Slower Adaptation of VO2 to Steady State of Submaximal Exercise with β-Blockade*

R. L. Hughson and G. A. Smyth
Department of Kinesiology, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

Summary. The kinetics of oxygen uptake (VO2) were assessed in 17 normal subjects with β-blockade and placebo. β-blockade was achieved with either 50 mg oral metoprolol or 40 mg oral propranolol, each twice per day. Tests were conducted on the cycle ergometer at work rates approximating 80% of the work rate at ventilatory anaerobic threshold. Work rate was initiated as a square wave starting from prior rest. Data obtained 48 h, 1 week, and 4 weeks after starting drug or placebo were pooled to increase the number of points for regression analysis of kinetic parameters. While there were no differences in the plateau values for VO2 with and without β-blockade, the rate of adaptation to steady state was significantly slower with β-blockade than with placebo (P < 0.05). This resulted in an increase of oxygen deficit by approximately 200 ml O2. Cardiac output measured by CO2 rebreathing was significantly reduced by β-blockade (metoprolol by 4.1%, propranolol by 12.2%, both P < 0.05). Blood lactate concentration was unaffected by β-blockade. It was concluded that the influence of β-blockade on the oxygen transport system was responsible for the significantly slower increase of VO2 to steady state in submaximal exercise.

Key words: β-adrenergic receptor blockade – Oxygen uptake – Oxygen deficit – Exercise

Introduction

The peak oxygen uptake (VO2) measured during exhausting exercise in normal man is reduced approximately 5% by β-adrenergic receptor blockade (Epstein et al. 1965; Hughson and MacFarlane 1981). Associated with this lower peak VO2 is a reduction in cardiac output of up to 15% (Epstein et al. 1965; Hansen et al. 1978) which must be at least partially compensated by a greater arterial to mixed venous O2 content difference [(a-v)O2 diff] resulting from blood flow redistribution (Hansen et al. 1978). As the peak VO2 is measured in a continuous incremental exercise test, it is not known how rapidly these circulatory adaptations take place during β-blockade.

At the onset of constant load exercise, VO2 increases rapidly toward a new steady state. While some investigators might argue that the rate at which VO2 adapts to the new level is limited by muscle metabolic mechanisms (Cerretelli et al. 1980; Pendergast et al. 1980), other evidence indicates that oxygen transport is critical. VO2 kinetics are slower when the inspired oxygen fraction is less than normal (Linnarsson 1974). Also, VO2 kinetics are slower in the transition from light to moderate exercise than rest to exercise, probably due to slower increases in heart rate and oxygen transport (Hughson and Morrissey 1982, 1983). It might be anticipated that VO2 kinetics should be slower due to the lower cardiac output and the requirements for blood flow redistribution with β-blockade (Hughson et al. 1978). Recently, Twentyman et al. (1981) have shown that at certain points in exercise, VO2 is lower with β-blockade than placebo. The purposes of the present study were to determine the kinetics of VO2 adaptation to steady state by a computerized regression technique, and to measure the cardiac output in the steady state of exercise during control conditions, and with two β-blockers, metoprolol and propranolol.

Methods

A total of 17 subjects took part in this study. Each subject received a medical examination to screen for possible contraindications to * Supported by the Ontario Heart Foundation

Offprint requests to: R. L. Hughson at the above address
The subjects, all male non-smokers, were recruited as two separate groups over consecutive four month periods. The first group (metoprolol, n = 9) had a mean ± 1 SD for age of 21 ± 1 years, weight of 71.2 ± 3.4 kg, ventilatory anaerobic threshold (Orr et al. 1982) of 2.200 ± 270 ml O₂·min⁻¹ and VO₂ max of 3,840 ± 165 ml O₂·min⁻¹. The second group (n = 8) had mean values of 21 ± 2 years, 70.4 ± 9.4 kg, 1,790 ± 300 ml O₂·min⁻¹ and 3,590 ± 150 ml O₂·min⁻¹. The lower VO₂ max in the second group was simply a reflection of the difference in volunteer populations; it did not reflect an attempt to recruit different subjects.

