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Relating pulmonary oxygen uptake to muscle oxygen consumption at exercise onset: in vivo and in silico studies

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Abstract Assessment of the rate of muscle oxygen consumption, UO_{2m} , in vivo during exercise involving a large muscle mass is critical for investigating mechanisms regulating energy metabolism at exercise onset. While UO_{2m} is technically difficult to obtain under these circumstances, pulmonary oxygen uptake, VO_{2p} , can be readily measured and used as a proxy to UO_{2m} . However, the quantitative relationship between VO_{2p} and UO_{2m} during the nonsteady phase of exercise in humans, needs to be established. A computational model of oxygen transport and utilization—based on dynamic mass balances in blood and tissue cells—was applied to quantify the dynamic relationship between model-simulated UO_{2m} and measured VO_{2p} during moderate (*M*), heavy (*H*), and very heavy (*V*) intensity exercise. In seven human subjects, VO_{2p} and muscle oxygen saturation, StO_{2m} , were measured with indirect calorimetry and near infrared spectroscopy (NIRS), respectively. The dynamic responses of VO_{2p} and StO_{2m} at each intensity were in agreement with previously published data. The response time of muscle

oxygen consumption, $\tau_{UO_{2m}}$, estimated by direct comparison between model results and measurements of StO_{2m} was significantly faster ($P < 0.001$) than that of pulmonary oxygen uptake, $\tau_{VO_{2p}}$, (*M*: 13 ± 4 vs. 65 ± 7 s; *H*: 13 ± 4 vs. 100 ± 24 s; *V*: 15 ± 5 vs. 82 ± 31 s). Thus, by taking into account the dynamics of oxygen stores in blood and tissue and determining muscle oxygen consumption from muscle oxygenation measurements, this study demonstrates a significant temporal dissociation between UO_{2m} and VO_{2p} at exercise onset.

List of symbols

A	Response of VO_{2p} , VO_{2m} , and UO_{2m} at the onset of exercise ($l O_2 \text{ min}^{-1}$)
A_{ss}	Response of VO_{2p} , VO_{2m} , and UO_{2m} at steady state condition ($l O_2 \text{ min}^{-1}$)
C_{Hb}	Concentration of Hb in the whole body ($g l^{-1}$)
$C_{rbc,Hb}$	Concentration of Hb in the red blood cell (mM)
$C_{mc,Mb}$	Concentration of Mb in myocyte (mM)
C_x^B	Bound oxygen concentration in artery, capillary, and tissue (mM)
C_x^F	Free oxygen concentration in artery, capillary, and tissue (mM)
C_x^T	Total oxygen concentration in artery, capillary, and tissue (mM)
H_{body}	Body height (m)
Hct	Hematocrit (fraction of red blood cells in blood) (–)
HR	Heart rate (beat min^{-1})
K_{Hb}	Hill constant at which Hb is 50% saturated by O_2 (mM^{-n})
K_{Mb}	Hill constant at which Mb is 50% saturated by O_2 (mM^{-1})
M_{body}	Body mass (kg)
MW_{Hb}	Molecular weight of hemoglobin ($g \text{ mol}^{-1}$)

