Attenuation of Exercise Conditioning by Beta-adrenergic Blockade

DAVID L. SABLE, M.D., H. L. BRAMMELL, M.D., MARK W. SHEEHAN, M.D., ALAN S. NIES, M.D., JOHN GERBER, M.D., AND LAWRENCE D. HORWITZ, M.D.

SUMMARY High levels of β-adrenergic stimulation accompany strenuous exercise, but the possibility that β-adrenergic blockade might prevent exercise conditioning has not been adequately investigated. We studied normal, sedentary men, ages 21–35 years, before and after 5 weeks of intensive aerobic conditioning. On a double-blind protocol, eight received placebo and nine propranolol throughout the conditioning period. A high level of β-adrenergic blockade was documented in all subjects receiving propranolol; individual mean plasma propranolol concentrations were 100–292 ng/ml. Both groups trained at comparable intensities. Graded maximal treadmill tests were performed before starting drugs or training, and were repeated 3–5 days after completing the conditioning period, when β-adrenergic blockade was no longer present. In subjects who received placebo, training increased exercise duration (16.4 ± 1.3 to 21.2 ± 1.5 minutes [± SEM], p < 0.01) and maximal oxygen uptake (43.6 ± 2.9 to 52.7 ± 3.2 ml/kg/min, p < 0.05). Subjects who received propranolol had only modest improvement in exercise duration (16.0 ± 0.6 to 17.3 ± 0.9 minutes, p < 0.05), and no significant change in maximal oxygen uptake (40.4 ± 1.4 to 40.9 ± 0.9 ml/kg/min). With training, diastolic pressure at maximal exercise decreased in subjects who received placebo (63 ± 3 to 48 ± 3 mm Hg, p < 0.05) but was unchanged in subjects who received propranolol. Training did not alter maximal heart rate in either group. Thus, high levels of β-adrenergic blockade markedly attenuated aerobic conditioning in these normal subjects. We conclude that β-adrenergic stimulation is essential in exercise conditioning.

ENDURANCE EXERCISE results in adaptive changes in the cardiovascular system known as training or conditioning effects. In normal subjects performing near-maximal exercise, the conditioning process results in greater physical work capacity, total body oxygen consumption, cardiac output, stroke volume and arteriovenous oxygen difference.1-5 At submaximal work loads, conditioning results in diminished myocardial oxygen consumption, lower heart rate and higher stroke volume.6-8 Similar changes occur with exercise training in many patients with coronary artery disease.4-6 The potentially favorable nature of these changes is the physiologic basis for the use of aerobic exercise programs in rehabilitating patients with coronary artery disease.

The mechanisms by which exercise-induced cardiovascular conditioning occurs are poorly understood. It is known, however, that a high level of sympathetic stimulation accompanies aerobic exercise of substantial intensity.12-14 In a recent study in dogs, regular intermittent infusions of a synthetic catecholamine, dobutamine, resulted in cardiovascular conditioning effects that resembled those achieved with regular intermittent aerobic exercise.15 These data indicate that repeated sustained sympathetic stimulation might be an important factor in exercise conditioning.

Beta-adrenergic blockade is widely used to treat coronary artery disease, and aerobic exercise is often prescribed in cardiac rehabilitation programs. If β-adrenergic stimulation is needed for exercise conditioning, then β blockade might be expected to interfere with this process. To test this hypothesis, we studied 17 healthy, sedentary men before, during and after an intensive 5-week aerobic exercise program. Using a double-blind protocol, eight subjects received placebo and nine propranolol during the training period. Conditioning effects were compared in the two groups by evaluating maximal treadmill performance while the subjects were not taking drugs before and after training.

