Acute effects of β blockade and exercise on mood and anxiety

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Abstract

Objective—To measure the previously reported β blocker induced adverse changes in mood state and anxiety measures, and to determine if prolonged aerobic exercise attenuates such mood modifications.

Methods—After 4 days of drug treatment with comparable doses of propranolol (40 and 80 mg), metoprolol (50 and 100 mg), or placebo, mood (POMS) and anxiety states (STAI) were assessed in healthy volunteers, before and after 1 h of treadmill walking exercise at 50% maximum oxygen uptake.

Results—Compared to placebo, resting "tension", "depression", and "total mood disturbance" were significantly higher on propranolol 80 mg, but all were reduced with exercise. "Fatigue" and "confusion" were also higher on propranolol, and were unaffected by exercise. "Fatigue" was also higher than placebo after exercise on metoprolol 100 mg. "Anxiety" was unaffected by drug treatment or exercise.

Conclusions—The evidence that β blockers, and particularly propranolol, have adverse effects on mood was confirmed. It would be preferable to prescribe a β blocker which does not adversely alter mood states. However, exercise significantly reduced the measures of "tension" and "depression" which were adversely increased by propranolol. Exercise prescription may therefore not only be compatible with β blockade, but a highly desirable adjuvant therapy.

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Key terms: β blockade; exercise; anxiety; mood

Exercise is increasingly encouraged as a means of increasing health,^{1,2} while physical inactivity is an established risk factor for coronary artery disease,^{3,4} stroke,⁵ and hypertension.⁶ Increased physical activity also increases personal "wellbeing",⁷ reduces weight,⁸ and reduces depression and anxiety.⁹ The mechanisms of psychological improvements with exercise remain elusive. It has been suggested that exercise releases endogenous opiates (β endorphins), which are responsible for the runner's "high".¹⁰ Others suggest that exercise may simply be a temporary escape from life's problems, and provides only temporary relief. Whatever the biochemical mechanism, exercise may have to be regular and frequent to achieve psychological benefits.¹¹

The type of exercise which is beneficial in reducing the risk of coronary heart disease is regular vigorous aerobic activity of long duration, for example above 50% $\dot{V}O_2$ max, for periods of more than 30 minutes, three times a week.³ This type of exercise is associated with many physiological improvements.¹²⁻¹⁶

Regular aerobic exercise is therefore recommended for most patients with risk factors for coronary heart disease such as hypertension and hyperlipidaemia and, with suitable supervision, is to be encouraged in those with established coronary artery disease, and as part of a postinfarct rehabilitation programme.¹⁷

Drugs also have an important role in reducing death from coronary heart disease and improving quality of life. β Blocking drugs are now well established in the control of hypertension and angina and are also beneficial in the primary and secondary prevention of myocardial infarction^{18,19} and prevention of sudden cardiac death.²⁰ Patients at risk of developing coronary heart disease and those surviving a myocardial infarct may be advised to take a β blocker and also to take more exercise, and a combination of β blockade and exercise is prescribed as treatment for hypertension.⁶ However, some β blockers have unwanted side effects²¹ such as increased fatigue,²²⁻²⁴ and an increased incidence of depression,²⁵⁻²⁷ which presents a dilemma for prescribing clinicians.²⁸

If compliance for drug taking and for an exercise regimen is to be achieved, then it is important that the drugs taken do not reduce the patient's motivation to exercise, either by increasing the physiological or psychological mechanisms of fatigue, or by adversely affecting mood. If such side effects of drugs are an unavoidable part of treatment, then exercise may be beneficial in offsetting the adverse mood changes that have been reported with some β blocker therapy.

Many studies that have attempted to investigate the relation between exercise and psychological variables have suffered from poor study design, poor quantification of fitness levels of participants (for example, using self reported activity levels), and poor quantification and replication of exercise intensity and type (see La Fontaine for review²⁹). This study addressed these problems by measuring rather than predicting the aerobic fitness potential of subjects (that is, the maximum oxygen uptake), calculating exercise intensity at 50% of each subject's maximum oxygen uptake, and carefully replicating energy expenditure and environment during each trial.

