Effects of β-Blockade and Exercise on Cardiovascular and Cognitive Functioning

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SUMMARY Twenty-four men with mild essential hypertension were assigned randomly to receive propranolol (n = 9), atenolol (n = 7), or a placebo (n = 8). All subjects participated in a 12-week study and provided physiological and behavioral data four times during the study: after a medication-free baseline period (Session 1); after 2 weeks of medication, without exercise (Session 2); after 8 weeks of continued medication while participating in a program of aerobic exercise (Session 3); and after 2 weeks of maintenance exercise without medication (Session 4). Subjects' maximal oxygen uptake increased significantly between Sessions 2 and 3, and the magnitude of this increase did not vary across the drug groups. Subjects' resting heart rates varied as a function of the presence of β-blocking medication, but there was in addition a reduction attributable to exercise training that did not vary across the drug groups. The decrease in blood pressure associated with β-blockade (Session 2) was not decreased any further by exercise training (Session 3). Despite an increase in blood pressure following the withdrawal of active medication (Session 4), blood pressure remained significantly lower compared with the Session 1 baseline level. Performance in a reaction-time test of short-term memory functioning improved slightly for all three groups between Sessions 1 and 2 and remained constant thereafter. The present findings demonstrate that hypertensive persons can achieve cardiorespiratory training effects despite the presence of β-blockade, that the combined effects of aerobic exercise training and β-blockade do not influence performance on this test of memory functioning, and that aerobic exercise may be a useful complement to pharmacological methods for maintaining reductions in blood pressure. (Hypertension 11: 470-476, 1988)

KEY WORDS hypertension • β-blockade • aerobic exercise • cognitive processes

HYPERTENSION is a major cardiovascular disease affecting 25% of the adult population in the United States. The physical consequences of hypertension include end-organ damage that can lead to kidney failure, stroke, and coronary heart disease. Hypertension may have behavioral consequences as well. In particular, hypertension-related deficits have been observed both on psychometric and on reaction-time (RT) measures of cognitive functioning.

Aerobic exercise is currently receiving attention as a behavioral method for lowering blood pressure. Although results have been somewhat inconsistent, recent studies have found that nonmedicated hypertensive subjects can reduce their blood pressure with exercise training. Cross-sectional studies, which have found that athletes and other active persons exhibit faster RTs than do sedentary persons, suggest that aerobic exercise may also enhance cognitive performance. Thus, aerobic exercise may represent a nonpharmacological intervention that could lead both to a reduction in blood pressure and to improvements in hypertensive persons' performance of cognitive tasks.

Many patients with hypertension are on concurrent pharmacological regimens that may affect their response to exercise training. β-Adrenergic antagonists (i.e., β-blockers) attenuate increases in heart rate and cardiac output and may therefore interfere with the effects of exercise training. Although studies of healthy adults and cardiac patients indicate that cardiorespiratory training effects can be achieved despite the presence of β-blockade, to our knowledge, the interaction of exercise training and β-blockade has not been studied previously in patients with hypertension. β-Blockade has also been reported to influence sub-
jectors' performance of cognitive tasks. β-blockade has been found to lead to some deficits during tests of memory (i.e., Wechsler-Russell Memory Scale), and on RT measures of sensory and motor functioning. In a previous study, we reported that 2 weeks of β-blockade (either atenolol or propranolol) had no short-term adverse effects on the performance of hypertensive subjects in a RT test of memory, as compared with hypertensive subjects assigned to a placebo group. Following the initial 2 weeks, these subjects also participated in an 8-week program of aerobic exercise, during which they continued to take their originally assigned medication. This was followed by a 2-week period during which they continued to exercise but discontinued their medication. In the present report we examine the cardiovascular and behavioral data for the atenolol, propranolol, and placebo groups that we obtained over the entire 12-week protocol. Two questions were of interest. The first was the potential differences between atenolol and propranolol in their effects on the cardiorespiratory response to an 8-week program of aerobic exercise. Although both of these β-blockers penetrate the central nervous system, propranolol crosses the blood-brain barrier more readily than does atenolol, presumably by virtue of the greater lipophilicity of propranolol. In addition, propranolol's blockade affects both cardiac and vascular receptors, whereas atenolol's blockade affects cardiac receptors relatively selectively. It is therefore possible that, in hypertensive persons, propranolol will limit the cardiorespiratory response to exercise training more than atenolol will. The second question was the combined effects of exercise and the different forms of β-blockade, versus exercise alone, on RT measures of memory function.

