Effects of selective and nonselective $\beta$-adrenergic blockade on mechanisms of exercise conditioning

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ABSTRACT Exercise conditioning involves adaptations in the heart, peripheral circulation, and trained skeletal muscle that result in improved exercise capacity. Since the specific influence of $\beta$-adrenergic stimulation on these various adaptations has not been clear, we studied the effect of $\beta_1$-selective and nonselective $\beta$-adrenergic blockade on the exercise conditioning response of 24 healthy, sedentary men after an intensive 6 week aerobic training program. Subjects randomly assigned to receive placebo, 50 mg bid atenolol, or 40 mg bid nadolol were tested before and after training both on and off drugs. Comparable reductions in maximal exercise heart rate occurred with atenolol and nadolol, indicating equivalent $\beta_1$-adrenergic blockade. Vascular $\beta_2$-adrenergic selectivity was maintained with atenolol as determined by calf plethysmography during intravenous infusion of epinephrine. All subjects trained at greater than 85% of maximal heart rate and 80% of VO$_2$-max determined on drug. VO$_2$-max increased after training 16 $\pm$ 2% (p < .05) in the placebo group and 6 $\pm$ 2% (p < .05) in the atenolol group, while there was no change in the nadolol group. At maximal exercise, subjects receiving placebo increased their exercise duration and oxygen pulse significantly greater than those receiving atenolol or nadolol. During submaximal exercise there were reductions in heart rate and heart rate–blood pressure product in all three groups, but these reductions were greater with placebo than with either drug. Leg blood flow during submaximal exercise decreased 24 $\pm$ 2% (p < .01) in the placebo group but was unchanged in the atenolol and nadolol groups. Lactates in arterialized blood during submaximal exercise were reduced equivalently in all three groups after training. Capillary/fiber ratio in vastus lateralis muscle biopsy specimens increased 31 $\pm$ 6% in the placebo group and 21 $\pm$ 6% in the atenolol group (both p < .05) and tended to increase in the nadolol group. Succinic dehydrogenase and cytochrome oxidase activities in muscle biopsy specimens increased equivalently in all three groups after training. Thus, although exercise conditioning developed to some extent in both drug groups, especially during submaximal exercise, these changes were less marked than that with placebo. While $\beta$-adrenergic blockade attenuated the exercise conditioning response, skeletal muscle adaptations including increases in oxidative enzymes, capillary supply, and decreases in exercise blood lactates were unaffected. Cardiac and peripheral vascular adaptations do appear to be affected by $\beta$-adrenergic blockade during training. Cardioselectivity does not seem to be important in modifying these effects.


AEROBIC EXERCISE TRAINING results in improved function of the heart, peripheral circulation, and skeletal muscle that results in enhanced physical work capacity.1–6 The relative importance of each adaptation and the factors that separately or together in-
ratory have shown that propranolol attenuates exercise conditioning. However, other investigators have not observed effects of β-blockade on exercise conditioning in healthy men. These conflicting results could represent differences in study design but may also reflect a differential effect of β-adrenergic blockade on the various mechanisms involved in exercise conditioning.

Since high heart rates and myocardial oxygen consumption during training appear to be requisites for optimal conditioning, the attenuation of exercise conditioning by propranolol could be caused in part by direct β-receptor blockade that inhibited cardiac adaptations. Since nonselective β-adrenergic receptor blockade also may alter skeletal muscle metabolism and peripheral vascular function, we considered the possibility that extracardiac adaptations could also be impaired. If so, cardioselective β-adrenergic blockers would be expected to be less detrimental during exercise training, since β-adrenergic receptors, which are modulators of peripheral vascular reactivity and carbohydrate metabolism in skeletal muscle, would be minimally affected. In prior studies, lactate metabolism during exercise was influenced more by nonselective than by β-selective adrenergic blockade, whereas hemodynamic and antilipolytic effects were similar with selective and nonselective β-adrenergic blockade.

We compared specific training-induced adaptations of skeletal muscle and the peripheral vasculature in healthy young men randomly assigned to groups with intact sympathetic control, cardioselective β-adrenergic blockade, or nonselective β-adrenergic blockade. We hypothesized that if skeletal muscle metabolic and vascular adaptations were inhibited by loss of β-sympathetic stimulation, selective β-adrenergic receptor blockade would attenuate exercise conditioning less than nonselective β-adrenergic blockade.

Methods

Study group. Twenty-four nonsmoking, healthy male volunteers, ages 21 to 35 years, participated in the study. Informed consent for all testing was obtained from each subject and the protocol was approved by the Human Subjects Committee of the University of Colorado Health Sciences Center. All subjects had not been exercising regularly and had resided in Denver for at least 6 months before the study. Each had a normal physical examination, resting electrocardiogram (ECG), and hematocrit. Before entry into the study, each subject underwent a graded maximal treadmill test to ensure a normal ECG and blood pressure response to exercise and to familiarize him with the treadmill protocol.

