

# Effects of prior heavy exercise on phase II pulmonary oxygen uptake kinetics during heavy exercise

MARK BURNLEY,<sup>1</sup> ANDREW M. JONES,<sup>2</sup> HELEN CARTER,<sup>3</sup> AND JONATHAN H. DOUST<sup>3</sup>

<sup>1</sup>Chelsea School Research Centre, University of Brighton, Eastbourne, East Sussex, BN20 7SP;

<sup>2</sup>Department of Exercise and Sport Science, Manchester Metropolitan University, Alsager, ST7 2HL;

and <sup>3</sup>School of Sport, Exercise and Leisure, University of Surrey Roehampton, London, SW15 3SN, United Kingdom

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**Burnley, Mark, Andrew M. Jones, Helen Carter, and Jonathan H. Doust.** Effects of prior heavy exercise on phase II pulmonary oxygen uptake kinetics during heavy exercise. *J Appl Physiol* 89: 1387–1396, 2000.—We tested the hypothesis that heavy-exercise phase II oxygen uptake ( $\dot{V}O_2$ ) kinetics could be speeded by prior heavy exercise. Ten subjects performed four protocols involving 6-min exercise bouts on a cycle ergometer separated by 6 min of recovery: 1) moderate followed by moderate exercise; 2) moderate followed by heavy exercise; 3) heavy followed by moderate exercise; and 4) heavy followed by heavy exercise. The  $\dot{V}O_2$  responses were modeled using two (moderate exercise) or three (heavy exercise) independent exponential terms. Neither moderate- nor heavy-intensity exercise had an effect on the  $\dot{V}O_2$  kinetic response to subsequent moderate exercise. Although heavy-intensity exercise significantly reduced the mean response time in the second heavy exercise bout (from  $65.2 \pm 4.1$  to  $47.0 \pm 3.1$  s;  $P < 0.05$ ), it had no significant effect on either the amplitude or the time constant (from  $23.9 \pm 1.9$  to  $25.3 \pm 2.9$  s) of the  $\dot{V}O_2$  response in phase II. Instead, this “speeding” was due to a significant reduction in the amplitude of the  $\dot{V}O_2$  slow component. These results suggest phase II  $\dot{V}O_2$  kinetics are not speeded by prior heavy exercise.

$\dot{V}O_2$  slow component; exercise transitions; lactate threshold; oxygen transport

IN RESPONSE TO A STEP TRANSITION from rest to constant-intensity moderate exercise [below the lactate threshold (LT)], pulmonary oxygen uptake ( $\dot{V}O_2$ ) increases to meet the augmented energetic requirement in three characteristic phases (43). After a short delay of  $\sim 20$  s, which reflects the transit time from the exercising muscles to the lungs (phase I), pulmonary  $\dot{V}O_2$  rises in a monoexponential fashion (phase II) to attain a steady state (phase III) within 2–3 min in healthy subjects. During heavy exercise [above the LT but below the maximal  $\dot{V}O_2$  ( $\dot{V}O_{2\max}$ )], a delayed increase in  $\dot{V}O_2$  that has relatively slow kinetics emerges after the phase II response (41). This  $\dot{V}O_2$  “slow component” causes  $\dot{V}O_2$  to increase above the steady-state value predicted from the extrapolation of the  $\dot{V}O_2$ -power output relationship

from moderate exercise intensities (5, 33). Grassi et al. (20) have reported that the phase II  $\dot{V}O_2$  time constant at the mouth is similar to that simultaneously measured across the exercising limb, and Poole et al. (35) showed that  $\sim 86\%$  of the  $\dot{V}O_2$  slow component could be accounted for by an increased leg  $\dot{V}O_2$  during heavy cycle exercise.

The physiological determinants of the phase II  $\dot{V}O_2$  kinetics during exercise are still debated (39).

It has been suggested that the time constant for pulmonary  $\dot{V}O_2$  in phase II closely reflects the time constant for  $O_2$  utilization in the exercising muscles (1, 4, 20, 36). It has been suggested that, during moderate exercise, these kinetics are primarily determined by enzymatic processes that result in a “metabolic inertia” relative to the steady-state energy demands of exercise (18–20). However, oxygen delivery to the muscle mitochondria may become an important determinant of the phase II time constant during heavy exercise (17, 31, 42). Support for this contention comes from the observation that a prior “warm-up” or “conditioning” bout of heavy-intensity cycling exercise results in a speeding of  $\dot{V}O_2$  kinetics during heavy exercise (16, 17, 31). Using a monoexponential model to describe the  $\dot{V}O_2$  response over 6 min of exercise, Gerbino et al. (17) found a significant reduction in the effective time constant of the  $\dot{V}O_2$  response in the second of two heavy exercise bouts separated by 6 min of recovery. MacDonald et al. (31) also demonstrated a net speeding of  $\dot{V}O_2$  on-kinetics [measured as a reduction in the mean response time (MRT)] when heavy exercise was preceded by an identical heavy exercise bout. It was suggested that the prior exercise resulted in an increase in  $O_2$  delivery during a second heavy bout and thus speeded the kinetics of  $\dot{V}O_2$  (17, 31). These investigators (17, 31) also reported that the  $\dot{V}O_2$  slow component was reduced by prior heavy exercise.

Because the  $\dot{V}O_2$  response to heavy exercise can be described as a three-phase process, the modeling of this response with a single dynamic parameter (the effective time constant for  $\dot{V}O_2$  or MRT) has been questioned

Address for reprint requests and other correspondence: M. Burnley, Chelsea School Research Centre, Univ. of Brighton, Gaudick Rd., Eastbourne, East Sussex, BN20 7SP, United Kingdom (E-mail: M.Burnley@bton.ac.uk).

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Table 1. *Subjects' physical characteristics*

Subject	Age, yr	Sex	Height, m	Mass, kg	LT, l/min	$\dot{V}O_{2peak}$ , l/min	$\dot{V}O_{2peak}$ , ml·kg <sup>-1</sup> ·min <sup>-1</sup>
1	21	M	1.82	65.8	2.65	4.10	62
2	25	F	1.71	66.8	1.59	2.85	43
3	33	M	1.76	81.2	1.69	3.65	45
4	31	M	1.85	79.5	1.95	3.70	46
5	32	M	1.71	71.2	2.31	3.62	51
6	27	F	1.61	58.6	2.04	3.08	53
7	36	M	1.74	77.0	1.99	3.30	43
8	22	M	1.76	69.4	2.27	3.78	54
9	22	M	1.79	66.1	3.08	4.50	68
10	29	M	1.74	72.4	2.50	3.89	54
Mean	29		1.75	70.8	2.21	3.65	52
SD	5		0.07	7.0	0.45	0.48	8

LT, lactate threshold;  $\dot{V}O_{2peak}$ , peak oxygen uptake; M, male; F, female.

(2). When previous investigators have modeled the heavy exercise  $\dot{V}O_2$  response during phase II and the slow component separately, the phase II time constant has been found to be slower (33) or unchanged (2, 8) compared with moderate-intensity exercise. Barstow et al. (2) showed that, when the exercise response was described with a monoexponential term, the time constant was systematically slowed as the power output was increased above the LT. However, this slowing of  $\dot{V}O_2$  kinetics above the LT was not related to a slowing of the phase II  $\dot{V}O_2$  kinetics but rather to the inclusion of the slow component term in the monoexponential model. When the  $\dot{V}O_2$  response was mathematically modeled using discrete exponential terms to describe the phase II and slow component responses, the phase II  $\dot{V}O_2$  kinetics were invariant during exercise bouts ranging from 35% to 100%  $\dot{V}O_{2max}$  (2). Therefore, describing the  $\dot{V}O_2$  response kinetics with a monoexponential model through the entire duration of exercise (17) or reporting the MRT (31) may be misleading if the goal is to establish the phase II  $\dot{V}O_2$  kinetics for heavy exercise.