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n	Hill coefficient (–)
OD	Oxygen deficit (l O ₂)
PS _{cap}	Permeability surface area product (l min ⁻¹)
Q_m	Muscle blood flow (l min ⁻¹)
Q_p	Cardiac output (l min ⁻¹)
$S_{cap,Hb}$	Oxygen hemoglobin saturation in blood capillary (–)
$S_{tis,Mb}$	Oxygen myoglobin saturation in muscle tissue (–)
StO _{2m}	Muscle oxygen saturation (–)
SV	Stroke volume (ml beat ⁻¹)
t	Time (min)
t_{ex}	Time at the end of exercise (min)
t_0	Time at the onset of the exercise (min)
UO_{2m}	Muscle oxygen utilization (l O ₂ min ⁻¹)
$V_{cap}, V_{mus}, V_{tis}$	Anatomical volume of capillary, muscle, and tissue (l)
V_{cap,O_2}, V_{tis,O_2}	Effective volume of O ₂ in capillary and tissue (l)
VCO_{2p}	Pulmonary carbon dioxide output (l - CO ₂ min ⁻¹)
V_I, V_E	Flow rate inspired and exhaled air (l - min ⁻¹)
VO_{2m}	Muscle oxygen uptake (l O ₂ min ⁻¹)
VO_{2p}	Pulmonary oxygen uptake (l O ₂ min ⁻¹)
$VO_{2p,peak}$	Maximum pulmonary oxygen uptake (l O ₂ min ⁻¹)
WR	Work rate (W)
W_{mc}	Myocyte volume fraction (–)
ΔQ_m	Amplitude of response of muscle blood flow (l min ⁻¹)
$\Delta UO_{2m}, \Delta VO_{2p}$	Amplitude of response of UO_{2m} and VO_{2p} (l O ₂ min ⁻¹)
ΔWR	Exercise incremental work rate (W)

Greek letters

η	Mechanical efficiency (–)
τ_A	Mean response time (s)
τ_{HR}	Time constant of heart rate (s)
τ_{PCr}	Time constant of the Phosphocreatine kinetics (s)
τ_{Q_m}	Time constant of the muscle blood flow rate (s)
$\tau_{UO_{2m}}$	Time constant of the muscle oxygen utilization (s)
$\tau_{VO_{2m}}$	Mean response time of the muscle oxygen uptake (s)
$\tau_{VO_{2p}}$	Mean response time of the pulmonary oxygen uptake (s)

Superscript

B	Bound oxygen concentration
F	Free oxygen concentration
H	Heavy condition
j	Exercise intensity
M	Moderate condition
R	Resting condition

T	Total oxygen concentration
V	Very heavy condition
W	Warm-up condition

Introduction

The regulation of cellular oxygen consumption in skeletal muscle during exercise (in vivo) depends on the dynamic interplay of electron flow, proton pumping, metabolic flux, ADP-dependent feedback control, and oxygen delivery (Chung et al. 2005). At the onset of exercise, the rate of ATP supply has to match the nearly instantaneous increase in the rate of ATP demand in order to satisfy the energy requirements of exercise. Thus, availability of sufficient oxidizable substrates (e.g., NADH) and oxygen, as well as of the reactants associated with ATP hydrolysis (i.e., ADP, phosphocreatine, creatine, inorganic phosphate) plays an important role in the regulation of oxygen consumption (Grassi 2005).

Although direct in vivo measurement of muscle oxygen consumption dynamics (UO_{2m}) is not feasible during exercise involving large muscle mass, pulmonary oxygen uptake (VO_{2p}) can be computed from measurable variables at the airway opening (Whipp et al. 2005) and may be used as a proxy to UO_{2m} . However, under nonsteady state conditions, VO_{2p} is unlikely to provide a reliable estimation of muscle oxygen consumption because of a potential dissociation between them at exercise onset (Behnke et al. 2005; Lador et al. 2006). To provide additional insight into muscle oxidative function, measurements can be made with respect to blood–tissue oxygen transfer directly from skeletal muscle (Poole et al. 2005). Indeed, the muscle oxygen uptake (VO_{2m}) kinetic response to exercise has been obtained in human subjects and showed no significance difference from VO_{2p} (Grassi et al. 1996). However, measurements of VO_{2m} are technically difficult and invasive in nature, which makes them undesirable for routine testing in human subjects. Moreover, the invasive procedures used to measure muscle blood flow (Q_m) and the arterial and femoral venous oxygen contents during the on-transient of a step change in work rate with sufficient time resolution (Andersen and Saltin 1985; Grassi et al. 1996; Poole et al. 1992) are prone to alter the VO_{2m} response (Behnke et al. 2005). In general, assessment of the kinetics of muscle oxygen utilization, oxygen content, and blood flow during work transitions requires proper utilization of the law of conservation of mass and thus accounting for changes in oxygen stores (Cerretelli and di Prampero 1987; di Prampero et al. 1983; Kemp 2005).

