Effects of prior heavy-intensity exercise during single-leg knee extension on \( V\dot{O}_2 \) kinetics and limb blood flow

Nicole D. Paterson, John M. Kowalchuk, and Donald H. Paterson. Effects of prior heavy-intensity exercise during single-leg knee extension on \( V\dot{O}_2 \) kinetics and limb blood flow. J Appl Physiol 99: 1462-1470, 2005. First published May 12, 2005; doi:10.1152/japplphysiol.00173.2005.—The effects of prior high-intensity exercise on \( \dot{O}_2 \) uptake (\( V\dot{O}_2 \)) kinetics of a second heavy exercise may be due to vasodilation (associated with metabolic acidosis) and improved muscle blood flow. This study examined the effect of prior high-intensity exercise on femoral artery blood flow (\( Q_{leg} \)) and its relationship with \( V\dot{O}_2 \) kinetics. Five young subjects completed five to eight repeats of two 6-min bouts of heavy-intensity one-legged, knee-extension exercise separated by 6 min of loadless exercise. \( V\dot{O}_2 \) was measured breath by breath. Pulsed-wave Doppler ultrasound was used to measure \( Q_{leg} \) and blood flow velocity data were fit using a monoexponential model to identify phase II and phase III time periods and estimate the response amplitudes and time constants (\( \tau \)). Phase II \( V\dot{O}_2 \) kinetics were speeded on the second heavy-intensity exercise [mean \( \tau \) (SD), 29 (10) s to 24 (10) s, \( P < 0.05 \)] with no change in the phase II (or phase III) amplitude. \( Q_{leg} \) was elevated before the second exercise [1.55 (0.34) l/min to 1.90 (0.25) l/min, \( P < 0.05 \)], but the amplitude and time course [\( \tau \), 25 (13) s to 35 (13) s] were not changed, such that throughout the transient the \( Q_{leg} \) (and \( \Delta Q_{leg}/\Delta V\dot{O}_2 \)) did not differ from the prior heavy exercise. Thus \( V\dot{O}_2 \) kinetics were accelerated on the second exercise, but the faster kinetics were not associated with changes in \( Q_{leg} \). Thus limb blood flow appears not to limit \( V\dot{O}_2 \) kinetics during single-leg heavy-intensity exercise nor to be the mechanism of the altered \( V\dot{O}_2 \) response after heavy-intensity prior exercise.

Femoral artery blood flow; priming exercise; oxygen uptake; primary component \( V\dot{O}_2 \) kinetics

The adjustment in pulmonary \( O_2 \) uptake (\( V\dot{O}_2 \)) at the onset of constant load exercise reflects the metabolic energy requirements and \( O_2 \) consumption of the exercising muscle (23, 36, 41). The physiological mechanisms of control, or limitations, to \( V\dot{O}_2 \) kinetics have been debated. During heavy-intensity exercise (compared with moderate), it has been proposed that \( O_2 \) delivery may be of greater importance in modulating the \( V\dot{O}_2 \) kinetics (22, 34, 35). Grassi et al. (19, 20) showed that increasing convective \( O_2 \) delivery and peripheral \( O_2 \) diffusion during rest to moderate-intensity exercise transitions in an isolated dog gastrocnemius preparation had no effect on muscle \( V\dot{O}_2 \) kinetics, but, at stimulation rates to mimic maximal \( V\dot{O}_2 \), faster \( O_2 \) delivery did hasten the kinetics (22). Nevertheless, during high-intensity exercise in humans \( O_2 \) delivery has been shown to be in excess of demand (i.e., \( V\dot{O}_2 \)), particularly early in the on-transient (2, 28). Alternatively, \( V\dot{O}_2 \) kinetics may be controlled and limited by the rate of response and the processes of muscle oxidative metabolism (22, 41, 43, 48). In addressing this debate, one experimental model that has received considerable attention is that of the effects of prior heavy-intensity exercise on a subsequent heavy exercise, with this perturbation altering the preexercise conditions of the second response and subsequently the overall kinetic responses.