Study design. Measurements of heart rate and blood pressure, expired gas analysis, and exercise duration were performed during a standardized, graded treadmill exercise test. Central circulatory adaptations were analyzed by correlating changes in oxygen consumption and heart rate. The peripheral circulatory and metabolic effects of exercise training were analyzed by measuring calf muscle blood flow during supine submaximal exercise, lactate production during graded treadmill exercise testing, and oxidative enzyme activity and capillary supply in skeletal muscle. Initial testing (test I) was performed before training and drug dosing (figure 1). After 5 days on

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Study design. Subjects underwent treadmill testing, plethysmography, and muscle biopsy before and after aerobic conditioning. Drug-treated subjects were tested 5 days after receiving drugs. All drugs were discontinued for 5 days before final testing (test IV). The aerobic conditioning program was 6 weeks in duration.
medication but before the beginning of exercise training, treadmill testing and venous occlusion plethysmography were repeated (test II). Those investigators and technical staff directly involved in testing or exercise training were blinded as to treatment. At the end of the sixth week of training, another treadmill test was performed while the subjects were taking medication (test III). All drugs were then discontinued while the subjects continued to exercise for 2 more days. Two to 4 days later, which was 4 to 6 days after discontinuation of all drugs, final testing was performed (test IV).

**Treadmill testing.** Each subject fasted at least 4 hr before testing. A 20-gauge catheter was inserted into a vein on the dorsum of the hand, after which the subjects rested supine in a quiet room for 30 min before heart rate and blood pressure were recorded. The hand with the intravenous line was wrapped with a heating pad and warmed to 43° C. This “arterialized” the venous blood, allowing blood lactate measurements that closely approximated arterial samples at rest and during exercise as previously described. We validated the presence of arterialized blood with our system by measuring PO2 at rest and during exercise in eight of the 24 subjects.

Maximal exercise testing to exhaustion was performed on a treadmill according to a graded protocol with 3 min stages. To increase sensitivity to detect differences in performance, we used relatively small increments in workload (table I). We sought a plateau in oxygen consumption at peak exercise, defined as a change of less than 2 ml/kg/min in oxygen consumption compared with the prior 30 sec measurement. Arm blood pressure measured by cuff sphygmomanometer and heart rate calculated from the ECG were recorded during the last 10 sec of each minute of exercise. Expired gas analysis was used to determine ventilation (Ve), oxygen consumption (VO2), and CO2 production (VCO2) every 30 sec during exercise as previously described. To determine the amount of oxygen delivered by each heartbeat, “oxygen pulse” was calculated by dividing the oxygen consumption by the heart rate at each level of submaximal exercise and at peak exercise.

“Arterialized” blood for lactate, assayed by an enzymatic spectrophotometric technique, was withdrawn before exercise, during the last 30 sec of each exercise stage, and at peak exercise. The lactate threshold (LT) was defined as the point at which blood lactate during exercise increased beyond the upper limits of normal for resting lactate (1.3 mmol/liter). VO2-LT was the oxygen consumption at which the lactate threshold occurred, and VO2-LT/VO2max × 100 was the percent of maximal oxygen consumption at which this occurred. During the last 10 sec of each exercise stage subjects were asked to identify a subjective level of perceived exertion using a modified Borg scale.

**Venous occlusion plethysmography.** Calf blood flow and vascular resistance during submaximal exercise were determined by a “stop-measurement” technique employing venous occlusion plethysmography as previously described. Each subject performed 3 min of supine bicycle exercise at 600 kg/m/min. The first measurement of flow was obtained at 2.5 sec after exercise, then every 5 sec for four measurements to determine the hyperemic response. The highest postexercise flow was used for analysis. Bicycle exercise was performed in triplicate to provide an average of three flow values. Subjects rested between exercise periods until heart rate and blood pressure returned to basal conditions. Mean arterial pressure was calculated as one-third of the pulse pressure added to the diastolic pressure. Calf vascular resistance was calculated by dividing mean blood pressure by blood flow and expressed as peripheral resistance units (PRU). Plethysmography was performed on alternate days from maximal exercise testing.

**Skeletal muscle analysis.** Skeletal muscle biopsy samples were obtained from the vastus lateralis by a percutaneous needle technique. One sample for histochemical and morphometric analysis was mounted in gum tragacanth on a block and quick-frozen in isopentane precooled in liquid nitrogen. Another sample was washed free of blood and loose connective tissue with sterile 0.9% saline was immediately frozen in liquid nitrogen and stored at −70° C for later biochemical analysis. Serial sections for histochemical analysis and plastic embedded sections were prepared by the cryostat retrieval technique. Muscle fiber type was determined with the pH 9.4 myosin-ATPase reaction. Mean values were calculated for each specimen for fiber type composition, capillary/fiber ratio, capillary density (capillaries/mm2), and fiber diameter. Muscle samples were also analyzed for activity of two oxidative enzymes, succinic dehydrogenase (SDH) and cytochrome oxidase. SDH was analyzed by the method of Chi et al. and cytochrome oxidase by the method of Wharton and Tzagoloff.

