Cardiovascular and Oxygen Uptake Kinetics During Sequential Heavy Cycling Exercises

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Catalogue Data

Key words: impedance cardiography, exercise transitions, cardiac output, prior exercise
Mots-clés: impédance, transition d’exercice, débit cardiaque, exercice précédent

Abstract/Résumé
The purpose of the present study was to assess the relationship between the rapidity of increased oxygen uptake (V\textsubscript{O\textsubscript{2}}) and increased cardiac output (CO) during heavy exercise. Six subjects performed repeated bouts on a cycle ergometer above the ventilatory threshold (~80% of peak V\textsubscript{O\textsubscript{2}}) separated by 10-min recovery cycling at 35% peak V\textsubscript{O\textsubscript{2}}. V\textsubscript{O\textsubscript{2}} was determined breath-by-breath and CO was determined continuously by impedance cardiography. CO and V\textsubscript{O\textsubscript{2}} values were significantly higher during the 2-min period preceding the second bout. The overall responses for V\textsubscript{O\textsubscript{2}} and CO were significantly related and were faster during the second bout. Prior heavy exercise resulted in a significant increase in the amplitude of the fast component of V\textsubscript{O\textsubscript{2}}, with no change in the time constant and a decrease in the slow component. Under these circumstances, the amplitude of the fast component was more sensitive to prior heavy exercise than was the associated time constant.

L’objectif de ce travail était d’évaluer la relation entre le taux d’ajustement de la consommation d’oxygène (V\textsubscript{O\textsubscript{2}}) et du débit cardiaque (CO) lors d’un exercice épuisant à charge constante. Six sujets ont répété un exercice continu de 6 min sur bicyclette ergométrique à ~80% de V\textsubscript{O\textsubscript{2}} pic séparé par 10 min à 35% V\textsubscript{O\textsubscript{2}} pic. CO était déterminé par

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un cardiographe à impédance. Les valeurs de CO et $\dot{V}O_2$ étaient significativement supérieures avant le début du deuxième exercice. Les réponses globales pour $\dot{V}O_2$ et CO étaient significativement corrélées, et plus rapides pendant le deuxième exercice. Le pré-exercice épuisant avait pour conséquence une augmentation significative de l’amplitude de la composante rapide de $\dot{V}O_2$, sans changement de sa constante de temps et une diminution de la composante lente. Dans ces circonstances, l’amplitude de la composante rapide était plus sensible au pré-exercice que l’était la constante de temps associée.

Introduction

When exercise starts from rest or light exercise, the oxygen uptake ($\dot{V}O_2$) response to a step increase in exercise intensity has been shown to have an initial increase (Phase I, which begins with the first breath and continues for 15 to 20 s), and thereafter an exponential increase to a steady state (Phase II). During high-intensity exercise (above the ventilatory threshold), the rate at which $\dot{V}O_2$ increases can be improved by an identical bout of priming exercise (Gerbino et al., 1996). This is manifested as an increased overall rate of change of $\dot{V}O_2$ with a reduction in the $\dot{V}O_2$ slow component, previously demonstrated to supplement the fundamental exponential $\dot{V}O_2$ responses (Scheuermann et al., 2001).

Burnley and colleagues (2000; 2001) addressed this issue further and demonstrated that the Phase II time constant ($\tau_2$) was actually unaltered by the prior exercise. They further suggested that, by accounting for the altered baseline at the onset of the second bout, this phase of the subsequent kinetics was identical between bouts. This exponential increase in $\dot{V}O_2$ during Phase II resembles first-order kinetics, suggesting that only one step is rate limiting. Phase II for $\dot{V}O_2$ may be explained by a limitation of either oxygen transport or activation of metabolic processes that govern muscle oxygen utilization (Hughson, 1990). But the extent to which peripheral or central factors limit $\dot{V}O_2$ kinetics is still debated (Grassi et al., 1998; Hughson et al., 1996; Perrey et al., 2001; Tschakovsky and Hughson, 1999). Without a detailed analysis of $\dot{V}O_2$ and cardiac output (CO) kinetics, the issue of metabolic inertia or oxygen delivery for heavy exercise remains unresolved.

To test this $\dot{V}O_2$-CO relationship at the onset of heavy exercise, a continuous CO measurement is needed. Since the standard method presently available (i.e., the $CO_2$ rebreathing method) for CO measurement during exercise requires steady-state conditions, it is impossible to apply it to the transient condition. Other noninvasive methods for determining CO are the Doppler ultrasound (Loeppky et al., 1981) which requires an experienced operator, or the impedance technique (Kubicek et al., 1966). For some researchers, impedance cardiography ($CO_{IMP}$) provides a reasonable estimate of the changes in CO, but for others this technique lacks accuracy and reliability (Bloch and Russi, 1997). Recently the reproducibility and accuracy of CO measured with a new $CO_{IMP}$ device, the PhysioFlow (PF-05, Manatec Biomedical, Paris) was demonstrated using a test/retest exercise procedure in comparison with the invasive Fick method during an incremental work test for trained subjects (Richard et al., 2001).

