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ALTERATIONS IN THE OXYGEN DEFICIT–OXYGEN DEBT RELATIONSHIPS WITH β-ADRENERGIC RECEPTOR BLOCKADE IN MAN

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SUMMARY

1. The effects of β-adrenergic receptor blockade (100 mg oral metoprolol) or matched placebo on gas exchange kinetics were studied in six males. Ventilation and gas exchange were monitored in four transitions for each treatment from loadless pedalling (0 W) to a selected work rate (100 W) and back to 0 W. Breath-by-breath data were averaged for analysis.

2. Oxygen uptake ($\dot{V}_{O_2}$) kinetics were significantly slowed at the onset of exercise and recovery by β-blockade. This resulted in larger oxygen deficit and oxygen debt (671 ± 115, 586 ± 87 ml O_2, respectively) for β-blockade than for placebo (497 ± 87, 474 ± 104 ml O_2). In addition, oxygen deficit was significantly larger than oxygen debt during β-blockade tests. These results can be explained by greater utilization of oxygen and creatine phosphate stores as well as anaerobic glycolysis at the onset of 100 W exercise with β-blockade.

3. Carbon dioxide output ($\dot{V}_{CO_2}$) kinetics were significantly slowed by β-blockade only at the onset of exercise.

4. Expired ventilation ($\dot{V}_E$) kinetics were not affected by β-blockade. At 0 W, $\dot{V}_E$ was significantly reduced by β-blockade. Heart rate was lower at all times with β-blockade. Kinetics of heart rate were not affected.

5. These data for $\dot{V}_{O_2}$ kinetics at the start and end of exercise indicate that even in moderate-intensity exercise, lactic acid production can contribute significantly to energy supply. The use of the term 'alactic' to describe the deficit and debt associated with this exercise is not appropriate.

INTRODUCTION

At the onset of exercise, oxygen uptake ($\dot{V}_{O_2}$) does not reach the required steady state immediately. Rather, it follows an exponential time course to attain steady state in approximately 3 min during moderate-intensity exercise (Henry, 1951; Henry & deMoor, 1956; Whipp, 1971). The inadequate supply of energy from aerobic sources at the onset of exercise must be met largely by utilization of creatine phosphate high-energy stores (Margaria, Edwards & Dill, 1933). As exercise intensity is increased progressively towards a maximum, an increasingly greater demand is also

placed on anaerobic glycolysis to supplement the insufficient aerobic energy supply (Margaria *et al.* 1933). The term oxygen deficit is used to describe this inadequate oxygen utilization at the onset of exercise.

Replenishment of energy stores and a return to resting conditions at the end of exercise requires oxygen consumption in excess of the base-line recovery conditions. In their classic paper, Margaria *et al.* (1933) described the process of recovery $\dot{V}_{O_2}$ as comprising an alactic oxygen debt following moderate exercise, and both an alactic and lactic oxygen debt after more strenuous exercise. Although the use of this terminology has been criticized (Stainsby & Barclay, 1970; Brooks, Hittleman, Faulkner & Beyer, 1971; Keul, Doll & Keppler, 1972), the fact remains that the initial deficit must be accounted for energetically in some manner.

The magnitude of the oxygen deficit is generally found to be approximately equivalent to that of the oxygen debt in moderate exercise (Whipp, Seard & Wasserman, 1970; Knuttgen & Klausen, 1971; Linnarsson, 1974). In heavier exercise, oxygen debt is found to exceed oxygen deficit in magnitude (Asmussen, 1946; Christensen & Hogberg, 1950). In contrast, Cerretelli, Shindell, Pendergast, di Prampero & Rennie (1977) reported that oxygen deficit exceeded the size of the fast component of oxygen debt. The reasons for these discrepancies could lie in extra post-exercise oxygen consumption for processes other than simple deficit repayment (Brooks *et al.* 1971) or in the variability of the recovery base line (Cowan & Solandt, 1937; Stainsby & Barclay, 1970).

