β_1 -selective and non-selective β -adrenoceptor blockade, anaerobic threshold and respiratory gas exchange during exercise

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1 The effect of oral doses of the β_1 -selective adrenoceptor antagonist atenolol (50 mg), the non-selective antagonist propranolol (40 mg) and placebo was investigated during exercise in a crossover comparison in six healthy but untrained subjects. Descriptors of ventilation, respiratory gas exchange, and arterialized blood lactate and glucose were obtained during steady state bicycle ergometric exercise at 20% and 60% of the subjects' previously determined maximal oxygen uptake ($\dot{V}O_2$ max).

2 At these work intensities, the previously reported increase of respiratory exchange ratio (RER) during non-selective β -adrenoceptor blockade was found to be trivial (placebo = 0.96 ± 0.03 s.e. mean; propranolol = 0.97 ± 0.01 ; atenolol = 0.97 ± 0.04 ; 60% $\dot{V}O_2$ max, 10 min exercise) and only present during the early minutes of effort. Oxygen uptake and carbon dioxide production did not differ between treatments.

3 Both drugs produced highly significant falls in peak expiratory flow (PEF) rates and tidal volume (V_T) which were compensated by an increase in respiratory rate. PEF, 60% $\dot{V}O_2$ max: placebo = 3.8 ± 0.3 l/s; propranolol 3.6 ± 0.3 l/s ($P < 0.03$); atenolol 3.1 ± 0.3 l/s ($P < 0.01$). V_T , 60% $\dot{V}O_2$ max: placebo 2.0 ± 0.1 l; propranolol 1.8 ± 0.2 l ($P < 0.05$); atenolol 1.7 ± 0.1 l ($P < 0.01$).

4 Arterialized lactate was significantly elevated during work at 20% and 60% $\dot{V}O_2$ max, but rose progressively at the 60% $\dot{V}O_2$ max load. Ventilation, oxygen uptake and ventilatory equivalent for carbon dioxide also rose progressively at this workload. Ventilatory equivalent for oxygen showed no significant rise. There were no treatment differences, either at the aerobic or anaerobic workloads. During steady state exercise, previously described determinants of anaerobic threshold (RER, O_2 ventilatory equivalent) appear not to be valid.

5 We conclude that normoglycaemic aerobic or anaerobic work is associated with a β_1 -adrenoceptor response which reduces airway resistance. Despite antagonism of lipolysis and hepatic glycogenolysis, β -adrenoceptor blockade does not appear to alter the pattern of substrate utilization.

Keywords atenolol propranolol respiratory gas exchange anaerobic threshold

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Introduction

Several studies have examined the effect of β -adrenoceptor blockade on respiratory gas exchange during exercise (Pearson *et al.*, 1979; Twentyman *et al.*, 1981; Petersen *et al.*, 1983; Tesch & Kaiser, 1983). In early investigations, considerable attention was devoted to the question of whether maximal oxygen uptake ($\dot{V}O_2$ max) was affected (Epstein *et al.*, 1965; Ekblom *et al.*, 1972) and although still a matter of controversy (e.g. Franz *et al.*, 1982) it now appears that a small impairment of $\dot{V}O_2$ max is produced (Pearson *et al.*, 1979; Petersen *et al.*, 1983; Tesch & Kaiser, 1983; Wilmore *et al.*, 1983). This is in keeping with the restriction of maximal cardiac output produced by β -adrenoceptor blockade (Epstein *et al.*, 1965).

In more recent investigations, inferences have been drawn regarding the metabolic effects of β -adrenoceptor blocking drugs from respiratory gas exchange data (Pearson *et al.*, 1979; Twentyman *et al.*, 1981). Most recently, Petersen and colleagues (1983) have claimed that alterations in respiratory gas exchange during exercise after β -adrenoceptor blockade were minimal (Petersen *et al.*, 1983). Changes in variables such as $\dot{V}O_2$ were thought to be due to an increased time constant for gas uptake secondary to the haemodynamic effects of β -adrenoceptor blockade. The majority of these studies have been undertaken with propranolol. Exceptions are Wilmore *et al.* (1983) (sotalol), Pearson *et al.* (1979) (metoprolol, propranolol) and Franz *et al.* (1982) (acebutolol, pindolol).