Since in vivo measurements of the dynamics of intracellular oxygen consumption during exercise are not possible yet (Behnke et al. 2005), inferences on the relationship between VO_{2p} and UO_{2m} may be made from the noninvasive assessment of measurable variables, such as VO_{2p} , blood flow (Engoren and Barbee

2005; Richard et al. 2004; Rowland and Obert 2002; Tordi et al. 2004) and muscle oxygenation (Bhambhani 2004; Cerretelli and Grassi 2001; Ferrari et al. 2004; Neary 2004; Rolfe 2000). In particular, near infrared spectroscopy (NIRS) can be used to monitor the relative concentrations of deoxyhemoglobin and deoxymyoglobin or tissue oxygen saturation, StO_{2m} , during dynamic exercise. In lieu of specific assessments of intracellular oxygenation, NIRS can provide information reflecting the balance between local muscle oxygen delivery and utilization within the interrogated tissue region (DeLorey et al. 2003; Grassi et al. 2003; MacPhee et al. 2005).

Currently, sufficient experimental data are available to quantify the relationship between $\dot{V}O_{2p}$ and UO_{2m} using a mathematical model that characterizes the major transport and reaction processes undergone by oxygen from room air to the contracting muscles via the cardiorespiratory system. In this study, we develop a computational model based on dynamic mass balances for oxygen to investigate the relationship between $\dot{V}O_{2p}$ and UO_{2m} dynamics at the onset of exercise. Experimental studies provide temporal profiles of $\dot{V}O_{2p}$ and StO_{2m} from the vastus lateralis muscle during constant work rate leg cycling on-transitions at three exercise intensities in healthy adolescents. Differences between the dynamic behavior of $\dot{V}O_{2p}$ and UO_{2m} during work transitions representative of moderate, heavy, and very heavy intensity exercise are analyzed using a computational model of oxygen transport and utilization that takes into account changes in both blood and muscle oxygen stores.

Methods

Experimental studies

Subjects

Seven male African-American adolescents were included in the study after having passed the participation criterion (peak $\dot{V}O_{2p} > 38 \text{ ml kg}^{-1} \text{ min}^{-1}$). Subjects were healthy, unmedicated, non-smokers, who were not involved in competitive athletics at the time of the study. All investigational procedures were approved by the University Hospitals of Cleveland Institutional Review Board and written informed consent was obtained from both subjects and their parents.

Resting measurements and exercise protocol

Subjects participated in tests on five occasions within a 2-week period. They were instructed to refrain from eating and exercising for 2 h prior to their scheduled exercise tests. All anthropometric measurements were obtained on day 1, prior to the maximal exercise test (see Table 1). Body height was measured with a standard, calibrated stadiometer, and body mass with a balance

beam scale (Seca, Vogel and Halke, Hamburg, Germany). Stage of maturation was estimated by self-assessment using the charts by Morris and Udry (Sheel et al. 2004), assuming that all subjects were post-pubertal (Stage 4–5). All exercise tests were carried out on an electronically braked cycle ergometer (Ergometrics 800, SensorMedics, Yorba Linda, CA, USA). The work rate transition time of the cycle ergometer to a step change was less than 2 s. Subjects were able to utilize the cycle ergometer digital display to monitor their pedaling frequency (rpm) throughout each test.

Testing took place approximately at the same time of the day for each subject. On day 1, the subjects performed a continuously incremental “ramp” test to determine peak pulmonary oxygen uptake ($\dot{V}O_{2p,peak}$) and ventilatory threshold (VT) (see Table 1). Three minutes of baseline data were collected for each subject sitting quietly on the cycle ergometer. Subjects then began a warm-up with 3-min of cycling at a 20 W work rate and of ~ 60 rpm frequency. Then the work rate was continuously increased (20 W min^{-1}) until the subjects reached voluntary exhaustion. Upon exhaustion, the work rate was reduced to 20 W, active recovery was maintained for 10 min, and a 5-min passive recovery followed while sitting quietly on the stationary bike.