The relations between the oxygen deficit and oxygen debt were examined in the present study in which work began from loadless pedalling (0 W) and finally went back to 0 W. The exercise intensity was chosen to remain below the ventilatory anaerobic threshold as defined by Wasserman, Whipp, Koyal & Beaver (1973) to minimize lactic acid production. In addition to a placebo condition, 100 mg oral metoprolol was given to examine the effects of β-adrenergic receptor blockade on gas exchange kinetics as well as the oxygen deficit and oxygen debt. Previous reports had indicated that the rate of adaptation of $\dot{V}_{O_2}$ to steady state was altered by β-blockade (Hughson, Rouleau & Jones, 1978; Twentyman, Disley, Gribbin, Alberti & Tattersfield, 1981; Petersen, Whipp, Davis, Huntsman, Brown & Wasserman, 1983) in such a way that oxygen deficit would be expected to increase. There have been no previous studies of the corresponding effects on oxygen debt. In addition to the $\dot{V}_{O_2}$ response under these conditions, expired ventilation ($\dot{V}_E$), carbon dioxide output ($\dot{V}_{CO_2}$), heart rate and blood lactate responses were observed.

METHODS

Subjects. Six healthy 20–22 year old males volunteered as subjects. Their physical characteristics are given in Table 1.

Full details of the experimental procedures were given to the subjects. This included a description of any possible side effects of β-blockers. The subjects signed a consent form approved by the Office of Human Research at the University. Prior to taking any medication, each subject underwent a medical examination to exclude any contra-indications to β-blockade.

Exercise testing. An initial progressive exercise test to exhaustion was conducted on each subject to determine maximal oxygen uptake ($\dot{V}_{O_2,max}$) and the ventilatory anaerobic threshold, assessed by multi-segment linear regression by the method of Orr, Green, Hughson & Bennett (1982). From these tests, a work rate below the ventilatory anaerobic threshold of all subjects was selected (100 W) for all subsequent testing.

Two hours prior to all tests the subjects took either 100 mg oral metoprolol or a matched placebo. The subjects were blinded as to which tablet they took. Each subject reported to the laboratory on four separate occasions. On two of these (one drug, one placebo), a catheter (Angiocath, 21 gauge) was inserted in a dorsal vein of a warmed hand for collection of arterialized blood in the final minute of 0 W and 100 W cycling to determine blood lactate concentrations. Each test session was identical in terms of exercise protocol. The subjects rode for 6 min at 0 W. Work rate was then increased as a square wave to 100 W for 6 min. The work rate was reduced to 0 W for a further 10 min before repeating the 6 min ride and 10 min 0 W recovery rate again. Thus, each subject performed a total of four transitions from loadless pedalling to 100 W and back to loadless pedalling for both drug and placebo.

TABLE 1. Physical characteristics of subjects

Subject	Age (yr)	Height (cm)	Weight (kg)	$\dot{V}_{O_2,max}$ (ml/min)	Ventilatory anaerobic threshold (ml O_2/min)
D.G.	20	183	68	2800	1550
E.C.	19	178	68	3250	2075
G.H.	20	180	75	3525	2175
K.B.	20	167	57	2525	1675
T.H.	23	177	75	3400	1800
T.N.	19	185	84	4000	2800
Mean	20·2	178·3	71·2	3250	2013
S.D.	1·5	6·3	9·1	527	452

Gas exchange analysis. Breath-by-breath analysis of ventilation and respiratory gas exchange was performed on a system designed specifically for this purpose. A computer (Microwat, Northern Digital, Waterloo, Canada) processed digital pulses from a volume turbine (VMM 110, Alpha Technologies, Laguna Beach, CA). The sample rate for analog signals from a respiratory mass spectrometer (Perkin Elmer MGA-1100A) and cardiotachometer (Hewlett Packard 7830A) was dictated by the arrival of a digital pulse from the volume turbine (i.e. it was proportional to ventilatory flow rate). Pulses from the turbine corresponded to approximately each 2 ml of volume. Prior calibration with a large syringe introduced correction factors for both inspired and expired volumes. Additional volume correction was according to measured temperatures of inspired air (21–22 °C) and expired air (31–33 °C). The algorithm of Beaver, Lamarra & Wasserman (1981) was used to correct $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ according to changes in lung gas stores and alveolar gas concentration. Sixteen variables for each breath were stored on disk for later analysis.

Data analysis. The four square-wave transitions from 0 W to 100 W for drug or placebo were superimposed. The data were averaged over 10 s periods to minimize the random fluctuations inherent in all breath-by-breath collections.

