Exercise Hemodynamics and Oxygen Delivery in Human Hypertension
Response to Verapamil

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SUMMARY To characterize the hemodynamic response to exercise and the effects of calcium channel antagonism in hypertensive subjects, invasive exercise hemodynamics were performed in the baseline state after intravenous infusion of verapamil and after 5 to 7 days of oral verapamil in 10 subjects with moderate to severe hypertension. We also assessed oxygen delivery and use and the response of the sympathetic nervous system by measuring plasma norepinephrine levels at rest and during exercise. Both routes of administration were associated with significant reductions of mean arterial pressure and systemic vascular resistance at rest and peak exercise (p < 0.05). Changes in heart rate were not statistically significant. Following oral administration of verapamil, stroke volume increased significantly in both the resting and exercise states. Pulmonary wedge pressure did not increase; in fact, the Frank-Starling relationship of cardiac performance actually was improved. Oxygen delivery and use were unchanged with both routes of administration. There was no significant difference in rest and exercise plasma norepinephrine levels following verapamil therapy. Thus, verapamil resulted in a significant reduction of mean arterial pressure, mediated by a significant reduction of systemic vascular resistance, following both intravenous and short-term oral administration. This reduction occurred without expression of left ventricular dysfunction and was not at the expense of increased oxygen use or enhanced sympathetic nervous systemic activity.

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KEY WORDS • cardiac performance • oxygen consumption • norepinephrine • hypertension • cardiac output • human • pulmonary wedge pressure • ergometry

The hemodynamic characteristics of hypertensive patients must be evaluated to clarify the impact of vasoconstriction on the heart and the peripheral circulation. However, resting hemodynamics provide only a static profile of the hypertensive patient and do not identify the cardiovascular changes that occur with daily activity. While noninvasive assessment of exercise performance offers additional information, it does not completely assess ventricular loading conditions, peripheral vascular responses, or the changes in oxygen delivery and use during maximal exercise. For these reasons, more extensive invasive assessments of cardiac performance and peripheral vascular responses to exercise are necessary.

Although the data base for rest and exercise hemodynamic responses to therapeutic maneuvers that reduce blood pressure and peripheral resistance remains limited, this hemodynamic profile is important, since it provides a means to assess the favorable and unfavorable responses to therapy occurring in larger groups of patients treated in the outpatient setting. For example, \( \beta \)-adrenergic blockade often results in long-term blood pressure reduction but is associated with a reduction of rest and exercise cardiac output. \(^1\)\(^2\) Calcium channel antagonists have provided a new approach to the therapy of hypertension \(^1\) and appear to reduce blood pressure by decreasing peripheral vascular resistance. \(^3\)\(^4\) A potential problem with this class of vasodilators, however, is the possibility of a negative inotropic effect, which could limit cardiac performance.
In the present study, we evaluated the rest and exercise hemodynamic responses and oxygen use in a group of untreated subjects with moderate to severe hypertension. We then studied the effects of blood pressure reduction by calcium channel antagonism with intravenous and oral administration of verapamil on rest and exercise hemodynamics and oxygen use.

Subjects and Methods

This study consisted of 10 subjects with moderate to severe hypertension. All gave written informed consent to participate and completed all phases of the study. There were 6 male and 4 female subjects, ranging in age from 42 to 73 years. At the time of entry into the study, all subjects were believed to have essential hypertension, although one subsequently was found to have hypersecretion of aldosterone due to bilateral adrenal hyperplasia. All subjects had had the clinical diagnosis of hypertension for at least 2 years. Nine of the 10 subjects had been receiving one or more combinations of medical therapy with unsatisfactory responses; one subject had chosen to refuse treatment. All subjects had funduscopic changes of grade I or II hypertensive retinopathy, and six had evidence of cardiac enlargement by either electrocardiogram or chest roentgenogram. None of the subjects were in the accelerated or malignant stages of hypertension. In addition, none had clinical evidence of congestive heart failure, renal impairment, or chronic lung disease. Occlusive carotid disease was excluded by physical examination and Doppler ultrasound evaluation. None of the subjects had a history of angina, previous myocardial infarction, or nitrate use. As part of the screening studies, all subjects underwent a maximal exercise treadmill test according to the standard Bruce protocol. During exercise, no symptoms or electrocardiographic changes compatible with coronary artery disease were elicited. All previous medications were tapered and discontinued 2 to 3 weeks before admission to the hospital to avoid carryover effects of previous therapy. All patients were admitted to the Adult Clinical Research Center of New York Hospital for the study and were maintained on a 100 mEq sodium diet.