Methods

Seventeen male volunteers, ages 21–35 years, participated in the study. None had a history of cardiac or pulmonary disease or hypertension. All were nonsmokers and had not exercised regularly for at least 1 year before the study. The subjects had normal cardiovascular physical examinations, chest roentgenograms and resting ECGs. Before entry into the study, each underwent a graded maximal treadmill test to document a normal electrocardiographic response to exercise. Oxygen consumption was calculated from expired gas analysis, as described below. Subjects were then separated into pairs with similar maximal oxygen consumptions. One member of each pair was randomized to treatment with propranolol and the other to placebo. The assignment of the subjects and the monitoring of plasma propranolol levels were done by two of the authors not otherwise involved in the day-to-day conduct of the study. Neither the subjects nor the other investigators knew which subjects received propranolol.

Initially, all subjects underwent a standardized battery of tests before starting propranolol or placebo (test 1). Each subject had fasted for 12 hours and had abstained from alcoholic beverages for at least 72
hours before testing. After body weight was recorded, a 16-gauge, 2-inch i.v. catheter (Angiocath, Deseret Company) was inserted in an antecubital vein. A slow i.v. infusion of normal saline solution was begun at a rate that prevented blood from clotting in the catheter. The subjects then rested supine alone in a quiet room for 30 minutes, after which heart rate, blood pressure, and ECG were recorded as resting data. Vital capacity and expired volume over the first second of forced expiration (FEV₁) were measured on a Stead-Wells Spirometer (Warren E. Collins, Inc.). Graded maximal treadmill testing was then performed on a Quinton treadmill (model 1849C) using 2-minute stages. The protocol was designed so that the estimated total oxygen consumption (VO₂) increased by 7 ml/kg/min at each of the first three stages, and by 3.5 ml/kg/min in each stage thereafter (table 1). Exercise was continued to exhaustion. The ECG was continuously monitored by telemetry on an oscilloscope. Blood pressure by cuff sphygmomanometry, heart rate, and ECG were recorded during the last 10 seconds of each minute of exercise, and during the last 10 seconds of each minute after exercise for 5 minutes. Expired gases were collected by a 13-liter Collins mouthpiece fitted to a Koegel valve. To measure ventilation, expired air was directed through a hot-wire anemometer into a mixing chamber. Expired carbon dioxide and oxygen were measured by continuous sampling from the mixing chamber, using a Beckman LB-2 carbon dioxide analyzer and a fuel-cell oxygen analyzer. Outputs from these analyzers were monitored on-line by a MicroNova computer (Data General Corporation). Each 30 seconds during exercise, printouts of minute ventilation, VO₂, and carbon dioxide production were obtained.

After test I, propranolol or placebo was taken orally by each subject four times daily in equal divided doses. Over a 1-week period, the dose of propranolol was adjusted to obtain a plasma level greater than 100 ng/ml 3 hours after a dose. This concentration of propranolol consistently produces a high level of β-adrenergic blockade in normal subjects, with maximal reduction of exercise tachycardia.16-18 The total daily dose necessary to attain this plasma level ranged from 160-640 mg. At the end of this week, a second battery of tests (test II), identical to the first, was given to assess the effects of propranolol on exercise performance before training and to establish a maximal drug-influenced heart rate that could be used for exercise prescription during training. Treadmill testing was begun 3 hours after the last dose of propranolol or placebo, and blood samples for propranolol measurement were taken immediately before treadmill exercise. The concentration of propranolol in plasma was determined using high-pressure liquid chromatography, as described by Aarons et al.19

After test II, the 5-week training period was begun. Subjects exercised three times per week in supervised, telemetry-monitored sessions. Each session began with 5 minutes of stretching and warm-up exercises. This was followed by 8 minutes of continuous exercise on each of three devices: motor-driven treadmill, bicycle ergometer, and steps (repeated step-ups using a single step of fixed height). Subjects were allowed 1–2 minutes of rest between the different modes of exercise. The average steady-state heart rate was recorded for each mode of exercise. A 20-minute run followed exercise on the devices. In addition to the supervised sessions, all subjects were required to exercise 2 days per week, monitoring and reporting their own steady-state pulse rate during 30–45 minutes of continuous running or bicycling. Compliance with medication was documented by weekly pill counts and by propranolol blood level measurements three times during the training.