Kinetic analyses of the $\dot{V}_E$, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and heart rate were performed as previously described by Hughson & Morrissey (1982, 1983) using a modification of the model of Linnarsson (1974). Below the ventilatory anaerobic threshold, a single-term exponential adequately described the kinetic behaviour of $\dot{V}_E$, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ in both placebo and drug conditions. The model for the onset of exercise is of the form:

$$f(t) = a(1 - e^{-(t-T_D/\tau)}),$$

where $f(t)$ represents the increment in $\dot{V}_E$, $\dot{V}_{O_2}$ or $\dot{V}_{CO_2}$ above the 0 W base line at any time t, a represents the change to plateau, T_D the time delay, and τ the time constant. The parameters a, T_D and τ were estimated by non-linear curve fitting. For each of $\dot{V}_E$, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$, the data were analysed for $t \geqslant 0{\cdot}25$ min only since data before this point reflect an increase due to a change in venous return and not altered muscle metabolism (Hughson & Morrissey, 1982, 1983; Whipp, Ward, Lamarra, Davis & Wasserman, 1982). Heart rate was analysed by the two-term exponential described by Linnarsson (1974).

The recovery data were analysed by the model of Linnarsson (1974). The equation was:

$$f(t) = a(e^{-(t-T_D/\tau)}).$$

All data points from the initiation of recovery were used, as a smooth decrease to base line is generally observed.

For this equation a was the difference between the steady-state exercise value of $\dot{V}_E$, $\dot{V}_{O_2}$ or $\dot{V}_{CO_2}$ and the recovery 0 W steady-state value. The last 2 min of each of 100 W or 0 W was taken to be steady state. The parameters T_D and τ were determined by non-linear regression.

The mean response time (Linnarsson, 1974; Hughson & Morrissey, 1982) was determined for the one-term exponential as the sum of $\tau + T_D$. This value represents the time taken to achieve 63% of the final steady-state response.

Oxygen deficit and oxygen debt. The oxygen deficit is defined as the difference between the required total oxygen cost of exercise and that actually measured. It is estimated as the product of the plateau parameter a and the mean response time (Henry, 1951; Whipp, 1971; Linnarsson, 1974). In the estimate of $\dot{V}_{O_2}$ kinetics described above, the first 15 s of data were omitted. This would be expected to lead to an error in the calculation of oxygen deficit (Whipp *et al.* 1982). Consequently, the mean response time for this calculation was determined with all data points.

The oxygen debt is the excess recovery oxygen uptake above the base line on completion of exercise. All data points were used in the kinetics model for recovery described above. It was estimated as the product of the plateau parameter a and the mean response time.

Statistical analysis. Each subject acted as his own control under the test conditions of placebo or drug. A paired Student's t test was used for all simple comparisons of two-sample means for placebo *vs.* drug. For the comparisons of more than two-sample means, an analysis of variance using the error term of subject by treatment was used. *Post-hoc* analysis was with the Student–Neuman–Keul test with the critical $P < 0.05$.

RESULTS

Steady-state responses

The $\dot{V}_{O_2}$ during loadless pedalling (0 W), was significantly lower with β-blockade than with placebo in the post-exercise recovery period ($P < 0.05$, Table 2). It was also lower in the pre-exercise period, but not at the selected value ($P = 0.054$). The $\dot{V}_{O_2}$ measured in the final 2 min of 100 W exercise was not significantly different with placebo or β-blockade.

No differences between drug and placebo were seen at either 0 W or 100 W exercise for $\dot{V}_{CO_2}$ (Table 2). The respiratory exchange ratio ($\dot{V}_{CO_2}/\dot{V}_{O_2}$) tended to be higher at the 0 W level with β-blockade compared with placebo; this difference was significant ($P < 0.05$) for pre-exercise only. During the final 2 min of exercise, the respiratory exchange ratio was the same for drug compared with placebo.

The expired minute ventilation ($\dot{V}_E$) was significantly lower with β-blockade than with placebo at 0 W both before and after exercise. During steady-state of exercise, $\dot{V}_E$ was not significantly different between conditions.

Heart rate was significantly reduced by β-blockade compared with placebo at both 0 W and 100 W exercise (Table 2).

Blood lactate concentration was not significantly different between placebo and β-blockade in the steady state of exercise at 100 W or recovery.

Kinetic analysis

$\dot{V}_{O_2}$. The onset of exercise response was significantly slower for $\dot{V}_{O_2}$ with β-blockade than for placebo (Table 3 and Fig. 1). The time constant for β-blockade (34.0 ± 8.2 s; $\bar{x} \pm$ S.D.) was slower than for placebo (23.7 ± 5.3 s; $P < 0.05$). The mean response time (= time constant + time delay) was also significantly slower (42.4 ± 7.1 *vs.* 32.5 ± 5.2 s).