Overall Study Design

After admission to the Clinical Research Center, subjects were observed for 3 to 5 days of stabilization. They then underwent two exercise hemodynamic studies, performed 5 to 7 days apart. During the first hemodynamic study, exercise responses in the baseline untreated state were obtained. In addition, verapamil was given intravenously to assess the immediate effects of blood pressure reduction on rest and exercise hemodynamics. The second study was performed following 5 to 7 days of oral verapamil therapy. All hemodynamic studies were performed in the morning after an overnight fast. Subjects were brought to the procedure room of the coronary care unit. A right heart catheter was placed percutaneously from an arm vein, and a cannula was placed percutaneously in the brachial artery of the same arm. A 30-minute equilibration period ensued, followed by the baseline upright exercise. After completing the baseline exercise, subjects returned to the supine position for 2 hours of rest. Verapamil was then administered intravenously (as outlined in the section Verapamil Administration) to assess its immediate effects on upright exercise. On completion of this second exercise study, subjects were allowed to recover from exercise, the verapamil infusion was discontinued, and they were returned to the Clinical Research Center.

Exercise Hemodynamic Protocol

Catheter placement was performed on a table designed for upright exercise. The subjects were elevated to a seated position, where they could comfortably pedal an electronically braked bicycle ergometer while the catheters were in place. Subjects rested in the seated position initially and then in the supine position, followed by the baseline upright exercise. On completion of the baseline exercise, subjects returned to the procedure room for repeat exercise hemodynamic study, using the contralateral arm for catheter placement. This study was performed to coincide with the peak blood pressure response to the orally administered verapamil.

Catheter and equipment placement was performed on a table designed for upright exercise. The subjects were elevated to a seated position, where they could comfortably pedal an electronically braked bicycle ergometer while the catheters were in place. Subjects rested in the seated position, then in the supine position, and then in the supine position.
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Determination of Hemodynamic and Respiratory Gas Parameters

Heart rate and all pressures were recorded continuously on a multichannel recorder. The heart rate was obtained from a precordial lead. Pressures were followed as phasic, but we obtained electronically dampened means recordings for exercise values and calculation of derived indices. Mean arterial pressure, pulmonary artery pressure, and right atrial pressure were continuously recorded (all pressures were expressed as mm Hg). Phasic and mean pulmonary wedge pressure (in mm Hg) were obtained at the end of the rest phase and each stage of exercise. Cardiac output was obtained in duplicate by the thermodilution technique and was expressed as cardiac index (in L/min/m²), correcting for body surface area. Stroke volume index, systemic vascular resistance (in dyn cm⁻⁵) and pulmonary vascular resistance (in dyn sec cm⁻⁵) were calculated from standard formulas. Measurements of respiratory gases was obtained by using a metabolic cart (SensorMedics, Anaheim, CA, USA). The metabolic cart provided a real-time digital display of the respiratory gases and calculated respiratory exchange ratio, as well as a printout of all data at 15-second intervals. The data that were analyzed included oxygen consumption (V̇O₂, expressed as ml/min), carbon dioxide production (V̇CO₂, expressed as ml/min), and the respiratory exchange ratio (V̇CO₂/V̇O₂, expressed as a 2-digit decimal).

Blood Sample Analysis

Plasma norepinephrine was analyzed by the radioenzymatic assay of Peuler and Johnson (values expressed as pg/ml). Blood oxygen saturation was analyzed using transmission spectrophotometry. Blood oxygen content was calculated by the formula blood oxygen content = blood oxygen saturation x hemoglobin x 1.34 and is expressed as volume percent. The arteriovenous oxygen difference was determined by subtracting the mixed venous oxygen content from the arterial oxygen content.

