs to be evaluated.

References

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