**Drug dosing.** After initial testing, subjects were stratified by maximal oxygen consumption into matched trios. Within each matched trio, subjects were randomly assigned to placebo or selective (atenolol) or nonselective (nadolol) β-adrenergic blockade categories. The subjects were blinded as to the type of medication they received. Drugs or placebo were administered twice a day to produce a more consistent level of β-adrenergic blockade during the exercise training sessions. Nadolol was prescribed in 40 mg bid doses and atenolol in 50 mg bid doses. After 5 days on medication, subjects performed a second treadmill test (test II) to determine the degree of β1-adrenergic blockade by measuring the reduction in heart rate at maximal exercise from that before drug therapy (test I). β2-Adrenergic blockade was determined by the change in calf vascular resistance during infusion of epinephrine before and after administration of drugs or placebo. Plasma drug levels were obtained by methods described previously.

**Exercise training.** After the initial two tests, all subjects began a 6 week exercise program. Three times per week they performed 50 min of circuit training during supervised, telemetry-monitored sessions. Circuit training consisted of 25 min of stationary bicycle exercise, 12.5 min of treadmill walking, and 12.5 min of stepping walks (repeated step-ups using a single step of fixed height). Subjects were allowed 1 to 2 min of partial recovery between devices. Two times per week they performed a 40 min run during which they monitored their own pulses and recorded their immediate postexercise heart rates at the completion of each run. All exercise training sessions began approxi-

**TABLE 1**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Time (min)</th>
<th>Speed (mph)</th>
<th>Grade (%)</th>
<th>METS (estimated)</th>
</tr>
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<tbody>
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<td>I</td>
<td>2</td>
<td>3.0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
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<td>4</td>
<td>5</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>3.75</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>3.75</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>V</td>
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<td>3.75</td>
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<tr>
<td>VI</td>
<td>3</td>
<td>3.75</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>VII</td>
<td>3</td>
<td>3.75</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>VIII</td>
<td>3</td>
<td>3.75</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>IX</td>
<td>3</td>
<td>3.75</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>X</td>
<td>3</td>
<td>4.2</td>
<td>15</td>
<td>13.6</td>
</tr>
<tr>
<td>XI</td>
<td>3</td>
<td>4.2</td>
<td>17.5</td>
<td>15.0</td>
</tr>
<tr>
<td>XII</td>
<td>3</td>
<td>4.2</td>
<td>20</td>
<td>16.5</td>
</tr>
</tbody>
</table>
mately 2 hr after the last dose of drug or placebo was taken. Compliance with medication was documented by weekly pill counts, heart rate during exercise, and a plasma drug level measurement on a sample obtained at an unannounced time during the exercise training period.

The subjects were required to train at 85% of the maximal heart rate attained during the treadmill test performed on medication. Mean training heart rate was obtained from the recorded heart rates during each exercise session for the entire 6 weeks of exercise training. \( \overline{V}O_2 \) during training was estimated from the training heart rate by extrapolation from the measurements of heart rate and \( \overline{V}O_2 \) obtained during the pretraining treadmill test performed on medication or placebo (test II). From the \( \overline{V}O_2 \) at the mean training heart rate, a percentage of \( \overline{V}O_2\text{max} \) (on medication) at which the subjects began their training was obtained. To estimate how much work was performed by each subject during an exercise session, the number of kilocalories per liter of oxygen consumed was determined by using the thermal equivalent of oxygen for the nonprotein respiratory exchange ratio from a standardized table. Respiratory exchange ratio and \( \overline{V}O_2 \) corresponding to the subjects’ training heart rates were taken from test II. The total number of kilocalories consumed during an exercise session were obtained by determining the product of \( \overline{V}O_2 \) at training heart rate times the number of kilocalories per liter of oxygen consumed times the total number of minutes of exercise. Also, perceived exertion scores were recorded during the exercise sessions with the modified Borg scale.28

**Statistical analysis.** Mean differences between tests in each subject group were determined by two-way analysis of variance with the Student-Newman-Keul test for multiple comparisons, with \( p < .05 \) considered significant. One-way analysis of variance, with the Student-Newman-Keul test for multiple comparisons, was used to determine significant mean differences among groups. Linear regression lines were used to summarize the heart rate response of each subject to levels of submaximal exercise representing 45% to 85% of \( \overline{V}O_2\text{max} \) on test I for each testing period. The regression coefficients for each subject were then treated as dependent variables and subjected to two-way analysis of variance. This was performed for each testing period. Changes in blood lactate during successive submaximal workloads were analyzed with parametric multivariate dose-response curve techniques.49 A polynomial computer model that accurately described the data was determined, and multivariate comparisons were made with the polynomial coefficients. Two-way repeated measures analysis of variance was used to determine the difference in blood lactate reduction after training or drug dosing among the three subject groups. All data are presented as mean ± SEM.

**Results**

**Characteristics of subjects.** There were no significant differences among the groups for age, weight, heart rate, \( \overline{V}O_2\text{max} \) or exercise duration before drug randomization or exercise training (table 2). A plateau in oxygen consumption at peak exercise occurred in 88 ± 1% of the placebo group, 78 ± 2% of the atenolol group, and 78 ± 2% of the nadolol group. There were no significant differences by two-way analysis of variance among the three subject groups for any of the four testing periods. Thus a true physiologic maximum oxygen consumption was achieved by the majority of the subjects.