Verapamil Administration

To determine the immediate hemodynamic response to reversal of vasoconstriction by calcium channel antagonism, we administered verapamil intravenously. With subjects in the supine position, verapamil was administered as a bolus of 0.15 mg/kg and the hemodynamic response was followed for 15 minutes. A verapamil infusion was then started at a rate of 1 mg/min. The infusion was titrated to maintain the maximal level of mean arterial pressure reduction observed during the bolus administration. The dose ranged between 1 and 2 mg/min. The infusion was continued for 20 to 30 minutes with the subjects in the supine position, throughout the transition to the seated rest position and throughout the exercise. Following recovery from exercise, the infusion was discontinued. When subjects were returned to their rooms after the first hemodynamic study, therapy with oral verapamil was initiated at a dose of 80 mg every 8 hours. This was increased to a dose that would reduce blood pressure to the normotensive range, as measured at the bedside. Verapamil therapy was continued for 5 to 7 days, up to the time of the second hemodynamic study. Two subjects received 80 mg, seven received 120 mg, and one received 160 mg, administered every 8 hours. The dose administered before the second hemodynamic study was the individualized dose each subject had been receiving for the prior 5 to 7 days.

Statistical Analysis

All data were entered into a UNIX-operated mainframe computer that uses the "S" data management system. Statistical analysis was performed using the BMDP statistical software program. Analysis of variance was used to compare all rest and peak exercise values; group values are expressed as the mean ± the standard error of the mean (SEM). In this way, we compared baseline values with all changes observed following intravenous and oral administration of verapamil. Correlations were by linear regression. Values were statistically significant if they achieved a p value of less than 0.05.

Results

Baseline Response to Exercise

Figure 1 shows the hemodynamic responses to exercise in the baseline untreated state. Heart rate increased from 79 ± 4 to 141 ± 9 beats/min. The increases of pressure included mean arterial pressure, from 137 ± 6 to 179 ± 8 mm Hg; right atrial pressure, from 1 ± 0.5 to 6 ± 2 mm Hg (not shown in figure); pulmonary artery pressure, from 17 ± 3 to 37 ± 3 mm Hg; and pulmonary wedge pressure, from 7 ± 2 to 19 ± 3 mm Hg (all changes p < 0.001). Systemic vascular resistance decreased from 2449 ± 149 to 1279 ± 87 dyn sec cm⁻⁵, and pulmonary vascular resistance decreased from 196 ± 26 to 132 ± 11 dyn sec cm⁻⁵ (both p < 0.01). The exercise-induced vasodilatation was accompanied by an increase in cardiac index, from 2.38 ± 1.11 to 5.85 ± 0.31 L/min/m² (p < 0.01), and an increase in stroke volume index, from 31 ± 2 to 42 ± 2 ml/m²/p (p < 0.01). There was a highly significant correlation between rest and exercise mean arterial pressure and cardiac index (r = 0.789, p < 0.001), which indicates that the increase in mean arterial pressure during exercise was mediated by an increase in cardiac output.

Effects of Calcium Channel Antagonism on Rest and Exercise Hemodynamics

Several changes in resting hemodynamics were observed during verapamil therapy (see Figure 1). There was no significant change in heart rate with either route of administration. Mean arterial pressure decreased from the baseline value of 137 ± 6 mm Hg to 104 ± 3 and 111 ± 4 mm Hg during intravenous and oral
FIGURE 1. Hemodynamic responses to exercise and subsequent intervention with verapamil therapy. The values shown represent baseline measurements (B), the immediate response to intravenous verapamil infusion (IV), and the response to 1 week of oral verapamil therapy. HR = heart rate, MAP = mean arterial pressure; PAP = pulmonary artery pressure; PWP = pulmonary wedge pressure; CI = cardiac index; SVI = stroke volume index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance.

However, stroke volume index increased to 37 ± 2 ml/m² (p < 0.05, compared with baseline). The predominant hemodynamic effect contributing to the reduction of blood pressure by verapamil was reduction of systemic vascular resistance. Compared with the baseline value of 2449 ± 142 dyn sec cm⁻², there was a respective reduction of systemic vascular resistance to 1552 ± 93 and 1813 ± 104 dyn sec cm⁻² with intravenous and oral administration of verapamil (both p < 0.05 compared with baseline). The reduction of pulmonary vascular resistance did not achieve statistical significance.

