The Effects of Verapamil on Training in Patients with Ischemic Heart Disease

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Verapamil is a calcium-channel blocking agent with antianginal and antiarrhythmic properties that have been widely studied. Its myocardial depressant effect is well known. The purpose of this study was to examine the effects of verapamil on the training response in patients with ischemic heart disease. The study group consisted of 41 male patients with a mean age of 53.3 ± 7.2 years who had suffered a myocardial infarction or had undergone coronary artery bypass surgery 8 to 12 weeks previously. They were chosen on a consecutive basis from eligible patients entering a cardiac rehabilitation program. With use of a double-blind technique, 21 patients were assigned to receive verapamil, 120 mg three times daily, while the other 20 were given an identical placebo. Each patient underwent exercise stress testing in the untreated state to permit comparison between tests performed on commencement and completion of training. The training effect was determined by comparing exercise response before and after the eight-week program. There was an increase in exercise duration (p<0.001) and a decrease in functional aerobic impairment (p<0.001), without difference between the two groups. Energy expenditure increased in both groups, but the highest level was achieved by those receiving active treatment (p<0.02). Heart rate for equal workload was significantly reduced after training (p<0.001), although this was lower in the placebo patients (p<0.001) and the patients who had a recent myocardial infarction (p<0.01). It appears that treatment with verapamil does not impair the development of a training effect in patients with ischemic heart disease who are undergoing organized training.

(Chest 1992; 101:411-15)

CABG = coronary artery bypass graft; MET = metabolic equivalent; MI = myocardial infarction

Exercise training is recommended for many patients with ischemic heart disease and has been shown to produce an increase in exercise tolerance and an improvement in the maximal rate of oxygen uptake and double product. Verapamil is commonly used in the treatment of angina pectoris and may have a prophylactic role. Verapamil, therefore, will be prescribed for many patients who are involved in exercise training, both supervised and unsupervised.

Verapamil has well-documented negative inotropic, negative chronotropic, and antianginal properties. Despite the negative inotropic properties, verapamil may have beneficial effects on exercise hemodynamics. Patton et al demonstrated no effect on exercise stroke volume or cardiac index in patients with coronary artery disease. In patients with exertional angina pectoris, verapamil increases exercise ejection fractions, presumably by ameliorating exercise-induced ischemia. The negative chronotropic properties are compensated for by reflex sympathetic activity as a result of peripheral vasodilatory effects.

The exercise training response in patients with ischemic heart disease differs from that in normal subjects. With ischemic heart disease, increases in cardiac output are attenuated, and there is a greater reliance on peripheral adaptations. Verapamil, by its antiischemic effects and peripheral vasodilation, may produce beneficial changes in exercise cardiac outputs and thus improve the training response.

This double-blind placebo-controlled study investigated the effects of verapamil on patients after myocardial infarction (MI) or coronary artery bypass graft (CABG) surgery who were participating in a structured exercise training program.

Patients and Methods

Patients

The study population comprised 41 male patients with a mean age of 53 ± 7.2 years. All these patients had suffered an MI or had undergone CABG surgery 8 to 12 weeks previously. The patients were chosen on a consecutive basis from those eligible patients entering a cardiac rehabilitation program.

On recruitment, patients were randomly allocated a number which corresponded to their treatment package. Patients and investigators were blinded as to whether treatment was verapamil or placebo. The placebo tablets were identical to the active. Twenty-one patients were given verapamil, 120 mg three times daily, while the other 20 were given placebo.

Patients were excluded from the study if they had congestive heart failure, significant cardiac conduction problems, hemodynamically significant valvular disease, hypertension, diabetes mellitus, serious renal or hepatic disease, or a history of serious allergy; if they were older than 65 years of age; or if they were receiving beta-blocking agents or digoxin. Informed consent was obtained from all patients.