The treatment schedule for the two groups was identical. Group 1 received metoprolol (50 mg, twice daily) and group 2 received propranolol (40 mg, twice daily). The study was conducted as a double-blind cross-over design with both groups also taking a matching placebo. One half of each group took the active drug first, then the placebo; the other half received the placebo and active drug in reverse order. Testing was conducted over four week periods for each of the drug or placebo phases. Each subject was tested three times on the active drug and three times on the placebo. These tests occurred 48 h, 1 week, and 4 weeks after commencing the drug or placebo phase. The last tablet was taken 3 h prior to the exercise tests.

Exercise was performed on an electrically braked cycle ergometer (Quinton 870) in the upright position. Based on the preliminary testing for ventilatory anaerobic threshold and VO₂ max, a work rate was selected for each subject equivalent to approximately 80–90% of the ventilatory anaerobic threshold. Exercise was preceded by 5–10 min of rest while breathing through a mouthpiece. When the subject had attained relative steady state as judged by monitoring mixed expired gas concentrations, exercise commenced on a verbal command given without prior warning. The ergometer was pre-set at the required resistance setting. The subjects exercised for 10 min. In the first 5 min of exercise, expired air was passed through a breathing valve to a 7.01 mixing chamber. Expired oxygen and carbon dioxide were monitored continuously by Applied Electrochemistry S-3A and Beckman LB-2 analyzer, respectively. Ventilation was monitored by a pneumotachograph. Oxygen uptake was calculated over 15-s intervals as previously described by allowing a volume delay of 151 to match mixed expired gases with the appropriate expired volume (Hughson et al. 1980). At the 8th min point of exercise, the carbon dioxide was sampled near the mouthpiece for determination of end-tidal PCO₂. Cardiac output was estimated during the 9th min by the CO₂ rebreathing technique of Jones et al. (1975).

There were no significant changes in the responses of submaximal exercise heart rate, blood pressure or ventilatory anaerobic threshold, or of maximal exercise heart rate or VO₂ in drug or placebo group over the four weeks of each study phase as determined by analysis of variance with a drug time error term (Smyth et al. unpublished 1982). Therefore, the results were pooled from the three drug or placebo tests for data analysis. This yielded a three-fold increase in the number of data points for the analysis of VO₂ versus time for each subject. The kinetics of VO₂ were determined as the rate of change of the increase above resting VO₂ to the new exercise steady state VO₂ (dVO₂(ss)). A single term exponential function of the form:

\[ V_O^2(t) = A' V_O^2(ss) \left(1 - e^{\frac{t - T_D}{r}}\right) \]

where \( V_O^2(t) \) is the VO₂ at any time t, \( T_D \) is a time delay and r is the time constant (Linnarsson 1974; Hughson and Morrissey 1982) was fitted to all data for t > 0.25 min (Hughson and Morrissey 1982). The mean response time (MRT) was calculated from this as the time at which the response passed 63% of its final plateau value. For this single term exponential, MRT was equal to \( r + T_D \).

Statistical analysis of kinetic parameters was performed by two way analysis of variance using the subject by drug or placebo comparison separately for each drug. Post-hoc analysis was with the Duncan multiple-range test. Steady state exercise variables were compared by paired Student’s t-tests using the mean value from the three tests for each treatment for the individual subjects.

### Results

The kinetic analysis of the oxygen uptake response is shown in Table 1. No significant effect of β-blocker, either metoprolol or propranolol, was seen on the steady state oxygen uptake. However, a significantly slower rate of adaptation of VO₂ to steady state was shown for both β-blockers. For metoprolol, the mean

### Table 1. Kinetic analysis of VO₂ in the transition from rest to exercise at 80% anaerobic threshold

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Metoprolol (n = 9)</th>
<th>Propranolol (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Active drug</td>
</tr>
<tr>
<td>ΔVO₂(ss)</td>
<td>1,291 ± 118</td>
<td>1,322 ± 194</td>
</tr>
<tr>
<td>(ml O₂·min⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time constant (r, s)</td>
<td>27.7 ± 8.1</td>
<td>35.9 ± 19.8</td>
</tr>
<tr>
<td>Time delay (TD, s)</td>
<td>6.6 ± 4.4</td>
<td>8.3 ± 6.7</td>
</tr>
<tr>
<td>Mean response time (MRT, s)</td>
<td>34.3* ± 6.1</td>
<td>44.1* ± 14.8</td>
</tr>
</tbody>
</table>

* Values are mean ± 1 SD
* P < 0.05, significantly different from corresponding placebo