**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Atenolol</th>
<th>Nadolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>28 ± 1</td>
<td>29 ± 1</td>
<td>31 ± 1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.7 ± 4.2</td>
<td>78.5 ± 3.3</td>
<td>79.2 ± 4.9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>130 ± 3</td>
<td>137 ± 4</td>
<td>128 ± 2</td>
</tr>
<tr>
<td>Submaximal exercise</td>
<td>39.8 ± 1.2</td>
<td>40.7 ± 1.6</td>
<td>42.7 ± 1.2</td>
</tr>
<tr>
<td>Maximal exercise</td>
<td>181 ± 3</td>
<td>186 ± 2</td>
<td>188 ± 2</td>
</tr>
<tr>
<td>( \overline{V}O_2\text{max} ) (ml/kg/min)</td>
<td>22.8 ± 0.8</td>
<td>23.3 ± 1.2</td>
<td>26.1 ± 1.0</td>
</tr>
</tbody>
</table>

Values are mean ± SE.

Submaximal heart rate was measured at 60% entry \( \overline{V}O_2\text{max} \).

Differences among groups were not significant.

**Documentation of \( \beta_1 \)-adrenergic blockade and selectivity.** There was no significant change in maximal heart rate between tests I and II in placebo-treated subjects. The reduction in maximal heart rate (test II) was \( 48 ± 3 \) (SE) beats/min with atenolol (\( p < .05 \)) and \( 48 ± 4 \) beats/min with nadolol (\( p < .05 \)). As we have shown previously in these same groups of subjects,37 epinephrine-induced \( \beta_2 \)-adrenergic stimulation resulted in a fall in calf vascular resistance for both the placebo and atenolol groups and an increase in the nadolol group. Mean plasma drug levels were \( 226 ± 29 \) ng/ml atenolol and \( 43 ± 9 \) ng/ml nadolol.

**Compliance with medication and training.** All subjects took greater than 90% of their tablets with no significant differences among the groups. Plasma levels of both drugs obtained during a random, unannounced time during training were not significantly different from pretraining values. Fatigue occurred in three subjects taking placebo, three subjects taking atenolol, and five subjects taking nadolol. One subject taking atenolol had intermittent diarrhea, and one subject taking nadolol complained of cold extremities. No symptoms were severe enough to require withholding or modification of the medication dosage. Each group attended 99% of their exercise training sessions. All three groups slightly exceeded the prescribed heart rate of 85% of maximal heart rate on test II (88% to 91%). Training oxygen consumptions and kilocalories, estimated by the heart rate–\( \overline{V}O_2 \) relationship on test II and time of exercise, were similar in each group (table 3). By perceived exertion ratings, all subjects trained at a similar, very heavy level.

Both drug groups exercised at a lower mean heart rate than the placebo group during training. The heart rate–blood pressure product \( \times 10^-2 \), an index of myocardial oxygen consumption, was significantly lower in both drug groups during training than in the placebo
TABLE 3
Training data

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Atenolol</th>
<th>Nadolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean training HR (beats/min)</td>
<td>160 ± 3</td>
<td>125 ± 2^&lt;</td>
<td>122 ± 3^&lt;</td>
</tr>
<tr>
<td>Mean % HR max (test II)</td>
<td>89 ± 1</td>
<td>90 ± 1</td>
<td>88 ± 1</td>
</tr>
<tr>
<td>Mean estimated VO₂ during training (ml/kg/min)</td>
<td>32.0 ± 1.1</td>
<td>33.1 ± 1.4</td>
<td>32.7 ± 0.6</td>
</tr>
<tr>
<td>Mean % VO₂max (test II)</td>
<td>81 ± 2</td>
<td>86 ± 1</td>
<td>80 ± 1</td>
</tr>
<tr>
<td>Mean HR–BP during training (× 10⁻²)</td>
<td>274 ± 10</td>
<td>206 ± 10^&lt;</td>
<td>185 ± 10^&lt;</td>
</tr>
<tr>
<td>Supervised hours of training</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circuit</td>
<td>14.9 ± 0.1</td>
<td>14.9 ± 0.1</td>
<td>14.7 ± 0.2</td>
</tr>
<tr>
<td>Run</td>
<td>7.9 ± 0.1</td>
<td>7.8 ± 0.1</td>
<td>8.0 ± 0.0</td>
</tr>
<tr>
<td>Mean estimated Kcal during training</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circuit</td>
<td>573 ± 29</td>
<td>639 ± 33</td>
<td>634 ± 36</td>
</tr>
<tr>
<td>Run</td>
<td>459 ± 23</td>
<td>512 ± 26</td>
<td>507 ± 29</td>
</tr>
<tr>
<td>Perceived exertion score at training HR</td>
<td>7.0 ± 0.5</td>
<td>8.0 ± 0.4</td>
<td>7.0 ± 0.3</td>
</tr>
</tbody>
</table>

HR = heart rate; HR–BP = heart rate–blood pressure product.
Values are mean ± SE.
Mean training heart rates and HR–BP for atenolol and nadolol were significantly less than for placebo (^<p < .05, one way ANOVA). Differences among groups were not significant for all other variables listed.