Subjects were required to exercise at or above a minimal heart rate, which was 75% of the maximal heart rate (HRmax) attained during treadmill exercise at test II. This minimal heart rate corresponded to a similar intensity of exercise for both propranolol and placebo subjects when calculated as VO₂ at 75% of HRmax divided by maximal VO₂, based on VO₂ measured at test II.

At the end of the fifth week of training, subjects performed a third battery of tests (test III) to assess the effects of training on exercise performance while the subject was receiving drugs. Drugs were then stopped, and the subjects continued to exercise 3 more days while residual body stores of drugs were metabolized. Then, 3–5 days after drugs had been stopped, a final battery of tests (test IV), identical to tests I, II, and III, was performed to evaluate the effect of drug withdrawal on exercise performance by comparison with test III.

Comparison of mean intragroup changes between the four test sessions was accomplished by two-way analysis of variance, using Student-Newman-Keul's test for multiple comparisons, with p < 0.05 considered significant. The mean differences between groups were compared by unpaired, two-tailed t-test. The results are reported as mean ± SEM.

### Results

#### Description of Subjects at Entry

Table 2 is a comparison of placebo and propranolol groups on entry into the study. There were no significant differences between groups in age, weight, percent body fat by skinfold measurement, initial maximal VO₂ (VO₂max), or treadmill exercise duration.

#### Compliance with Medication and Training

Subjects in both groups reported excellent compliance with the prescribed dosage schedules. Compli-

---

### Table 1. Protocol for Maximal Treadmill Testing

<table>
<thead>
<tr>
<th>Stage</th>
<th>Time (min)</th>
<th>Speed (mph)</th>
<th>Grade (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2</td>
<td>3.0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>3.4</td>
<td>4</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>3.75</td>
<td>6</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>3.75</td>
<td>8</td>
</tr>
<tr>
<td>V</td>
<td>2</td>
<td>3.75</td>
<td>10</td>
</tr>
</tbody>
</table>

After stage V, speed remained unchanged and grade increased by 2%.
TABLE 2. Comparison of Placebo and Propranolol Groups at Entry into the Study

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.5 ± 1.3</td>
<td>27.2 ± 1.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.6 ± 4.1</td>
<td>76.6 ± 2.2</td>
</tr>
<tr>
<td>%BF</td>
<td>20.5 ± 1.5</td>
<td>20.9 ± 1.4</td>
</tr>
<tr>
<td>VO₂ max (ml/kg/min)</td>
<td>43.6 ± 2.9</td>
<td>40.4 ± 1.4</td>
</tr>
<tr>
<td>Exercise duration (min)</td>
<td>16.4 ± 1.3</td>
<td>16.0 ± 0.6</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

Differences between groups are not significant.

Abbreviations: %BF = percent body fat by skinfold measurement; VO₂ max = maximal oxygen consumption.

ance was confirmed by weekly counts of each subject’s remaining pill supply, by retrospective observation of heart rates during exercise sessions, and by measured blood levels of propranolol. Mean propranolol blood levels ranged from 100-292 ng/ml during the 5-week training period.

Propranolol and placebo subjects participated in 91% of the monitored training sessions. The intensity of training was also similar in the two groups. Mean steady-state heart rate during training sessions was 85 ± 1% of HRmax for the placebo group, and 93 ± 1% for the propranolol group. Based on VO₂ measurements at test II, these heart rates corresponded to a mean steady state VO₂ of 33.3 ± 2.2 ml/kg/min (75 ± 3% of VO₂ max) for the placebo group, and 32.5 ± 2.4 ml/kg/min (79 ± 3% of VO₂ max) for the propranolol group. Each group trained at a level of approximately 10 metabolic equivalents (1 met = VO₂ of 3.5 ml/kg/min).