The contradictory data from previous investigations prompted the present study which investigated possible metabolic and respiratory effects of non-selective or β_1 -selective adrenoceptor blockade and differed from earlier investigations in several respects. First, the effects of oral atenolol 50 mg (currently the most selective β_1 -adrenoceptor antagonist) were compared with both oral propranolol 40 mg and placebo during bicycle ergometric exercise using a rigorous crossover design. Low doses of these drugs were used to attempt to ensure β_1 -adrenoceptor selectivity of atenolol and to minimize membrane stabilising effects of propranolol. This design has been used successfully in previous studies (McLeod *et al.*, 1983, 1984). Secondly, a highly accurate micro-processor-controlled system (Beckman MMC Horizon), able to give instantaneous data such as expiratory flow rates, was used to measure respiratory variables, and respiratory gas exchange. Thirdly, the effects of exercise at work loads corresponding to 20% and 60% $\dot{V}O_2$ max were measured sequentially at 30 s intervals for

up to 10 min of exercise to avert errors which could be produced by changes in time constants for gas uptake or elimination. Finally, arterialised venous samples were drawn during exercise for lactate and glucose measurements, and correlation with the respiratory data.

Methods

Six healthy untrained adult subjects (five men and one woman) aged 24 to 36 years were studied on four separate occasions during upright bicycle ergometric exercise. All were medical laboratory staff, all were familiar with exercise protocols and venepuncture. During the first exercise session, maximal oxygen uptake was determined by analysis of mixed expired gas using a Beckman Mobile Metabolic Cart (MMC Horizon, Beckman PMO, Anaheim, CA, USA). Subsequent exercise sessions were performed at workloads corresponding to 20% and 60% of this $\dot{V}O_2$ max value. After a gap of 3–4 weeks, subjects were restudied at weekly intervals 2 h after the oral ingestion of either propranolol 40 mg, atenolol 50 mg, or matching placebo in the fasting state. Tablets were administered using a Latin square design double-blind crossover protocol. One hour prior to exercise, subjects attended the exercise laboratory where ECG monitoring electrodes and the headpiece containing a Hans-Rudolph mouthpiece and non-return valves were fitted. A 21 g butterfly needle was placed in the same dorsal vein of the same hand for each study, its tip oriented distally. The needle was flushed with saline and the hand, wrapped in a paper glove, was rested in an enclosed box heated to 80°C to arterialize the venous blood (Forster *et al.*, 1972). Since validation studies indicated that 30 min were required for maximal arterialization, the subject rested on the bicycle for this period. Exercise then commenced at 20% $\dot{V}O_2$ max and was maintained at this level for 10 min, followed by a further 10 min at 60% $\dot{V}O_2$ max. Respiratory data were collected every 30 s, and the measurements at 5 and 10 min of exercise were used for final analysis. The subject then rested on the bicycle for a further 20 min. Blood samples were taken 5 min and immediately before exercise, after 5 and 10 min of each workload, and at 1, 2, 5, 10 and 20 min post exercise. Blood samples were analysed for lactate and glucose by enzymatic methods using a centrifugal analyzer as previously described (McLeod *et al.*, 1983). All exercise sessions were conducted in an air conditioned exercise laboratory (temperature 19–20°C) and all began at the same time of day (08.00 h). Units of

assays are reported as measured; the conversion factors are: lactate—8.9 mg/100 ml = 1 mmol/l; glucose—18 mg/100 ml = 1 mmol/l; propranolol—259 ng/ml = 1 μ mol/l; atenolol—266 ng/ml = 1 μ mol/l.