In the earlier studies, a prior bout of heavy-intensity cycling exercise was shown to speed the overall \( V\dot{O}_2 \) kinetics [mean response time (MRT)] on a second heavy-intensity bout (18, 34). It was suggested that the metabolic acidosis associated with the high-intensity warm-up exercise resulted in vasodilatation with improved muscle perfusion and/or enhanced \( O_2 \) off-loading from hemoglobin during the subsequent exercise. Recently, Burnley et al. (10-13) have reported that phase II \( V\dot{O}_2 \) kinetics (i.e., primary time constant, \( \tau_2 \)) was not speeded by prior heavy-intensity cycling exercise, but, rather, the phase II amplitude was increased and the slow component \( V\dot{O}_2 \) decreased. An unaltered \( \tau_2 \) by prior heavy-intensity exercise has been interpreted to imply that the likely effect of metabolic acidosis of increasing \( O_2 \) delivery did not overcome a limitation (10-13), although the unchanged \( \tau_2 \) could also be interpreted to suggest that the rate-limiting factor of muscle \( O_2 \) utilization was not affected (39). Nevertheless, in contrast to these leg cycling studies, Rossiter et al. (42), using knee-extension exercise, found an actual speeding of the phase II \( V\dot{O}_2 \) kinetics, with no change in the amplitude of the phase II response, and a small reduction in the slow component \( V\dot{O}_2 \). Other studies of knee-extension exercise also have found a reduced phase II time constant (\( \tau \)) with prior heavy exercise (17, 26, 51). In cycling, prior heavy-intensity exercise has been shown to speed the \( V\dot{O}_2 \) kinetics of subsequent exercise in older adults (14, 44) and in young subjects with initially “slow” \( V\dot{O}_2 \) kinetics (24).

Doppler ultrasound has provided a tool to noninvasively measure limb blood flow continuously during exercise transients and the steady state. The hypothesis that prior high-intensity leg exercise might result in improved muscle perfusion (measured by Doppler) and affect the \( V\dot{O}_2 \) kinetics during the subsequent exercise on-transient was the focus of two recent studies (17, 26), which, however, yielded conflicting data. Hughson et al. (26), on the basis of a single trial in each subject, observed that an elevated muscle blood flow on the second heavy-intensity exercise allowed a higher \( V\dot{O}_2 \) (and...
faster MRT) throughout the second exercise. Fukuba et al. (17) concluded that faster phase II \( \dot{V}O_2 \) kinetics in a second high-intensity exercise were not associated with a similar modulation in the limb blood flow. Therefore the purpose of the present study was to examine the effect of a prior bout of high-intensity exercise on the response and relationship of \( \dot{V}O_2 \) kinetics and femoral artery blood flow \( (Q_{leg}) \) [\( Q_{leg} \), Doppler ultrasound of mean blood velocity (MBV), and imaging of arterial diameter]. One-legged knee-extension (KE) exercise was used with a heavy-intensity exercise bout preceded by a heavy-intensity “warm-up” bout. We hypothesized that 1) with a prior bout of exercise the \( \dot{V}O_2 \) kinetics would be faster (shorter phase II \( \tau \)) at the onset of a second step of exercise (as per Rossiter et al., Ref. 42); 2) \( Q_{leg} \) would be elevated before the second exercise bout; however, this greater blood flow would not be maintained throughout the exercise on-transient; 3) the speeding of the \( \dot{V}O_2 \) kinetics would not be related to the time constant of the adaptation of the increase in \( Q_{leg} \) \( (\tau Q_{leg}) \); and 4) the prior exercise would elicit a smaller \( \dot{V}O_2 \) slow component on the subsequent exercise with a proportional reduction in the magnitude of the phase III blood flow. Thus the overall hypothesis was that despite a prior hyperemia on the second exercise, blood flow was not the limitation for the rate of increase in \( \dot{V}O_2 \) or the mechanism of faster \( \dot{V}O_2 \) kinetics on the second exercise bout.

**METHODS**

**Subjects.** Five healthy, young subjects (3 men, 2 women) completed all testing. All were recreationally active but not in systematic training or competitive sport. Each gave written, informed consent. The study was approved by the University Review Board for Health Sciences Research Involving Human Subjects. Subjects were instructed not to perform exercise on the days of testing and to refrain from caffeine for 12 h before the tests.

**Exercise protocols.** After an acclimatization visit to the laboratory, on the second day subjects performed incremental single-leg KE exercise to fatigue (\( \dot{V}O_2 pkKE \)). The KE ergometer was custom built (see Bell et al., Ref. 8) after that described by Andersen et al. (1). The KE exercise involved active quadriceps contraction against a resistance (set on cycle ergometer), followed by passive return of the leg to the flexed position. The test consisted of 2 min of “loadless” exercise followed by 1 min at a resistance of 100–500 g (3–15 W) depending on subject size and fitness. Work rate was then increased every 1 or 1.5 min, to ensure the test produced fatigue in 8–12 min. The subjects performed the KE exercise at a rate of 30 extensions per minute, with timing established by a metronome. Fatigue was reached when subjects could no longer maintain the rate of 30 extensions per minute despite verbal encouragement. The \( \dot{V}O_2 pkKE \) test provided data to estimate the appropriate heavy-intensity work rate.