Side Effects of Drug Treatment

Seven subjects noted unpleasant symptoms which they attributed to medication. One who was receiving placebo reported excessive fatigue and lack of energy. The other six were receiving propranolol at doses of 40-120 mg four times daily. Five of the latter subjects had difficulty concentrating while studying or reading and a general decrease in energy level. The sixth complained of light-headedness and fatigue while skiing at an altitude of 9000 feet, symptoms he had not experienced previously at that altitude. No symptoms were severe enough to require withholding medication or decreasing doses. The severity of symptoms did not correlate with plasma propranolol concentrations or the amount of training effect achieved in any subject.

Effects of Training in the Placebo Group

Comparison of maximal treadmill performance before and after training in the placebo group (tests I and IV) showed a mean increase in VO₂ max from 43.6 ± 2.9 to 52.7 ± 3.2 ml/kg/min (p < 0.05), a 21% improvement (fig. 1). Exercise duration increased from 16.4 ± 1.3 to 21.2 ± 1.5 minutes (p < 0.01), a 29% improvement (fig. 2). Ventilation at maximal exercise (VEmax) increased from 111 ± 8 to 144 ± 9 l/min (p < 0.01), a 30% increase (fig. 3). Resting heart rate (HRrest) tended to decrease, but the change was not statistically significant. HRmax, resting systolic and diastolic blood pressures (SPrest, DPrest) did not change significantly. Systolic blood pressure at maximal exercise (SPmax) was unchanged after training, but diastolic blood pressure at maximal exercise (DPmax) decreased from 63 ± 3 to 48 ± 3 mm Hg (p < 0.05).

The increase in VO₂ max and exercise duration occurred primarily between tests II and III (i.e., during the exercise training period) (fig. 1). VE max also increased between tests II and III, but in addition increased between tests I and II (p < 0.05) and between tests III and IV (p < 0.05) (fig. 3). There were no changes in resting vital capacity or FEV1 at any of the four test sessions.

Effects of β-adrenergic Blockade Before Training

After β blockade was achieved but before training commenced (test I vs test II), there were significant decreases in HRrest (63 ± 4 to 51 ± 4 beats/min, p < 0.05), HRmax (189 ± 2 to 130 ± 3 beats/min, p < 0.05), SPmax (176 ± 4 to 140 ± 5 mm Hg, p < 0.05), and exercise duration (16.0 ± 0.6 to 15.0 ± 0.8 minutes, p < 0.05). There were no significant changes resulting from the initial β-adrenergic blockade in VO₂ max, VE max, DP max, DP rest or SP rest.

Effect of Training in the Propranolol Group

Comparison of tests I and IV in the propranolol group shows the effect of training on maximal treadmill performance when subjects were tested in the absence of β-adrenergic blockade, first at entry into the study and then at the conclusion of the study after the drug had been stopped. VO₂ max remained unchanged after the 5-week training program (figs. 1 and 4A). There was no significant difference in VO₂ max between the groups before training (test I), but a highly significant difference (p < 0.002) after training.

**Figure 1.** Effect of exercise training on maximal oxygen consumption (VO₂ max). Brackets represent mean ± SEM. I = before training or drug; II = during drug administration before training; III = during drug administration after training; IV = without drug after training.
Exercise duration in the propranolol group increased slightly (16.0 ± 0.6 to 17.3 ± 0.9 minutes, p < 0.05). There was no significant difference in exercise duration between groups at test I, but a significant difference (p < 0.05) at test IV after training. VEmax in the propranolol group increased by 20%, from 117 ± 9 to 140 ± 10 l/min (p < 0.05). VCO₂max increased from 42.7 ± 2.0 to 48.9 ± 2.5 ml/kg/min, a 15% increase (p = 0.06). HRrest, HRmax and DPmax were unchanged. SPmax was significantly increased after training (176 ± 4 to 186 ± 5 mm Hg, p < 0.05).