Previous work examining the potential intensity-dependent effect of prior heavy exercise used prior moderate and heavy exercise of same duration (Bearden and Moffatt, 2001; Burnley et al., 2000; Scheuermann et al., 2001) and different
unloaded recovery duration between repeated bouts (Burnley et al., 2001). All of
these studies found an unaltered $\tau_2$ in Phase II, suggesting that the rate-limiting
factor(s) of muscle $O_2$ utilization was not affected by the prior high-intensity exer-
cise. But it has been shown that an elevated baseline may speed $\dot{V}O_2$ kinetics (Davis
et al., 1972; Di Prampero et al., 1989). Among all these studies, only Bearden and
Moffatt (2001) examined $\dot{V}O_2$ and heart rate (HR) kinetics during repeated bouts
of heavy cycling with an elevated baseline. They demonstrated that HR (and
presumably $CO$) kinetics can be dissociated from $\dot{V}O_2$ kinetics in exercise transitions
from an elevated baseline (~35% $\dot{V}O_2$ peak). However, they estimated $CO$ by
Stringer’s linear regression (Stringer et al., 1997). To confirm the efficacy of the
priming exercise on the cardiovascular system, at least an indirect determination
of $CO$ kinetics would be needed, which would support the speculations about the
rate of $O_2$ delivery to the exercising muscles.

In order to have a better insight into the effect of prior exercise on the $\dot{V}O_2$
and $CO$ responses of subsequent high-intensity exercise, we replicated in part the
methods of Bearden and Moffatt (2001), except that we measured $CO$ kinetics by
the PhysioFlow impedance device. We examined the effect of a 6-min prior high-
intensity cycling exercise (~80% $\dot{V}O_2$ peak) on the $\dot{V}O_2$ and $CO$ kinetics of a simi-
lar 6-min subsequent high-intensity cycling exercise separated by 10-min recov-
ery cycling at 35% $\dot{V}O_2$ peak. We tested the hypothesis that the faster overall rate of
increase in $\dot{V}O_2$ during the second bout would be accompanied by faster increases
in $CO$.

**Methods**

Six healthy men volunteered for the study. Each was accustomed to cycle-ergom-
eter exercise but none of the men were competitive athletes. Mean age was 26 ± 2
years; height was 175.8 ± 1.8 cm; body mass was 69.9 ± 3.8 kg. Possible risks and
benefits were explained, and written informed consent was obtained from each
subject prior to all testing. The study complies with the Helsinki declaration for
human experimentation. The subjects’ physical characteristics are listed in Table 1.

**Table 1  Subjects’ Physical Characteristics**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yrs)</th>
<th>Height (m)</th>
<th>Body mass (kg)</th>
<th>VT (L·min$^{-1}$)</th>
<th>Peak $\dot{V}O_2$ (L·min$^{-1}$)</th>
<th>Peak $\dot{V}O_2$ (ml·kg·min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>1.78</td>
<td>70.0</td>
<td>3.21</td>
<td>4.30</td>
<td>61.4</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>1.79</td>
<td>65.0</td>
<td>2.77</td>
<td>3.90</td>
<td>60.0</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>1.66</td>
<td>51.6</td>
<td>2.20</td>
<td>2.96</td>
<td>57.3</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>1.77</td>
<td>83.0</td>
<td>3.07</td>
<td>4.16</td>
<td>50.1</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>1.80</td>
<td>75.8</td>
<td>2.72</td>
<td>3.71</td>
<td>48.9</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>1.75</td>
<td>73.8</td>
<td>3.12</td>
<td>4.40</td>
<td>59.5</td>
</tr>
<tr>
<td>Mean</td>
<td>26</td>
<td>1.76</td>
<td>69.9</td>
<td>2.85</td>
<td>3.90</td>
<td>56.2</td>
</tr>
<tr>
<td>SEM</td>
<td>2</td>
<td>0.02</td>
<td>3.8</td>
<td>0.13</td>
<td>0.18</td>
<td>1.9</td>
</tr>
</tbody>
</table>
Subjects reported to the laboratory in a rested and hydrated state on two occasions at approximately the same time of day (±2 hr). On the day of the tests, subjects were asked to consume only a light meal and to abstain from caffeinated beverages. Tests were separated by at least 2 days. The ergometer seat was adjusted so that the subjects’ legs were almost fully extended when the pedals were at their lowest point. Room temperature was about 23 °C and the test environment was maintained free of noise and other potential distractions.