The heavy-intensity work rate was calculated to elicit a \( \dot{V}O_2 \) corresponding to \( \sim 80\% \dot{V}O_2 pkKE \). The protocol consisted of 6 min of loadless exercise (L1) followed by a 6-min step of high-intensity exercise (H1), a 6-min recovery of loadless exercise (L2), a 6-min step of high-intensity exercise (H2), and 6 min of loadless recovery (L3). Subjects performed five to eight repeats of the constant-load KE exercise with each trial performed on separate days. Measurements from the individual trials were averaged to improve the signal-to-noise ratio and to improve the confidence in the modeling parameters of the response.

**Measurement.** \( \dot{V}O_2 \) was measured breath by breath. A bidirectional, low-resistance, low-dead-space (90 ml) turbine and volume transducer (Alpha Technologies VMM-110) was used to measure inspired and expired airflow. The turbine was calibrated with a 3-liter syringe. Respired gases were measured at the mouth and analyzed for fractional concentrations of \( O_2, CO_2 \), and \( N_2 \) by a mass spectrometer (Perkin-Elmer MGA-1100). The mass spectrometer was calibrated daily against precision-analyzed gas mixtures. The time delay for a square-wave bolus of gas to pass from the turbine to the analysis system was determined, and the gas concentrations were time aligned to match gas volumes. The analog signals from the mass spectrometer and turbine transducer were sampled at 50 Hz and stored on a computer for off-line breath-by-breath computations and later analysis. Pulmonary \( \dot{V}O_2 \) was calculated using algorithms of Beaver et al. (6). Heart rate was monitored using an ECG with the electrodes in a modified V5 configuration.

Femoral artery MBV was measured by Doppler ultrasound (Vingmed CFM 750) utilizing a 7.5-mHz pulsed-wave sector probe. The probe was hand held by an investigator over the femoral artery distal to inguinal ligament (avoiding probing near the femoral artery bifurcation), and the probe position was maintained to optimize the auditory and visual cues of the MBV throughout the test. MBV was measured during at least four, and up to six, repetitions (of the five to eight trials), and the data for all trials were ensemble averaged for an individual to yield a single response. The QRS complex of the ECG tracing was used to discern the beat-by-beat MBV waveforms. MBV was calculated by integrating the total area under the MBV profile for each beat. Arterial diameter images were recorded by using the Vingmed CFM 750, during one trial for each subject. Measurements of the images for vessel diameter were made by two observers to ensure that no interobserver differences existed. Arterial diameters were measured every 2 min throughout the test. It was shown that arterial diameter did not change throughout the test; thus an average diameter measurement during L1 for each subject was used to represent the arterial diameter for calculation of blood flow. \( Q_{leg} \) was calculated as \( Q_{leg} = MBV \times \pi r^2 \) (where \( r \) is radius and MBV is the averaged MBV throughout the test for each subject).

Blood samples were obtained during one of the constant-load trials for measurement of blood lactate. The samples were taken from the dorsal vein of the hand, using a Teflon catheter (Angiocath, 21 gauge) and heparinized syringes (3 ml). The hand and forearm were heated with a warm heating pad and a heat lamp to arterialize the venous blood samples. Samples were taken at 3 and 6 min of L1, at 3 and 6 min of H1, at 6 min of L2, at 3 and 6 min of H2, and at 6 min of L3. Samples were immediately analyzed or put in an ice bath and analyzed shortly thereafter. Lactate concentrations ([La]; mmol/l) were determined using a blood gas-electrolyte analyzer (Nova Stat Profile 9 Plus gas-electrolyte analyzer, Nova Biomedical Canada). Calibration was performed before and throughout the analysis procedure.

**Data analysis.** Breath-by-breath pulmonary \( \dot{V}O_2 \) data were initially examined by using the model fitting software of Origin 41 with the purpose of removing data points representing “noise.” A preliminary fit was done for each square-wave trial, and data points lying outside a 99% confidence interval of the fit were removed. The \( \dot{V}O_2 \) data then were interpolated to 1-s intervals, time aligned, and ensemble averaged for each subject. Beat-by-beat MBV data were edited manually by visual inspection to remove beats when the signal had been lost or very low signals were obtained. Next, the data were interpolated to 2-s intervals (1 contraction cycle), time aligned, and ensemble averaged for each subject. The MBV data were fit by use of the Origin 41 software, and points lying outside the 99% confidence interval of fit were removed. The \( \dot{V}O_2 \) and MBV data then were averaged over an 8-s interval, and these averaged data sets for each subject were modeled to estimate the parameters of the response by using a monoequponential model as follows:

\[
Y(t) = A_0 + A(1 - e^{-t/\tau\times TD/t})
\]