Subjects and Methods

Two of the 26 subjects who completed the initial assessment did not complete the exercise training and were excluded from the analysis. The remaining subjects were 24 men (20 white, 4 black) between the ages of 26 and 54 years (mean age, 42.17 ± 8.0 (SD) years) who had mild essential hypertension. Before their participation, these subjects had demonstrated diastolic blood pressures between 90 and 110 mm Hg on four occasions during a 1-week period. On these occasions blood pressure was measured every other minute using standard cuff sphygmomanometry. A practice test without oxygen uptake was performed initially, and subsequent exercise tests with oxygen uptake were performed four times: before starting drug treatment.
Exercise Training

Between Sessions 2 and 3, subjects exercised 5 days per week for 8 consecutive weeks. On four days, subjects exercised on a stationary bicycle, and on the fifth day they exercised on a treadmill. Each training session was supervised by an exercise physiologist, nurse, or other trained personnel. Each session consisted of 10 to 15 minutes of warm-up exercises followed by 40 minutes of continuous cycling or walking and jogging at an intensity of 70 to 85% VO2max, as determined at the time of the initial (Time 1) treadmill test. No subject missed more than three training sessions in the 8-week training period.

Memory-Search Task

The memory test was a version of the Sternberg memory-search paradigm. This is a test of short-term memory functioning that requires subjects to decide, on each trial, whether or not a visually presented probe digit was a member of a set of digits held in memory. The presentation of the stimuli and measurement of subjects' response times were controlled by microcomputer (Apple, Cupertino, CA, USA). The stimuli were presented on a video monitor that used a P31 green phosphor. Subjects used two keys, located on opposite sides of the microcomputer keyboard, as response keys. The yes and no response keys were assigned to the subject's dominant and nondominant hands, respectively.

A memory set composed of the digits 0 to 9 was presented on the viewing screen at the beginning of each trial. Each memory set contained either two, four, or six digits. Subjects viewed the memory set for as long as they wished and then pressed the space bar on the microcomputer keyboard, which erased the memory set and brought a 1-second warning signal to the center of the viewing screen. The offset of this signal was followed immediately by the appearance of a probe digit, which remained on the screen until either the yes or no key was pressed. The recorded RT represented the difference in milliseconds between the onset of the probe and the keypress response. The yes or no response erased the probe and brought a new memory set to the screen. At each session, subjects performed one block of practice trials and five blocks of test trials. Each block contained a randomized sequence of 36 trials, six for each combination of memory-set size and response. For each subject, the assignment of the yes or no response to a particular memory set was alternated across sessions, and trial block order was varied both within and across sessions. Both the memory test and the physiological assessments were conducted at four points in time, as already described, but on separate days.

To perform the memory-search task subjects had to identify the probe, perform some comparison between the probe and memory-set items, reach a decision, and select a response. Subjects' RT to the probe is typically an increasing linear function of the size of the memory set. This linear function allows different processing components of task performance to be distinguished. The slope of the line of best fit relating RT to set size is the average increase in RT per memory-set item. The slope thus represents the average duration of the internal comparison between the probe and each memory-set item. The intercept of this linear function represents the combined durations of other components not associated with memory comparison: probe identification, yes or no decision, and response selection. If, for example, mean RT was 500 msec for a memory-set size of two items, 600 msec for a set size of four items, and 700 msec for a set size of six items, then the linear function relating RT to set size would be y = 50x + 400. Thus, in this case the average duration of the comparison stage would be 50 msec per item, and the combined durations of the remaining processing components would be 400 msec.