Previous work investigating the effects of prior heavy exercise has either not measured the phase II  $\dot{V}O_2$  kinetics (17) or has not used these kinetics in the physiological interpretation of the data (31). Therefore, the purpose of the present study was to test the hypothesis that specifically the phase II  $\dot{V}O_2$  response to heavy exercise could be speeded by prior heavy exercise. We replicated the methods of Gerbino et al. (17), except that we also used a triple exponential model to describe the  $\dot{V}O_2$  response to heavy exercise (3). This model partitioned the  $\dot{V}O_2$  response into its constituent parts, allowing the phase II  $\dot{V}O_2$  kinetics and the slow component to be characterized separately. This enabled us to determine whether the reduction in the effective time constant for  $\dot{V}O_2$  or MRT reported in previous studies (17, 31) was due to a true speeding of the phase II  $\dot{V}O_2$  kinetics or was the result of a reduction in the  $\dot{V}O_2$  slow component.

## METHODS

**Subjects.** Ten healthy, active volunteers (8 men) gave written, informed consent to participate in this study, which was

approved by the University of Brighton Ethics Committee. The physical and aerobic performance characteristics of the subjects are presented in Table 1.

**Experimental design.** The subjects visited the laboratory on five occasions over a 2-wk period. The first visit was used to determine the LT and the peak oxygen uptake ( $\dot{V}O_{2peak}$ ), whereas the other visits were used to complete the experimentation. All subjects reported to the laboratory rested, (having performed no strenuous activity in the preceding 24 h), well hydrated, and having abstained from food, alcohol, and caffeine in the 3 h before testing. Tests were conducted in a well-ventilated laboratory at the same time of day for each subject ( $\pm 2$  h), at a comfortable temperature (18–21°C).

**Measurement of LT and  $\dot{V}O_{2peak}$ .** All testing was performed on an electrically braked cycle ergometer (Jaeger ER 800, Wurtzberg, Germany), which controlled external power output independent of pedal cadence. Each subject, therefore, self-selected a cadence of between 70 and 90 rpm and maintained this throughout all tests ( $\pm 2$  rpm). LT and  $\dot{V}O_{2peak}$  were determined from an incremental cycle protocol, similar in design to that used previously in runners (9), in which subjects exercised to volitional exhaustion. The tests began at a power output of 50–100 W, and the power output was increased by 25 W every 4 min. At the end of each 4-min stage, a blood sample ( $\sim 25$   $\mu$ l) was collected from the fingertip into a capillary tube for immediate analysis of blood lactate concentration ([lactate]) using an automated lactate analyzer (YSI Stat 2300, Yellow Springs Instruments, Yellow Springs, OH). The 4-min stages were terminated when blood [lactate] increased by 1 mM or more in two consecutive stages. The subjects completed between six and nine of these stages. When the 4-min stages were completed, the power output increased incrementally by 25 W every minute until the subjects reached volitional exhaustion. Throughout the incremental test, pulmonary gas exchange was measured breath-by-breath, as described below. The steady-state  $\dot{V}O_2$  for a given power output was taken as that measured over the last 30 s of each 4-min stage, whereas  $\dot{V}O_{2peak}$  was determined as the highest value recorded in any 30-s period before the subject's volitional termination of the test. The LT was determined as a sudden and sustained increase in blood [lactate] above resting levels from visual inspection of individual plots of blood [lactate] vs.  $\dot{V}O_2$  by two experienced, independent reviewers (28).

**Experimental tests.** The power outputs for the experimental trials were set at 80% of the  $\dot{V}O_2$  at LT for the moderate-intensity bouts and half-way between the  $\dot{V}O_2$  at LT and  $\dot{V}O_{2peak}$  for the heavy-intensity bouts [50% $\Delta$ , that is LT + 0.5

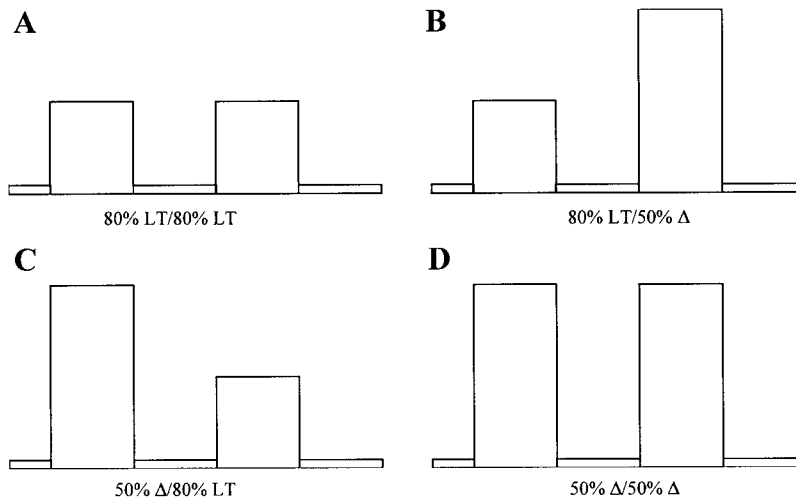


Fig. 1. Schematic representation of the experimental protocol. After 3 min of cycling at 20 W, subjects performed a square-wave transition to a power output calculated to require 80% of lactate threshold (LT; moderate exercise) or halfway between LT and maximal oxygen uptake ( $\dot{V}O_2$ ) (50% $\Delta$ ; heavy exercise). After 6 min of recovery cycling at 20 W, the subjects again completed a square-wave transition to either 80% LT or 50% $\Delta$ , before completing another 6 min of recovery cycling at 20 W. Protocols performed were moderate followed by moderate exercise (A), moderate followed by heavy (B), heavy followed by moderate (C), and heavy followed by heavy (D).

$\times (\dot{V}O_{2\text{ peak}} - \text{LT})$ . These power outputs were determined by linear regression of  $\dot{V}O_2$  on power output, using the sub-LT stages from the incremental test.

The experimental tests were identical in design to those of Gerbino et al. (17). Subjects initially performed 3 min of baseline pedaling at 20 W (the lowest intensity available on the ergometer), followed by a square-wave increase to a constant power output of either 80% LT or 50% $\Delta$  for 6 min, followed by an abrupt decrease in power output back to 20 W for 6 min. This exercise-recovery square wave was repeated immediately, resulting in a “double square-wave” protocol (Fig. 1). Immediately before and after each square-wave transition, a fingertip blood sample was taken, from which the increase in blood [lactate] during exercise ( $\Delta[\text{lactate}]$ ) was calculated.

Four variations of the double square-wave protocols were performed: 1) two bouts at 80% LT; 2) a bout at 80% LT followed by a bout at 50% $\Delta$ ; 3) a bout at 50% $\Delta$  followed by a bout at 80% LT; and 4) two bouts at 50% $\Delta$ . To improve the signal-to-noise ratio and to facilitate curve fitting, subjects performed each of these variations on two separate occasions. To achieve this in four laboratory visits, subjects performed two protocols in each visit, in a pseudorandom design. The subjects were not aware of which tests they would be performing, only that the total test duration would be 27 min and that the tests would be similar in design. At least 1 h separated each test, and subjects performed a maximum of two heavy-intensity bouts in any laboratory visit. As a result, the consecutive bouts of heavy exercise (50% $\Delta$  intensity) were always performed 1 h after the consecutive bouts of moderate exercise (80% LT intensity). At least 24 h separated each laboratory visit.