Gas and ventilation measurements

Evaluations of the Beckman MMC system have been published previously (Wilmore *et al.*, 1976; Kannagi *et al.*, 1983). Advantages of the microprocessor controlled system are that both the volumetric and gas analysis systems can be rapidly and accurately calibrated immediately prior to use. This was done in each study. In addition, three highly trained athletes, capable of exercising at a constant workload of up to 60% $\dot{V}O_2$ max were studied during steady state exercise at 20% to 50% $\dot{V}O_2$ max to assess the reproducibility of the various measured and derived variables of the analyzer. During these studies, four variables were measured. These were: ventilation (dependent on total rotations of the jewelled turbine mechanism); peak flow (an instantaneous value dependent on rate of turbine rotation); $\dot{V}O_2$ (dependent on measurement of ventilation and accuracy of polarographic O_2 electrode); RER (dependent additionally on accuracy of infrared CO_2 analyzer). During the drug studies, measurements were made of oxygen uptake, carbon dioxide production, respiratory exchange ratio, ventilatory equivalents for O_2 and CO_2 (ratio of gas uptake or elimination to total ventilation), peak expiratory flow, tidal volume, and respiratory frequency. All these measurements were made during normal spontaneous ventilation.

Data analysis

Differences between the three treatments were compared by analysis of variance. Comparisons between measurements made at 5 and 10 min of exercise on each treatment were made by paired Student's *t*-test.

Ethical approval

This study was approved by the Human Studies ethical committee of Duke University.

Results

Treatment effects

There were no differences between propranolol, atenolol or placebo in rest or exercise values for oxygen uptake, carbon dioxide production,

respiratory exchange ratio and ventilatory equivalents for oxygen or carbon dioxide (Table 1). Both β -adrenoceptor blocking drugs produced highly significant reductions in peak expiratory flow, even at the lower work level. There was a small reduction in tidal volume after propranolol and a larger reduction in tidal volume after atenolol (Table 1, Figure 1). These effects appeared to be compensated by an increased respiratory frequency after β -adrenoceptor blockade, and partly by an inconsistent overall reduction in ventilation after the two drugs.

There were no differences between treatments in arterialized concentrations of lactate during exercise (Table 2). During the recovery phase, lactates showed a trend towards lower values on propranolol. Glucose concentrations were slightly higher on atenolol than placebo at peak exercise, and glucose concentrations on propranolol were somewhat lower than either of these two values although these differences just failed to reach statistical significance. These effects have been noted before by us, and are very much larger during more intense or more prolonged exercise (McLeod *et al.*, 1983; 1984).

Respiratory variables and lactate

During steady state exercise at 20% $\dot{V}O_2$ max, lactates were significantly elevated from resting values and there was no difference between the 5 and 10 min values. At 60% $\dot{V}O_2$ max, there were significant differences between the 5 and 10 min values. Lactate increased by a similar amount (approximately 12 mg/100 ml) on all three treatments. Similarly, ventilation, $\dot{V}O_2$, and CO_2 VE increased with continued exercise. O_2 VE did not increase significantly. During this period, RER declined considerably, since $\dot{V}CO_2$ remained unchanged.

Drug concentrations and β -adrenoceptor blocking effect

Atenolol concentrations ranged from 186 to 748 ng/ml; total propranolol concentrations were between 5 and 33 ng/ml. In previous studies, similar concentrations of atenolol and propranolol were obtained. β_1 -adrenoceptor blockade as assessed by reduction in exercise heart rates was almost identical for the non-selective and β_1 -selective adrenoceptor antagonists (McLeod *et al.*, 1983; 1984). In the present investigation, atenolol was somewhat more potent as a β_1 -adrenoceptor antagonist as assessed by effect on exercise heart rate. Both drugs however produced significant β -adrenoceptor blockade (Table 3).

Table 1 Measurements of respiratory gas exchange, ventilatory characteristics, and arterialized lactate and glucose after placebo, propranolol 40 mg, and atenolol 50 mg.