From ramp exercise data, $\dot{V}O_{2p,peak}$ and VT were determined for each participant. The VT was determined using the V-slope method (Beaver et al. 1986). From these two parameters ($\Delta = \dot{V}O_{2p,peak} - VT$) was calculated and used to determine the individual work rates for each of the exercise intensity domains. For subject participation in the remainder of the protocol, $\dot{V}O_{2p,peak}$ values had to be within 2 SD of the predicted adolescent (14–18 year) based on Cooper et al. (1984) (Boys: $38\text{--}62 \text{ ml kg}^{-1} \text{ min}^{-1}$). On the other days, subjects performed a series of eight square-wave exercise tests at selected work rates, which corresponded to about: (a) 90% VT (moderate, WR^M), (b) VT + 25% of Δ (heavy, WR^H), and (c) VT + 75% of Δ (very heavy, WR^V) (Table 1). Each exercise test, regardless of intensity, followed the same procedure for baseline, warm-up, active recovery, and passive recovery as described in the day 1 maximal exercise test. During moderate exercise, upon completing the warm-up, subjects exercised for 5 min at the pre-determined work rate. During heavy exercise, subjects were asked to pedal until they had achieved a steady state, defined as 2 min of less than 5% change in $\dot{V}O_{2p}$. Finally, during the very heavy exercise bouts, subjects were asked to pedal until they could no longer maintain the pedaling frequency despite vigorous encouragement. All tests were carried out at a pedaling frequency equal to 60 rpm. Instructions to begin and end testing were given by voice without warning. “Steady state” values were calculated by averaging data recorded over the last 30 sec of exercise for moderate- and heavy-intensity tests and over the last 15 s for very heavy exercise. A break of 1.0–1.5 h was observed between exercise-bouts performed on a single day.

Table 1 Physical characteristics and exercise-related parameters for each human subject

Physical characteristic	M1	M2	M3	M4	M5	M6	M7	Mean \pm SD	CV (%)
Age (year)	15	15	17	16	15	16	17	15.8 \pm 0.85	5
Body height, H_{body} (m)	1.65	1.83	1.80	1.72	1.76	1.78	1.72	1.75 \pm 0.06	3
Body mass, M_{body} (kg)	51.4	69	79.1	60.5	70.9	77.3	60.9	67 \pm 9.95	15
$\dot{V}O_{2p}$ at VT ($l\ O_2\ \text{min}^{-1}$)	1.15	1.93	1.75	1.19	1.36	1.89	1.67	1.56 \pm 0.32	20
$\dot{V}O_{2p,\text{peak}}$ ($l\ O_2\ \text{min}^{-1}$)	2.13	3.65	3.02	3.01	2.80	3.18	3.32	3.01 \pm 0.47	16
WR at VT (W)	84	141	134	78	101	129	132	114.1 \pm 25.95	23
Peak WR (W)	169	272	214	200	214	209	243	217.3 \pm 32.59	15
WR^M (W)	75	125	120	70	90	115	120	102.1 \pm 23.2	23
WR^H (W)	105	175	150	110	130	150	160	140 \pm 25.98	18
WR^V (W)	150	235	190	170	185	190	215	190.7 \pm 27.9	15