Several changes in exercise hemodynamics also were observed during verapamil therapy. There was no significant change in heart rate at peak exercise during verapamil therapy. The maximal blood pressure achieved during peak exercise decreased from 179 ± 8 to 135 ± 7 mm Hg with intravenous administration of verapamil (p < 0.05). Although maximal blood pressure during peak exercise was decreased to 154 ± 7 mm Hg after 1 week of verapamil therapy, this decrease was not statistically significant compared with baseline values. As with the resting state, there was no significant change of right atrial pressure, pulmonary artery pressure, or pulmonary wedge pressure during maximal exercise with either route of administration. Exercise cardiac index was not significantly changed by either intravenous or oral administration of verapamil, but exercise stroke volume index increased. Stroke volume index increased with both intravenous (45 ± 2 ml/m²) and the week-long oral therapy (49 ± 3 ml/m²; p < 0.05 compared with baseline). The systemic vascular resistance during maximal exercise was significantly decreased during verapamil therapy, from 1278 ± 100 to 963 ± 66 and 996 ± 76 dyn sec cm⁻² with intravenous and oral administration of verapamil, respectively (both p < 0.05 compared with baseline). The reduction of pulmonary vascular resistance did not achieve statistical significance.

The respiratory gas profile during exercise and in response to verapamil is summarized in Table 1. There

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Intravenous</th>
<th>Oral (1 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂ (ml/min)</td>
<td>234 ± 21</td>
<td>243 ± 21</td>
<td>205 ± 19</td>
</tr>
<tr>
<td>Rest</td>
<td>Exercise</td>
<td>1200 ± 675</td>
<td>1239 ± 659</td>
</tr>
<tr>
<td>VO₂ (ml/min)</td>
<td>182 ± 24</td>
<td>170 ± 15</td>
<td>146 ± 16</td>
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<tr>
<td>Rest</td>
<td>Exercise</td>
<td>1224 ± 210</td>
<td>1250 ± 213</td>
</tr>
<tr>
<td>RER (VO₂/VO₂)</td>
<td>0.72 ± 0.02</td>
<td>0.69 ± 0.01</td>
<td>0.70 ± 0.03</td>
</tr>
<tr>
<td>Rest</td>
<td>Exercise</td>
<td>0.99 ± 0.04</td>
<td>0.98 ± 0.05</td>
</tr>
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Values are means ± SEM. VO₂ = oxygen consumption, VO₂ = carbon dioxide production; RER = respiratory exchange ratio.
was no significant change of oxygen consumption, carbon dioxide production, or respiratory exchange ratio during verapamil therapy. Resting values of oxygen consumption at baseline, during intravenous infusion of verapamil, and during oral therapy with verapamil were 234 ± 21, 243 ± 21, and 205 ± 19 ml/min, respectively; during maximal exercise, oxygen consumption was 1200 ± 675, 1239 ± 659, and 1136 ± 519 ml/min, respectively. Resting values of carbon dioxide production were 182 ± 24, 170 ± 15, and 146 ± 16 ml/min, respectively; carbon dioxide production during maximal exercise was 1224 ± 210, 1250 ± 213, and 1239 ± 187 ml/min, respectively.

Cardiac Performance During Exercise

The relationship of pulmonary wedge pressure to stroke volume index is shown in Figure 2. There was an appropriate increase of pulmonary wedge pressure and stroke volume index during exercise in the baseline state, which was not significantly changed with intravenous administration of verapamil. However, this relationship was significantly improved with 1 week of oral therapy with verapamil (p < 0.05). Thus, there was an upward shift of the Frank-Starling relationship during oral therapy with verapamil, which indicates an overall improvement of cardiac performance in the setting of a decrease in systemic vascular resistance. The resistance/flow relationship is shown in Figure 3, where the changes with exercise and verapamil therapy are given for individual subjects. Overall, systemic vascular resistance was inversely correlated with cardiac index (r = -0.844, p < 0.001).

After 1 week of oral therapy with verapamil, there was a leftward shift of this relationship in both the resting and exercise states.

