Demonstration of Training Effect During Chronic $\beta$-adrenergic Blockade in Patients with Coronary Artery Disease

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SUMMARY Attenuation of exercise-induced increases in heart rate and cardiac output by chronic $\beta$-adrenergic blockade has been thought to compromise benefit of exercise training in patients with coronary artery disease (CAD). To assess this important issue, 35 CAD patients were evaluated by a 3-month walk-jog-cycle training program: 14 patients received no $\beta$ blocker (group 1), 14 received propranolol, 30–80 mg/day (group 2), and seven patients received propranolol, 120–240 mg/day (group 3). The extent of CAD, resting heart rate before training blood pressure and $V_O_2$ max were similar ($p = NS$) in each group. The maximal exercise heart rate (mean $\pm$ SD, 147 $\pm$ 21 beats/min in group 1 vs 120 $\pm$ 10 beats/min in group 2 and 115 $\pm$ 12 beats/min in group 3) was not significantly different between groups. The $V_O_2$ max before training was 25 $\pm$ 5.0 ml/kg/min in group 1 vs 23 $\pm$ 3.2 ml/kg/min in group 2 and 26 $\pm$ 2.8 ml/kg/min in group 3 ($p = NS$). Training consisted of three 1-hour periods per week at a heart rate of 70–85% of the maximal pretraining heart rate. In each group, $V_O_2$ increased ($p < 0.05$) after training: group 1, 27%; group 2, 30%; group 3, 46%. The double product was unchanged after training ($p = NS$) in each group.

These data indicate that substantial training effects may be achieved in CAD patients despite therapeutic doses of $\beta$ blockers and a reduced training HR. Thus, there appears to be no indication to reduce $\beta$ blockers in CAD patients engaged in cardiac rehabilitation.

EXERCISE CONDITIONING is valuable therapy for certain patients with coronary artery disease and chronic stable angina pectoris. In appropriately selected patients, exercise training results in an increase in exercise tolerance, maximal rate of oxygen uptake ($V_O_2$ max) and double product. Beta-adrenergic blockade produces attenuation of the usual increase in heart rate and blood pressure during exercise, and consequently, has important therapeutic benefits in many patients with angina pectoris. In this manner, $\beta$-blocking agents prolong exercise tolerance by affording greater external work performance concomitant with reduced cardiac work and myocardial oxygen requirements.

Despite the widespread clinical usage of $\beta$-adrenergic blocking drugs in coronary artery disease and the common practice of prescribing exercise conditioning programs to patients with ischemic heart disease, many of whom are receiving $\beta$-blocking agents, objective data concerning the effect of these drugs on the patient’s ability to achieve a training effect are lacking. It has been presumed that chronic exercise during therapeutically imposed limitation in heart rate and cardiac output responses would prohibit an optimal beneficial training effect.

One study showed that exercise training provided no additional benefit in patients receiving $\beta$ blockers, whereas another study suggested that an improvement in exercise capacity may be achieved by coronary patients engaged in an exercise program despite the presence of $\beta$ blockade.

The present investigation, carried out in 35 patients who had documented coronary artery disease and were receiving no, moderate or large doses of propranolol, was designed to examine the effects of chronic $\beta$-adrenergic blockade on the ability to derive a cardiovascular training effect from an exercise conditioning program.

Materials and Methods

Patient Population

Thirty-five male patients enrolled in The Methodist Hospital cardiac rehabilitation program were evaluated. Each patient had coronary heart disease confirmed by a documented myocardial infarction or selective coronary arteriography. Twenty-five patients had previous myocardial infarctions and 12 patients had undergone coronary artery bypass surgery. The decision to use propranolol and the dosage administered were at the discretion of each patient’s physician; however, no alteration in therapy was allowed during the rehabilitation program so that propranolol as well as other medications were maintained constant. The study population was divided into three groups: group 1 consisted of 14 patients who received no $\beta$-blockade therapy during the 3-month exercise program, group 2 consisted of another 14 patients who received low-dose propranolol (30–80 mg/day), and group 3 consisted of seven patients who received high-dose propranolol (120–240 mg/day).

Among the 14 group 2 patients, eight were taking...
propranolol because of angina, three after a myocardial infarction and two because of hypertension; in one patient the drug was given after coronary bypass surgery. Of the seven group 3 patients, four were receiving propranolol for angina pectoris, two after a myocardial infarction and one after coronary bypass. In addition, each patient taking propranolol received a constant dose for at least 2 weeks before entry into the study.

Before the initiation of exercise training, all patients underwent a maximal graded treadmill stress test using the Bruce protocol.9 Treadmill exercise was terminated because of angina in four patients in group 1, four patients in group 2 and in one patient in group 3; fatigue or dyspnea was the reason for stopping in 10 group 1, 10 group 2 and six group 3 patients. Heart rate and systolic blood pressure at rest and at peak exercise were recorded, and the maximal double product was calculated. Aerobic capacity (\(\text{VO}_2\) max) was estimated from the duration of exercise by a standard regression equation: 
\[
\text{VO}_2\text{ max for males} = 3.88 + (0.056 \times \text{duration of exercise in seconds}).
\]
Exercise for the training period was prescribed for each patient according to the initial exercise test results by selecting a training heart rate of 70–85% of the peak heart rate during maximal stress.