Initially all subjects underwent an incremental exercise test on a mechanically braked cycle ergometer (Monark 818 E, Stockholm, Sweden) to allow for estimation of peak oxygen uptake (VO₂ peak) and ventilatory threshold (VT). After sitting for 3 minutes at rest, the subjects began the test at a power output of 30 W during a 2-min period; the power output was increased in 30-W increments every minute until the subjects reached volitional exhaustion. The pedaling cadence was fixed at 60 rpm and maintained throughout all tests (±5 rpm). Pulmonary gas exchange was measured breath-by-breath, as described below. VO₂ peak was determined as the highest value recorded in any 30-s period prior to the subject’s volitional termination of the test. The VO₂ at VT was determined as the breakpoint in the plot of CO₂ output (VCO₂) as a function of VO₂, where the slope becomes >1 (V-slope method) (Beaver et al., 1986).

On the second day, each subject completed an exercise protocol consisting of one minute at rest followed by 5-min baseline cycling at 35% VO₂ peak, then two constant-load work bouts (Bout 1 and Bout 2) at a work rate corresponding to 80% VO₂ peak, separated by 10 min of baseline recovery cycling. Throughout the exercise test the subjects were asked to keep a constant pedaling cadence of ~60 rpm. The pedaling cadence was displayed to the subject.

Before and during the exercise bouts, VO₂ was measured continuously on a breath-by-breath basis by means of a computerized O₂–CO₂ analyzer-flowmeter combination (CPX/D Medical Graphics, St. Paul, MN). The composition of the expired gas was evaluated by means of a thermal O₂ analyzer (Zirconium cell) and an infrared CO₂ analyzer. The CPX system was calibrated immediately before and after each experimental run with air and precision-analyzed gas mixture. All gases were passed through a condenser to control water vapor pressure before analysis. The response time for O₂ and CO₂ concentrations, depending on the capillary length, was less than 70 and 110 ms, respectively. The required tolerance of repeated calibration was ±1%. Respiratory flow was measured continuously by means of a dry gas meter (pneumotach) based on the Pitot tube principle (Porszasz et al., 1994), which was calibrated before each experiment by means of a 3-L syringe (Hans Rudolph 5530, Kansas City, MO) and connected to a mouthpiece. Expired gas volumes were corrected to standard temperature and pressure dried.

Values of stroke volume (SV) and CO were estimated noninvasively by the PhysioFlow impedance device based on analysis of instant thoracic impedance variations, using six electrodes (two for ECG measurement of HR and four for COIMP). Two sets of electrodes (Ag/AgCl, Dorvit Skintact, FS 50, Innsbruck, Austria), one transmitting and one sensing, were applied to each subject at the left base of the neck and along the xiphoid. Another set of electrodes was used to monitor a single electrocardiographic signal (ECG; CM5 position). The PhysioFlow concept and the methodology have been described in a recent study (Charloux et al., 2000,
Appendix I). Briefly, the four COIMP electrodes are used to transmit and receive a very low electric current of 3.6 mA (peak to peak) and 75 kHz frequency. Unlike traditional impedance methods, the positioning of electrodes is not critical, nor are special electrodes or skin cleansing required. Measured parameters are HR, contractility index (CI), and thoracic flow inversion time (TFIT) (active period of left ventricular ejection). SV is then derived from CI and TFIT, and CO measurement is based on the following formula including HR, a stroke volume index (SVi), and body surface area (BSA):

\[
\text{CO (L·min}^{-1}) = \text{HR (beats·min}^{-1}) \times \text{SVi (ml·min}^{-2}) \times \text{BSA (m}^2)
\]

With this impedance device, a first evaluation of SVi is computed during a calibration procedure that is performed with the subject in the resting condition. This evaluation retains the largest impedance variation achieved during systole and the largest rate of variation of the impedance signal. To allow for the achievement of a single averaged signal for each 5 cardiac cycles, impedance signals were time-aligned by computer according to the peak of the QRS complex of the ECG (ensemble-averaging technique). The COIMP PhysioFlow device for CO determination was validated recently by comparison with the invasive direct Fick method during a progressive maximal test (Richard et al., 2001). There was a high correlation between CO values determined by impedance and by direct Fick methods during progressive maximal exercise tests in individual subjects \((r = 0.94, p < 0.01)\). This correlation indicates that the adopted impedance cardiography should provide a reliable estimate of CO during exercise and quantitative information on the time course of change in CO.