In the recovery from 100 W to 0 W exercise, again both the time constant and mean response time for β-blockade (36.9 ± 2.9 and 38.0 ± 4.8 s, respectively) were slower

TABLE 2. Mean values ± 1 S.D. for six subjects measured in steady-state conditions of pre-exercise (0 W), exercise (100 W) and post-exercise (0 W) with and without β-blockade

Variable		Placebo	Drug	Significance
Pre-exercise	$\dot{V}_{O_2}$	662 ± 56	594 ± 46	n.s.
Exercise	$\dot{V}_{O_2}$	1558 ± 51	1532 ± 37	n.s.
Post-exercise	$\dot{V}_{O_2}$	642 ± 67	609 ± 47	$P < 0.05$
Pre-exercise	$\dot{V}_{CO_2}$	542 ± 43	538 ± 36	n.s.
Exercise	$\dot{V}_{CO_2}$	1405 ± 81	1400 ± 33	n.s.
Post-exercise	$\dot{V}_{CO_2}$	560 ± 39	570 ± 38	n.s.
Pre-exercise	r.e.r.	0·87 ± 0·04	0·91 ± 0·02	$P < 0.05$
Exercise	r.e.r.	0·90 ± 0·05	0·91 ± 0·04	n.s.
Post-exercise	r.e.r.	0·88 ± 0·05	0·94 ± 0·05	n.s.
Pre-exercise	$\dot{V}_E$	16·2 ± 2·5	15·3 ± 2·1	$P < 0.05$
Exercise	$\dot{V}_E$	33·5 ± 2·9	31·8 ± 2·0	n.s.
Post-exercise	$\dot{V}_E$	17·0 ± 2·3	16·3 ± 2·3	$P < 0.05$
Pre-exercise	h.r.	77·7 ± 12·1	64·3 ± 9·4	$P < 0.01$
Exercise	h.r.	116·8 ± 11·4	91·0 ± 8·4	$P < 0.001$
Post-exercise	h.r.	81·8 ± 11·4	64·0 ± 6·7	$P < 0.01$
Exercise	La	1·14 ± 0·43	1·30 ± 0·65	n.s.
Post-exercise	La	1·12 ± 0·49	0·90 ± 0·54	n.s.

Units for $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are ml/min s.t.p.d., for $\dot{V}_E$ l/min b.t.p.s., for heart rate (h.r.) beats/min, and for blood lactate (La) mM; r.e.r. = respiratory exchange rate; n.s. = not significant. Statistical analysis by paired Student's t test.

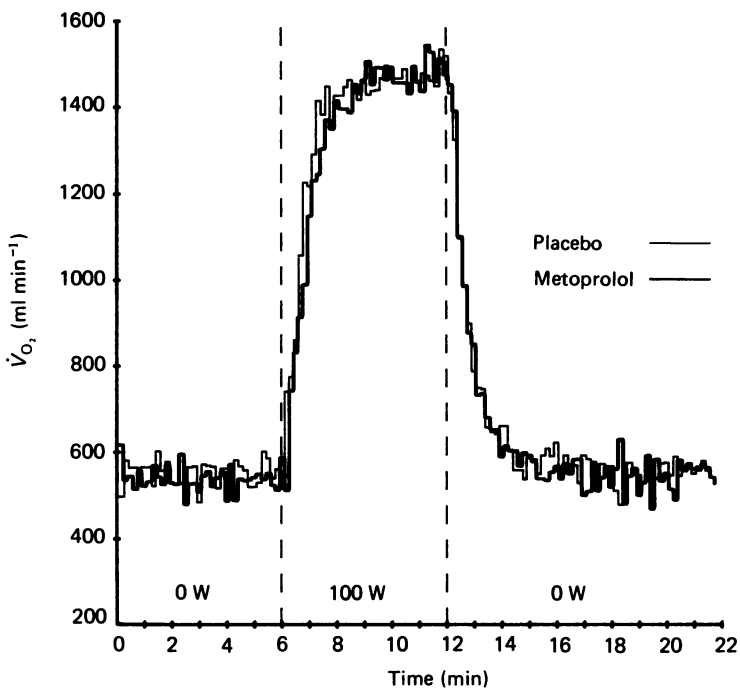

Fig. 1. Effect of 100 mg oral metoprolol (heavy line) or placebo (light line) on the $\dot{V}_{O_2}$ response in 0 W loadless pedalling, 100 W exercise and 0 W recovery. Each line represents the mean response of four tests in each of six subjects.