The exercise training program consisted of 1-hour sessions 3 days a week for 12 weeks. Each class consisted of a warm-up period of calisthenics, 40 minutes of walking, jogging and cycling, and a cool-down period. A repeat maximal treadmill exercise test using the Bruce protocol was performed after the 12-week training period.

Each group participated in equivalent numbers of training sessions. Thus, of the 36 possible training periods, the mean attendance was 31 sessions for group 1, 32 sessions for group 2 and 31 sessions for group 3. Patients who attended fewer than 25 sessions were not included in the investigation.

Statistical analyses were carried out using \(t\) tests for paired and unpaired data. The data are presented as mean ± sd.

**Results**

The clinical characteristics of each group are summarized in table 1. The proportions of patients with previous myocardial infarction, current angina pectoris and coronary bypass surgery were similar (\(p > 0.05\)) in each group. Six patients in group 1, seven in group 2 and three in group 3 had a previous myocardial infarction and angina pectoris.

The measured and derived indexes obtained at rest and exercise in the three groups are summarized in table 2. There were no statistically significant differences between the groups with regard to resting heart rate and blood pressure before or after training. Total treadmill exercise duration before training was similar (\(p > 0.05\)) in each group. Additionally, maximal ST-segment depression measured 0.08 second after the J point was similar (\(p > 0.05\)) in each group before training: 0.93 ± 0.3 mm, 1.21 ± 0.4 mm and 0.83 ± 0.3 mm in groups 1, 2 and 3, respectively. Heart rate, but not systolic blood pressure, determined at peak exercise was significantly (\(p < 0.05\)) attenuated in groups 2 and 3 compared with group 1. There were no differences (\(p > 0.05\)) in peak heart rate, systolic blood pressure or double product during exercise in group 2 compared with group 3 before or after training. Similarly, there were no intragroup differences in these exercise variables determined before and after the training protocol.

In each group, the absolute treadmill exercise duration was greater after training than before training (all \(p < 0.05\)) (figs. 1–3). Each group exhibited a substantial and significant (\(p < 0.05\)) increase in \(\text{VO}_2\) after training (table 2). The mean absolute increments in exercise duration after training were similar (\(p > 0.05\)) in each group.

The mean training heart rate in the groups receiving propranolol was substantially less than in controls. However, the average amount of exercise performed during each training session was equivalent (\(p > 0.05\)) in each group: 5.2 ± 1.84 mets, 5.1 ± 1.15 mets and 5.1 ± 1.17 mets in groups 1, 2 and 3, respectively.

The 35 patients in this study had no complications during the exercise training periods or as a result of propranolol therapy.

**Discussion**

Some investigators have speculated that physical conditioning programs in coronary heart disease patients receiving \(\beta\)-adrenergic blocking agents may not be beneficial.3,7 This opinion is supported by the results of studies in which the acute i.v. administration of \(\beta\) blockers to normal subjects caused a decline in exercise tolerance, peak heart rate and left ventric-
TABLE 2. Effect of Propranolol on Exercise Training

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Resting heart rate</td>
<td>74 ± 22</td>
<td>73 ± 23</td>
<td>71 ± 10</td>
</tr>
<tr>
<td>(beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak ex heart rate</td>
<td>147 ± 21</td>
<td>152 ± 17</td>
<td>120 ± 10†</td>
</tr>
<tr>
<td>(beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting systolic BP</td>
<td>121 ± 19</td>
<td>118 ± 20</td>
<td>124 ± 17</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
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<tr>
<td>Peak ex systolic BP</td>
<td>157 ± 24</td>
<td>168 ± 28</td>
<td>165 ± 18</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise test duration</td>
<td>7.1 ± 1.9</td>
<td>9.8 ± 1.9*</td>
<td>6.3 ± 1.8</td>
</tr>
<tr>
<td>(min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak ex double product</td>
<td>23,100 ± 3,779</td>
<td>25,600 ± 4,281</td>
<td>19,863 ± 3,225</td>
</tr>
<tr>
<td>(beats/min × mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO2 max (ml/kg/min)</td>
<td>25.1 ± 5.0</td>
<td>31.9 ± 9.5*</td>
<td>23.2 ± 3.2</td>
</tr>
<tr>
<td>Goal training heart</td>
<td>117 ± 19</td>
<td>98 ± 14</td>
<td>93 ± 12†</td>
</tr>
<tr>
<td>rate (mean beats/min)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Values are mean ± SD.
Abbreviations: ex = exercise; BP = blood pressure.
* p < 0.05 vs value before training.
† p < 0.05 vs group 1.