The kinetics of \(\dot{V}O_2\) and CO were estimated independently for each test. The individual responses during transitions were linearly interpolated to yield data points at each 1-s interval. Occasional errant data points (e.g., due to a cough, sneeze, or sigh) were deleted from the data set if they fell more than ±4 standard deviations outside the mean value for the 30-s interval that bracketed the breath in question (Lamarra et al., 1987). These data were then smoothed using a 5-point moving-average procedure to reduce the noise so as to enhance the underlying characteristics (Koga et al., 1999). Steady-state values were obtained by averaging the cardiovascular data over a 2-min exercising baseline period, between the 5th and 6th minutes of the 6-min heavy bouts, and during the last 2 minutes of the 10-min recovery period. We adopted the guideline that a period equivalent to four overall rates (as determined by mean response time, MRT) will yield virtually steady-state conditions.

To facilitate comparisons, the time courses of \(\dot{V}O_2\) and CO at the onset of exercise were described in terms of exponential functions that were fit to the data by using nonlinear-regression techniques. The computation of best-fit parameters was chosen by the program so as to minimize the sum of the squared differences between the fitted function and the observed response, using specially-built fitting software. A smaller mean square error indicated a better fit. The goodness-of-fit was also evaluated by the flat profile of the residual plot (i.e., signifying a good fit to measured data) being no longer sustained (see Figure 1), as judged by visual inspection. Inspection of the raw data suggested that CO responded as either a one- or two-component exponential. The time course of the \(\dot{V}O_2\) response after the
onset of exercise was described in terms of a three-component exponential function. The three-component model equation, which incorporates the one- and two-component models, is the following:

\[ Y(t) = BL + A_1 \left[1 - e^{-\left(t - TD_1\right) / \tau_1}\right] + A_2 \left[1 - e^{-\left(t - TD_2\right) / \tau_2}\right] + A_3 \left[1 - e^{-\left(t - TD_3\right) / \tau_3}\right] \]

where \( Y(t) \) is the dependant variable; \( BL \) is the baseline value; \( TD_1, TD_2, \) and \( TD_3 \) are the time delays from the onset of exercise to the onset of the responses of the first, second, and third component, respectively; \( A_1 \) is the change in \( Y \) above \( BL \) in the first component whereas \( A_2 \) and \( A_3 \) represent the change in \( Y \) for times after \( TD_2 \) and \( TD_3 \) to a predicted steady-state, respectively; \( \tau_1, \tau_2, \) and \( \tau_3 \) represent the time constants for each component. If the three-component model was used, \( TD_2 \) differed from \( TD_3 \). From these parameters the time to 63% of the increase in the variable under investigation (MRT) was calculated as a weighted sum of the time delay and time constant for each component according the generalized equation:

\[ MRT = \frac{A_1}{A_1 + A_2 + A_3} \cdot (TD_1 + \tau_1) + \frac{A_2}{A_1 + A_2 + A_3} \cdot (TD_2 + \tau_2) + \frac{A_3}{A_1 + A_2 + A_3} \cdot (TD_3 + \tau_3) \]

MRT was calculated for both the \( \dot{V}O_2 \) and CO responses. Following the procedures outlined previously (Lamarra et al., 1987), we calculated the 95% confidence intervals for estimation of Phase II \( \dot{V}O_2 \) kinetics, as determined by \( \tau_2 \).

### STATISTICAL ANALYSIS

Differences between Bout 1 and Bout 2 were tested for statistical significance by a two-tailed paired \( t \)-test. A simple linear regression was performed to show relationships between pairs of variables. Difference between baseline, end-exercise, and end-recovery time points during Bouts 1 and 2 for SV, CO, and HR were analyzed by one-way analysis of variance with the Student-Newman-Keuls post hoc test. The level of significance was set at \( p < 0.05 \). All data presented are expressed as the mean ± SE throughout.

### Results

The incremental test data showed that the VT occurred at 73 ± 1% of \( \dot{V}O_2 \) peak and resulted in power outputs of 225 ± 15 W. Actual work rates were baseline 35.8 ± 1.2% \( \dot{V}O_2 \) peak or 48.9 ± 1.7% VT, and heavy exercise asymptote was 78.9 ± 1.6% \( \dot{V}O_2 \) peak.