Results

Extent of β-Blockade

The mean heart rate during exercise treadmill testing, at an oxygen uptake of 2.5 L/min was 21% lower during drug treatment in both the propranolol and atenolol groups, indicating a high degree of β-blockade. Similar results were obtained when the heart rate was monitored during the exercise training sessions. The heart rate at an oxygen uptake of 2.5 L/min was unchanged after the 2 weeks of placebo treatment, indicating a high reproducibility of the test protocol. Maximal heart rates were reduced 24% for both the propranolol group and the atenolol group. The maximal heart rate was unchanged in the placebo group.

Physiological and Behavioral Data

The subjects' VO2max during exercise treadmill testing, resting heart rate, systolic and diastolic blood pressures, and mean RT in the memory-search task were each analyzed in a separate univariate analysis of variance (ANOVA). In these ANOVAs, drug group (propranolol, atenolol, placebo) was a between-subjects variable and session (1–4) was a within-subjects variable. For each dependent variable, a significant interaction between drug group and session was followed by the separate comparison of adjacent sessions for each group. The comparison across adjacent sessions provided information regarding the short-term effects of β-blockade alone (Sessions 1 and 2), long-term exercise training concurrent with β-blockade (Sessions 2 and 3), and the effects of withdrawal of β-blockade in trained subjects (Sessions 3 and 4). This overall analysis, in which the session variable included all four assessments, was followed by an additional ANOVA that included only Sessions 1 and 4. Because all subjects were medication-free at both the first and last testing sessions, the comparison of Sessions 1 and
**Maximal Oxygen Consumption**

Subjects’ mean \( \text{VO}_2\text{max} \) values during exercise treadmill testing are presented in Table 1. The ANOVA of these data for all four sessions yielded both a significant main effect of session (\( F_{3,63} = 30.54, p < 0.0001 \)) and a significant group \( \times \) session interaction (\( F_{6,63} = 2.95, p < 0.01 \)). The session main effect was not significant between Sessions 1 and 2. However, the effect of exercise was reflected in the increase in \( \text{VO}_2\text{max} \) from Session 2 (3.04 L/min) to Session 3 (3.43 L/min; \( F_{1,21} = 29.80, p < 0.0001 \)) and in the further increase from Session 3 to Session 4 (3.58 L/min; \( F_{1,21} = 5.89, p < 0.02 \)). The group \( \times \) session interaction was not significant either between Sessions 1 and 2 or between Sessions 2 and 3. This interaction was significant between Sessions 3 and 4 (\( F_{1,6} = 6.52, p < 0.006 \)), because the atenolol group exhibited a 0.40 L/min increase in \( \text{VO}_2\text{max} \) across Sessions 3 and 4 (\( F_{1,6} = 19.20, p < 0.005 \)), whereas the change between these sessions was not significant for either of the other groups. The main effect of group was not significant at either Session 3 or Session 4.

The ANOVA of Sessions 1 and 4 yielded only a significant main effect of session (\( F_{1,21} = 58.18, p < 0.0001 \)), reflecting the higher \( \text{VO}_2\text{max} \), averaged over group, at Session 4 (3.58 L/min) relative to Session 1 (3.12 L/min).