Measurements of pulmonary gas exchange

Prior to exercise and before data collection, a facemask (8940 Series, Hans Rudolph Inc., Kansas, MO, USA) was properly fitted and sealed with a gel to minimize gas leaks. In order to measure gas exchange, subjects breathed through a mass flow sensor (hot-wire anemometer) from which two sample lines transported expired air to a metabolic measurement system (VMax 29, SensorMedics, Yorba Linda, CA, USA), which was calibrated before each test using a 3-l syringe. Subjects were given several minutes to familiarize themselves with the breathing apparatus in order to minimize non-physiological results. The oxygen and carbon dioxide analyzers were calibrated before each testing session with known compositions of gases. Before, during, and after exercise testing and recovery periods, ventilatory respiration V_E (BTPS), pulmonary oxygen uptake $\dot{V}O_{2p}$ (STPD), pulmonary carbon dioxide output $\dot{V}CO_{2p}$ (STPD), and a 3-lead electrocardiogram (SensorMedics) were continuously monitored. Blood pressure was taken with an automated cuff (Tango, SunTech Inc.) every 3 min during the maximal exercise test. Calculations of $\dot{V}O_{2p}$ and $\dot{V}CO_{2p}$ were based on the expired gas under the assumption that the fractional concentration of inspired and expired nitrogen are equal (Auchincloss et al. 1966) then no changes of gas lung stores were considered.

Measurements of muscle oxygenation

Local muscle oxygen saturation time profiles, $StO_{2m}(t)$, of the right quadriceps vastus lateralis muscle were obtained with NIRS (Inspectra™ model 325 tissue spectrometer, Hutchinson Technology, Hutchinson, MN, USA). The spectrometer consists of four photomultiplier tubes coupled to interference filters having center wavelengths of 680, 720, 760, and 800 nm. The receiver and source optical fibers (optodes) have a separation distance of 25 mm and are molded into plastic optode housing. A closed cell polyethylene foam light scattering calibrator, Plastazote® LD 45 (Zotefoams Inc, Walton, KY, USA), was used to capture reference light intensity at each wavelength prior to placing the 25 mm reflectance probe on the tissue measurement site. Calibration

was performed prior to the start of each experiment. The experimental data obtained from the metabolic cart and NIRS were synchronized for any condition change by a simultaneous event marker on both devices. The work rate was controlled by a computer that operated the cycle ergometer and metabolic cart simultaneously.

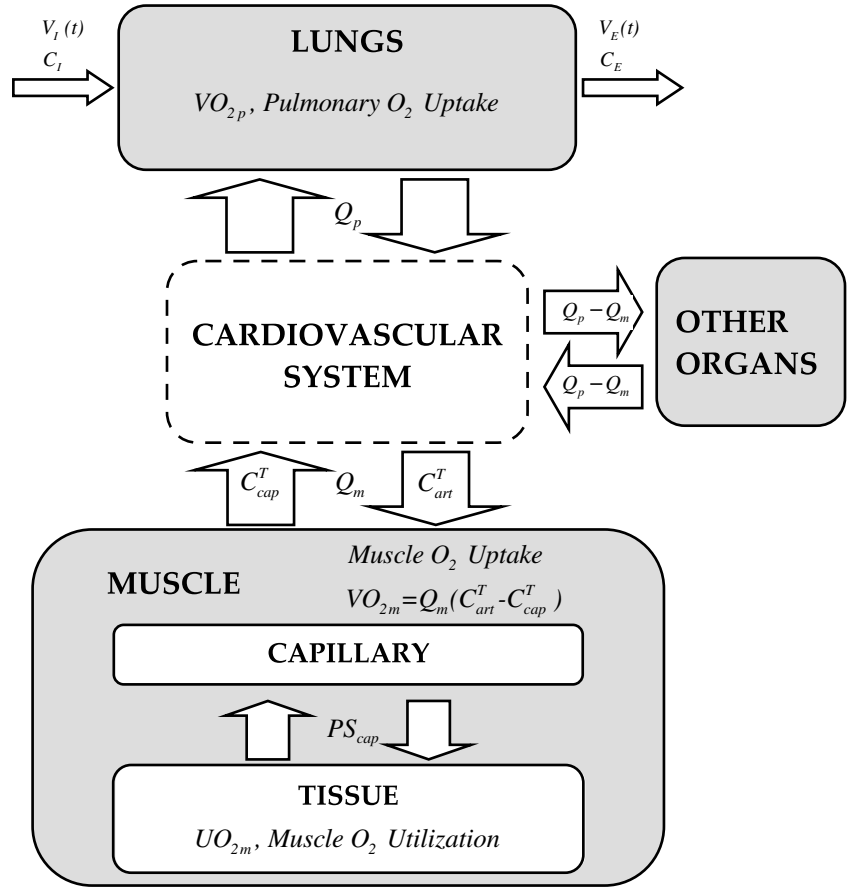
For estimating muscle oxygen saturation, StO_{2m} , a continuous wave near-infrared algorithm was used (Myers et al. 2005). Optodes were placed on the right vastus lateralis muscle, midway between the right iliac crest and the right lateral condyle. To ensure the exact same positioning of the optodes for a given subject, a fiberglass measuring tape was used to measure their distance as described above. This distance was recorded before the subject's first exercise test. This was used as a reference to position the optode before each of the subsequent exercise tests. Optodes were contained in an optically dense, polyethylene foam shield especially designed to assure a tight fitting around the probe optode housing. This shield prevented optodes from sliding along the skin surface during motion and minimized ambient light noise.