where \( Y(t) = \dot{V}O_2 \) or MBV at time \( t \), \( A_0 \) is the baseline \( \dot{V}O_2 \) or MBV, \( A \) is the asymptotic value to which \( \dot{V}O_2 \) or MBV is assumed to project, \( \tau \) is the time constant of the response, and TD is the time delay. In heavy-intensity exercise the \( \dot{V}O_2 \) response shows three phases (I, II,
III, as detailed in Refs. 13, 38, 42. The model-fitting strategy used (Rossiter et al., 41, 43) was designed to identify the phase II component (for VO₂ for our purposes). For the VO₂ data, initially a fitting window from 30 s after exercise onset (eliminating phase I) to end-exercise (6 min) was used. The window was then iteratively extended back toward the exercise onset (i.e., t = 0) until the “goodness of the fit” deteriorated, determined by three factors: 1) the flatness of the residual plot and deviations from the zero line, 2) a sudden increase in the χ² value, and 3) a sudden increase in the value of τ as data from phase I were included in the fitting window. The phase I-II transition was taken as that time point just before the time where these sudden changes occurred. Once the start point of phase II was determined it was then used to fit to 60 s and the window was then again lengthened (toward end exercise). The determinants mentioned above were again used, in this case to establish the onset of the phase III VO₂ slow component.

The magnitude of the phase I plus phase II amplitude was determined from the VO₂ at the end of L1 or L2 to the end of phase II (for H1 and H2, respectively). The total amplitude was the VO₂ from L1 to end of exercise for H1 (6 min) and L2 to end of exercise for H2. The averages were taken from the last 24 s of the response. The amplitude of the phase III or slow component was calculated as the difference between the VO₂ at the end of phase II (determined by fitting of VO₂) and end exercise. The slow component was also calculated as the difference between the VO₂ at minute 3 after the onset of exercise and end exercise [ΔVO₂(6–3)] as used in previous papers. Each time represented the average of three data points (i.e., 24 s).

MBV data were fit for each subject, using the same approach as for the VO₂ data to isolate the phase II and a phase III responses. The only difference was that for MBV data the fitting window for phase II was started from 8 s (allowing for a potential phase I of blood flow increase because of the muscle pump). Absolute mean blood flows (Qleg) were calculated from the MBV data at specific time points. Additionally, the MBV and Qleg data were examined in each of the recovery (L2 and L3) periods to assess any hyperemia.

Statistics. Data are expressed as means and SD. The data of the H1 and H2 responses were compared using a one-way repeated-measures ANOVA. Differences in the parameters for VO₂ and MBV across the two steps were assessed using two-way ANOVA with post hoc Newman-Keuls tests. The relationship of VO₂ and Qleg responses was tested by Pearson-product moment correlation. The level of significance was set at P < 0.05.

RESULTS

For the five subjects [3 men, 2 women; mean age 22.4 (1.1) yr; height 1.76 (0.09) m; mass 77.4 (15.5) kg] on the one-leg KE exercise the average peak work rate achieved was 30.0 (8.7) W, with a VO₂pkKE of 1.10 (0.18) l/min. The mean work rate for the heavy-intensity protocol averaged 21.9 (3.3) W, and this elicited an end-exercise (H1, 6 min) VO₂ of 0.89 (0.22) l/min, or 80.4 (6.1)% of VO₂pkKE. A blood lactate concentration of 3.5 mmol/l at the end of H1 confirmed that the work rate was in the heavy-intensity domain. The use of single-leg KE exercise provided an amplitude of the VO₂ response of 0.41 l/min [approximately the same as Rossiter et al. (40) for quadriceps exercise, ΔVO₂ of 0.47 l/min] sufficient for model fitting.

VO₂ response. The typical VO₂ response (shown as 8-s averages) for the entire protocol of L1, H1, L2, H2, and L3 is shown in Fig. 1A, with the model fits and residuals. The VO₂ on-transient parameter estimates of H1 and the subsequent heavy-intensity, H2, are shown in Table 1. There was no difference in the baseline (L1 and L2) VO₂ between steps (H1, 0.48 l/min; H2, 0.50 l/min, Table 1). The fit window determined from the modeling procedures to define the phase II interval of the VO₂ response was from 26 to 98 s after the onset of H1, and 23 to 97 s after the onset of H2. The amplitudes of the VO₂ increase from L1 to phase II of H1, and L2 to phase II of H2 (i.e., combined phase I + II amplitude) were not different (H1, 0.32 l/min; H2, 0.33 l/min, Table 1). The phase II τVO₂ of H2 (24 s) was shorter than that of H1 (29 s) (P = 0.048) (Table 1). All subjects showed faster phase II kinetics on H2, and there was a significant correlation of the H1 and H2 τ (r = 0.92, P = 0.03). With the five to eight repeats of the protocol, the 95% confidence interval of the on-transient τ₂ averaged 2 s (with a range of 1–4 s).