The responses in a single subject along with the residuals to a step increase in work rate corresponding to 80% \( \dot{V}O_2 \) peak (Bouts 1 and 2) are presented in Figure 1. At the onset of the second bout of heavy exercise, the mean baseline \( \dot{V}O_2 \) response was significantly elevated by 73 ml·min\(^{-1}\) (Table 2; \( p < 0.05 \)) above that preceding the first bout. The kinetics (\( \tau_2 \)) of the primary fast component during Bout 2 was similar to that for Bout 1 (\( p = 0.123 \)). The 95% confidence interval for the estimation of Phase II \( \tau_2 \) was 3.2 s for Bout 1 and 2.7 s for Bout 2. These data were based on one transition and mean response amplitudes during Phase II from 853 to 1370 ml·min\(^{-1}\). The amplitude at the end of Phase II (i.e., \( A_1 + A_2 \)) was higher in Bout 2 as a consequence of prior heavy exercise (\( p = 0.024 \)). The absolute \( \dot{V}O_2 \) amplitude at the end of Phase II (i.e., \( BL + A_1 + A_2 \)) was also significantly
increased after prior heavy exercise ($p < 0.01$), due in part to the elevated baseline $\dot{VO}_2$ (Table 2). The amplitude of the $\dot{VO}_2$ slow component ($A_3$) was significantly reduced ($p < 0.01$) by prior heavy exercise (Table 2 and Figure 1). Prior heavy exercise (Bout 1) was associated with a speeding ($p < 0.05$) of the MRT in Bout 2 (Table 3). Due to the elevation in absolute VO$_2$ response at the end of Phase II and the reduced $\dot{VO}_2$ slow component, the $\dot{VO}_2$ values recorded at the end of exercise were similar between these two exercise bouts ($p = 0.424$, Table 3).

The CO kinetics from baseline to heavy exercise is shown for the two bouts in Figure 2. The increase in CO during heavy exercise did not differ between Bouts
Table 2  Parameter Estimates for \( \dot{V}O_2 \) Responses to Repeated Bouts of Heavy Exercise

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Bout 1</th>
<th>Bout 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL (ml·min(^{-1}))</td>
<td>1390 ± 80</td>
<td>1462 ± 88*</td>
</tr>
<tr>
<td>( A_1 ) (ml·min(^{-1}))</td>
<td>462 ± 55</td>
<td>465 ± 51</td>
</tr>
<tr>
<td>TD(_1) (s)</td>
<td>0.5 ± 0.1</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>( \tau_1 ) (s)</td>
<td>7 ± 1</td>
<td>5 ± 1</td>
</tr>
<tr>
<td>( A_1 + A_2 ) (ml·min(^{-1}))</td>
<td>1409 ± 71</td>
<td>1526 ± 72*</td>
</tr>
<tr>
<td>TD(_2) (s)</td>
<td>22 ± 1</td>
<td>21 ± 1</td>
</tr>
<tr>
<td>( \tau_2 ) (s)</td>
<td>25 ± 1</td>
<td>23 ± 0</td>
</tr>
<tr>
<td>BL + ( A_1 + A_2 ) (ml·min(^{-1}))</td>
<td>2798 ± 145</td>
<td>2989 ± 155*</td>
</tr>
<tr>
<td>( A_3 ) (ml·min(^{-1}))</td>
<td>436 ± 81</td>
<td>287 ± 57*</td>
</tr>
<tr>
<td>TD(_3) (s)</td>
<td>120 ± 5</td>
<td>114 ± 1</td>
</tr>
<tr>
<td>( \tau_3 ) (s)</td>
<td>121 ± 2</td>
<td>120 ± 1</td>
</tr>
</tbody>
</table>

Note: Values are mean ± SEM; \( n = 6 \) subjects.
*Significantly different from Bout 1, \( p < 0.05 \).

Table 3  Baseline Cycling Exercise, Amplitude of Increase at 6 min of Exercise, and Time to 63\% (MRT) of Increase in CO and \( \dot{V}O_2 \) to Repeated Bouts of Heavy Exercise

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Baseline (L·min(^{-1}))</th>
<th>Amplitude (L·min(^{-1}))</th>
<th>MRT (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO Bout 1</td>
<td>9.6 ± 0.7</td>
<td>7.3 ± 0.9</td>
<td>62 ± 8</td>
</tr>
<tr>
<td>CO Bout 2</td>
<td>11.5 ± 1.1*</td>
<td>8.1 ± 0.8</td>
<td>44 ± 6*</td>
</tr>
<tr>
<td>( \dot{V}O_2 ) Bout 1</td>
<td>1.4 ± 0.1</td>
<td>1.8 ± 0.1</td>
<td>83 ± 10</td>
</tr>
<tr>
<td>( \dot{V}O_2 ) Bout 2</td>
<td>1.5 ± 0.1*</td>
<td>1.8 ± 0.1</td>
<td>64 ± 6*</td>
</tr>
</tbody>
</table>

Note: Values are mean ± SEM; \( n = 6 \) subjects.
*Significantly different from Bout 1, \( p < 0.05 \).
Figure 2. Cardiac output (CO) in a single subject to repeated heavy cycling transitions. First (Bout 1, top panel) and second (Bout 2, bottom panel) transitions from 35% to 80% peak \( \dot{V}O_2 \) are shown. Exercise begins at 0 min. —— = beat-by-beat interpolated to second-by-second CO; —— = line of best fit. Residuals at the base of each panel appear randomly distributed about the line of best fit.