**Measurement of pulmonary gas exchange.** Pulmonary gas exchange was measured breath-by-breath throughout all tests. Subjects wore a nose clip and breathed through a mouthpiece connected to a low resistance ( $0.65 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}^{-1}$  at 8.5 l/s) turbine volume transducer for the measurement of inspiratory and expiratory volumes (Interface Associates). The turbine was calibrated using a 3-liter calibration syringe (Hans-Rudolph). The dead space volume of the mouthpiece was 90 ml. A 2-m-long capillary tube was used to continuously draw gas from the mouthpiece into a mass spectrometer (CaSE QP9000, Morgan Medical, Kent) at a rate of 60 ml/min. The mass spectrometer was tuned to measure  $O_2$ ,  $CO_2$ , and  $N_2$  concentrations at a rate of 50 Hz and was calibrated before each test using gases of known concentration. Volume and

concentration signals underwent time alignment and analog-to-digital conversion, and breath-by-breath values for  $\dot{V}O_2$ , carbon dioxide output ( $\dot{V}CO_2$ ), and expired ventilation were calculated and displayed online. Heart rate was continuously monitored using short-range telemetry (Polar Sports Tester, Kempele, Finland).

**Data analysis.** The breath-by-breath data were linearly interpolated to provided second-by-second values. For each subject, the two performances of each protocol were time aligned and averaged to provide one set of second-by-second data for each variation of the protocol. The  $\dot{V}O_2$  responses were modeled using iterative nonlinear regression techniques in which minimizing the sum of squared error was the criterion for convergence. The time course of the  $\dot{V}O_2$  response after the onset of exercise [ $\dot{V}O_2(t)$ ] was described in terms of a two- (moderate-intensity) or three- (heavy-intensity) component exponential function. Each exponential curve was used to describe one phase of the response. The first phase began at the onset of exercise, whereas the other terms began after independent time delays (3)

$$\dot{V}O_2(t) = \dot{V}O_2(b) + A_0 \times (1 - e^{-t/\tau_0})$$

phase I (cardiodynamic component)

$$+ A_1 \times (1 - e^{-(t - TD_1)/\tau_1}) \quad \text{phase II (primary component)}$$

$$+ A_2 \times (1 - e^{-(t - TD_2)/\tau_2}) \quad \text{phase III (slow component)}$$

where  $\dot{V}O_2(b)$  is the baseline  $\dot{V}O_2$  measured in the 3 min preceding the onset of exercise;  $A_0$ ,  $A_1$ , and  $A_2$  are the asymptotic amplitudes for the exponential curves;  $\tau_0$ ,  $\tau_1$ , and  $\tau_2$  are the time constants; and  $TD_1$  and  $TD_2$  are the time delays (Fig. 2). The phase I response was terminated at the onset of phase II (at  $TD_1$ ), and given the value for that time (defined  $A_0$ ). The amplitude of the primary response ( $A_1$ ) was defined as the increase in  $\dot{V}O_2$  from baseline to the end of phase II (i.e.,  $A_0' + A_1$ ). The amplitude of the  $\dot{V}O_2$  slow component was determined as the increase in  $\dot{V}O_2$  from  $TD_2$  to the end of exercise (defined  $A_2'$ ) rather than from the asymptotic value ( $A_2$ ), which may lie beyond physiological limits. In addition to the time constants describing each exponential term, a mono-exponential curve was fit from 25 s after exercise onset to the end of exercise [the effective  $\dot{V}O_2$  time constant ( $\tau\dot{V}O_2$ )], after Gerbino et al. (17). The MRT was calculated as the weighted sum of all three phases, yielding a value that represents the time taken to attain 63% of the overall  $\dot{V}O_2$  response (31). The inclusion of these parameters allowed comparison of the

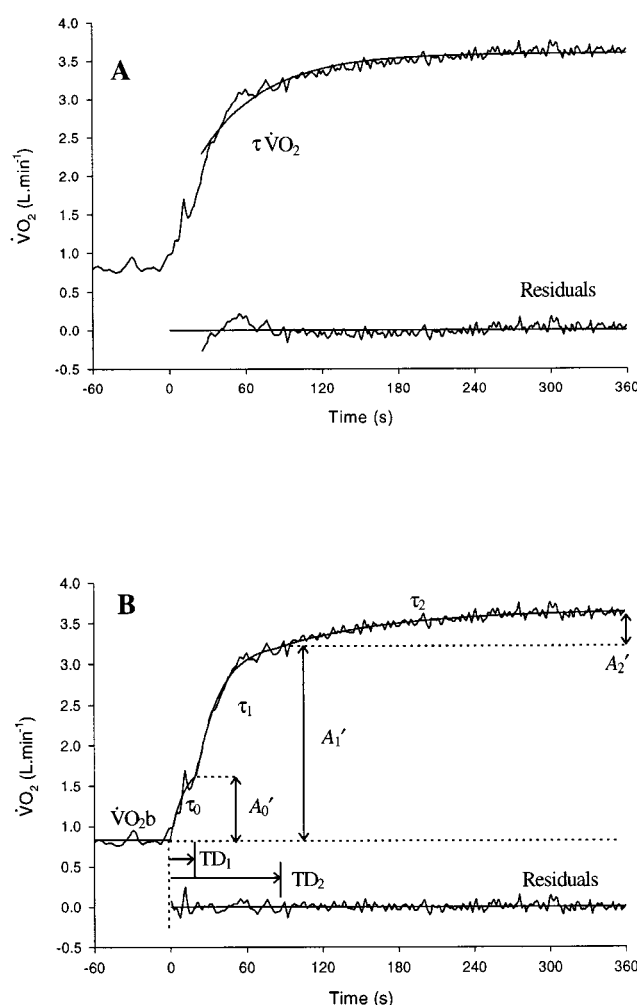


Fig. 2. Example of the  $\dot{V}O_2$  response to heavy-intensity exercise. A: response fitted with a monoexponential curve from 25 s after the onset of exercise. Residuals at the foot of the graph show clear trends throughout the exercise period. B: the same response fitted with the triple exponential model, with response parameters superimposed. Residuals at the foot of this graph appear randomly distributed about the line of best fit.  $\tau \dot{V}O_2$ , effective  $\dot{V}O_2$  time constant;  $\tau_0$ ,  $\tau_1$ , and  $\tau_2$ , time constants;  $\dot{V}O_{2b}$ , baseline  $\dot{V}O_2$  measured in the 3 min before onset of exercise;  $A_0'$ ,  $A_1'$ , and  $A_2'$ , amplitudes for exponential curves (see text);  $TD_1$  and  $TD_2$ , time delays.

effects of prior exercise on the phase II  $\tau$  ( $\tau_1$ ) with the effects on the overall  $\dot{V}O_2$  kinetics ( $\tau \dot{V}O_2$ , MRT). We did not attempt to model the  $\dot{V}CO_2$  kinetics of heavy exercise with a model similar to that of  $\dot{V}O_2$ , because the evolution of  $CO_2$  at the lung under these conditions is unlikely to be resolved into three distinct exponential components, owing to the potential of the buffering of lactate and hyperventilation to distort the truly aerobic output of  $CO_2$  at the lung (10). We therefore interpreted the time course of  $\dot{V}CO_2$  relative to the modeled  $\dot{V}O_2$  responses by using the pattern of change in respiratory exchange ratio (R) observed, assuming a constant muscle RQ (42).

**Statistical analysis.** To determine the “goodness of fit” of the models used to describe the  $\dot{V}O_2$  responses to heavy exercise, the residuals of each three-phase model were compared with those of the two-phase model applied to heavy exercise by means of an *F* test. The two-phase modeling approach was analogous to the monoexponential modeling

procedure employed by Gerbino et al. (17), because a single curve was used to describe both the phase II and the slow component of the  $\dot{V}O_2$  responses. This quantitative comparison was necessary because the original procedure used by Gerbino et al. (17) described fewer data (which began 25 s after the onset of exercise) than the triple exponential model (which began at exercise onset).