The phase III slow-component VO₂ amplitudes for H1 and H2 were not significantly different [end of phase II VO₂ to the
Table 1. Kinetic parameters for \( \dot{V}O_2 \) during heavy-intensity single-leg knee-extension exercise following prior heavy exercise

<table>
<thead>
<tr>
<th></th>
<th>( H1 ) ( \dot{V}O_2 ), l/min</th>
<th>( H2 ) ( \dot{V}O_2 ), l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (A0)</td>
<td>0.478 (0.101)</td>
<td>0.496 (0.097)</td>
</tr>
<tr>
<td>Amplitude (A1+A2)</td>
<td>0.317 (0.082)</td>
<td>0.334 (0.104)</td>
</tr>
<tr>
<td>A0 + (A1+A2)</td>
<td>0.794 (0.173)</td>
<td>0.830 (0.189)</td>
</tr>
<tr>
<td>TD, s</td>
<td>5.5 (9.4)</td>
<td>6.2 (8.1)</td>
</tr>
<tr>
<td>( t_2, s )</td>
<td>29.0 (10.2)</td>
<td>23.9 (9.6) (( P = 0.048 ))</td>
</tr>
<tr>
<td>A3 {end-exercise } [A0 + (A1+A2)]</td>
<td>0.098 (0.054)</td>
<td>0.108 (0.056)</td>
</tr>
<tr>
<td>( A_{12} {[A1+A2] + A3} )</td>
<td>0.414 (0.123)</td>
<td>0.436 (0.139)</td>
</tr>
<tr>
<td>End exercise</td>
<td>0.892 (0.218)</td>
<td>0.932 (0.226) (( P = 0.031 ))</td>
</tr>
</tbody>
</table>

Values are means (SD). \( H1 \), first heavy-intensity exercise; \( H2 \), second heavy-intensity exercise; A0, baseline \( O_2 \) uptake (\( \dot{V}O_2 \)); A1, A2 amplitude of phase I and phase II \( \dot{V}O_2 \); TD, time delay of monoeponential fit; \( t_2 \), time constant of phase II monoeponential fit; A3, amplitude of phase III (slow component) \( \dot{V}O_2 \); \( A_{12} \), total \( \dot{V}O_2 \) amplitude from baseline (A0) to end-exercise \( \dot{V}O_2 \).

Table 2. Kinetic parameters for MBV and Qleg responses during heavy-intensity single-leg knee-extension exercise following prior heavy exercise

<table>
<thead>
<tr>
<th></th>
<th>( H1 ) MBV, cm/s</th>
<th>( H1 ) Qleg, l/min</th>
<th>( H2 ) MBV, cm/s</th>
<th>( H2 ) Qleg, l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (A0)</td>
<td>53.7 (22.0)</td>
<td>1.55 (0.34)</td>
<td>66.0 (25.1) (( P = 0.040 ))</td>
<td>1.90 (0.25) (( P = 0.018 ))</td>
</tr>
<tr>
<td>Amplitude (A1+A2)</td>
<td>76.3 (25.6)</td>
<td>2.35 (0.89)</td>
<td>80.9 (22.4)</td>
<td>2.62 (1.13)</td>
</tr>
<tr>
<td>A0 + (A1+A2)</td>
<td>130.0 (41.6)</td>
<td>3.90 (0.92)</td>
<td>146.9 (26.9)</td>
<td>4.52 (1.11)</td>
</tr>
<tr>
<td>TD, s</td>
<td>-0.1 (5.7)</td>
<td></td>
<td>-2.5 (8.6)</td>
<td></td>
</tr>
<tr>
<td>( t_2, s )</td>
<td>24.5 (12.5)</td>
<td></td>
<td>34.5 (13.4)</td>
<td></td>
</tr>
<tr>
<td>A3 {end-exercise } [A0 + (A1+A2)]</td>
<td>23.1 (10.6)</td>
<td>0.72 (0.37)</td>
<td>11.6 (7.9)</td>
<td>0.37 (0.26)</td>
</tr>
<tr>
<td>( A_{12} {[A1+A2] + A3} )</td>
<td>99.4 (20.8)</td>
<td>3.08 (0.85)</td>
<td>92.5 (18.0)</td>
<td>3.00 (1.23)</td>
</tr>
<tr>
<td>End exercise</td>
<td>153.6 (39.1)</td>
<td>4.62 (0.89)</td>
<td>158.4 (22.0)</td>
<td>4.89 (1.20)</td>
</tr>
</tbody>
</table>

Values are means (SD). Abbreviations are as in Table 1, for mean blood velocity (MBV) and femoral artery flow (Qleg) rather than for \( \dot{V}O_2 \).
impede blood flow throughout the exercise, whereas in knee extension only (with passive flexion) there is a muscle relaxation phase that would allow flow between each contraction.