Effect of training on treadmill performance in the placebo group. As a result of training, maximal oxygen consumption in the placebo subjects increased 16% from 39.8 ± 1.2 (test I) to 46.0 ± 2.1 ml/kg/min (test IV), (p < .01), (figure 2, A). Weight was unchanged during training. At maximal exercise, oxygen pulse, the amount of oxygen delivered per heartbeat, increased 16% from 15.9 ± 0.8 to 18.4 ± 0.9 ml/beat (p < .01), (figure 2, B). Exercise duration increased 25% from 22.8 ± 0.8 to 28.6 ± 1.2 min (p < .01), (figure 2, C). There was no change in maximal heart rate after training.

Resting heart rate–blood pressure product decreased from 73 ± 3 to 66 ± 4 × 10⁻² (p < .05).

At equal levels of submaximal exercise there were reductions in heart rate, heart rate–blood pressure product, respiratory exchange ratio (VCO₂/VO₂), and perceived exertion score and a rise in oxygen pulse as a result of training (all p < .05) (table 4, figure 3). Thus the placebo group showed conclusive evidence of training during maximal and submaximal exercise.

Effects of β-blockade before training. Heart rates during submaximal exercise were reduced by equivalent amounts with both atenolol and nadolol (figure 3). Both drugs also significantly reduced the heart rate–blood pressure product during submaximal and maximal exercise. VO₂max decreased 6% with atenolol from 40.7 ± 1.6 to 38.5 ± 1.4 ml/kg/min (p < .01), whereas there was no significant change with nadolol (figure 2, A). Exercise duration and respiratory exchange ratio were unchanged with both drugs (figure 2, C). Oxygen pulse during submaximal and maximal exercise.

FIGURE 2. Effects of exercise training on maximal oxygen consumption (VO₂max) (A), maximal oxygen pulse (B), and exercise duration (C). I = before training or drug; II = during drug administration before training; III = during drug administration after training; IV = without drug after training. Brackets represent mean ± SE. *p < .05 compared with test I.
exercise increased significantly with both drugs (figure 2, B).

Effect of training on treadmill performance in the drug groups. Comparison of tests I and IV in the drug groups demonstrated the effects of training in the absence of β-adrenergic blockade. VO₂max in the atenolol group increased from 40.7 ± 1.6 to 43.1 ± 1.2 ml/kg/min (p < .05, figure 2, A). VO₂max in the nadolol group tended to increase (42.7 ± 1.2 vs 45.0 ± 1.2 ml/kg/min), but this change was not significant (p = .1, figure 2, A). Thus, whereas the placebo group had a 16% increase in VO₂max with exercise training, the atenolol group had only a 6% increase and the nadolol group a 5% increase, both less than in the placebo group (p < .05, figure 2, A). As in the placebo group, no significant changes in body weight occurred in the atenolol group; in the nadolol group weight decreased from 79.2 ± 4.9 to 77.5 ± 4.3 kg (p < .05).

Oxygen pulse at maximal exercise did not increase in either drug group (figure 2, B), although it increased in the placebo group. There was an 18% improvement in exercise duration in the atenolol group (p < .05) and a 10% improvement in the nadolol group (p < .05, figure 2, C) as compared with a 26% increase in placebo subjects (figure 2, C).

Neither drug group had a significant change in maximal heart rate after training. Heart rate decreased during several levels of submaximal exercise after training in both drug groups (p < .05, figure 3), and there were no significant differences between the atenolol and nadolol groups. The decreases in heart rate during submaximal workloads were significantly greater in the placebo group than in either of the drug groups (p < .05, figure 3); for example, at 60% VO₂max (stage 4) the placebo group had a 17 beats/min reduction in heart rate, whereas both drug groups had an 8 beats/min decrease.

### TABLE 4

Submaximal exercise performance

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th></th>
<th>Atenolol</th>
<th></th>
<th>Nadolol</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>130 ± 3</td>
<td>113 ± 4&lt;sup&gt;A,B&lt;/sup&gt;</td>
<td>137 ± 4</td>
<td>130 ± 4&lt;sup&gt;A&lt;/sup&gt;</td>
<td>128 ± 2</td>
<td>120 ± 4&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td>HR-BP (x 10⁻²)</td>
<td>202 ± 9</td>
<td>176 ± 9&lt;sup&gt;A,B&lt;/sup&gt;</td>
<td>227 ± 14</td>
<td>213 ± 9&lt;sup&gt;A&lt;/sup&gt;</td>
<td>199 ± 10</td>
<td>181 ± 11&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td>Oxygen pulse (ml/beat)</td>
<td>13.4 ± 0.7</td>
<td>15.2 ± 0.8&lt;sup&gt;A,B&lt;/sup&gt;</td>
<td>14.4 ± 0.7</td>
<td>14.3 ± 0.9</td>
<td>15.0 ± 0.8</td>
<td>15.7 ± 1.0</td>
</tr>
<tr>
<td>Respiratory exchange ratio</td>
<td>0.85 ± 0.01</td>
<td>0.81 ± 0.01&lt;sup&gt;A,B&lt;/sup&gt;</td>
<td>0.84 ± 0.01</td>
<td>0.86 ± 0.01</td>
<td>0.84 ± 0.01</td>
<td>0.85 ± 0.01</td>
</tr>
<tr>
<td>Perceived exertion</td>
<td>4.3 ± 0.3</td>
<td>3.4 ± 0.2&lt;sup&gt;A&lt;/sup&gt;</td>
<td>4.0 ± 0.3</td>
<td>3.3 ± 0.5&lt;sup&gt;A&lt;/sup&gt;</td>
<td>4.1 ± 0.5</td>
<td>3.5 ± 0.3&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values are means ± SE.