TABLE 3. Parameters estimated for $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, $\dot{V}_E$ and heart rate (h.r.) for onset and recovery from exercise both with and without β-blockade

	$\dot{V}_{O_2}$ kinetics				$\dot{V}_{CO_2}$ kinetics				$\dot{V}_E$ kinetics				H.r. kinetics			
	$\dot{V}_{O_2}$ onset		$\dot{V}_{O_2}$ recovery		$\dot{V}_{CO_2}$ onset		$\dot{V}_{CO_2}$ recovery		$\dot{V}_E$ onset		$\dot{V}_E$ recovery		H.r. onset		H.r. recovery	
Parameter	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug
a	934* ±38	934* ±25	920* ±34	923* ±36	840* ±108	889* ±44	845* ±88	837* ±51	16·6* ±3·8	17·6* ±0·9	16·5* ±3·1	15·5* ±1·5	38·8* ±7·4	27·3† ±4·6	38·8* ±7·5	26·7† ±4·2
τ(s)	23·7* ±5·3	34·0†‡ ±8·2	31·1† ±5·7	36·9‡ ±2·9	63·8* ±12·5	92·0* ±49·8	58·8* ±10·3	68·7* ±14·9	72·1* ±17·6	74·7* ±27·4	64·3* ±17·3	73·5* ±30·6	—	—	—	—
T_D(s)	8·8* ±1·1	8·4* ±2·7	−0·4† ±3·1	1·1† ±2·5	5·5* ±8·6	−3·2* ±26·4	−3·6* ±5·6	−1·8* ±5·0	43·7* ±14·4	11·5* ±6·7	2·8* ±9·0	8·6* ±7·4	—	—	—	—
M.r.t.(s)	32·5* ±5·2	42·4† ±7·1	30·7* ±7·5	38·0‡ ±4·8	69·3* ±5·9	88·8† ±25·9	55·3* ±9·0	66·9* ±13·0	75·7*† ±14·5	86·3† ±28·3	67·0* ±20·4	82·2*† ±30·4	28·8* ±7·7	26·0* ±4·3	15·8† ±2·0	16·2† ±3·0

Units for a: $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ = ml/min s.t.p.d.; $\dot{V}_E$ = l/min b.t.p.s.; h.r. = beats/min. M.r.t. = mean response time.

Statistical comparison for each kinetic analysis was conducted on both onset and recovery for placebo and drug by the Student–Newman–Keul test where means with the same symbol are not significantly different ($P < 0·05$).

than for the corresponding placebo values (31·1 ± 5·7 and 30·7 ± 7·5 s) ($P < 0·05$, Table 3).

The time delay parameter for $\dot{V}_{O_2}$ kinetics was unaffected by β-blockade *vs.* placebo; however, it was significantly longer for the onset of exercise compared with recovery.

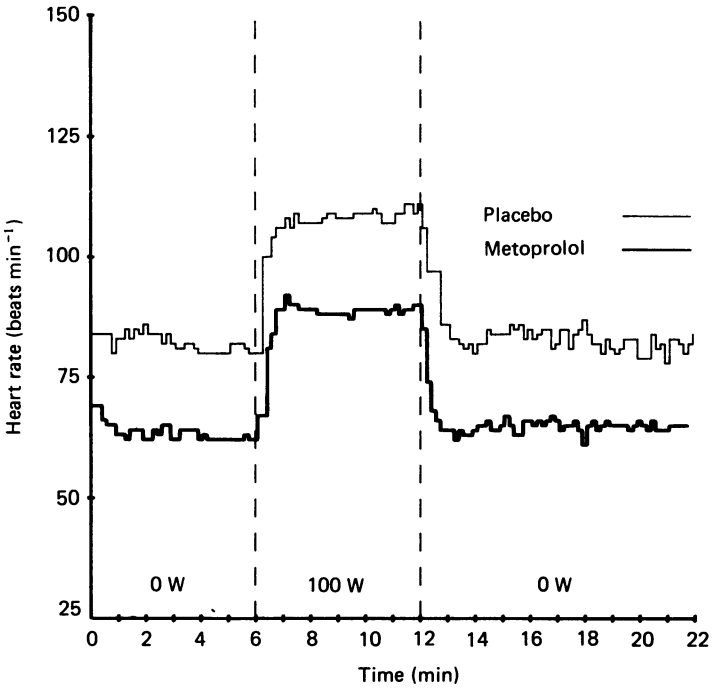

Fig. 2. Effect of 100 mg oral metoprolol (heavy line) or placebo (light line) on the heart rate response in 0 W loadless pedalling, 100 W exercise and 0 W recovery. Each line represents the mean response of four tests in each of six subjects.