		Placebo	Propranolol	Atenolol
$\dot{V}O_2$ (ml min ⁻¹ kg ⁻¹)	Rest	4.3 ± 0.1	4.0 ± 0.1	4.3 ± 0.4
	20%—5 min	14 ± 0.7	14 ± 0.7	13 ± 0.6
	20%—10 min	14 ± 0.8	14 ± 0.7	14 ± 0.8
	60%—5 min	29 ± 2.6	30 ± 2.3	26 ± 1.4
	60%—10 min	31 ± 2.4 [†]	31 ± 2.0 [†]	28 ± 1.6 [†]
$\dot{V}CO_2$ (ml min ⁻¹ kg ⁻¹)	Rest	3.4 ± 0.2	3.3 ± 0.1	3.4 ± 0.3
	20%—5 min	12 ± 0.6	11 ± 0.5	11 ± 0.7
	20%—10 min	12 ± 0.7	12 ± 0.6	12 ± 0.7
	60%—5 min	30 ± 2.4	30 ± 2.0	27 ± 1.8
	60%—10 min	30 ± 2.4	30 ± 2.0	27 ± 1.9
RER	Rest	0.78 ± 0.02	0.80 ± 0.02	0.78 ± 0.01
	20%—5 min	0.83 ± 0.02	0.82 ± 0.02	0.81 ± 0.03
	20%—10 min	0.84 ± 0.02	0.87 ± 0.01	0.84 ± 0.01
	60%—5 min	1.01 ± 0.03	1.03 ± 0.03	1.01 ± 0.04
	60%—10 min	0.96 ± 0.03 [†]	0.97 ± 0.01 ^{††}	0.97 ± 0.04 [†]
O ₂ VE (l/l)	20%—5 min	27 ± 2	26 ± 2	25 ± 2
	20%—10 min	26 ± 2	27 ± 1	25 ± 2
	60%—5 min	28 ± 2	27 ± 2	28 ± 2
	60%—10 min	29 ± 2	28 ± 3	29 ± 3
CO ₂ VE (l/l)	20%—5 min	32 ± 2	29 ± 2	31 ± 1
	20%—10 min	31 ± 2	30 ± 2	30 ± 1
	60%—5 min	27 ± 1	27 ± 1	28 ± 1
	60%—10 min	29 ± 1 [†]	29 ± 3 [†]	31 ± 3 [†]
$\dot{V}E$ (l/min)	20%—5 min	24 ± 2	23 ± 2	22 ± 1
	20%—10 min	25 ± 2	24 ± 2	23 ± 1
	60%—5 min	54 ± 4	53 ± 3	50 ± 4
	60%—10 min	29 ± 5 [†]	58 ± 3 [†]	54 ± 3 [†]
Peak flow (l/s)	20%—10 min	1.9 ± 0.3	1.5 ± 0.2*	1.6 ± 0.2*
	60%—10 min	3.8 ± 0.3	3.6 ± 0.3*	3.1 ± 0.3**
Tidal volume (l)	20%—10 min	1.2 ± 0.1	1.1 ± 0.1	1.1 ± 0.1
	60%—10 min	2.0 ± 0.1	1.8 ± 0.2	1.7 ± 0.1**
Respiration rate (min ⁻¹)	20%—10 min	22 ± 2	22 ± 1	21 ± 2
	60%—10 min	30 ± 1	34 ± 4	32 ± 4
Lactate (mg/dl)	Rest	11 ± 2	10 ± 1	10 ± 1
	20%—5 min	14 ± 1	14 ± 1	17 ± 3
	20%—10 min	13 ± 1	13 ± 1	15 ± 3
	60%—5 min	43 ± 3	47 ± 3	45 ± 6
	60%—10 min	55 ± 6 [†]	53 ± 7	57 ± 9 [†]
Glucose (mg/dl)	Rest	87 ± 4	89 ± 2	91 ± 2*
	20%—5 min	87 ± 4	86 ± 2	87 ± 1
	20%—10 min	86 ± 4	85 ± 3	89 ± 2
	60%—5 min	90 ± 4	83 ± 1*	88 ± 2
	60%—10 min	88 ± 4	85 ± 3	91 ± 3

$\dot{V}O_2$ —Oxygen uptake; $\dot{V}CO_2$ —Carbon dioxide uptake; RER—respiratory exchange ratio (carbon dioxide production/oxygen uptake); O₂VE—ventilatory equivalent for oxygen (litres ventilation per litre oxygen uptake); CO₂VE—ventilatory equivalent for carbon dioxide; VE—ventilation.

*, **, †, †† Treatment different from placebo by ANOVA, $P < 0.05$, 0.01 respectively. †, †† 10 min difference from 5 min reading by paired t -test, $P < 0.05$, 0.01 respectively.