The exercise load was 60% VO₂max on the entry treadmill (test I). Determinations were done before training (test I) and after training (test IV) in an unblocked state.

*<sup>p</sup> < .05 by two-way ANOVA for difference from pretraining state.

*<sup>p</sup> < .05 by one-way ANOVA for difference between placebo and both drug groups.

![FIGURE 3](http://circ.ahajournals.org/)

**Figure 3.** Effects of exercise training on heart rate during submaximal exercise. Comparison of test periods by subject group. *<sup>p</sup> < .05 by two-way ANOVA for tests II, III, and IV compared with test I in the atenolol and nadolol groups, and <sup>p</sup> < .05 for tests III and IV compared with test I in the placebo group. **<sup>p</sup> < .05 by one-way ANOVA for differences between placebo and both drug groups comparing test IV to test I.**
reduction. Perceived exertion score and heart rate–blood pressure product decreased significantly during submaximal exercise in both drug groups ($p < .05$), whereas oxygen pulse and respiratory exchange ratio did not change (table 4). The placebo group had significant changes in all these variables.

Comparison of tests II and III demonstrated the effects of training under the influence of β-adrenergic blockade. $\text{VO}_{2}\text{max}$ and exercise duration increased in the atenolol group (figure 2, A) but there was no significant change in the nadolol group. Oxygen pulse, heart rate, heart rate–blood pressure product and respiratory exchange ratio did not change during submaximal and maximal exercise in either group.

Comparison of tests III and IV demonstrated the effects of withdrawal of atenolol and nadolol on exercise performance after training. There were no significant changes in $\text{VO}_{2}\text{max}$ or exercise duration in either drug group 5 days after withdrawal of medication (figure 2). Oxygen pulse during maximal and submaximal exercise decreased in both drug groups. Maximal heart rate increased from 143 ± 3 to 187 ± 2 beats/min ($p < .05$) in the atenolol group and from 143 ± 4 to 189 ± 3 ($p < .05$) in the nadolol group. Heart rate also increased during submaximal exercise in both drug groups (figure 3).

**Effects on blood lactate.** The lactate responses to submaximal loads representing 45% to 85% $\text{VO}_{2}\text{max}$ in test I were similar and well described by quadratic curves (figure 4). In the study performed with β-adrenergic blockade before training (test II), the nadolol group had significantly lower lactate values than either the placebo or the atenolol group ($p < .05$). Analysis of training in the absence of β-adrenergic blockade (test IV) demonstrated significant reductions ($p < .05$) in blood lactate values during submaximal exercise for all three subject groups (figure 4). Two-way repeated measures analysis of variance of the change in lactate between tests I and IV did not demonstrate significant differences among the three groups. Comparison of tests II and III demonstrated significant reductions in blood lactate during submaximal exercise in both drug groups, indicating that this effect of training occurred while the subjects were under the influence of β-adrenergic blockade. At maximal exercise, blood lactates did not change significantly among the subject groups in any testing period.

The oxygen consumption ($\text{VO}_{2}\text{-LT}$) and percent $\text{VO}_{2}\text{max}$ at which lactates rose above resting values are shown in table 5. There was a significant increase in $\text{VO}_{2}\text{-LT}$ for all three subject groups after training. These changes were seen both with the subjects on β-

**TABLE 5**

Lactate threshold

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Atenolol</th>
<th>Nadolol</th>
</tr>
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<tbody>
<tr>
<td>$\text{VO}_{2}\text{-LT}$ (l/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test I</td>
<td>1.55±0.09</td>
<td>1.74±0.11</td>
<td>1.67±0.12</td>
</tr>
<tr>
<td>II</td>
<td>1.57±0.09</td>
<td>1.71±0.11</td>
<td>1.65±0.15</td>
</tr>
<tr>
<td>III</td>
<td>1.96±0.18*</td>
<td>1.94±0.10*</td>
<td>2.02±0.09*</td>
</tr>
<tr>
<td>IV</td>
<td>2.03±0.17*</td>
<td>1.98±0.15*</td>
<td>2.04±0.16*</td>
</tr>
<tr>
<td>% $\text{VO}_{2}\text{max}$-LT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test I</td>
<td>52±1</td>
<td>55±3</td>
<td>50±3</td>
</tr>
<tr>
<td>II</td>
<td>54±2</td>
<td>57±3</td>
<td>51±5</td>
</tr>
<tr>
<td>III</td>
<td>59±2*</td>
<td>60±2</td>
<td>61±3</td>
</tr>
<tr>
<td>IV</td>
<td>61±3*</td>
<td>58±2</td>
<td>58±2</td>
</tr>
</tbody>
</table>

*p < .05 for difference from test I, no significant between-group differences for any testing period for either $\text{VO}_{2}\text{-LT}$ or % $\text{VO}_{2}\text{max}$-LT.
blockade (test III) and after withdrawal of β-blockade after training (test IV). Although only the placebo group showed a significant increase in percent VO₂ max at which this lactate threshold occurred, there was a tendency toward similar changes in both drug groups. Thus both mean blood lactate values during submaximal exercise and lactate threshold data indicated a favorable and similar result of training in all three subject groups.