$\dot{V}_{CO_2}$. The $\dot{V}_{CO_2}$ kinetics at the onset of exercise tended to be slower for β-blockade than for placebo as evidenced by the greater mean value for the time constant and mean response time. The difference was significant only for the mean respose time.

In recovery, the $\dot{V}_{CO_2}$ kinetics were not significantly changed by β-blockade.

No differences were observed for the plateau (*a*) or the time delay parameters for β-blockade compared with placebo, and for onset of exercise *vs.* recovery.

$\dot{V}_E$. There were no significant differences for any of the estimated kinetic parameters comparing drug with placebo for either the onset of exercise or recovery.

As $\dot{V}_E$ did not change significantly at the onset of exercise, but $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ kinetics were both slowed by β-blockade, the decrease in end-tidal P_{O_2} and increase in end-tidal P_{CO_2} normally seen at the onset of exercise occurred more slowly.

Heart rate. The heart rate response is indicated graphically in Fig. 2. Although there was a marked difference in steady-state responses with placebo and β-blockade, there were no differences in kinetics. Table 3 shows the mean response time only, since a two-component exponential model was used.

Oxygen deficit and oxygen debt. Table 4 presents the results from the analysis of

oxygen deficit and oxygen debt estimated from the product of the mean response time and the response plateau (a). This mean response time was calculated separately with all data points as described by the Methods.

The administration of metoprolol compared with placebo caused both the oxygen deficit and the oxygen debt to be larger. The magnitude of the oxygen debt was not significantly different from that of the oxygen deficit for the placebo tests; however, a significantly larger oxygen deficit than oxygen debt was observed with β-blockade.

TABLE 4. Mean values ± 1 S.D. of oxygen deficit and oxygen debt with and without β-blockade

	Placebo	Drug
Oxygen deficit (ml)	497 ± 87*	671 ± 115†
Oxygen debt (ml)	474 ± 104*	586 ± 87‡

Statistical comparison of all four means by Student–Newman–Keul test. Means with the same symbol are not significantly different ($P < 0.05$).

DISCUSSION

The rate of adaptation of $\dot{V}_{O_2}$ to the steady state of exercise and recovery were both significantly slowed by β-blockade with metoprolol. The magnitude of the oxygen deficit and oxygen debt were therefore both significantly greater for β-blockade than the corresponding placebo values. In addition, with β-blockade the oxygen deficit was larger than the oxygen debt. These data expand on the earlier observations of slower adaptation to the steady state of exercise for $\dot{V}_{O_2}$ with β-blockade (Hughson *et al.* 1978; Twentyman *et al.* 1981; Petersen *et al.* 1983).

Kinetic analysis of gas exchange in the present study followed the method described by Hughson & Morrissey (1982, 1983) for the onset of exercise. This model is appropriate for analysis of the time course of changes due to muscle metabolism, since a time lag exists corresponding to the circulatory transit from muscle to lungs (Linnarsson, 1974; Hughson & Morrissey, 1982); however, omission of the initial data points makes it an inappropriate model for calculation of oxygen deficit (Whipp *et al.* 1982). Consequently, the kinetic parameters for oxygen deficit were calculated separately with all data points included. For recovery gas exchange kinetics and oxygen debt calculation, all data points were included.

The rate-limiting step for the increase of $\dot{V}_{O_2}$ at the onset of exercise has not been identified definitely. Some authors argue for limitation at the point of oxygen utilization (Cerretelli, Rennie & Pendergast, 1980; Whipp & Mahler, 1980). Hughson & Morrissey (1983) have presented results which were interpreted as evidence for a rate-limiting step at oxygen transport. If this is the limiting step, it might be expected that β-blockade would slow the adaptation of $\dot{V}_{O_2}$ to steady state. Such results have been found in the present study as well as by Twentyman *et al.* (1981) and Petersen *et al.* (1983). Until the kinetics of cardiac output, and indeed local muscle blood flow, can be compared in studies of placebo and β-blockade in man, a definite conclusion cannot be reached. Other authors (Twentyman *et al.* 1981; Morrisson, Kumana, Rudnick, Haynes & Jones, 1982; Petersen *et al.* 1983) have suggested a slower

adaptation of oxygen transport as a consequence of β-blockade. In dogs, β-blockade does not alter the time constant for the cardiac output response, but it does significantly reduce the absolute cardiac output at any time in exercise (Versteeg, P. G. A., personal communication). The heart-rate kinetics in the present study behaved in a similar manner, with no difference in mean response time between placebo and β-blockade. Petersen *et al.* (1983) have reported no change in heart-rate kinetics with β-blockade at a moderate work rate, and slower kinetics at a heavy work rate.