The muscle oxygenation StO_{2m} , is considered to represent an averaged values coming from hemoglobin and myoglobin based on capillary and tissue volumes. In the present study, StO_{2m} values are reported as relative changes from warm-up values at 20 W to values during exercise of various intensities and normalized with respect to warm-up condition.

Mathematical model formulation

A schematic representation (Fig. 1) emphasizes oxygen utilization and transport processes in the lungs and skeletal muscle. Processes in the lungs are linked to those in muscle and other organs by cardiovascular system. A mathematical model of oxygen dynamics in skeletal muscle is derived from mass balances that describe oxygen concentration dynamics in capillary bed and tissue compartments. This model assumes perfect mixing and a constant capillary-tissue transport coefficient PS_{cap} (i.e., the product of permeability and surface area). Variables and symbols are defined in the "List of Symbols". The oxygen mass balances relate the dynamic

Fig. 1 Oxygen utilization and transport between lungs and skeletal muscle



responses of total oxygen (C_{cap}^T, C_{tis}^T) to free oxygen (C_{cap}^F, C_{tis}^F) in the capillaries and tissues:

$$V_{cap} \frac{dC_{cap}^T}{dt} = Q_m (C_{art}^T - C_{cap}^T) - PS_{cap} (C_{cap}^F - C_{tis}^F) \quad (1)$$

$$V_{tis} \frac{dC_{tis}^T}{dt} = PS_{cap} (C_{cap}^F - C_{tis}^F) - UO_{2m}. \quad (2)$$

The muscle blood flow (Q_m) and oxygen utilization rate in muscle (UO_{2m}) have distinct dynamics depending on exercise intensity: moderate (M), heavy (H), and very heavy (V). At steady-state, these equations yield skeletal muscle oxygen uptake, which can also be derived using the Fick principle:

$$VO_{2m} = Q_m (C_{art}^T - C_{cap}^T) = PS_{cap} (C_{cap}^F - C_{tis}^F) = UO_{2m}. \quad (3)$$

To relate the total oxygen concentration C_x^T to free oxygen concentration C_x^F ($x = art, cap, tis$), we consider oxygen in free and (hemoglobin) bound forms in arterial and capillary blood ($C_{art}^F, C_{cap}^B; C_{cap}^F, C_{cap}^B$) and in free and (myoglobin) bound forms in muscle tissue (C_{tis}^F, C_{tis}^B). We assumed that (a) the free oxygen concentration in the red blood cell is equal to that in the plasma and that (b) the free oxygen concentration in myocyte is equal to that within the interstitial fluid. Consequently, the total oxygen concentrations in arterial and capillary

blood and in muscle tissue are the sums of the corresponding free and bound oxygen concentration as:

$$C_{cap}^T = C_{cap}^F + C_{cap}^B \quad (4)$$

$$C_{tis}^T = C_{tis}^F + C_{tis}^B \quad (5)$$

which are related by local chemical equilibrium. In blood the relation is

$$C_{cap}^B = 4 \text{ Hct } C_{rbc, Hb} S_{cap, Hb} = 4 \text{ Hct } C_{rbc, Hb} \frac{K_{Hb} (C_{cap}^F)^n}{1 + K_{Hb} (C_{cap}^F)^n}. \quad (6)$$