The responses to square-wave bouts of the same exercise intensity (moderate or heavy) were compared using a one-way repeated-measures ANOVA with post hoc Bonferroni-adjusted paired-samples confidence intervals. These bouts were compared on the basis of the effect of prior exercise on the responses. For example, the relevant heavy exercise responses were the first bout of heavy exercise in the  $2 \times 50\% \Delta$  trial (no prior exercise), the second of these two heavy bouts (prior heavy exercise), and heavy exercise after prior moderate exercise (prior moderate exercise). The *F* ratios were interpreted as demonstrating a significant main effect when  $P < 0.05$ .

## RESULTS

The mean ( $\pm$  SD)  $\dot{V}O_{2\text{peak}}$  value was  $52.0 \pm 8.0$  ml·kg<sup>-1</sup>·min<sup>-1</sup>, with LT occurring at  $60 \pm 7\%$  of  $\dot{V}O_{2\text{peak}}$ . These data yielded power outputs of  $110 \pm 40$  and  $230 \pm 50$  W for the moderate- and heavy-intensity bouts, respectively.

*F* tests confirmed the superiority of the triple exponential model compared with a double exponential fit incorporating a single curve describing phase II and the slow component responses (*F* value range 15.67–316.62, where  $F > 5.42$ ,  $P < 0.001$ ). Figure 2A shows the monoexponential curve fitting procedure according to Gerbino et al. (17), whereas Fig. 2B shows the triple exponential model according to Barstow et al. (3) in a typical subject. It is evident from the residual plots at the foot of each graph that the triple exponential model provided a qualitatively superior fit compared with that of the monoexponential, which showed a clear trend in the residuals throughout the curve fitting. The monoexponential curve fit provided a particularly poor description of the  $\dot{V}O_2$  response between ~25 and 80 s (phase II). In contrast, the triple exponential model yielded essentially white residuals throughout the exercise transition.

Prior exercise, whether of moderate or heavy intensity, had no effect on the  $\dot{V}O_2$  response to moderate exercise (Table 2; Fig. 3). Specifically, Table 2 shows that neither the amplitude ( $A_1'$ ) nor the kinetics ( $\tau_1$ ) of the phase II response to moderate exercise were altered by prior exercise ( $A_1'$ ,  $F_{2,9} = 0.02$ ,  $P = 0.98$ ;  $\tau_1$ ,  $F_{2,9} = 1.11$ ,  $P = 0.35$ ). A steady-state  $\dot{V}O_2$  was attained within ~2 min for all moderate exercise conditions.

Moderate exercise had no effect on the  $\dot{V}O_2$  response to subsequent heavy exercise (Table 3, Fig. 3). At the onset of the second of the two bouts of heavy exercise, the baseline  $\dot{V}O_2$  response was significantly elevated by ~100 ml/min above that preceding the first bout ( $F_{2,9} = 10.85$ ,  $P = 0.001$ ; Table 3, Fig. 3). The phase II time constant ( $\tau_1$ ) was not altered by prior heavy exercise ( $F_{2,9} = 0.22$ ,  $P = 0.80$ ; Table 3). The amplitude at the end of the heavy exercise phase II response ( $A_1'$ ) was also unaffected by prior heavy exercise ( $F_{2,9} = 2.03$ ,

Table 2. Oxygen uptake responses to moderate intensity exercise

	No Prior Exercise	Prior Moderate	Prior Heavy
$\dot{V}O_2(b)$ , l/min	$0.95 \pm 0.03$	$0.93 \pm 0.03$	$0.99 \pm 0.03$
Phase I			
$A'_0$ , l/min	$0.24 \pm 0.06$	$0.22 \pm 0.05$	$0.30 \pm 0.05$
$\tau_0$ , s	$14.9 \pm 1.1$	$9.9 \pm 2.1$	$12.7 \pm 2.3$
Phase II			
$TD_1$ , s	$24.1 \pm 2.3$	$24.7 \pm 1.9$	$15.0 \pm 3.1$
$A'_1$ , l/min	$0.79 \pm 0.13$	$0.79 \pm 0.14$	$0.79 \pm 0.13$
$\tau_1$ , s	$15.6 \pm 2.5$	$20.4 \pm 3.6$	$16.4 \pm 2.9$
MRT, s	$30.5 \pm 2.0$	$34.9 \pm 2.9$	$26.8 \pm 2.1$

Values are means  $\pm$  SE.  $\dot{V}O_2(b)$ , baseline  $\dot{V}O_2$ ;  $A'_0$  and  $A'_1$ , amplitudes at the end of phase I and II, respectively;  $TD_1$ , time delay before onset of phase II;  $\tau_0$  and  $\tau_1$ , time constants for the two exponential components; MRT, mean response time.

$P = 0.16$ ). However, the absolute  $\dot{V}O_2$  amplitude at the end of phase II [ $\dot{V}O_2(b) + A'_1$ ] was significantly increased after prior heavy exercise ( $F_{2,9} = 9.64$ ,  $P = 0.001$ ) due, in part, to the elevated baseline  $\dot{V}O_2$  (Table 3).

The amplitude of the  $\dot{V}O_2$  slow component ( $A'_2$ ) was consistently and significantly reduced by prior heavy exercise ( $F_{2,9} = 31.26$ ,  $P < 0.001$ ; Table 3, Fig. 3). This reduction in the  $\dot{V}O_2$  slow component, and the nonsignificant changes in the phase II response profile, led to a significantly lower net end-exercise  $\dot{V}O_2$  ( $F_{2,9} = 14.00$ ,  $P < 0.001$ ). This effect is most clearly demonstrated in Fig. 4, which shows the absolute (Fig. 4A) and net (Fig. 4B)  $\dot{V}O_2$  responses to the  $2 \times 50\% \Delta$  protocol. Figure 4A shows that the absolute  $\dot{V}O_2$  at the end of phase II was higher in the second bout due, in part, to the higher

Table 3. Oxygen uptake and blood lactate responses to heavy exercise

	No Prior Exercise	Prior Moderate	Prior Heavy
$\dot{V}O_2(b)$ , l/min	$0.95 \pm 0.04$	$0.97 \pm 0.03$	$1.05 \pm 0.04^\dagger$
Phase I			
$A'_0$ , l/min	$0.55 \pm 0.02$	$0.40 \pm 0.02$	$0.55 \pm 0.08$
$\tau_0$ , s	$14.8 \pm 1.8$	$13.1 \pm 2.4$	$12.9 \pm 1.3$
Phase II			
$TD_1$ , s	$20.2 \pm 1.2$	$17.7 \pm 1.4$	$19.0 \pm 1.1$
$A'_1$ , l/min	$1.84 \pm 0.16$	$1.89 \pm 0.11$	$1.89 \pm 0.16$
$\tau_1$ , s	$23.9 \pm 1.9$	$24.9 \pm 2.3$	$25.3 \pm 2.9$
Slow component			
$TD_2$ , s	$106.4 \pm 9.5$	$115.2 \pm 17.8$	$114.6 \pm 11.2$
$A'_2$ , l/min	$0.27 \pm 0.02$	$0.24 \pm 0.05$	$0.10 \pm 0.02^\dagger$
$\tau_2$ , s	$269.2 \pm 17.7$	$261.3 \pm 14.6$	$261.8 \pm 20.4$
Overall response			
$\dot{V}O_2(b) + A'_1$ , l/min	$2.79 \pm 0.17$	$2.86 \pm 0.14$	$2.94 \pm 0.18^*$
EE $\dot{V}O_2$ , l/min	$2.10 \pm 0.17$	$2.13 \pm 0.16$	$1.99 \pm 0.17^\dagger$
MRT, s	$65.2 \pm 4.1$	$61.8 \pm 4.5$	$47.0 \pm 3.1^\dagger$
$\tau \dot{V}O_2$ , s	$45.0 \pm 3.8$	$42.5 \pm 3.3^*$	$35.3 \pm 2.3^\dagger$
BL [lactate] (mM)	$1.1 \pm 0.1$	$0.6 \pm 0.1$	$2.6 \pm 0.2^\dagger$
$\Delta$ [lactate] (mM)	$2.8 \pm 0.3$	$3.6 \pm 0.3$	$1.6 \pm 0.1^\dagger$