The 35% increase in oxygen deficit in β-blockade must mean significant changes in the energy supply mechanisms at the onset of exercise. Three factors could account for this increase in oxygen deficit. In conjunction with the reduction in cardiac output with β-blockade is a decrease in mixed venous oxygen content (Epstein, Robinson, Kahler & Braunwald, 1965; Reybrouck, Amery & Billiet, 1977). This factor could account for approximately one-quarter of the increased oxygen deficit. It is unlikely that the oxygen stores of myoglobin would play a role in oxygen deficit since the myoglobin dissociation curve dictates high saturation to extremely low values of P_{O_2} (Farhi, 1964). The remaining oxygen deficit must be accounted for by creatine phosphate depletion or anaerobic glycolysis, or a combination of these two. After allowing for changes in oxygen stores, an oxygen deficit of approximately 125 ml (5·5 mmol) must be accounted for. This is equivalent to 33 mmol high-energy phosphate.

The magnitude of the oxygen debt should indicate which of the above mechanisms is more likely. The oxygen debt for β-blockade was significantly larger than that for placebo. This observation is opposed to the finding of a smaller oxygen debt in dogs during β-blockade (Barnard & Foss, 1969; Cain, 1971). This probably indicates differences in the hormonal control of metabolism in different species (Juhlin-Dannfelt, Terblanche, Fell, Young & Holloszy, 1982). Studies of muscle creatine phosphate repletion in animals (Piiper & Spiller, 1970) and man (Harris, Edwards, Hultman, Nordesjö, Nylind & Sahlin, 1976) show the similarity of the time course for the high-energy phosphates and oxygen debt. Thus, it would be expected that the larger oxygen debt with β-blockade reflects a greater steady-state depletion of creatine phosphate during exercise.

Exercise of the intensity studied in the present experiments is generally considered to have strictly a so-called alactic oxygen debt (Margaria *et al.* 1933; Henry, 1951). The attainment of steady-state $\dot{V}_{O_2}$ in recovery equivalent to the pre-exercise level supports this, as does the absence of any pattern of the residuals about the best-fit line obtained with a single-term exponential. However, the oxygen deficit was significantly larger than the oxygen debt for the β-blockade tests; in the placebo tests, the difference between oxygen deficit and debt was not significant. Linnarsson (1974) had similar results, with oxygen deficit exceeding oxygen debt in hypoxia but not normoxia. In a separate experiment, Linnarsson, Karlsson, Fagraeus & Saltin (1974) found both greater creatine phosphate depletion and increased intramuscular lactate in submaximal exercise with hypoxia. It is possible to account energetically for the greater oxygen deficit than oxygen debt in the β-blockade tests by anaerobic glycolysis in the deficit period. Cerretelli *et al.* (1977) also suggested significant involvement of anaerobic glycolysis at the onset of moderate exercise. They observed

an increase in blood lactate in post-exercise resting recovery. That the present study did not see an increase in steady-state recovery lactate can be accounted for by enhanced lactate metabolism as an aerobic substrate in moderate and 0 W exercise (Newman, Dill, Edwards & Webster, 1937). It was assumed in the present study that the 100 W work rate of the subjects during β-blockade remained below the ventilatory anaerobic threshold. This was not measured, since previous studies have shown no alteration with β-blockade (Hughson & MacFarlane, 1981; MacFarlane, Hughson, Green, Walters & Ranney, 1983). A recent study has reported a lower ventilatory threshold (Petersen *et al.* 1983). The reason for this difference is not clear but should have little effect on the present results.

The preceding discussion certainly questions the validity of the use of 'alactic' to describe the oxygen deficit at the onset of exercise. Even though a single-term exponential function adequately fits the data (Henry, 1951; Whipp, 1971; Whipp & Wasserman, 1972), more complex biochemical processes are probably occurring than those hypothesized by Henry (1951).