**Resting Heart Rate**

Subjects’ mean resting heart rates are presented in Table 1. The ANOVA of these data for all four sessions yielded a significant main effect of session (\( F_{3,63} = 35.98, p < 0.0001 \)). The mean resting heart rate was 83.88 beats/min at Session 1, 69.46 beats/min at Session 2, 62.79 beats/min at Session 3, and 71.79 beats/min at Session 4. The overall group \( \times \) session interaction was also significant (\( F_{6,63} = 5.96, p < 0.0001 \)). Between Sessions 1 and 2, both the main effect of session (\( F_{1,21} = 42.93, p < 0.0001 \)) and the group \( \times \) session interaction (\( F_{2,21} = 9.21, p < 0.001 \)) were significant. The mean resting heart rate for the placebo group remained unchanged across Sessions 1 and 2, whereas heart rate declined significantly across these sessions for both the propranolol group (\( F_{1,8} = 53.79, p < 0.0001 \)) and the atenolol group (\( F_{1,6} = 17.04, p < 0.006 \)). As noted, this reduction reflects the effectiveness of \( \beta \)-blockade. Between Sessions 2 and 3, the main effect of session was significant (\( F_{1,21} = 12.99, p < 0.002 \)) as the result of a 6.67 beats/min decrease in heart rate that did not vary significantly across groups. The group \( \times \) session interaction was again significant between Sessions 3 and 4 (\( F_{2,21} = 8.81, p < 0.0002 \)). Across these last two sessions, heart rate remained unchanged for the placebo group, but with the withdrawal of the \( \beta \)-blocking medication, there was a significant increase in heart rate both for the propranolol group (\( F_{1,8} = 26.82, p < 0.0008 \)) and for the atenolol group (\( F_{1,6} = 36.85, p < 0.0009 \)).

The comparison of Sessions 1 and 4 yielded only a significant main effect of session (\( F_{1,21} = 35.47, p < 0.0001 \)), reflecting the lower mean heart rate at Session 4 relative to Session 1.

**Systolic Blood Pressure**

The mean systolic blood pressure values are presented in Table 1. In the ANOVA of all four sessions there was a significant main effect of session (\( F_{3,63} = 25.10, p < 0.0001 \)). Systolic blood pressure, averaged across groups, ranged from 149.42 mm Hg at Session 1 to 133.83 mm Hg, 130.33 mm Hg, and 136.25 mm Hg at Sessions 2, 3, and 4, respectively. In the four-session ANOVA there was a marginally significant interaction between session and group (\( F_{6,63} = 2.16, p < 0.06 \)). Between Sessions 1 and 2, there was a significant effect of session (\( F_{1,21} = 54.40, p < 0.0001 \)) and a marginally significant group \( \times \) session interaction (\( F_{2,21} = 2.79, p < 0.08 \)), which represented the fact that the decrease in systolic blood pressure across sessions was greater for the two active drug groups than for the placebo group. Between Sessions 2 and 3, neither the main effect of session nor the group \( \times \) session interaction was significant. The withdrawal of \( \beta \)-blocking medication between Sessions 3 and 4 led to a significant increase in systolic pressure overall (\( F_{1,21} = 23.01, p < 0.0001 \)), which varied across the three groups (\( F_{2,21} = 8.81, p < 0.002 \)). Systolic pressure did not change significantly for the placebo group between Sessions 3 and 4, whereas there was a significant increase both for the propranolol group (\( F_{1,8} = 14.73, p < 0.005 \)) and the atenolol group (\( F_{1,6} = p < 0.02 \)).

In the ANOVA of Sessions 1 and 4, only the main effect of session (\( F_{1,21} = 20.11, p < 0.0002 \)) was significant, reflecting the lower mean systolic pressure at Session 4 relative to Session 1.
Diastolic Blood Pressure

The mean diastolic blood pressure values are presented in Table 1. The ANOVA of all four sessions yielded a significant main effect of session ($F_{3, 21} = 28.87, p < 0.0001$). The overall decline in diastolic pressure from 96.67 to 86.25 mm Hg between Sessions 1 and 2 was significant ($F_{1, 21} = 68.05, p < 0.0001$). The mean diastolic pressure remained unchanged between Sessions 2 and 3, but there was a significant increase in diastolic pressure from 85.75 mm Hg at Session 3 to 87.83 mm Hg at Session 4 ($F_{1, 21} = 4.57, p < 0.05$). In the four-session ANOVA the main effect of group was marginally significant ($F_{3, 21} = 2.92, p < 0.08$), because diastolic pressure was lower overall for the atenolol group (86.07 mm Hg) than for either the propranolol group (88.39 mm Hg) or the placebo group (92.63 mm Hg).