Values are means  $\pm$  SE. EE  $\dot{V}O_2$ ,  $\dot{V}O_2$  amplitude above baseline at the end of exercise (i.e., net EE  $\dot{V}O_2$ );  $TD_1$  and  $TD_2$ , time delays;  $\tau_0$ ,  $\tau_1$ ,  $\tau_2$ , time constants associated with the exponential terms; MRT, mean response time;  $\tau \dot{V}O_2$ , effective time constant; BL [lactate], baseline blood lactate concentration;  $\Delta$ [lactate], increase in blood lactate concentration during exercise. \*Significantly different from no prior exercise ( $P < 0.05$ );  $^\dagger$ significantly different from no prior exercise and prior moderate ( $P < 0.05$ ).

baseline  $\dot{V}O_2$ . However, the absolute  $\dot{V}O_2$  at the end of exercise ( $3.05 \pm 0.17$  l/min, or 84% of  $\dot{V}O_{2\text{ peak}}$ , range 75–95% of  $\dot{V}O_{2\text{ peak}}$ ) was similar between the two bouts due to the smaller slow component in the second bout.

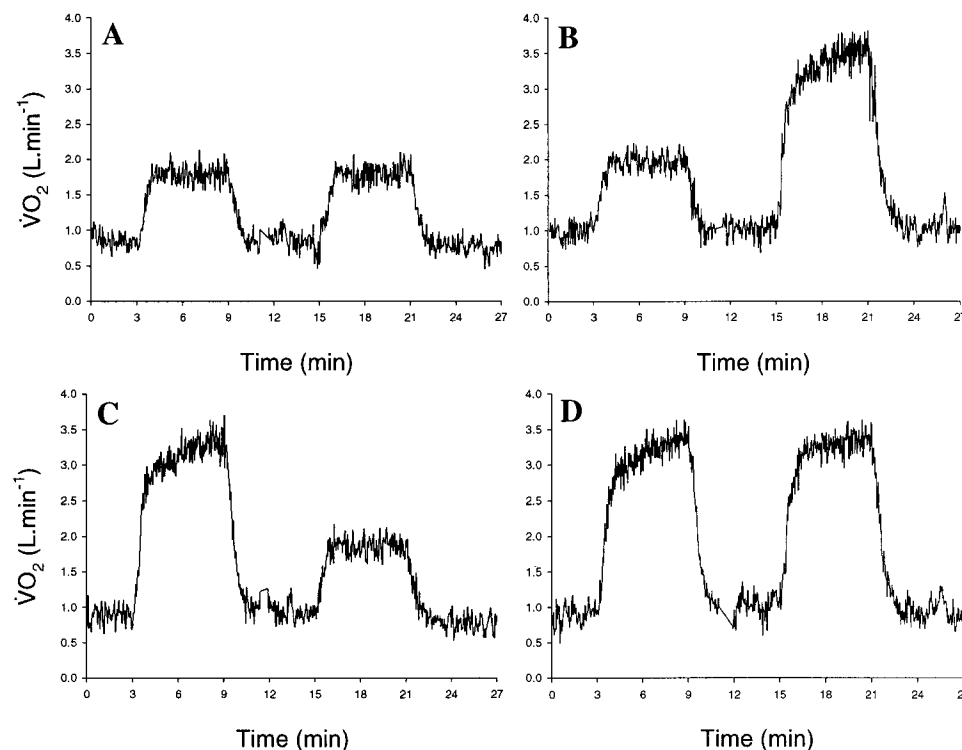


Fig. 3.  $\dot{V}O_2$  responses to the double square-wave protocols in a typical subject (subject 8). Consecutive bouts of moderate exercise (A), consecutive bouts of heavy exercise (D), moderate exercise followed by heavy exercise (B), and heavy exercise followed by moderate exercise (C) are shown.

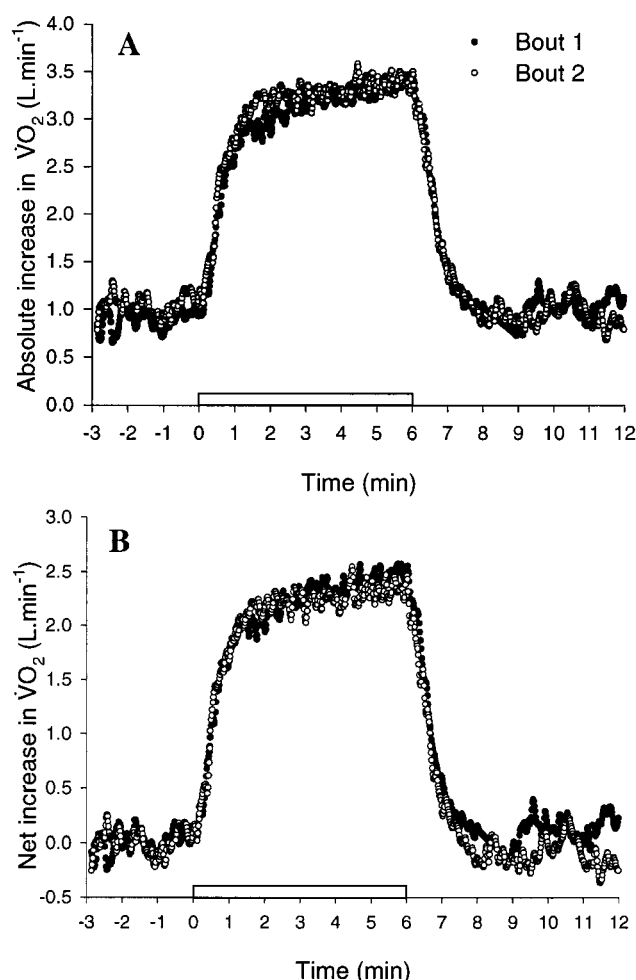


Fig. 4. Absolute (A) and net (B) response to the first (*bout 1*) and second (*bout 2*) bouts of heavy exercise in a representative subject (*subject 8*). In A, note the higher absolute  $\dot{V}O_2$  at the end of phase II for *bout 2*. Note also that the  $\dot{V}O_2$  slow component response is smaller for *bout 2* so that the absolute end-exercise  $\dot{V}O_2$  values (and, indeed, the off-transient response) are similar in the two bouts. In B, the data are normalized to provide the same baseline  $\dot{V}O_2$ . Note that the  $\dot{V}O_2$  response through phases I and II is almost identical in the two bouts. Note also that the reduced slow component in *bout 2* leads to a lower net end-exercise  $\dot{V}O_2$ . The phase II time constant ( $\tau_1$ ) for this subject was 27.3 s during *bout 1* (95% CI = 25.9–28.7 s) and 27.5 s during *bout 2* (95% CI = 26.1–28.9 s). These data have been treated with a 5-s rolling average to improve clarity. Bars above x-axis denote duration of each exercise bout.

The smaller  $\dot{V}O_2$  slow component response in the second bout can be seen more clearly when the difference in baseline  $\dot{V}O_2$  between the bouts is accounted for (Fig. 4B).

Although prior heavy exercise did not affect phase II  $\dot{V}O_2$  kinetics, both the effective time constant ( $\tau\dot{V}O_2$ ) and the MRT of the overall  $\dot{V}O_2$  response were significantly reduced in the second of the two heavy exercise bouts (Table 3). However, the MRT appears to be more closely related to the relative amplitude of the slow component than to the phase II  $\dot{V}O_2$  kinetics (Fig. 5). The MRT and the  $\tau\dot{V}O_2$  were significantly correlated ( $r = 0.87$ ;  $P < 0.001$ ). These results indicate that although both the MRT and the  $\tau\dot{V}O_2$  reflect the overall

time course of the  $\dot{V}O_2$  response to the end of exercise, neither specifically reflects the phase II  $\dot{V}O_2$  kinetics.