**Vascular effects of training.** Calf blood flow during submaximal supine exercise decreased 24% after training in the placebo group, 36.5 ± 2.6 to 27.9 ± 1.5 ml/100 ml/min (p < .05), but there was no change in either drug group (figure 5). Calf vascular resistance rose 22% after training in the placebo group, from 3.2 ± 0.2 to 3.9 ± 0.3 PRU (p < .05), whereas it was unchanged in the drug groups. Thus only the placebo group had significant changes in calf blood flow and vascular resistance during supine submaximal exercise after exercise training.

**Effects on skeletal muscle.** The mean percent type I fibers before training was 31 ± 3% in the placebo group, 39 ± 3% in the atenolol group, and 41 ± 5% in the nadolol group (p = NS). After training there were also no significant differences in percent type I fibers in the vastus lateralis muscle of any subject group.

Capillary-to-fiber ratio increased after training by 31% in the placebo group and 21% in the atenolol group but was not significantly changed in the nadolol group (figure 6). Fiber diameter increased in the placebo and nadolol groups but not in the atenolol group with exercise training.

Mitochondrial oxidative enzyme activity increased significantly (p < .05) after training in all three subject groups (figure 7). SDH increased 70% in the placebo group, 46% in the atenolol group, and 44% in the nadolol group, whereas cytochrome oxidase increased 65% in the placebo group, 58% in the atenolol group, and 33% in the nadolol group. There were no significant differences among the three subject groups in the magnitude of the increases in oxidative enzyme activities after training.

**Discussion**

Both drug groups had an equivalent degree of β-adrenergic blockade representing 80% of maximal blockade for the age group. The vascular response to intravenous epinephrine documented cardioselectivity with atenolol in the dose used in this study. The main difference during training between the placebo group and the two drug groups was that the latter exercised at a lower heart rate and heart rate–blood pressure product, resulting in lower estimated myocardial oxygen consumption. All other aspects of training, including percent of maximal heart rate, percent of VO₂ max, estimated kilocalories expended, and perceived exer-

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**FIGURE 5.** Effects of exercise training on calf blood flow and vascular resistance. Subjects were studied while off medication. P = placebo; A = atenolol; N = nadolol. *p < .05 for percent change from pretraining level by two-way ANOVA.

**FIGURE 6.** Effects of exercise training on capillary/fiber ratio and fiber diameter in vastus lateralis muscle. Subjects were studied while off medication. Open bar = before training; hatched bar = after training. *p < .05 for difference from pretraining by two-way ANOVA. p = NS for difference among subject groups by one-way ANOVA.
tion score, indicated that all three groups performed an equivalent amount of work during training.

Subjects in the atenolol and nadolol groups had attenuated conditioning responses in certain cardiopulmonary measurements. The placebo group had greater increases in VO₂ max, maximal oxygen pulse, and exercise duration than either drug group. Although both drug groups had reductions in heart rate and heart rate–blood pressure product during submaximal exercise after training, these were less marked than in the placebo group. Oxygen pulse increased after training during submaximal and maximal exercise only in the placebo group. Since oxygen pulse reflects changes in either stroke volume or arteriovenous oxygen difference, some attenuation of either the cardiac or peripheral adaptations to training occurred in the drug groups.

However, neither ß-adrenergic blocker attenuated certain well-recognized skeletal muscle adaptations that occurred as a result of exercise training. All three groups had significant increases in the skeletal muscle oxidative enzymes SDH and cytochrome oxidase. There were similar increases in the capillary supply of a trained muscle in the placebo and atenolol groups. Only the nadolol group did not have a significant increase in capillary/fiber ratio after training. Although a true difference with nonselective blockade cannot be excluded, this group had the highest pretraining capillary/fiber ratio. Recent studies in man and animals also have presented evidence that skeletal muscle metabolic improvement with exercise training is independent of sympathetic nervous influence.41,42 Therefore, ß-adrenergic blockade during training does not appear to appreciably alter these classic aspects of skeletal muscle conditioning.

Blood lactate levels during submaximal exercise were reduced significantly in all three groups. The lower blood lactates presumably reflect either decreased lactate production because of improved skeletal muscle oxidative capacity or increased lactate clearance.43,44 Although the percent VO₂ max at which the lactate threshold occurred increased significantly only in the placebo group, there was a trend toward increases of similar magnitude in both drug groups. The improved skeletal muscle oxidative enzyme capacity and capillary supply may explain the rightward shift in the lactate curves.