The overall rate of increase in CO with the transition from 35% to 80% \( \dot{V}O_2 \) peak determined by the MRT was significantly faster in Bout 2 (Table 3, \( p = 0.048 \)). CO and SV comparisons are given in Figure 3. SV did not differ significantly across conditions. CO was significantly higher during the exercise baseline in Bout 2 compared to Bout 1 (Table 3 and Figure 3, \( p < 0.05 \)). The 2-min baseline (99 ± 2 vs. 111 ± 3 bpm) and end-exercise (158 ± 5 vs. 170 ± 7 bpm) values for HR were significantly higher (\( p < 0.05 \)) in Bout 2. As shown in Table 3, during the baseline preceding Bout 2, CO remained some 18% above the control value and HR remained ~12 bpm above the control value. The sustained increase in HR (12%) therefore only accounted for approximately two-thirds of the residual increase in CO. There was a trend for SV to increase, but the level of significance was not reached.
**Figure 3.** Stroke volume (SV) and cardiac output (CO). Base = 2-min period cycling baseline; EX = last minute exercise value; 1 = Bout 1; 2 = Bout 2. Data are mean (±SE) values for six subjects.

*Significantly different from Base 1 at $p < 0.05$; # Significantly different from Base 2 at $p < 0.05$.

**Figure 4.** Relationship between mean response time (MRT) for oxygen uptake is shown as a function of MRT for cardiac output during Bouts 1 and 2, with 95% confidence intervals of the regression (---). Regression equation (-----) is $Y = 0.90X + 25.6$ ($r = 0.806$, $SEE = 11.9$, $p < 0.01$).
The relationship between the time course (MRT) of increase in $\overline{V}O_2$ and CO at the onset of heavy cycling exercise (Bouts 1 and 2) is shown in Figure 4. The overall regression equation describing the repeated bouts of heavy cycling tests was $\text{MRT-}$\,$\overline{V}O_2 = 0.90 \text{MRT-CO} + 25.6$, $r = 0.81 \,(p < 0.01)$. As shown in Figure 4, the MRT for CO was consistently and appreciably shorter than $\overline{V}O_2$ (intercept of the regression equation of 25.6; $SE = 11.7; \, p = 0.045$). Also, the correlation showed that 65% of the variability of the MRT for CO could be explained by the MRT of $\overline{V}O_2$ ($r^2 = 0.65; \, SEE = 11.9$).

**Discussion**

One major finding in the present study was that the overall kinetics (i.e., MRT) for both $\overline{V}O_2$ and CO were significantly accelerated by repeated heavy cycling exercise. The time course of change, given by the MRT, was 28% faster for $\overline{V}O_2$ and 23% faster for CO in the second exercise bout compared with the first heavy exercise. However, it appears that the acceleration of overall $\overline{V}O_2$ kinetics in Bout 2 was due to a less pronounced slow-component amplitude and an increase in the net amplitude of the Phase II rather than a speeding of the Phase II $\overline{V}O_2$ kinetics. While we observed a lack of speeding of the kinetics of the primary $\overline{V}O_2$ response, our results indicate that adaptation of aerobic metabolism during high-intensity exercise might be improved by the availability of O$_2$.

**METHODOLOGICAL CONSIDERATIONS**

Limitations to the methodology used in the present study include, first of all, instrumental constraints. In 1966 Kubicek et al. described a method of calculating stroke volume (i.e., cardiac output) from the thoracic impedance signal. However, special electrodes, specific configuration, skin cleansing, and measurements for estimating one cylinder or truncated cone model were essential for obtaining the true value of stroke volume, but they could also induce some error in this assessment. Recently a new thoracic impedance method, the PhysioFlow, has become available. This device is the result of technical improvements in software and hardware; a new generation of analog technology allows the PhysioFlow to improve signal filtering and stability and provides better data processing. The basic equation for calculating SV has been modified profoundly in order to overcome the difficult evaluation of variables such as blood resistivity, the distance between recording electrodes, and the basal thoracic impedance used in the Kubicek equation.

The PhysioFlow has been validated against accepted reference methods such as “direct” Fick (Charloux et al., 2000; Richard et al., 2001). Validations were obtained at rest and during exercise up to maximal effort on the cycle ergometer, both in healthy subjects and in patients suffering from cardiac or pulmonary diseases. Further reproducibility has also been tested thoroughly; the greatest variation observed between two comparable CO impedance measurements was 16%. However, the estimation accuracy of CO in the present study may have been limited by the lack of repeated data collections and we must consider the result of CO MRT carefully. But in the present study, a low intersubject CO variability after full data analysis was similar (coefficient of variation [CV] from 17% at rest to 22% at
6-min exercise) to that previously observed using CO\textsubscript{Imp} methods during multiple repetitions of exercise (Grassi et al., 1997; Koga et al., 1996).