Exercise Tolerance Testing

Exercise tolerance tests were carried out on a treadmill, following the standard Bruce protocol. Patients were exercised until one or more of the following end points were achieved: 55 percent of the...
Table 1—Patient Characteristics in Placebo and Active-Treatment Groups*

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 20)</th>
<th>Active (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>55.7 ± 6.1</td>
<td>50.3 ± 7.2</td>
</tr>
<tr>
<td>Recent M1</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Recent CABG</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Attendance, %</td>
<td>87</td>
<td>94</td>
</tr>
<tr>
<td>Resting ECG findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior MI</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Inferior MI</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>No Q waves</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Exercise-induced ischemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>After</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

*Unless noted otherwise, values are numbers of patients.

maximal heart rate predicted for the patient's age,11 exhaustion, chest pain, or serious ventricular arrhythmias. The following measurements were assessed and compared: exercise duration, heart rates required for performing equal workloads, energy expenditure in metabolic equivalents (METs), and functional aerobic impairment.11 Heart rate for equal workload was calculated by comparing the peak heart rate in the first test with the corresponding rate at the same exercise duration in the second test. Exercise-induced ischemia was considered significant at 1-mm horizontal or downsloping ST-segment depression 80 ms from the J point in comparison with the resting ECG. Patients were exercised in the untreated state; the first test was before treatment started, and the second test was five days after treatment ended.

Exercise Training

Exercise training took place twice weekly for eight weeks. For each patient a target rate, 85 percent of that achieved in the initial exercise test, was achieved. The workload was adjusted individually during training to maintain this heart rate constantly. Patients exercised in groups for 4 min each on a treadmill, bicycle ergometer (twice, but not consecutively), handcrank, and Master's steps, with a 1-min rest period between each activity. Each session started and ended with a 5-min period of light calisthenics. Continuous ECG monitoring was carried out, and blood pressure was measured before and after each session.

Statistical Analysis

Statistical analysis was performed by using analysis of variance for repeated measures. Where applicable, three-factor interaction—between active and placebo, between MI and CABG, and before and after training—was used to assess the effects of these factors on the measured variables.

RESULTS

An evaluation of the exercise training response was performed by assessing exercise duration, heart rates for equal workload, energy expenditure, and functional aerobic impairment achieved in the first and second exercise tolerance tests by the verapamil and placebo groups. The verapamil and placebo groups were divided further into those patients with a recent MI and those with recent CABG surgery. The verapamil and placebo groups were of similar functional ability (Table 1). All 41 patients completed the program, and no serious cardiac events occurred during the study period.

**Figure 1.** Increase in exercise duration following training. There was no significant difference between the verapamil and placebo groups (p<0.001).

**Exercise Duration**

There was a significant increase in exercise duration from 5.8 to 9.4 METs (p<0.001), without any interaction from treatment or from whether patients were post-CABG or post-MI (Fig 1).

**Heart Rate for Equal Workload**

There was a significant decrease in heart rate for equal workload from 141.8 to 124.0 beats/min (p<0.001). Heart rate for equal workload was significantly lower in those patients receiving placebo as compared to verapamil (128.6 and 137.2 beats/min, respectively) (p<0.001) and in those patients with a recent MI as compared to recent CABG surgery (127.3 and 138.5 beats/min, respectively) (p<0.01) (Fig 2).

**Energy Expenditure**

Three-factor interaction demonstrated significant changes for energy expenditure (p<0.02). The verapamil MI group achieved higher levels of energy expenditure (7.6 before and 10.2 METs after) than the placebo MI group (6.8 before and 9.7 METs after). The verapamil CABG group achieved higher levels of

**Figure 2.** Reduction in heart rate for equal workload following training. There was no significant difference between the verapamil and placebo groups (p<0.001).

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energy expenditure (7.4 before and 10.3 METs after) than the placebo CABG group (7.7 before and 9.2 METs after) (Fig 3).

Functional Aerobic Impairment

There was a significant decrease in functional aerobic impairment from 32.4 percent to −1.5 percent (p<0.001), without any interaction from treatment or from whether patients were post-CABG or post-MI (Fig 4).

Bicycle Ergometer Workload

The workload achieved during training on the bicycle while on treatment was analyzed. The average workload achieved for the first three sessions was compared with that for the last three sessions. There was a significant increase in workload from 50.7 to 60.6 W after training (p<0.001), without any interaction from whether patients were receiving verapamil or placebo, or whether they were post-CABG or post-MI.