In Fig. 3A the modeled mean response parameters for $V_{O2}$ and $Q_{leg}$ show that although there was a higher initial femoral artery blood flow before H2, combined with a slightly (40%) slower Qleg kinetics, the Qleg during the first 45 s of the exercise on-transient was almost identical on H2 compared with H1. The $\Delta Q_{leg}/\Delta V_{O2}$ (Fig. 3B) was ~7.4 at the end of phase II (~90 s) in both H1 and H2, with this ratio rising throughout the on-transient in H2 (vs. exceeding the steady-state value and falling throughout the transient in H1). Thus the change in $O_2$ delivery during the exercise transient from loadless to heavy-intensity exercise was the same in H1 and H2 (Fig. 3C), and the calculated change in venous $O_2$ return actually increased over the first 45 s in H1 but more slowly over the first 90 s in H2 (Fig. 3C). Thus in H2 the smaller early change in initial blood flow was not only compensated by a greater $O_2$ extraction, but also over the first 90 s it resulted in a faster $V_{O2}$ kinetics.

On the first heavy-intensity exercise transient blood flow kinetics was similar to the $V_{O2}$ kinetics (25 and 29 s, respectively). Fukuba et al. (17) observed faster blood flow kinetics in the first heavy-intensity exercise, as observed previously for moderate-intensity exercise (8); however, on the second heavy exercise transition blood flow and $V_{O2}$ kinetics did not differ, and in our study blood flow kinetics of H2 (35 s) were not faster than the $V_{O2}$ kinetics (24 s). The Qleg-$V_{O2}$ kinetics was not significantly correlated (Fig. 2). There were no associations of the Qleg responses with the shorter $\tau V_{O2}$ after the prior exercise.

Other observations in the literature have also suggested that the effect of prior heavy exercise could not be ascribed to the alleviation of an $O_2$ delivery limitation. Burnley et al. (12) observed an elevated HR and greater near-infrared spectroscopy-derived oxyhemoglobin saturation and total hemoglobin in the vastus lateralis in the baseline period before the onset of the second heavy exercise (as also observed by Fukuba et al., Ref. 16) consistent with an increased muscle perfusion, but with no change in the primary $\tau V_{O2}$. It was concluded that the primary $V_{O2}$ kinetics was not limited by $O_2$ availability during heavy exercise. Krustup et al. (28) and Bangsbo et al. (2) have provided data that $O_2$ delivery exceeds muscle $O_2$ consumption during high-intensity exercise, at least early (up to 30 s) into the on-transient. Our data also suggest that $O_2$ delivery exceeds muscle $O_2$ consumption, as shown by a rise in the calculated venous $O_2$ return, over the first 30 s of the first exercise transient (Fig. 3C). In fact in the second heavy-intensity exercise transient the venous $O_2$ return rose over the first 90 s of the transient.

The mechanism of the speeding of the fundamental $V_{O2}$ kinetics remains elusive; although our data suggest that the faster kinetics is not dependent on greater blood flow to the exercising limb, there remains the possibility of considerable heterogeneity of local muscle blood flow. Richardson et al. (40), using an MRI technique, noted that relative to the local steady-state metabolism during plantar flexion exercise there are regions of significant under- and overperfusion with the blood flow varying fourfold in regions of similar metabolic activity. Prior exercise with the hyperemia before a second high-intensity exercise and enhanced vascular control of the
local distribution of the blood flow could conceivably reduce
the blood flow/VO₂ mismatch in the exercising muscle. This
was observed by DeLorey et al. (14) in relation to speeded
kinetics after prior exercise in older adults, accompanied by a
slower near-infrared spectroscopy-derived muscle deoxygena-
tion. The effect of metabolic acidosis in enhancing O₂ off-
loading from hemoglobin during the transient of the second
exercise also remains plausible. Thus the present data indicate
that blood flow to the exercising limb was not the limitation for
the rate of increase in VO₂, or, despite a prior hyperemia on the
second exercise, the mechanism of faster VO₂ kinetics on the
second exercise bout. Nevertheless, a limitation of O₂ delivery
to the active muscle fibers or the matching of perfusion and O₂
delivery to metabolism and O₂ utilization remain plausible
explanations of an O₂ delivery limitation to VO₂ kinetics in
heavy exercise.