The blood [lactate] response to heavy exercise is presented in Table 3. During the consecutive bouts of heavy exercise, blood [lactate] increased by  $2.8 \pm 0.3$  mM above baseline after the first bout and was still significantly elevated at the start of the second bout. Heavy exercise resulted in similar end-exercise blood [lactate] irrespective of the prior exercise condition ( $3.9 \pm 0.2$  mM after no prior exercise,  $4.2 \pm 0.3$  mM after prior moderate exercise, and  $4.4 \pm 0.3$  mM after prior heavy exercise;  $F_{2,9} = 2.02$ ,  $P = 0.16$ ). However,  $\Delta$ [lactate] was significantly smaller in the second of the two bouts of heavy exercise ( $F_{2,9} = 41.08$ ,  $P < 0.001$ ).

Figure 6 illustrates the pulmonary gas exchange responses to the consecutive heavy exercise bouts in one subject. The R response to the first bout of heavy exercise showed a transient overshoot (R increased above 1.0), followed by a decline over the last 4 min of exercise as  $\dot{V}CO_2$  stabilized and  $\dot{V}O_2$  continued to rise. In contrast to these responses, in the second heavy exercise bout, R evidenced a transient undershoot (reflecting a smaller increase in  $\dot{V}CO_2$  relative to that of  $\dot{V}O_2$ ), followed by a relatively stable R until the end of exercise due to a smaller slow component rise in  $\dot{V}O_2$ .

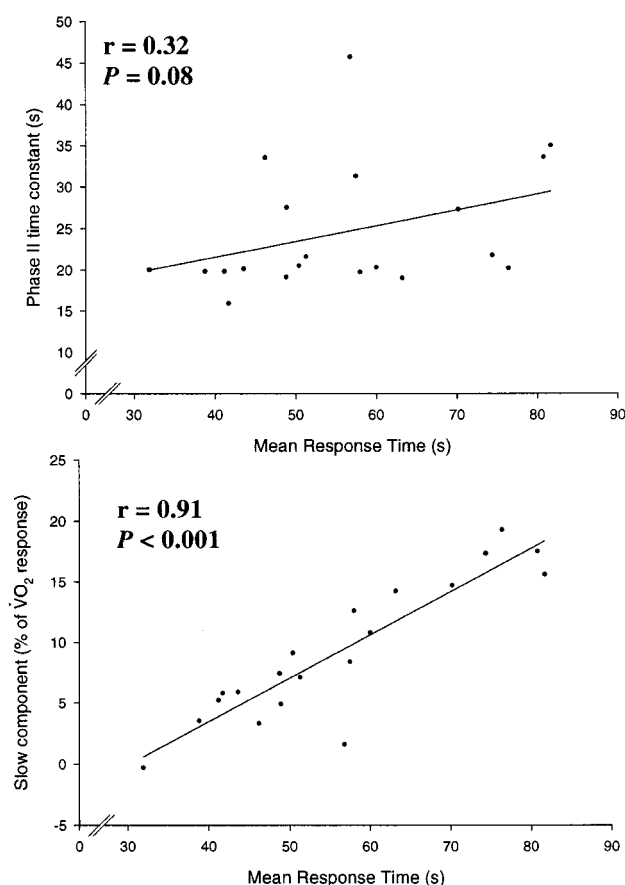


Fig. 5. Relationship between the mean response time and the time constant for the phase II exponential response ( $\tau_1$ ; top), and between mean response time and relative contribution of the slow component to the end-exercise  $\dot{V}O_2$  (bottom).

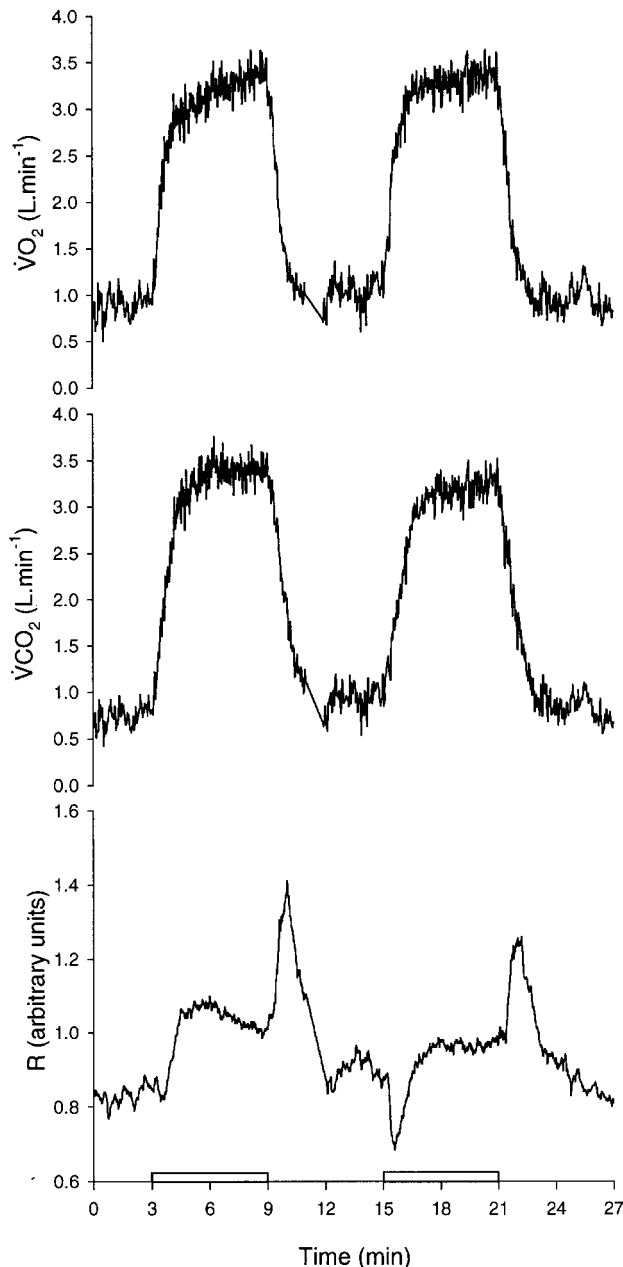


Fig. 6. Pulmonary gas exchange responses to double square-wave heavy exercise in a representative subject (*subject 8*). Note the similar early  $\dot{V}O_2$  response, the smaller  $\dot{V}O_2$  slow component response, the attenuation of the early carbon dioxide output ( $\dot{V}CO_2$ ) response, and the resulting transient undershoot in respiratory exchange ratio ( $R$ ) during the second bout of exercise. Bars above  $x$ -axis denote duration of each exercise bout.

## DISCUSSION

Our results demonstrate that neither prior moderate exercise nor prior heavy exercise had any effect on the  $\dot{V}O_2$  kinetics during subsequent moderate exercise. Furthermore, the  $\dot{V}O_2$  kinetics during heavy exercise were not affected by prior moderate exercise. However, the  $\dot{V}O_2$  kinetics during heavy exercise were affected by a prior bout of heavy exercise. The most important effect of the prior heavy exercise was to significantly

reduce the amplitude of the  $\dot{V}O_2$  slow component. In support of previous work (17, 31), we found that prior heavy exercise led to a significant reduction in the effective time constant ( $\tau\dot{V}O_2$ ) and the MRT in the second of the heavy exercise bouts. Importantly, however, this speeding of the overall kinetics was not the result of any speeding in the phase II  $\dot{V}O_2$  kinetics, which describe the response in approximately the first 2 min of exercise, but of the reduced amplitude of the  $\dot{V}O_2$  slow component and the consequently lower net end-exercise  $\dot{V}O_2$ . This finding that the time constant for the phase II exponential response during heavy exercise was not affected by prior heavy exercise contradicts previous reports (17, 31) and therefore questions the interpretation that muscle  $\dot{V}O_2$  on-kinetics are primarily limited by  $O_2$  delivery during heavy exercise.