Second, one could argue that the number of transitions between rest and exercise is not sufficient for accurately assessing the parameters of the model used for \( \dot{V}O_2 \) kinetics. For heavy and very heavy exercise intensities as in the present study, “noise” associated with a single transition could readily account for the 10% variation seen in the individual \( \tau_2 \) estimates, and the possibility of “real” variation on different occasions cannot be excluded (Özyener et al., 2001). The latter study used three repetitions at exercise intensities that manifested a slow phase of \( \dot{V}O_2 \), and the kinetic parameters estimated from the model fits showed high reproducibility for Phase II.

For the \( \dot{V}O_2 \) slow component, we demonstrated recently that estimated CV by the bootstrap method (see Borrani et al., 2001), especially those of the two critical parameters TD\( \textsubscript{3} \) and A\( \textsubscript{3} \), were relatively small (~10%), suggesting an accurate determination of the critical parameters even if a single transition was performed. Moreover, it is not possible to exclude the fact that the breath-by-breath variability may have biological significance, although Lamarra et al. (1987) suggested stochastic properties of the breath-by-breath noise. In the present study, the lack of relationship between the residuals and the time of exercise (\( p > 0.05 \)) support the view of the previous authors. Even if the single transition may be spoiled by inherent noise, we found a single transient to be sufficient in our subjects, as the amplitude of response was associated with a good signal-to-noise ratio (Figure 1).

\( \dot{V}O_2 \) KINETICS WITH PRIOR HEAVY EXERCISE

Comparing favorably with recent studies on the effect of prior exercise on \( \dot{V}O_2 \) kinetics (Burnley et al., 2000; 2001; Scheuermann et al., 2001), our data showed that the effect of prior exercise on \( \dot{V}O_2 \) kinetics increases the absolute amplitude of \( \dot{V}O_2 \) at the end of Phase II and is associated with a reduction in the amplitude of the slow component. The present study indicated that the net amplitude of the Phase II response was also increased by prior heavy exercise followed by 10 min of recovery, unlike the 12-min recovery period previously used (Burnley et al., 2001). Furthermore, it is clear from the present study that Phase II \( \dot{V}O_2 \) kinetics are not speeded by prior heavy exercise followed by 10-min recovery at a moderate-intensity exercise. Thus the faster MRT in repeated heavy transitions does not appear to be the result of faster initial Phase II kinetics, regardless of baseline work rate (Bearden and Moffatt, 2001; Burnley et al., 2000).

By manipulating perfusion pressure in cycle exercise (supine vs. upright positions) to examine the effect of \( O_2 \) delivery of large-muscle-mass exercise, Koga et al. (1999) found an opposite response to that shown in the present study during the second bout of heavy exercise; that is, Koga et al. found a significant reduction in the amplitude of Phase II and an increase in the amplitude of the slow component. Their results and the present findings suggest that the amplitude of \( \dot{V}O_2 \) at the end of Phase II itself may be more sensitive than Phase II \( \dot{V}O_2 \) kinetics to changes in \( O_2 \) delivery. Initially Gerbino et al. (1996), and later MacDonald et al. (1997), proposed that the effect of prior heavy exercise depends on the alleviation of a limitation in \( O_2 \) delivery. Our results show that while an increase in oxygen deliv-
ery (represented by CO) can modulate the required amplitude at the end of Phase II in the second exercise bout, the rate of adjustment of this phase was unaltered. These data support the work of Grassi et al. (1998) in that Phase II VO₂ kinetics were not speeded even if prior heavy exercise presented higher CO and a more favorable distribution of blood flow to the exercising muscles. To interpret these results correctly, one should ask whether the first exercise bout was indeed effective in determining more favorable conditions with regard to the rate of adjustment of O₂ delivery to the muscle fibers. The measurements carried out in the present study allow at least a partial answer. Indeed, during the 2-min baseline period preceding the second exercise bout, HR and CO values were significantly higher than during the homologous period before the first exercise bout (see Figure 2), and the pattern of CO adaptation results in a faster adjustment to steady state (Table 3). Note that CO was regulated in part by HR because SV was at, or nearly at, the exercising level during the cycling baseline (Figure 3).