The ANOVA of Sessions 1 and 4 yielded only a significant main effect of session ($F_{1, 21} = 38.16, p < 0.0001$), as a consequence of the lower diastolic pressure at Session 4 relative to Session 1.

Memory-Search Performance

The data of primary interest in the memory-search task were the mean RTs associated with correct responses. Preliminary analyses of these data demonstrated that the increase in RT over memory-set size was 99% linear. Therefore, subsequent analyses were performed on the slope (i.e., memory comparison component) and intercept (i.e., encoding and response components) of these RT functions, obtained for each subject in each experimental condition. The data were averaged over response type, which yielded 60 test trials for each memory-set size at each testing session.

Slope and Intercept Values

The mean slope and intercept values of the RT functions are presented in Table 2. The ANOVA of all four sessions did not yield any significant effects. The ANOVA of the slope values for Sessions 1 and 4 yielded only a significant main effect of session ($F_{1, 21} = 7.0, p < 0.02$), which reflected the relatively slower rate of search associated with the first testing session. There were no significant effects in the intercept values for Sessions 1 and 4.

Error Rates

The mean percentage of errors in the memory-search task, averaged over memory-set size, response, and session, was 2.22% for the propranolol group, 2.16% for the atenolol group, and 2.17% for the placebo group. Further analyses of the error data indicated that the changes in error rate were consistent with the RT data and that subjects were not trading speed for accuracy in the memory-search task.

Reliability

Because there were no significant variations in the slope and intercept values as a function of group assignment, the reliability of these measures was examined. The most appropriate comparison points are Sessions 2 and 3, when the presence or absence of medication was constant for each subject. The test-retest reliability over this 2-month interval was +0.76 ($p < 0.0001$) for the slope values and +0.50 ($p < 0.0133$) for the intercept values.

Discussion

Subjects’ participation in the program of aerobic exercise led to significant improvements in cardiorespiratory variables. The increase in $V_{O_{2}}$max between Sessions 2 and 3 was equivalent for the propranolol, atenolol, and placebo groups. Although there was a further increase in $V_{O_{2}}$max between Sessions 3 and 4 that was restricted to the atenolol group, this differential change across groups was not sufficiently pronounced to lead to a significant difference among the groups at Session 4. The present results thus demonstrate that hypertensive subjects resemble normotensive subjects in their ability to achieve benefits in cardiorespiratory fitness, despite the presence of either nonselective or selective β-blockade. The differences between atenolol and propranolol in their physiological properties did not lead, during long-term administration, to differential effects in the increase in $V_{O_{2}}$max associated with aerobic exercise training.

The magnitude of the changes in resting heart rate between Sessions 1 and 4 was influenced more by the presence and withdrawal of β-blockade than by exercise. There was a significant decrease in heart rate between Sessions 2 and 3, however, that did not vary across the groups and consequently represents the bradycardia associated with exercise training. In addition, the heart rate at Session 4 was lower than at...
Session 1, and the difference in heart rate between Sessions 1 and 4 did not vary significantly across groups.

Blood pressure was also responsive primarily to β-blockade. Both systolic and diastolic pressures decreased in the presence of β-blockade (between Sessions 1 and 2) and increased following the withdrawal of medication (between Sessions 3 and 4). Although blood pressure did not change significantly between Sessions 2 and 3, both systolic and diastolic blood pressures were lower at Session 4 than at Session 1, and this decrease did not vary across groups. At Session 4, following 10 weeks of exercise (the last 2 weeks of which were drug-free), the average blood pressure value was 136/88 mm Hg, compared with 149/97 mm Hg at Session 1. Thus, consistent with previous studies,10,11 our data suggest that regular exercise can reduce blood pressure in hypertensive subjects to normotensive levels. Aerobic exercise may therefore be a useful complement to pharmacological therapy in maintaining the reduction in blood pressure introduced by β-blockade.