Discussion

This double-blind placebo-controlled study demonstrates that verapamil in a dose of 120 mg three times daily does not affect the exercise training response in a group of patients with ischemic heart disease. There was a significant increase in exercise duration (p<0.001) and a decrease in functional aerobic impairment (p<0.001), without difference between the verapamil and placebo groups. There was a significant reduction in heart rate for equal workload (p<0.001), although this was lower in those patients who were receiving placebo compared to verapamil (p<0.001) and in those with a recent MI compared to recent CABG surgery (p<0.01). Energy expenditure increased, and this was highest in those patients receiving verapamil (p<0.02); this has not been demonstrated previously.

The aim of this study was to evaluate the effects of verapamil on the development of a training response over an eight-week training program. To evaluate this training response, patients were exercised off treatment to allow direct comparisons of the two exercise tests. Both groups were comparable for age, sex, previous MI, recent CABG surgery, and exercise-induced ischemia (Table 1). The dose of verapamil of 120 mg three times daily was used in order to produce the maximum effect.

The exercise tests, from which all observations were made, were performed according to the Bruce protocol. It is recognized that multistage exercise testing is the most informative type of testing procedure for evaluating physical work capacity or change in functional ability. The Bruce protocol increases speed and gradient every 3 min, but the weight-adjusted oxygen uptake increases almost linearly with time. Duration of exercise with this protocol has been shown to be highly correlated with directly measured VO2max in men with heart disease.

The precise mechanism of the exercise training response has not been fully elucidated. However, in healthy patients it is known to result in greater work capacity, VO2max, cardiac output, stroke volume, and systemic arteriovenous oxygen difference. At submaximal workloads, conditioning results in lower myocardial VO2, lower heart rate, and higher stroke volume. In patients with ischemic heart disease, the increase in stroke volume is impaired, and there is a greater reliance on increasing the systemic arteriovenous oxygen difference.

Verapamil has well-documented negative inotropic effects, but it is considered that this is compensated for by its vasodilatory effects on afterload. This is probably why it has no effect on exercise stroke volume or cardiac index in patients with coronary artery disease. In patients with exertional angina pectoris, it will increase exercise ejection fraction, presumably by ameliorating exercise-induced ischemia. The negative chronotropic effects are compensated for by reflex sympathetic activity. For these reasons, we
postulated that verapamil may increase exercise cardiac output to a greater degree than would be expected in this group of patients and thus improve the training response.

No consistent benefit in the exercise training response was demonstrated in this study. Those patients receiving active treatment did achieve higher levels of energy expenditure in the second test, but the placebo MI group achieved the same increase in energy expenditure between the two tests as the verapamil CABC group (2.9 METs). Heart rates for equal workload were higher in the verapamil group than in the placebo group and were higher in the CABC group than in the MI group. The verapamil and CABC groups achieved the highest energy expenditure in the first test, and the heart rate for equal workload in the first test was taken as the maximum heart rate in that test. Thus, the higher heart rate for equal workload reflects a greater intensity of exercise.

An increase in exercise stroke volume has been demonstrated in patients with stable angina pectoris, and the relief of exercise-induced ischemia appears to be the primary mode by which verapamil improves cardiac function. However, the presence of symptomatic or silent ischemia was not required to enter this study and consequently was not prevalent (Table 1). It has also been demonstrated that despite the beneficial effects of verapamil on exercise cardiac output in patients with angina pectoris, there is a reflex reduction in peripheral oxygen extraction.16 Cardiac output and peripheral oxygen extraction were not measured as part of the study protocol; deductively, however, our results suggest that the reduction in peripheral oxygen extraction may offset any increase in cardiac output. This observation needs further study.

Beta-blockers reduce exercise capacity acutely,17 although there are conflicting reports as to whether they affect the exercise training response. The literature in this area is contradictory. Studies have demonstrated an attenuated submaximal and maximal exercise response with endurance training.18 Others have observed a full training response when beta-blockers are compared to placebo.19,20 The reasons for these discrepancies are not entirely clear, but these studies were done on different patient populations, with different beta-blockers and different dosages.

In contrast, while calcium-channel blockers differ in structure and pharmacologic effects on calcium channels,21 verapamil,17 nifedipine,22 and diltiazem23 have all been documented not to affect acute exercise capacity, and nifedipine has no effect on the exercise training response.24 This homogeneous response of the calcium-channel blockers studied thus far is confirmed in our study, indicating that the beneficial effects of exercise training on coronary artery disease are not deleteriously affected by concomitant calcium-channel blocker therapy.

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