Alternatively, intracellular mechanisms may explain the rate
of response of oxidative phosphorylation, and prior exercise
may “prime” these regulators. After the onset of muscle con-
traction, intracellular (25) and microvascular Po₂ (7) was
shown to decrease exponentially after a time delay, whereas
the time delay, but not the time constant, before the fall in Po₂
was reduced by prior contractions, consistent with a faster
activation of mitochondrial respiration and muscle O₂ con-
sumption after prior exercise. Hogan (25) suggested that the
delay in activation of oxidative phosphorylation was related to
the rate of adaptive changes in putative regulators of mitochon-
drial respiration ([ADP], [ATP]/[ADP][Pi], where brackets
denote concentration), the rate of phosphocreatine (PCr) hy-
drolysis, the cytosolic Ca²⁺ level, or NADH availability, and
that one of these regulators could be activated to a greater
degree in the second “exercise” bout. Specifically, it was
highlighted that a more active state of the pyruvate dehydro-
genase complex before the second bout would result in greater
delivery of acetyl CoA and consequently more rapid delivery
of NADH to the electron transport chain and an accelerated
onset of oxidative phosphorylation. However, whereas a
“priming” of muscle enzymes (i.e., pyruvate dehydrogenase)
was associated with a decrease in muscle glycogen and PCr
breakdown and lactate accumulation (46), faster VO₂ kinetics
have not been demonstrated in humans (3, 21, 27), although
Rossiter et al. (43) reported a lower VO₂ amplitude. Possible
changes in other muscle enzymes or metabolic intermediates
cannot be discounted. Nevertheless, that prior heavy arm ex-
ercise speeds the VO₂ kinetics on subsequent leg cycling (9, 31)
argues against local changes in muscle metabolism being the
mechanism of speeded VO₂ kinetics; however, Fukuba et al.
(16) found no effect of prior heavy exercise with a different
muscle group.

Our findings of faster phase II VO₂ kinetics, and no change
in the primary component amplitude after prior heavy-intensity
KE exercise, although in basic agreement with those of Ros-
siter et al. (42) and Fukuba et al. (17), contrast with the reports
of others who used cycling exercise (5, 10–13, 16, 31, 32, 45),
with the exception of Tordi et al. (47). These studies have
consistently reported that the phase II VO₂ was unaltered by prior
heavy exercise, but rather the amplitude of the phase II VO₂
(target amplitude, 4) was increased (5, 10–13, 39, 50) with the
amplitude of the slow component VO₂ reduced (by usually
~50%). We observed a significantly greater (but small, 40
ml/min) end-exercise VO₂ for the second exercise, as did
Hughson et al. (26), whereas end-exercise \( \dot{V}O_2 \) was unchanged in the other two leg-extension studies (17, 42) and unchanged (5) or lower (13, 31) in cycle studies. An explanation for the differences in the majority of findings regarding the effects of prior heavy-intensity cycling exercise vs. knee-extension exercise is not clear. Rossiter et al. (42) noted that one difference was use of supine exercise compared with upright cycling, but in our data the KE was performed in the upright posture. The relative intensity of the exercise might be important. In the previous “leg-extension” studies (17, 42) the heavy-intensity exercise was somewhat lower at 70–75% of work peak and elicited a slow component \( \dot{V}O_2 \) of \( \sim 8–13\% \) of the total response amplitude. However, the relative intensity of our protocol (80% of peak \( \dot{V}O_2 \) for one-leg KE exercise and a slow component of 24% of the total amplitude) appears similar to the cycle studies of Burnley et al. (11, 13) (\( \sim 85\% \) of cycling \( \dot{V}O_2 \max \), and a slow component amplitude of \( \sim 14\% \) of the total amplitude). Regarding intensity, discrepancy still exists in comparing the results of those who have used higher relative intensities as to whether the \( \dot{V}O_2 \) kinetics are accelerated (47), or not (10, 31, 42).

Another possibility to explain the different responses in leg-extension vs. cycling exercise relates to the mass used. It has been suggested that an increase of the primary \( \dot{V}O_2 \) amplitude of a second heavy exercise bout may result from the recruitment of fatigued fibers, which may produce little or no tension but have an energetic cost, and the recruitment of additional motor units to maintain the power output (10). With cycling, Burnley et al. (10) found an increase of the integrated electromyogram (EMG) signal (averaged over three leg muscles) over the first 2 min of exercise, suggesting greater motor unit recruitment accompanying the increased primary \( \dot{V}O_2 \) amplitude of the second heavy exercise. In the present study, with KE requiring use of predominantly the quadriceps, the ability to recruit additional nonfatigued motor units from within the quadriceps muscle group involved in the exercise for the second heavy exercise compared with the first is less likely, whereas with cycling Burnley et al. (10) found, for example, that there was an increased activity of the gluteus maximus on the second bout. Nevertheless, EMG of the vastus lateralis (45), or from four muscle groups during cycling (47), in contrast to Burnley et al. (10), showed no significant effect of the prior exercise on the muscle activation. Thus the more isolated quadriceps muscle mass involved in the KE of the present study may preclude the ability to recruit additional nonfatigued motor units and to increase phase II \( \dot{V}O_2 \) amplitude on the second heavy-intensity exercise. Hughson et al. (26) observed no difference of the integrated EMG between the two heavy-intensity work bouts of their leg-extension/flexion protocol. From the present data, the \( \dot{V}O_2 \) elicited at end exercise for H2 was significantly higher than for H1, but only by 40 ml/min, suggesting that recruitment of additional muscle groups was not a major factor. Also related to the muscle mass involved it is interesting that Koga et al. (29) reported for heavy exercise a greater primary component gain for one-leg than two-leg cycling, with no difference in the per-leg \( \dot{V}O_2 \) slow component. With our one-legged KE exercise, the “target” amplitude may be reached on the first heavy-intensity work rate, and on the second there is no “need” for further muscle unit recruitment.