Muscle metabolism during 100 W exercise was not significantly altered by β-blockade, as shown by no difference between placebo and β-blockade for $\dot{V}_{O_2}$, respiratory exchange ratio or blood lactate. There was however, a significant reduction of $\dot{V}_{O_2}$ in the 0 W recovery with β-blockade. The majority of reports of $\dot{V}_{O_2}$ during exercise with β-blockade indicate no effect (Epstein *et al.* 1965; MacFarlane *et al.* 1983); others have previously proposed a decrease in $\dot{V}_{O_2}$ (Brundin, 1979; Pearson, Banks & Patrick, 1979). However, these latter papers measured $\dot{V}_{O_2}$ in the non-steady state of exercise. It is possible that the major mechanism responsible for the lower $\dot{V}_{O_2}$ in the face of unchanged $\dot{V}_{CO_2}$ was a shift to greater carbohydrate utilization as indicated by the higher respiratory exchange ratio with β-blockade, as suggested by Pearson *et al.* (1979). A reduction in free fatty acids in the blood might be expected in long duration exercise following β-blockade (Lundborg, Aström, Bengtsson, Fellenius, von Schenck, Svensson & Smith, 1981) but is not always found in shorter duration exercise (Nilsson, Hansson & Hökfelt, 1978). During moderate exercise, the rate of glycogenolysis does not appear to be influenced by β-blockade (Harris, Bergström & Hultman, 1972; Juhlin-Dannfelt *et al.* 1982), perhaps because of the major role played by intracellular inorganic phosphate concentration (Chasiotis, Sahlin & Hultman, 1982) as opposed to conversion of phosphorylase *b* to *a*, which is inhibited by β-blockade in perfused rat muscle (Richter, Ruderman & Galbo, 1982).

$\dot{V}_{CO_2}$ kinetics in the present study followed a similar trend to those of $\dot{V}_{O_2}$ for the onset of exercise. That is, β-blockade resulted in slower $\dot{V}_{CO_2}$ kinetics than did placebo. This is probably a consequence of two factors, the most apparent being that metabolic production of carbon dioxide was delayed due to the slow rise in $\dot{V}_{O_2}$. The second factor is that with the lower cardiac output during β-blockade, the venous content of carbon dioxide must increase, resulting in a greater store. Petersen *et al.* (1983) observed a slight slowing of $\dot{V}_{CO_2}$ kinetics; however, incomplete results may have precluded statistical significance. In recovery from exercise, the $\dot{V}_{CO_2}$ kinetics were not significantly slower with β-blockade than with placebo. Although the slower return of $\dot{V}_{O_2}$ to base-line recovery will keep $\dot{V}_{CO_2}$ elevated, a major factor influencing recovery $\dot{V}_{CO_2}$ kinetics should be the return of carbon dioxide stores back to base-line levels. If the kinetics of cardiac output recovery from 100 W to 0 W cycling are similar

in the placebo and β-blocked conditions, then release of carbon dioxide from stores would be expected to be similar for the two conditions.

$\dot{V}_E$ kinetics tended to be slower for both onset of exercise and recovery with β-blockade in comparison with placebo. However, the differences were not significant. There was a significant reduction in the steady-state ventilation in the pre- and post-exercise periods due to β-blockade. This was in spite of no difference in $\dot{V}_{CO_2}$, the normal stimulus for breathing. In the recent literature, a controversy exists as to whether β-blockade causes a blunting of the ventilatory response to carbon dioxide with publications supporting (Mustchin, Gribbin, Tattersfield & George, 1976; Patrick & Pearson, 1980) and opposing (Leitch, Hopkin, Ellis, Clarkson, Merchant & McHardy, 1980) this hypothesis. In exercise, β-blockade has not been associated with an altered ventilatory response in the steady state (Pearson *et al.* 1979; Leitch *et al.* 1980; Conway, 1982), but it has been shown to lower ventilation at the onset of exercise (Conway, 1982). The present results suggest an attenuation of ventilatory responses in very light exercise (0 W) due to β-blockade, but less effect during 100 W exercise.

β-adrenergic receptor blockade with 100 mg oral metoprolol significantly altered some of the cardiorespiratory adaptations to exercise. The most significant change was in the rate of adaptation of $\dot{V}_{O_2}$ to steady state at the onset of exercise where β-blockade significantly slowed the response. As a consequence, greater utilization of oxygen and creatine phosphate stores, and probably also anaerobic glycolysis, were required to meet the energy requirements. In recovery from exercise, $\dot{V}_{O_2}$ returned to steady state more slowly as the greater recovery $\dot{V}_{O_2}$ repayed the oxygen deficit. The size of the oxygen debt was less than the measured oxygen deficit with β-blockade. The most probable explanation was that some energy in the deficit period at the start of exercise must have come from anaerobic glycolysis with lactate production.

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