CARDIOVASCULAR RESPONSE

In the present study we used an elevated baseline (~35% VO₂ peak) to speed systemic metabolic recovery and VO₂ kinetics (Bearden and Moffatt, 2001). Unlike Bearden and Moffatt (2001), we found that τ₂ values of 25 s generally reported using a light or unloaded baseline (Barstow et al., 1996; Burnley et al., 2000; Engelen et al., 1996), suggesting that a speeding of overall VO₂ kinetics by an elevated baseline is not a universal conclusion. In fact, Hughson and Morissey (1983) observed a slower kinetics of VO₂ in the transition from light to moderate exercise than in the transition from rest to moderate exercise. It is important to note that overall VO₂ kinetics in the present study were dissociated (Figure 4, intercept of 25.6 significantly different from 0, p < 0.05) of CO kinetics with a baseline of moderate exercise. That is, the MRT for CO was consistently shorter than that for VO₂ (Table 3 and Figure 4).

Regression analysis of individual MRT values for VO₂ vs. CO (r = 0.81) did support our hypothesis that the overall increase in VO₂ was linked to the rate of increase in cardiac output across a range of values achieved with two conditions. When the response rate of an O₂ delivery process is compared to the rate of VO₂ response to a change in work rate, the O₂ delivery mechanism is usually determined to be faster (De Cort et al., 1991; Eriksen et al., 1990). These results have been interpreted as indicating that bulk O₂ delivery to the exercising muscle is adequate at the onset of exercise to meet the O₂ demands of the muscle. Given the approximately linear relationship between metabolic rate (VO₂) and each of HR, CO, and muscle blood flow (Rowell, 1993), the O₂ utilization hypothesis requires that O₂ demand must somehow be “anticipated” so that O₂ supply can be precisely matched or exceed the demand by feed-forward control (Hughson et al., 2001). However, inferences on convective O₂ delivery to muscles must rely on a main assumption: the time course of blood flow to the active muscles could be reasonably estimated on the basis of CO time course. This assumption holds if perfusion to active skeletal muscles accounts for most of the increase in CO at the on-transition. Although this would seem reasonable, it could not be directly tested. The issue of whether muscle tissue VO₂ is limited at the beginning of exercise, either by O₂ delivery or by intramuscular control mechanisms beyond the capillary level,
is not yet completely clarified. Rather it seems that the adaptation of aerobic metabolism should be viewed as resulting from the integration of factors which determine the rate of adaptation of the cellular metabolic state, enzyme activation, and mitochondrial O$_2$ supply (Tschakovsky and Hughson, 1999). The rate of increase in oxidative phosphorylation can be appreciated from MRT.

A more rapid overall increase in VO$_2$, which we found in the second exercise, would mean that a greater proportion of total ATP resynthesis occurred through oxidative phosphorylation, or that this proportion through oxidative phosphorylation remained the same but there was a greater ATP requirement during the early part of exercise. Thus it would appear that faster overall VO$_2$ kinetics was attributable in part to a faster adjustment of convective O$_2$ transfer. However, since the kinetics of CO were faster than those of VO$_2$ under both the control (Bout 1) and experimental (Bout 2) conditions, O$_2$ was available in excess of metabolic demand and suggest that metabolic control was a rate-limiting step for VO$_2$ response. Taken together, the previous comments suggest that the apparent inertia to mitochondrial flux at the onset of exercise seems to be governed not only by oxygen supply to muscle but also by substrate delivery and/or availability. In this repeated-exercise procedure, the major limiting factor(s) of VO$_2$ kinetics at the onset may be an unsolvable problem.

Finally, it is not clear why the $\tau_2$ observed for VO$_2$ kinetics was unchanged. This could be explained by an increase in motor unit recruitment (Bearden and Moffatt, 2000) at the onset of the second bout of exercise, resulting in an increase in VO$_2$ at the end of Phase II, even though the work rates had not changed in Bouts 1 and 2. This would require an increase in bulk O$_2$ supply to meet the increased O$_2$ demand, without necessarily altering the rate of adjustment of VO$_2$ toward the end of Phase II (Burnley et al., 2001; Scheuermann et al., 2001). The mechanisms responsible for the unchanged $\tau_2$ require additional research.

**Conclusion**

In conclusion, prior heavy exercise resulted in an increase in the amplitude without a change in the kinetics of Phase II VO$_2$ response, and a reduced VO$_2$ slow component during subsequent heavy exercise following 10 min of exercise recovery. Combined measurement of cardiac output and VO$_2$ kinetics revealed: (a) a significant positive correlation between the overall rate of increase in CO and VO$_2$ during the on-transitions of the sequential exercise protocol; and (b) a faster overall response for both CO and VO$_2$ during the second exercise bout. From the above considerations, it would be reasonable to conclude that the priming effect of moderate exercise enabled a better adaptation of the oxidative metabolic processes at the onset of heavy exercise.

**References**


Received October 3, 2001; accepted in final form May 27, 2002.