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The acute effects of two β blockers at comparable therapeutic doses, propranolol 40 and 80 mg and metoprolol 50 and 100 mg, and the acute effects of exercise on mood and anxiety state were examined.

Methods

SUBJECTS

Twenty healthy subjects, 10 male and 10 female, were recruited from the University of Birmingham student population. All subjects were clinically examined. No haematological or biochemical abnormalities were found, and no subject was excluded on medical grounds. All subjects gave informed written consent before proceeding with the trial, which had previously been approved by The Central Birmingham Health Authority ethics committee.

PROTOCOL

Maximum oxygen uptake ($\dot{V}O_{2\max}$) was measured for all subjects to determine aerobic fitness potential. On another day, subjects then completed a habituation walk on a motorised treadmill for 1 h, at 50% of measured $\dot{V}O_{2\max}$. Mood state and state anxiety questionnaires were completed before and after the habituation trial for familiarisation purposes.

For the treatment phase of the study, subjects undertook five 1 h treadmill walks at 50% $\dot{V}O_{2\max}$, separated by at least 7 d, with each of the following treatments taken orally: placebo; metoprolol 50 mg; metoprolol 100 mg; propranolol 40 mg; propranolol 80 mg.

Treatment order was randomised for each group of four subjects according to a Latin square arrangement. The study was randomised, crossover, and double blind, with each subject completing all five treatments.

Treatments were taken twice daily (am and pm) for the 4 d, with a final dose on the morning of the trial. Subjects arrived at the Clinical Investigation Unit after overnight fast, having monitored and replicated diet and activity closely over each 5 d trial period. The final dose of the drug/placebo, and a 1 MJ carbohydrate meal were consumed upon arrival, followed by cannula insertion (for blood sampling) and 90 min supine rest before the start of exercise. Euhydration was maintained by drinking 150 ml of water every 15 min.

PSYCHOLOGICAL MEASURES

Fifteen minutes before each exercise trial subjects completed Profile of Mood State (POMS³⁰) and State Anxiety (STAI³¹) questionnaires. The POMS consists of 65 five point adjective rating scales measuring six identifiable mood or affective states: tension-anxiety; depression-dejection; anger-hostility; vigour-activity; fatigue-inertia; and confusion-bewilderment. Each adjective, for example, "hopeless", requires a response ranging from "not at all" (score 0) to "extremely" (score 4).

The STAI questionnaire can be used to measure state or trait anxiety or both. This study used the Y-1 form only, which measures state anxiety, or how the subject feels "right now". The questionnaire consists of 20 state-

Group means for total energy expenditure (kJ), on drugs and placebo.

Treatment		Mean	SD
Placebo	20	1890.1	556.0
Metoprolol 50 mg	20	1907.2	552.8
Metoprolol 100 mg	20	1876.4	548.4
Propranolol 40 mg	20	1887.9	546.5
Propranolol 80 mg	20	1870.3	551.3

ments such as "I feel calm", and requires a response ranging from "not at all" (score 1) to "very much so" (score 4).

POMS and STAI questionnaires were completed again 15 min after exercise completion. Subjects were left to complete the questionnaires on their own, and explanation of specific terms in the questionnaires were given only if requested.

ENERGY EXPENDITURE

Expired air was collected in a Douglas bag at 15 min intervals throughout the 1 h exercise period. Energy expenditure was calculated from the $\dot{V}O_2$ and $\dot{V}CO_2$.^{32,33}

STATISTICAL ANALYSES

All data were initially analysed by a two factor repeated (within) measures analysis of variance (ANOVA); means comparisons were used to determine differences between treatments, with F values adjusted using the Scheffe method for multiple comparisons. A P value of <0.05 was chosen as significant. Data are presented as means(SD).