The primary focus of the present study was on the potential effects of relatively selective and nonselective β-blockade, as compared with the placebo control group, and consequently a no-exercise control group was not included. In the absence of this latter control, the reduction in blood pressure that occurred between Sessions 1 and 4 cannot be attributed entirely to exercise. Chesney et al.23 reported that reductions in blood pressure were associated with repeated assessments, in the absence of any other intervention. However, the reductions observed by Chesney et al.23 were 9 mm Hg systolic and 6 mm Hg diastolic after 18 weeks. In the present project, medication-free assessments separated by 12 weeks indicated a reduction by 13 mm Hg systolic and 9 mm Hg diastolic.

In a previous study18 we noted that the presence of β-blockade over a 2-week interval did not affect memory-search performance in mild hypertensive subjects. The present data extend the previous findings by demonstrating that β-blockade over an additional 8 weeks (Sessions 2 and 3) did not affect memory-search performance significantly. There was a significant decrease in the slope value (i.e., increase in search rate) between Sessions 1 and 2, but because this decrease was constant across the three groups, it represents a practice-related improvement rather than an effect of β-blockade. No change in either the slope or the intercept values was evident from Session 2 to Session 4, suggesting that neither exercise alone nor exercise and β-blockade combined affected the RT measures.

The conclusion that exercise and β-blockade do not influence memory-search RT is limited by the relatively small number of subjects in each treatment condition. Nevertheless, there was significant test-retest reliability for the RT measures, especially the slope values, and in the analysis of all four sessions, the main effect of session was significant for the slope values even though the difference between the largest and smallest mean slope value at each session was only 14 msec. In a recent study of normotensive subjects, we have also found that aerobic exercise does not significantly alter performance in the present version of the memory-search task, despite significant improvements in aerobic capacity.24 It consequently appears that a short-term program of aerobic exercise training does not alter memory-search performance in either hypertensive or normotensive subjects. Although the potential influence of aerobic exercise on cognitive function deserves further empirical investigation, the present results suggest that previously reported improvements in RT performance associated with exercise, especially differences between self-selected groups of exercisers and nonexercisers,12 may be influenced significantly by preexisting cohort differences between subject groups.

It is not likely that the constancy across sessions in the memory-search data is due to there being no room for improvement in subjects’ performance (i.e., a floor effect). We have recently compared the Session 1 data from the present subjects with the baseline data from 28 age-matched normotensive men who, in the context of a separate research project, also performed the memory-search task (D.J. Madden and J.A. Blumenthal, unpublished observations, 1987). In this comparison, the mean duration of memory comparison exhibited by the hypertensive subjects (i.e., RT slope) was significantly slower than that exhibited by the normotensive subjects. This hypertension-related slowing is consistent with previous reports suggesting a relation between hypertensive status and RT performance25 and demonstrates that there was room for improvement in the present subjects’ level of performance. In the present experiment, however, the changes in cardiovascular functioning associated with β-blockade, aerobic exercise, and the combined effects of these two variables did not affect memory-search performance.

In summary, the present findings suggest that 1) the cardiorespiratory fitness of hypertensive persons can be improved with aerobic exercise training; 2) β-blockade does not prevent this improvement; 3) blood pressure may be normalized (i.e., < 140/90 mm Hg) by β-blockade and aerobic exercise; and 4) changes in cardiovascular functioning associated with exercise training and β-blockade do not affect hypertensive subjects’ performance in the memory-search task. In view of the relatively small number of subjects participating in the present project, the potential effects of repeated blood pressure assessments, and the absence of a no-exercise control group, the present findings should be viewed as preliminary to larger-scale studies. Future studies should include both additional subjects and appropriate control groups to evaluate the extent to which blood pressure and cognitive functioning may be modified in hypertensive persons.

References
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