Figure 1 Peak expiratory flow and tidal volume measurements during exercise on the three treatments (□ placebo, ■ propranolol, ▨ atenolol). The fall in both variables is more pronounced at the higher exercise intensity, and is in proportion to the degree of β_1 -adrenoceptor blockade as evidenced by the effect on exercise heart rate. Values are mean $\pm$ 1 s.e. mean *, **significant treatment difference from placebo by ANOVA, $P < 0.05$, < 0.01 respectively.

Beckman MMC gas analysis system validation data

Representative data from a prolonged exercise study in one athlete are shown in Table 3. Coefficients of variation (CV) generally were considerably below 10%. The variability seen appears to derive largely from differences in flow and ventilation from one analysis period to the next (30 s). When these values appear as numerator and denominator of the variables, there is excellent reproducibility. RER for example consistently shows a CV of 3% or less.

When 1 min samples were compared, the CV for the other variables fell by 30%.

Discussion

This investigation supports a recent study indicating minimal effect of β -adrenoceptor blockade on patterns of substrate utilization as reflected in the relative uptake and elimination of oxygen and carbon dioxide (Petersen *et al.*, 1983). The majority of effects on energy metabolism due to catecholamines appear to be

Table 2 Heart rates at the data points on the three treatments. Both atenolol and propranolol heart rates differ from placebo at all points ($P < 0.01$). During exercise, atenolol produced a significantly greater degree of blockade than propranolol ($P < 0.01$).

	Heart rate (beats min^{-1})		
	Placebo	Propranolol	Atenolol
Rest	74 $\pm$ 5	61 $\pm$ 4	63 $\pm$ 4
20% $\dot{V}O_2$ max—5 min	97 $\pm$ 7	82 $\pm$ 4	77 $\pm$ 5
20% $\dot{V}O_2$ max—10 min	99 $\pm$ 7	84 $\pm$ 5	78 $\pm$ 5
60% $\dot{V}O_2$ max—5 min	143 $\pm$ 8	119 $\pm$ 5	104 $\pm$ 5
60% $\dot{V}O_2$ max—5 min	152 $\pm$ 7	121 $\pm$ 5	108 $\pm$ 5

Table 3 Validation studies. Date obtained during prolonged continuous study in an athlete exercising at different workloads. CV calculated from 10 consecutive 30 s measurements after reaching steady state heart rate at each work load. CVs for 1 min sampling times are smaller.

% $\dot{V}O_2$ max	20%		30%		40%		50%	
	Mean	CV%	Mean	CV%	Mean	CV%	Mean	CV%
Peak flow (1/s)	1.1	7	1.4	10	1.7	10	2.1	13
RER	0.80	2	0.85	2	0.84	3	0.87	2
$\dot{V}O_2$ (STPD 1/min)	0.96	5	1.20	4	1.50	3	1.90	1
$\dot{V}E$ (1/min)	21.2	7	27.5	6	35.1	6	42.5	4

β_2 -adrenoceptor mediated, and thus are mostly due to the hormonal actions of adrenaline (Arnold *et al.*, 1968; Stanton *et al.*, 1972; McLeod *et al.*, 1983, 1984; Rizza *et al.*, 1980; Loubatieres *et al.*, 1971). These effects are blocked by propranolol. In the present study, neither propranolol nor atenolol modified oxygen consumption or carbon dioxide production. Our previous investigations however have strongly suggested that propranolol but not atenolol impairs hepatic glucose release (McLeod *et al.*, 1983, 1984). In addition, both drugs in the same dosage as the present study markedly lowered free fatty acid (FFA) concentrations. If, during steady state exercise, changes in oxygen consumption and RER are trivial between treatments, this implies that although the source of origin or substrates may be affected, the overall pattern of substrate utilization is not altered by β_1 - or β_2 -adrenoceptor blockade. This would suggest that enhanced intramuscular glycogenolysis and fat breakdown combine to maintain the normal pattern of energy utilization during short term exercise (Felig & Wahren, 1975). There is evidence for enhanced intramuscular glycogenolysis during exercise after propranolol which would support this concept (Juhlin-Dannfelt *et al.*, 1982).