The fundamental difference between the present study and that of Gerbino et al. (17) was the mathematical modeling procedure used to analyze the data. Gerbino et al. (17) described the  $\dot{V}O_2$  response to heavy exercise with a monoexponential term beginning 25 s after exercise onset. In contrast, the present study used a mathematical model that began at the onset of exercise and featured three exponential terms and two independent time delays to describe the  $\dot{V}O_2$  response (3). Because the monoexponential modeling procedure used a single curve to describe two phases of the response, it was unlikely that this approach would yield a good representation of the  $\dot{V}O_2$  response data. This was indeed the case, as shown in Fig. 2A, in which the residuals associated with the monoexponential fit systematically deviated from the fitted line throughout the fitting window, in contrast to the superior fit of the triple exponential shown in Fig. 2B. When the monoexponential descriptors of the  $\dot{V}O_2$  kinetics of heavy exercise ( $\tau\dot{V}O_2$ , MRT) were interpreted after prior heavy exercise, a speeding was certainly apparent (Table 3). However, this was not a consequence of a speeding of the phase II  $\dot{V}O_2$  kinetics, which did not change after prior heavy exercise (Table 3; Fig. 4), but rather reflected a reduction in the amplitude of the  $\dot{V}O_2$  slow component. The 63% reduction in the slow component (from 0.27 to 0.10 l/min, on average) caused a lower net end-exercise  $\dot{V}O_2$ . In a situation in which there is no true speeding of the  $\dot{V}O_2$  kinetics, a lower end-exercise  $\dot{V}O_2$  amplitude will naturally lead to an earlier attainment of 63% of the total response (measured as the  $\tau\dot{V}O_2$  or MRT). Barstow et al. (2) showed that the  $\dot{V}O_2$  time constant in phase II did not differ for exercise below and above the LT. However, a monoexponential description of the entire exercise  $\dot{V}O_2$  response resulted in slower overall  $\dot{V}O_2$  kinetics as exercise intensity increased above the LT due to the inclusion of the  $\dot{V}O_2$  slow component in the monoexponential term (2). The results of the present study suggest that previous findings of speeded  $\dot{V}O_2$  kinetics after prior heavy exercise (17) resulted from the employment of a monoexponential modeling procedure rather than from a true speeding of phase II kinetics. Therefore, the  $\tau\dot{V}O_2$  or the MRT

should not be used to intuit the  $\dot{V}O_2$  kinetics of the phase II response during heavy exercise.

It has been suggested that the delivery and distribution of  $O_2$  to the working muscles might be one of the principal rate-limiting steps to muscle  $\dot{V}O_2$  kinetics during heavy exercise in many situations (24, 39). Evidence for this includes the slower  $\dot{V}O_2$  kinetics that are observed in hypoxia (13, 25), with  $\beta$ -blockade (23), during supine exercise (27), and in the transition from prior moderate exercise (26). In light of this, Gerbino et al. (17) favored a vascular, as opposed to a muscle enzymatic, limitation to the  $\dot{V}O_2$  kinetics during heavy exercise and argued that an improved muscle blood flow would speed the kinetics by increasing the availability of oxygen. However, the lack of a speeding of phase II  $\dot{V}O_2$  kinetics in the present study indicates that either prior heavy exercise did not improve  $O_2$  delivery or that an increase in  $O_2$  delivery had no effect on the phase II kinetics during heavy exercise. The former seems unlikely, given that studies utilizing near-infrared spectroscopy have found evidence for residual vasodilation at the onset of the second bout of heavy exercise using identical protocols (15, 40). However, it has been argued that, in "normal" exercise conditions, there is no  $O_2$  delivery limitation to phase II  $\dot{V}O_2$  kinetics because the kinetics of  $O_2$  delivery to exercising muscle are faster than either muscle or pulmonary  $\dot{V}O_2$  kinetics (12, 20).

Two recent studies by Grassi et al. (18, 19) provide strong evidence that improved  $O_2$  delivery does not affect phase II  $\dot{V}O_2$  kinetics. In electrically stimulated isolated dog gastrocnemius muscle, improvements in both convective and diffusive  $O_2$  delivery had no effect on the phase II  $\dot{V}O_2$  kinetics. It was shown that, even when exercise commenced with a muscle blood flow equal to that required during steady-state exercise,  $\dot{V}O_2$  kinetics were unchanged compared with a situation in which increases in muscle blood flow were spontaneous (18). Using the same muscle preparation, Grassi et al. (19) demonstrated that enhancing the potential for peripheral diffusion by increasing the driving pressure for  $O_2$  from the muscle capillaries to the mitochondria did not speed  $\dot{V}O_2$  kinetics. These studies suggest that intrinsic inertia of oxidative metabolism in the muscle cell is the primary limitation to  $\dot{V}O_2$  kinetics at the onset of heavy exercise. This inertia in the muscle oxidative machinery may be determined by intracellular levels of putative metabolic controllers (1) or by the activation of mitochondrial enzymes (38). The results of Grassi et al. (18, 19) are consistent with models of respiratory control, in which a single reaction with first-order kinetics controls muscle  $\dot{V}O_2$  (32), and with observations of a close temporal relationship between the monoexponential fall in muscle phosphocreatine concentration and the monoexponential rise in pulmonary  $\dot{V}O_2$  (1, 36). Our data support the work of Grassi et al. (18, 19) in that the phase II  $\dot{V}O_2$  kinetics were not speeded even if it is assumed that prior heavy exercise increased bulk  $O_2$  delivery to the active muscle.

The profiles of  $\dot{V}CO_2$  and R were used by Gerbino et al. (17) to support their suggestion that the speeded monoexponential  $\dot{V}O_2$  kinetics were the result of an improved muscle blood flow. However, phase II  $\dot{V}O_2$  kinetics were not speeded by prior heavy exercise, and therefore the blunted  $\dot{V}CO_2$  and  $\Delta[\text{lactate}]$  responses cannot be ascribed to a speeding of these kinetics, or a reduction in the initial oxygen deficit of heavy exercise. The  $\dot{V}CO_2$  response during heavy exercise is very difficult to interpret, due to the influence of  $CO_2$  stores dynamics (11), bicarbonate buffering of lactate, and additional  $CO_2$  clearance as a consequence of hyperventilation in response to metabolic acidosis (10), all of which distort the expression of aerobically generated  $CO_2$  output in the pulmonary signal. However, the blunted  $\dot{V}CO_2$  responses in the second heavy exercise bout (Fig. 6) have been noted previously (6, 17) and have been interpreted as indicating a reduced buffering of lactate during the second heavy exercise bout, consistent with the reduced  $\Delta[\text{lactate}]$  observed in the present study (Table 3). Though we can present no evidence that  $CO_2$  storage (tissue and blood  $CO_2$  capacitance;  $CO_2$  fixed as bicarbonate) did not change, we consider it unlikely that an exercise-induced change in  $CO_2$  stores would yield a response like that shown in the second exercise bout in Fig. 6. Due to the similarity of the phase II time constant for  $\dot{V}O_2$  between the two heavy exercise bouts, neither the rate nor the amount of  $CO_2$  stored from these mechanisms would have been increased in the second heavy exercise bout (11). This reiterates previous findings that suggest that the reduction in the  $\dot{V}CO_2$  response, relative to that of  $\dot{V}O_2$ , during the second heavy exercise bout reflected a reduced bicarbonate buffering of lactate (6, 17).