Results

AGE AND WEIGHT AND $\dot{V}O_{2\max}$

The mean age of males (n=10) was 24(6.3) years, and of females (n=10), 23.2(2.3) years. Males were significantly heavier than the females [75.6(9.5) v 63.0(7.4) kg, $P = 0.01$], and had higher values for $\dot{V}O_{2\max}$ [55.4(4.7) v 39.5(3.0) ml kg⁻¹ min⁻¹, $P = 0.01$]. The overall mean $\dot{V}O_{2\max}$ of 47.4 ml kg⁻¹ min⁻¹ indicated that the subjects were moderately fit but not specifically endurance trained.

ENERGY EXPENDITURE DURING EXERCISE TRIALS

Males (n = 10) expended significantly more energy than females (n = 10) over the 1 h exercise period [2358.9 v 1421.3 kJ, $P = 0.0001$], but there were no significant differences between treatments (table).

POMS: "TENSION"

Overall, there were significant differences between treatments ($P = 0.01$) and "tension" was lower after exercise than before ($P = 0.01$). Before exercise, compared to placebo, "tension" was increased only on propranolol 80 mg ($P = 0.01$). "Tension" was significantly lower after exercise on propranolol 80 mg ($P = 0.05$). After exercise, there were no significant differences from placebo. The data are shown in fig 1.

POMS "DEPRESSION"

There were significant differences between treatments ($P = 0.01$). Before exercise, compared to placebo, "depression" was signifi-

Figure 1 POMS "tension" before and after 1 h exercise at 50% of maximum oxygen uptake. ** $P = 0.01$ v placebo. † $P = 0.05$ v pre-exercise value.

Figure 2 POMS "depression" before and after 1 h exercise at 50% of maximum oxygen uptake. ** $P = 0.01$ v placebo. †† $P = 0.01$ v pre-exercise value.

Figure 3 POMS "anger" before and after 1 h exercise at 50% of maximum oxygen uptake. There were no significant differences from placebo or from before to after exercise.

there were no significant differences from placebo. The data are shown in fig 2.

POMS "ANGER"

For "anger" there were no significant differences between treatments or between pre- and postexercise. The data are shown in fig 3.

POMS "VIGOUR"

Overall, there were significant differences between treatments ($P = 0.01$). Before exercise, compared to placebo, there were no significant differences. Exercise did not change "vigour". After exercise, "vigour" was lower than placebo on propranolol 40 mg ($P = 0.05$) and propranolol 80 mg ($P = 0.05$). The data are shown in fig 4.

POMS FATIGUE

Overall there were significant differences between treatments ($P = 0.01$). Before exercise, subjects on propranolol 80 mg reported more "fatigue" than on placebo ($P = 0.01$). Exercise did not produce any significant changes in "fatigue". After exercise, compared to placebo, significantly more fatigue was reported on propranolol 80 mg and metoprolol 100 mg. The data are shown in fig 5.

POMS "CONFUSION"

Overall there were significant differences between drug treatments ($P = 0.01$). Before exercise, subjects on propranolol 80 mg reported more "confusion" than on placebo ($P = 0.01$). Exercise did not produce any significant changes in "confusion". After exercise, compared to placebo, subjects on propranolol 80 mg still reported more "confusion" than on placebo ($P = 0.01$). The data are shown in fig 6.

TOTAL MOOD DISTURBANCE (TMD)

A global assessment of mood state is calculated by summing tension, depression, anger, vigour (negative), fatigue, and confusion. This is Total Mood Disturbance (TMD).

Overall there were significant differences between treatments ($P = 0.01$). Subjects on propranolol 80 mg showed significantly greater TMD than on placebo ($P = 0.01$) before and after exercise. Exercise had no significant effect on TMD (fig 7).

STATE ANXIETY (STAI)

There were no significant differences in state anxiety (STAI) between treatments or between before and after exercise. The data are shown in fig 8.

Discussion

The results of this study confirm an increase in reported depression while taking propranolol.²⁵⁻²⁷ POMS "depression" was significantly greater than placebo while taking propranolol 80 mg. Of particular interest is the effect of one hour of treadmill walking on reported depression: scores were no longer significantly higher than placebo following exercise. This beneficial effect of regular exercise on mood has previously been demonstrated in clinically depressed patients.³⁴ While this study

cantly increased on propranolol 80 mg ($P = 0.01$). Exercise lowered "depression" on propranolol 80 mg ($P = 0.01$), but after exercise

Figure 4 POMS "vigour" before and after 1 h exercise at 50% of maximum oxygen uptake. * $P = 0.05$ v placebo.