A comparison of tests II and III shows the effects of training on maximal treadmill performance under the influence of β-adrenergic blockade. Exercise duration improved slightly with training (15.0 ± 0.8 to 16.6 ± 0.8 minutes, p < 0.05) (fig. 2). There were no significant changes in VO₂max, VEmax, VCO₂max, HRrest, HRmax or DPmax.

The effect of propranolol on maximal exercise performance after training was assessed by comparing tests III and IV. After withdrawal of β-adrenergic blockade, VEmax increased from 114 ± 9 to 140 ± 10 l/min (p < 0.05), HRmax increased from 137 ± 3 to 189 ± 2 beats/min (p < 0.05), and HRrest increased from 49 ± 3 to 62 ± 4 beats/min (p < 0.05). There were no significant differences in VO₂max, exercise duration, VCO₂max, DPmax, SPrest or DPrest (figs. 3 and 4). There were no changes in resting vital capacity or FEV₁ at any of the test sessions.

Discussion

Despite extensive documentation of the cardiovascular effects of exercise conditioning, the mechanisms by which this process occurs are unknown. Cardiovascular conditioning is achieved through sustained and repeated exercise periods during which HR, arterial pressure, cardiac output and VO₂ are substantially increased above resting values. High levels of sympathetic nervous system activity occur with such exercise and contribute to these increments in cardiovascular performance. Whether pharmacologic blockade of the β-adrenergic receptors, through which sympathetic cardiac effects are mediated, prevents or attenuates cardiovascular conditioning is the subject of this study.

We used a double-blind protocol in which the experimental group was subjected to β-adrenergic blockade during training, but maximal exercise performance was evaluated before and after the training period when no β-adrenergic blockade was present. The unmedicated subjects unequivocally achieved a conditioning effect, demonstrated by large increases in VO₂max and exercise duration. In addition, DPmax was reduced. The overall effect of training in the propranolol group is seen in the comparison of tests I and IV, which were performed in the absence of β blockade. VO₂max was unchanged by training and the increase in exercise duration (8%) was very small compared with that in the control group (29%). Thus, little or no cardiovascular conditioning was achieved when β-adrenergic stimulation during exercise training was blocked by propranolol.

In contrast to its effect on VO₂max in the two groups, training resulted in comparable increases in VEmax in both groups (figs. 3 and 4C). In the propranolol group, the largest change in VEmax occurred between tests III and IV, which were performed after training, before and after stopping propranolol. The few additional days of training between these tests do not account for this change. We
suspect that propranolol may have suppressed VE\textsubscript{max} through subtle effects on bronchiolar smooth muscle that were not detectable in our resting measurements. Alternatively, chronic propranolol administration may have diminished the release of lactic acid from skeletal muscle, as reported previously,\textsuperscript{20, 21} resulting in lower blood PCO\textsubscript{2} and a lesser stimulus to ventilation.

In the placebo group, there was a tendency toward small increases in VO\textsubscript{2}\textsubscript{max}, exercise duration, VE\textsubscript{max}, and VCO\textsubscript{2}\textsubscript{max} between tests I and II and between tests III and IV (figs. 1, 2 and 3). No training occurred during the week between tests I and II, and there were only two days of training between tests III and IV. These changes are probably due to familiarization with the testing equipment and environment, and perhaps to the subjects' desire to improve upon their previous performances. Such a "learning" effect, which does not represent a true conditioning response, occurs in serial exercise testing.\textsuperscript{22, 23}

Resting heart rates in both groups at the initiation of the study were lower than those generally reported in unconditioned subjects. These heart rates were obtained only after the subjects had rested supine in a quiet room for 30 minutes. Since these are substantially more basal conditions than are usually practiced for recording HR\textsubscript{rest}, we believe that the slower rates we reported are explained by the protocol.