However, extrapolation of these findings to patients with coronary artery disease and angina pectoris, in whom exercise tolerance may be reduced by the development of myocardial ischemia, may be misleading. We found a 31% improvement in exercise capacity in 20 coronary artery disease patients receiving propranolol in moderately large doses (160–320 mg/day) in a double-blind, crossover study. The present investigation shows that an unequivocal training effect can be obtained in coronary heart disease patients despite the administration of propranolol; improvement in maximal aerobic capacity was comparable to that in a control group of patients with coronary heart disease who were not receiving propranolol. The improvement in VO2 max was most marked in the patients receiving the higher doses of propranolol.

Our findings are in agreement with those of Obina et al., who reported 17 patients with angina pectoris who showed sequential improvement in exercise capacity by the addition of propranolol followed by a conditioning program. The inability of other workers to show an additive effect to β blockade by training 29 patients with angina pectoris may have been due to inadequate exercise (15 minutes of active exercise twice weekly) in patients receiving prindolol, 5 mg three times daily.

The patients in this investigation achieved adequate β blockade compared with the control group, as evidenced by the marked attenuation of maximal
heart rate response to exercise before and after the 3-month training program (table 2). Despite attenuated peak heart rate and peak double product during exercise, both propranolol-treated groups had improved exercise tolerance at least comparable to that in the control patients. These increases in peak exercise tolerance occurred in the propranolol-treated groups despite training at significantly reduced heart rates, which were determined by the maximal heart rate response to exercise before training. Thus, group 1 trained at a mean heart rate of 117 beats/min and groups 2 and 3 trained at mean heart rates of 98 and 93 beats/min, respectively. Group 3 patients tended to be younger and slightly fewer had had a myocardial infarction. Thus, our data suggesting that a greater training effect occurred with larger doses of propranolol should be interpreted with caution. The finding of principal importance, however, is that patients who received therapeutic quantities of a β blocker and underwent a 12-week exercise program can achieve a training effect. Hence, chronic administration of a β-blocking agent does not prevent improvement in exercise tolerance. Whether it actually improves the ability to derive a training effect from exercise can only be speculated. Further, one must consider the possibility that β-adrenergic blockade per se contributed to improved exercise tolerance to a greater extent than regular exercise training itself. This consideration does not seem likely, however, because patients in groups 2 and 3 had received propranolol for a mean of 7 months. Thus, the improvement in exercise tolerance in these two groups appears to relate to the exercise program.

Normal subjects increase their exercise capacity during physical training by augmenting cardiac output and redistributing cardiac output to actively exercising muscles, with consequent widening of the arteriovenous oxygen difference. Although peak double product may or may not be increased by training in normals, exercise conditioning prolongs the time required to achieve peak double product.

In coronary patients, exercise training may result in a greater double product and extend the exercise time required to achieve the peak double product. In the present study, peak exercise double product was not increased by training in the patients receiving propranolol. Thus, there is no evidence that cardiac performance was improved by exercise training in the propranolol-treated patients. However, because exercise duration and calculated VO₂ max were significantly increased (table 2), an unequivocal training effect resulted. We therefore suggest that the extended exercise tolerance resulted from peripheral alterations, which may be related to redistribution of blood flow, enhanced oxygen extraction by skeletal muscles or facilitated release of oxygen by hemoglobin.

Certain limitations of the present investigation should be discussed. The patients were not randomly assigned to one of the three groups, but rather, were assigned to a particular group based on the propranolol dosage prescribed by each patient's physician. Therefore, certain intrinsic bias with regard to the type of patient likely to receive no moderate or large doses of a β-blocking agent are probably reflected in our study groups. Another possibility is that without propranolol, patients in groups 2 and 3 may have achieved even greater benefit from the training program. However, these issues do not detract from the observation that a training effect in coronary artery disease patients may occur despite the presence of modest to large doses of a β-adrenergic blocking agent. The relative magnitude of improvement in exercise tolerance in each group is less important than the finding that patients receiving propranolol chronically can achieve a training effect. The mechanism for achieving this benefit at reduced training cardiac work loads cannot be determined from the present data.

In conclusion, the overall beneficial effects of exercise training consisting of extended exercise duration at reduced cardiac work loads may be accomplished despite β-adrenergic blockade and the resultant attenuated training heart rate. Cardiac rehabilitation does not appear to be contraindicated in patients receiving large therapeutic doses of propranolol. Finally, because of the beneficial effects of β-adrenergic blockade on angina pectoris, the possibility of a protective action against mortality after myocardial infarction and the desirability of limiting exercise double product in patients with symptomatic coronary artery disease, it may be preferable for many patients with severe coronary heart disease engaged in exercise training programs to receive β-adrenergic blockers.

Acknowledgement

The authors gratefully acknowledge the secretarial skills of Donna Chapman and Sharon Bonnot.

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Demonstration of training effect during chronic beta-adrenergic blockade in patients with coronary artery disease.
C M Pratt, D E Welton, W G Squires, Jr, T E Kirby, G M Hartung and R R Miller

Circulation. 1981;64:1125-1129
doi: 10.1161/01.CIR.64.6.1125

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