Although our measurements of oxidative enzymes, capillary supply, and lactate production did not support effects of selective or nonselective ß-adrenergic blockade on skeletal muscle conditioning, there could have been some alterations we did not measure. In particular, since a decrease in respiratory exchange ratio during submaximal exercise occurred only in the placebo group, the usual shift to preferential utilization of fat rather than carbohydrate as an energy substrate after training may have been absent or blunted with ß-adrenergic blockade. Lack of certain metabolic alterations may explain why the normal training-induced reduction in muscle blood flow during submaximal exercise was not seen in our subjects receiving ß-blockers. Since neither the atenolol nor nadolol group demonstrated a significant change in calf blood flow or vascular resistance during submaximal exercise after exercise training, ß₁-adrenergic selectivity does not appear to be important in this adaptation.

We propose that loss of stimulation of cardiac ß₁-adrenergic receptors results in decreased myocardial oxygen consumption and decreased myocardial adaptations due to exercise training by our regimen. Since the physical work and oxygen consumption by the skeletal muscles were unaffected by ß-adrenergic blockade, in general, normal adaptation to aerobic exercise training occurred in these organs. Animal studies suggest that ß-adrenergic stimulation is more important for glycogenolysis in the heart as compared
with skeletal muscle and in skeletal muscle both muscle contraction and β-adrenergic stimulation exert a dual control in glycogenolysis. The intensity of exercise also may determine the rapidity of cardiac adaptation to training in animals. Low-intensity exercise produces the same skeletal muscle metabolic effects as high-intensity exercise, but only high-intensity exercise produces cardiac changes during short-term exercise periods. Since exercise under the influence of β-adrenergic blockade occurs at a lower myocardial oxygen consumption, this may explain some of the hemodynamic attenuation observed.

The similar effects of β₁-selective and nonselective blockade also support the concept that the major cause of the reduced conditioning effects may be limitation in cardiac adaptations. Evidence for potentially beneficial cardiac changes with exercise training in both animals and man have been reported. These include increases in ventricular mass, increased contractility, and improved biochemical utilization of high-energy substrates. Although we did not measure any direct indexes of cardiac function, since β-adrenergic blockade did not attenuate skeletal muscle conditioning, we propose that the cardiac adaptations to training were attenuated, resulting in smaller increases in stroke volume and cardiac output. Cardiac hemodynamic studies on healthy subjects training under the influence of β-adrenergic blockade have not been performed, although a recent study suggested that increases in ventricular mass did not occur during exercise training with β-adrenergic blockade. Since β₁-adrenergic stimulation also controls fat mobilization in adipose tissue, diminished ability to utilize fat as an energy substrate during β-adrenergic blockade could also be a factor in the attenuation of exercise conditioning.

Several studies have not shown significant attenuation of exercise conditioning by β-adrenergic blockade in healthy subjects. There are several explanations why this apparent discrepancy may have occurred. First, the mean VO₂max in our subjects before training is higher than that in most of the other studies, although it is within the predicted values in a sedentary population normalized for age and sex (Table 6). Subjects with a higher VO₂max have been shown to train more by cardiac improvement with only a small increase in peripheral oxygen extraction. In previously sedentary subjects, cardiac and peripheral changes occurred equally. Both the current study and a previous study at our institution used higher levels of β-adrenergic blockade than other investigators, yet these doses are clinically relevant. In some studies training may have been too limited in control groups to ascertain whether differences occurred with β-adrenergic blockade. Finally, in other studies subjects were trained from 8 to 12 weeks on β-adrenergic blockade, while our subjects trained for only 6 weeks. Our short, very intensive training period seems to have resulted in a greater attenuation than longer, less intense programs. Increased duration of exercise training may eventually result in cardiac and peripheral vascular conditioning effects.

Although cardiac adaptations may be an important aspect of exercise conditioning in healthy young men, they may be less important for conditioning in patients with coronary artery disease. Several studies of patients with coronary disease have reported substantial exercise training effects without evidence of attenuation by β-adrenergic blockade. Conditioning in these patients may depend more on skeletal muscle adaptations and less on cardiac adaptations than in healthy subjects, and β-adrenergic blockade would be expected to have minimal effects.

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### References


### Table 6

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Atenolol</th>
<th>Nadolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual VO₂max (subjects)</td>
<td>39.8 ± 3.4</td>
<td>40.7 ± 4.5</td>
<td>42.7 ± 3.4</td>
</tr>
<tr>
<td>Predicted VO₂max (ml/kg/min)</td>
<td>45.4 ± 5.7</td>
<td>44.9 ± 5.7</td>
<td>44.3 ± 5.7</td>
</tr>
<tr>
<td>% predicted VO₂max</td>
<td>88 ± 7</td>
<td>91 ± 11</td>
<td>98 ± 6</td>
</tr>
</tbody>
</table>

Values are mean ± SD for predicted values. Predicted values are derived from regression equations of Hossack and Bruce: VO₂max = 58.33 - 0.457 (age).
Effects of selective and nonselective beta-adrenergic blockade on mechanisms of exercise conditioning.
E E Wolfel, W R Hiatt, H L Brammell, M R Carry, S P Ringel, V Travis and L D Horwitz

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