We conclude that \(\beta\)-adrenergic blockade with propranolol markedly attenuates the cardiovascular conditioning effects of exercise in normal subjects, and that \(\beta\)-adrenergic stimulation may be the major physiologic mechanism contributing to cardiovascular conditioning through dynamic exercise. Further investigation is necessary to determine if these findings apply to patients receiving propranolol for treatment of coronary artery disease or hypertension, and to determine if less complete levels of \(\beta\)-adrenergic blockade or selective \(\beta\)\textsubscript{1} blockade permits a portion of the cardiovascular conditioning response to occur.

Acknowledgment

We are grateful for the excellent technical support provided by S. Arlene Niccoli, R.N., Barbara Morgan, R.P.T., Sidney Fee, R.P.T., Sandra Stoll, O.T.R., and William Orr, biomedical engineer.

References

Reversal of Exercise-induced Hemodynamic and Electrocardiographic Abnormalities after Coronary Artery Bypass Surgery

RADHA J. SARMA, M.D., AND MIGUEL E. SANMARCO, M.D.

SUMMARY Forty patients (35 men and five women) who experienced hypotension during maximal symptom-limited exercise test were retested after a 12 ± 4-month interval. Mean age was 53.5 years. All patients had multiple-vessel disease. Seventeen patients underwent coronary artery bypass surgery because of disabling angina, and 23 patients without disabling angina continued under medical management. At entry, there were no significant differences in age, left ventricular function or exercise performance between the medical and surgical groups.

At follow-up, the surgical group showed an average increase in the exercise duration of 2.2 ± 1.7 minutes ($p < 0.001$), maximal heart rate of $17 ± 15$ beats/min ($p < 0.001$), maximal systolic blood pressure of 26 ± 23 mm Hg ($p < 0.001$) and maximal rate-pressure product of 60 ± 41 ($p < 0.001$). These measurements did not change significantly in the medically managed group.

Exercise-induced hypotension is apparently caused by ischemic left ventricular dysfunction, since in the majority of patients, it is reversible after successful revascularization. This observation is supported by the lack of improvement in a comparable group of patients managed without surgery.

EXERCISE-INDUCED blood pressure abnormalities are associated with severe coronary artery disease. Although the mechanism of exertional hypotension is not known, it has been postulated to be secondary to ischemic left ventricular dysfunction. Several studies have demonstrated reversal of the hypotensive response after coronary revascularization, but it is not clear whether a medical program can achieve similar long-term results.

In this retrospective study, we assessed the long-term effects of medical management or coronary revascularization on serial exercise testing in patients with exertional hypotension.

Patients and Methods

Forty patients (35 men and five women) who experienced an abnormal blood pressure response during maximal symptom-limited treadmill exercise test and had repeat testing at 12 ± 4 months were studied. The average age was 53 years (range 36–73 years). An abnormal blood pressure response to exercise was defined as either a failure of the systolic blood pressure to increase at least 10 mm Hg after the first minute of exercise (five patients) or an initial rise in systolic blood pressure but subsequent fall of more than 20 mm Hg during continued exercise (35 patients).

Each patient was exercised using the Bruce multistage treadmill protocol. Before the test, blood pressure and heart rate were taken with the patient supine, sitting and upright. Blood pressure and heart rate were then recorded at 1-minute intervals during exercise, immediately after exercise and every minute thereafter for 5–10 minutes. The ECG was continuously monitored and a recording was obtained at the end of each minute using bipolar leads X, Y, modified Lewis and V₆. Patients exercised to a symptom-limited end point, such as severe angina pectoris, fatigue or shortness of breath. Medications were not stopped before exercise testing. At the time of the initial test six patients were taking antihypertensive medications and three were taking propranolol. At repeat testing, four
Attenuation of exercise conditioning by beta-adrenergic blockade.
D L Sable, H L Brammell, M W Sheehan, A S Nies, J Gerber and L D Horwitz

Circulation. 1982;65:679-684
doi: 10.1161/01.CIR.65.4.679

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/65/4/679.citation