The phase III \( \dot{V}O_2 \), the “slow component” of \( \dot{V}O_2 \) increase, is of delayed onset (\( \sim 90–120 \) s) (8, 37, 38, 42), and results in a \( \dot{V}O_2 \) increase above the end-exercise value predicted from the work rate-\( \dot{V}O_2 \) relationship for moderate-intensity exercise (i.e., “excess” \( \dot{V}O_2 \)). As noted earlier, others have found the slow component to be reduced (usually by \( \sim 50\% \)) on the second heavy-intensity exercise (5, 13, 16, 18, 31, 32, 34, 45), although Tordi et al. (47) did not see a significant reduction. For leg-extension exercise we found no change in the slow component amplitude in the first to second heavy-intensity exercise. Rossiter et al. (42) reported a small reduction in the \( \dot{V}O_2 \) slow component (\( \sim 20 \) ml/min) and a lesser depletion of muscle PCR on the second exercise. Fukuba et al. (17) found a small reduction [\( \Delta \dot{V}O_2(6–3) \sim 20 \) ml/min], and Hughson et al. (26) found a nonsignificant reduction in their “modeled” slow component amplitude but a significant reduction in the \( \Delta \dot{V}O_2(6–3) \) (40 ml/min). The \( \dot{V}O_2 \) slow component has been suggested to relate to an increased motor unit recruitment and/or recruitment of type II fiber (4, 49). A lack of change in the muscle recruitment between exercise bouts would be consistent with our data during the leg-extension exercise of no reduction in the slow component \( \dot{V}O_2 \). On the second heavy-intensity exercise, Tordi et al. (47) and Scheuermann et al. (45) could not identify from EMG a changed recruitment or power frequency change related to the fiber type recruited. Hughson et al. (26) also found no change in the integrated EMG during the leg extension/flexion exercise across the two heavy-intensity exercise bouts, but a slightly higher mean power frequency on the second bout. Alternatively, from results of Endo et al. (15) that the reduction in the \( \dot{V}O_2 \) slow component was correlated to the residual preexercise blood [La], it was suggested that a lactic academia is a prerequisite for a reduction in the slow component on the subsequent exercise bout. As single-leg exercise induced a relatively smaller increase of blood [La] compared with two-leg or cycle exercise, a reduction in the slow component amplitude may not occur or may be small. The present data did demonstrate that the slow component, excess, \( \dot{V}O_2 \) in both H1 and H2 was accompanied by an increase in Qleg and \( \dot{O}_2 \) delivery. With a slightly (but not significantly) smaller phase III \( \dot{O}_2 \) flow amplitude in the second step, the end-exercise blood flows were similar (4.89 l/min on H2 vs. 4.62 l/min on H1) with a \( \Delta Q\text{leg}/\Delta \dot{V}O_2 \) of \( \sim 7.0 \) for the two steps. The similarity of the slow component phase \( \Delta Q\text{leg}/\Delta \dot{V}O_2 \) on H1 and H2 and to that of the primary component is consistent with the proposal that “oxygen delivery to the tissues, not blood flow per se, is the controlled variable producing exercise hyperemia” (Laughlin et al., Ref. 33).

Thus prior heavy-intensity leg-extension exercise elicited faster \( \dot{V}O_2 \) kinetics on a subsequent heavy exercise, but despite an initially higher limb blood flow on the second step there was not a significant increase in blood flow (\( \dot{O}_2 \) delivery) to the exercising limb during the exercise transient or steady state. Thus the faster \( \dot{V}O_2 \) kinetics on the second heavy-intensity KE exercise appears unrelated to limb blood flow but could be the effect of 1) better regional distribution of blood flow to metabolically active fibers, 2) prior acidemia on the \( \dot{O}_2 \)-hemoglobin dissociation overcoming a diffusion limitation, and/or 3) changes in processes of oxidative metabolism of enhanced substrate provision or enhanced enzyme activity.
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REFERENCES