Figure 5 POMS "fatigue" before and after 1 h exercise at 50% of maximum oxygen uptake. * $P = 0.05$, ** $P = 0.01$ v placebo. There were no significant changes from before to after exercise.

Figure 6 POMS "confusion" before and after 1 h exercise at 50% of maximum oxygen uptake. ** $P = 0.01$ v placebo. There were no significant changes from before to after exercise.

confirmed the antidepressant effect of acute exercise only in the short term, similar long term (exercise over six weeks) antidepressant effects have been shown in depressed subjects, but not in normal individuals.³⁵ It should be noted that the mean pre-exercise score of 7.0 on the "depression" scale while taking propranolol 80 mg is still well within the range for normal subjects. The POMS manual³⁰ gives mean "depression" scores of 22.3 (males) and 28.0 (females) for psychiatric patient populations. There is no suggestion that the subjects in this trial were clinically depressed while taking propranolol, only that scores of "depression" were significantly increased compared to placebo.

The measure of "tension" was also significantly increased on propranolol 80 mg. If "tension" is representative of a state of increased anxiety, then this finding contradicts the use of the drug to treat the somatic symptoms of anxiety. However, as with "depression", exercise also reduced "tension" to a level that was no different from placebo.

The changes in "depression" and "tension" could possibly reflect plasma concentration of the drug (propranolol reaches a peak in plasma concentration 1.5–2 h after oral administration, which then declines slowly). Although this explanation must be considered, the trend was for these measures to fall with exercise on all treatments including placebo, suggesting that exercise did have a real effect on these mood states. Furthermore, drug elimination tends to be slowed rather than enhanced by exercise, because of reduced hepatic circulation.

The lack of significant changes in depression and other POMS measures on placebo and other treatments is understandable, as scores were normal pre-exercise on all treatments other than propranolol 80 mg. The lack of effect of exercise on anxiety state is also unsurprising as this was also normal before exercise. The fact that subjects underwent a familiarisation trial would have attenuated any increased anxiety due to apprehension about the trials, and the Latin square design of the study ensured that order effects (which were not present anyway) did not influence the results. It has previously been suggested that the benefits of exercise are greatest in those who are more depressed or more anxious,²⁷ and the results of this study appear to support this hypothesis. It is possible that the POMS and STAI are not sufficiently sensitive to measure small changes in mood and anxiety states when scores are within the normal range.

Propranolol 80 mg also significantly increased "fatigue" before and after exercise, reduced "vigour" (as did propranolol 40 mg) after exercise, and increased "confusion" before and after exercise, suggesting that the central effects of propranolol are wide ranging. Propranolol at both doses was also the only treatment to cause an overall change in total mood disturbance. Metoprolol 100 mg also increased fatigue before and after exercise, but this was the only statistically significant effect of the drug on psychological variables measured, and could, as with propranolol, reflect

Figure 7 POMS "TMD" before and after 1 h exercise at 50% of maximum oxygen uptake. ** $P = 0.01$ v placebo. There were no significant changes between before and after exercise.

Figure 8 State anxiety (STAI) before and after 1 h exercise at 50% of maximum oxygen uptake. There were no significant differences from placebo and no significant changes over time.

the peripheral physiological fatigue after exercise on β blockade rather than any central effect.

CONCLUSION

The evidence that β blockers, and particularly propranolol, have adverse effects on mood was confirmed. The adverse effects on mood were significantly greater with propranolol than metoprolol. Exercise was beneficial in restoring some mood state measures to those recorded on placebo.

If a β blocker must be prescribed, and the therapeutic benefits of propranolol and metoprolol are comparable, then adverse mood changes are likely to be fewer with metoprolol than propranolol.

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