Oxygen Use and Circulating Catecholamines During Calcium Channel Antagonism

Cardiac performance improved during verapamil therapy, but this improvement could have been at the expense of increased systemic oxygen consumption or increased peripheral oxygen extraction. We therefore analyzed oxygen consumption compared with cardiac index and systemic vascular resistance at all stages of therapy (Figure 4). Oxygen consumption was well correlated with the cardiac index achieved during peak exercise. There was no change in this relationship with verapamil therapy, which resulted in a significant overall correlation (r = 0.827, p < 0.001). Oxygen consumption was inversely correlated with systemic vascular resistance for both rest and exercise determinations (r = -0.735, p < 0.001). There was also no change in this relationship during verapamil therapy. We were also able to obtain simultaneous cardiac output, oxygen consumption, and arteriovenous oxygen differences in six of the subjects studied (Figure 5). For both rest and exercise values, cardiac output and oxygen consumption during calcium channel antagonism were comparable to the pretreatment baseline values. In this setting, the arteriovenous oxygen difference was the same, or slightly decreased, by verapamil therapy. Thus, there was no apparent increase in peripheral oxygen extraction with verapamil therapy.

Figure 6 shows the relationship of cardiac index and plasma norepinephrine levels at rest and during maximal exercise. The plasma norepinephrine values observed in this study were closely correlated to the level of cardiac index achieved (r = 0.847, p < 0.001). There was no apparent difference between baseline values and those following calcium channel antago-
Discussion

The response to exercise in this group of hypertensive subjects revealed an increase of mean arterial pressure that was associated with a decrease of systemic vascular resistance and an increase of the heart rate and stroke volume index components of cardiac index. Furthermore, the measurement of pulmonary wedge pressure throughout exercise enabled a more accurate assessment of ventricular loading conditions and the detection of potential left ventricular failure. Despite the exercise-induced decrease of systemic vascular resistance, the absolute level of systemic vascular resistance achieved remained higher than that reported for normal subjects, which indicates persistently abnormal vascular tone. In this respect, the impact of drug intervention on rest and exercise vasoconstriction is a central issue to the profile of antihypertensive therapy.

Calcium channel antagonists provide a new approach to the therapy of hypertension. These agents have diverse chemical structures and mechanisms of action. They are believed to have a negative inotropic mechanism, which suggests that the improvement in cardiac performance was not at the expense of increased sympathetic nervous system activity.
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The present study also demonstrated that the improvement in overall systemic flow was not accompanied by potentially deleterious effects. Thus, the improved cardiac performance was not at the expense of increased oxygen consumption, which could adversely affect long-term cardiac performance. In addition, there was no increase in oxygen extraction, as both rest and exercise arteriovenous oxygen difference with verapamil therapy actually showed a tendency to decrease, rather than increase. Finally, there was no apparent reflex increase in sympathetic nervous system activity. While the assessment of sympathetic activity in clinical studies is difficult, the lack of change in the heart rate response to exercise and the concentration of circulating plasma norepinephrine are strong evidence that there was no increased sympathetic stimulation to account for the improvement in cardiac performance.

The findings in this study are in contrast to the reported exercise hemodynamic responses to β-adrenergic blockade in hypertension. The immediate and long-term response to β-adrenergic blockade is a reduction of cardiac output, which has been demonstrated that the higher the resting cardiac index before β-adrenergic blockade, the greater the reduction of cardiac index with therapy. Systemic vascular resistance increases when therapy is initiated, but it either remains elevated or returns toward the baseline values during long-term therapy. Lund-Johansen has performed the most extensive evaluation of the exercise response to β-adrenergic blockade. Short-term studies, short-term follow-up, and long-term follow-up all have indicated that β-adrenergic blockade causes a reduction of rest and exercise cardiac output. While the ability to vasodilate during exercise is not impaired by β-adrenergic blockade, the level of resistance achieved is not improved, compared with the pretreatment values. Direct comparisons remain limited, but it appears that calcium channel antagonism has a more favorable hemodynamic profile during exercise than does β-adrenergic blockade.

In summary, immediate and short-term administration of verapamil was associated with effective reduction of blood pressure, mediated by a reduction of systemic vascular resistance. This effect occurred without expression of left ventricular dysfunction; in fact, cardiac performance actually improved. This improvement was not at the expense of increased oxygen use or enhanced sympathetic activity. Because of the beneficial hemodynamic profile during blood pressure reduction with verapamil, and its beneficial effects in angina and cardiac arrhythmias, verapamil may be particularly desirable in those patients whose hypertension is accompanied by clinical evidence of coronary artery disease.

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