The effects of the two drugs on the spirometric variables were surprising. Nonetheless, there was clear evidence of a reduction in peak expiratory flow by both atenolol and propranolol, in proportion to their β_1 -adrenoceptor blocking potency. This is in contrast to the differences observed between the drugs at rest (Astrom & Vallin, 1974). During exercise at this intensity, adrenaline elevation is minimal (McLeod *et al.*, 1983). These data therefore suggest that noradrenaline is the predominant agonist in the exercise response at work intensities up to 60% $\dot{V}O_2$ max.

Although β_1 -adrenoceptors are in the minority in the lung, animal experiments suggest they have functional importance (Carswell & Nahorski, 1983). In an earlier study, Kumana *et al.* (1974) suggested that practolol did not reduce peak flow rate to the same extent as propranolol during exercise. Our study implies that some of this difference may have been due to partial agonist action. McDevitt (1977) has commented on discrepancies in other studies examining the effect of β -adrenoceptor blockade on respiratory function. Our experiments potentially explain the discrepancies noted when exercise-induced changes in respiratory measurements are used to attempt to demonstrate cardioselectivity in man (McDevitt, 1977). Further support for our suggestions comes from earlier work (Woods *et al.*, 1979; Oh *et al.*, 1978). Both of these groups found a tendency for all β -adrenoceptor blocking drugs except those possessing partial agonist activity to diminish exercise-induced increases in peak expiratory flow rate. These workers adduced from their data that the test was a poor discriminant of β_1 -adrenoceptor antagonist selectivity. Our data however suggest that the reason underlying this is that the effect of exercise at these intensities on airway resistance is, partly at least, mediated by β_1 -adrenoceptors.

The term 'anaerobic threshold' (Wasserman *et al.*, 1983) has been used to indicate that level of exercise beyond which significant anaerobic metabolism with accumulation of lactate in the blood occurs. Buffering by bicarbonate results in increased CO_2 loss over and above that produced by metabolism. This results in a non-linear relationship between ventilation (which is stimulated by the increased CO_2 production)

and oxygen uptake as workload increases. However, measurement of this point from expired gas measurements depends on a number of assumptions and is controversial (Green *et al.*, 1983; Wasserman, 1983; Hughes *et al.*, 1982; Brooks, 1983). In addition, it appeared to us that this concept ignored present understanding of skeletal muscle fibre heterogeneity. Fast glycolytic skeletal muscle fibres, when recruited, have the capacity to outstrip available oxygen supply and produce large amounts of lactate. In contrast, slow twitch (oxidative) fibres are essentially oxygen-coupled (Clausen, 1976). Blood lactate concentration therefore is affected by training which enhances lactate clearance (Donovan & Brooks, 1983), and by the degree of recruitment of fast-glycolytic fibres. Our data indicate significant though small elevations of lactate at low exercise intensity, an effect consistently denied by one group of workers (Wasserman & Whipp, 1975). A characteristic of exercise beyond the anaerobic threshold is a continuing rise in oxygen consumption, despite a constant level of external work (Wasserman, 1982). This occurred in all our subjects at 60% $\dot{V}O_2$ max. Oxygen uptake, ventilation, CO_2VE , and lactate all increased. However, CO_2 production was unchanged. It is noteworthy however, that on all

three treatments the O_2VE did not rise significantly. β -adrenoceptor blocking drugs are alleged to depress anaerobic threshold by over 20% (Petersen *et al.*, 1983) but our data indicated that neither drug produced disproportionate increases in lactate or oxygen consumption. Our measurements concur with data which indicate that ventilatory measurements do not reflect true anaerobiosis as determined from either blood lactate or intramuscular lactate (Green *et al.*, 1983).

In conclusion, the major finding of our study is the unexpected observation that β_1 -adrenoceptors despite their numerical minority may modulate bronchial tone during exercise. Previous human exercise studies including our own indicate that β -adrenoceptor blockade reduces lipolysis in adipose tissue (β_1 -effect) and hepatic glucose release (β_2 -effect). During short term exercise in this study however, we show that although β -adrenoceptor blockade is present, the patterns of substrate utilization (lipid vs carbohydrate) as reflected by respiratory gas exchange data, are unaffected by β_1 - or non-selective β -adrenoceptor blockade. Additionally, our data obtained during exercise on all three treatments, reinforce doubts about the measurement of 'anaerobic threshold' as reflected by gas exchange data.

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