An interesting observation in the present study was the reduction in the amplitude of the  $\dot{V}O_2$  slow component in the second of the two heavy exercise bouts. It has been suggested that the recruitment of low-efficiency type II fibers during heavy exercise is the most likely explanation for the  $\dot{V}O_2$  slow component phenomenon (3, 34, 41). Therefore, the reduced amplitude of the  $\dot{V}O_2$  slow component that we observed may be related to the recruitment of fewer type II fibers in the second exercise bout. It is possible that greater  $O_2$  availability at the onset of exercise, as a result of prior warm-up exercise (17), may facilitate the rapid establishment of an intracellular environment that allows tighter metabolic control later in exercise (7, 22). Metabolic systems under tighter control evidence the achievement of a given rate of mitochondrial respiration with a smaller disturbance in intracellular homeostasis (21, 22). This effect is commonly seen after exercise training (7), and there is also evidence that warm-up exercise reduces the magnitude of phosphocreatine depletion during high-intensity exercise (30). Therefore, it is possible that the reduced amplitude of the  $\dot{V}O_2$  slow component we observed in the second of the two bouts of heavy exercise reflected a more rapid establishment of intracellular homeostasis in the second bout, leading to the recruitment of fewer type II

fibers as the bout progressed. In support of this hypothesis, an increase in the amplitude of the phase II  $\dot{V}O_2$  response and a reduction in the slow component term have been shown in subjects with a high proportion of type I fibers (3) and in subjects breathing hyperoxic gas mixtures (31). The scenario of a tighter metabolic control leading to a reduced recruitment of type II muscle fibers might also explain the reduced  $\Delta[\text{lactate}]$  response seen in the second of the two heavy exercise bouts. An alternative explanation is that a greater total muscle mass (comprising both principal fiber types), representative of the muscle mass required to meet the exercise challenge, is engaged at the start of the second exercise bout. This would reduce the force required by each muscle fiber and might reduce the rate of fatigue and the recruitment of additional type II fibers.

An alternative explanation for the smaller  $\dot{V}O_2$  slow component in the second of the two heavy exercise bouts is an increased mechanical efficiency of working muscle consequent to an elevated muscle temperature. It is known that the increase in muscle temperature caused by heavy exercise can persist well into recovery (37), so it is likely that muscle temperature was elevated in our subjects during the second bout of heavy exercise. The unchanged  $A_1'$  and the lower  $A_2'$  and end-exercise  $\dot{V}O_2$  we observed after heavy exercise is similar to the responses described by Koga et al. (29) for subjects whose legs were prewarmed by  $\sim 3^\circ\text{C}$  before the completion of a heavy exercise bout. Koga et al. (29) also reported that, in the control condition (no prewarming of the legs), 6 min of heavy exercise (at 50% $\Delta$ ) increased muscle temperature by  $3.4^\circ\text{C}$ . It has been suggested that rising muscle temperature might cause the slow component by decreasing the phosphorylation potential and increasing the rate of mitochondrial respiration by a  $Q_{10}$  (the effect of increased temperature on enzyme-catalyzed reactions) effect (44). However, the reduction in the  $\dot{V}O_2$  slow component after preheating the leg muscles compared with the control condition observed by Koga et al. (29) contradicts this hypothesis. In contrast, Ferguson et al. (14) showed that pulmonary  $\dot{V}O_2$  was increased throughout heavy cycling exercise at 60 rpm after lower limb muscle warming. These authors speculated that the effect of increased muscle temperature could be explained by an acute transformation of type I fibers towards faster properties (37), resulting in an increase in energy turnover at the same exercise intensity. This is difficult to reconcile with the reduced net end-exercise  $\dot{V}O_2$  and the smaller slow component observed in the present study and that of Koga et al. (29). The mechanism for the attenuated slow component response when muscle temperature is increased, either by external heating (29) or by performing prior heavy exercise (present study; 17, 31), remains to be firmly established.

In our subjects, 6 min of recovery from heavy exercise (pedaling at 20 W) was insufficient for  $\dot{V}O_2$  to return to preexercise baseline levels (Fig. 3). This partial recovery of  $\dot{V}O_2$  after 6 min of recovery from the first heavy exercise bout has been reported previously (17, 31). In our subjects, this incomplete recovery

meant that the second heavy exercise bout began while baseline  $\dot{V}O_2$  was still elevated. Although this did not affect the net  $\dot{V}O_2$  response in phase II ( $A_1'$ ), because this reflects the anticipated exercise  $\dot{V}O_2$  (41), it meant that the absolute  $\dot{V}O_2$  at the end of phase II [ $\dot{V}O_2(b) + A_1'$ ] was significantly higher in the second heavy exercise bout. Part of the additional oxygen cost of the recovery processes from the first heavy exercise bout would presumably still be present in the second exercise bout and would be superimposed on the exercise  $\dot{V}O_2$  responses. When the absolute  $\dot{V}O_2$  responses in the first and second bouts of heavy exercise were superimposed (Fig. 4A), the difference in the baseline  $\dot{V}O_2$  caused any absolute exercise  $\dot{V}O_2$  in phase II to be reached earlier for the second bout of exercise. At face value, this could be interpreted as a speeding of the  $\dot{V}O_2$  kinetics. However, when the baseline  $\dot{V}O_2$  is normalized and the relative  $\dot{V}O_2$  response is plotted (Fig. 4B), it can be seen that this effect is caused simply by differences in  $\dot{V}O_2$  amplitude and not by any change in the time constant for the  $\dot{V}O_2$  response in phase II. Thus it is important to the correct interpretation of the  $\dot{V}O_2$  kinetic response that the elevated baseline  $\dot{V}O_2$  before the second of two bouts of heavy exercise be considered. Although the net end-exercise  $\dot{V}O_2$  response was significantly lower in the second heavy exercise bout, owing to the reduced slow component, the elevated baseline  $\dot{V}O_2$  in the second bout meant that the absolute end-exercise  $\dot{V}O_2$  was similar between the bouts [ $\dot{V}O_2(b) + \text{end-exercise } \dot{V}O_2 = \sim 3.05 \text{ l/min}$ ; Table 3]. However, the increased baseline  $\dot{V}O_2$  in the second heavy exercise bout did not appear to significantly affect the  $\dot{V}O_2$  slow component response. The magnitude of the increase in baseline  $\dot{V}O_2$  was less than the reduction in the slow component, and these changes were not related ( $r = 0.37$ ,  $P = 0.3$ ).

In conclusion, prior moderate or heavy exercise did not influence the  $\dot{V}O_2$  response during moderate-intensity exercise. Furthermore, prior moderate exercise did not alter the  $\dot{V}O_2$  response to heavy-intensity exercise. Using a mathematical model that was able to discriminate between the fundamental exponential  $\dot{V}O_2$  response and the  $\dot{V}O_2$  slow component, we found no evidence that the phase II  $\dot{V}O_2$  response during heavy exercise could be speeded by a prior bout of heavy exercise. This contrasts with earlier studies that suggested a speeding of  $\dot{V}O_2$  kinetics after prior heavy exercise when a monoexponential function was used to describe the  $\dot{V}O_2$  kinetic response (17, 31). The present study suggests that the overall speeding of  $\dot{V}O_2$  kinetics noted previously is primarily related to a reduction in the amplitude of the  $\dot{V}O_2$  slow component and not to a measurable speeding of the phase II  $\dot{V}O_2$  kinetics. The perception that the response is speeded may also be an artifact of the elevated baseline  $\dot{V}O_2$  in the second heavy exercise bout. Although it is likely that prior heavy exercise improved  $O_2$  delivery to the muscle due to the effects of residual acidosis on muscle blood flow and the oxyhemoglobin dissociation curve, our results suggest that such an improvement in  $O_2$  availability had no effect on the  $\dot{V}O_2$  on-kinetics in the first few

minutes of exercise. Instead, prior heavy exercise caused a marked reduction in the amplitude of the  $\dot{V}O_2$  slow component in the second of two bouts of heavy exercise.

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