In tissue the relation is

$$C_{tis}^B = W_{mc} C_{mc, Mb} S_{tis, Mb} = W_{mc} C_{mc, Mb} \frac{K_{Mb} C_{tis}^F}{1 + K_{Mb} C_{tis}^F}. \quad (7)$$

These relations depend on Hb and myoglobin (Mb) concentrations in red blood cell and myocyte ($C_{rbc, Hb}, C_{mc, Mb}$) and their respective volume fractions (Hct, W_{mc}) and oxygen saturations ($S_{cap, Hb}, S_{tis, Mb}$). In Eqs. 6 and 7, one mole of Hb and one mole of Mb binds to four moles and one mole of oxygen, respectively (Dash and Bassingthwaite 2006). The Eqs. 4 and 6 are also valid for arterial oxygen concentrations.

Combining Eqs. 1, 4 and 6 yields the concentration dynamics of the free oxygen in the capillaries:

$$\frac{dC_{\text{cap}}^{\text{F}}}{dt} = \frac{Q_{\text{m}}(C_{\text{art}}^{\text{T}} - C_{\text{cap}}^{\text{T}}) - PS_{\text{cap}}(C_{\text{cap}}^{\text{F}} - C_{\text{tis}}^{\text{F}})}{V_{\text{cap},\text{O}_2}}. \quad (8)$$

The effective volume (or volume of distribution) of oxygen in capillary ($V_{\text{cap},\text{O}_2}$) accounts for the binding space of oxygen in Hb

$$V_{\text{cap},\text{O}_2} = V_{\text{cap}} \left\{ 1 + \frac{4 \text{Hct } C_{\text{rbc,Hb}} K_{\text{Hb}} n (C_{\text{cap}}^{\text{F}})^{n-1}}{[1 + K_{\text{Hb}} (C_{\text{cap}}^{\text{F}})^n]^2} \right\}. \quad (9)$$

Combining Eqs. 2, 5, and 7 yields the concentration dynamics of free oxygen in the myocytes:

$$\frac{dC_{\text{tis}}^{\text{F}}}{dt} = \frac{PS_{\text{cap}}(C_{\text{cap}}^{\text{F}} - C_{\text{tis}}^{\text{F}}) - UO_{2\text{m}}}{V_{\text{tis},\text{O}_2}}. \quad (10)$$

The effective volume (or volume of distribution) of oxygen in tissue ($V_{\text{tis},\text{O}_2}$) accounts for the binding space of oxygen in Mb

$$V_{\text{tis},\text{O}_2} = V_{\text{tis}} \left\{ 1 + \frac{W_{\text{mc}} C_{\text{mc,Mb}} K_{\text{Mb}}}{[1 + K_{\text{Mb}} C_{\text{tis}}^{\text{F}}]^2} \right\}. \quad (11)$$

In response to a step increase in work rate, we assume that the dynamic response of oxygen consumption $UO_{2\text{m}}$ and blood flow Q_{m} are exponential (Binzoni et al. 1999; Miyamoto et al. 1982):

$$\begin{aligned} UO_{2\text{m}}(t) &= UO_{2\text{m}}^{\text{W}} + \Delta UO_{2\text{m}} [1 - \exp(t_0 - t)/\tau_{UO_{2\text{m}}}] \\ Q_{\text{m}}(t) &= Q_{\text{m}}^{\text{W}} + \Delta Q_{\text{m}} [1 - \exp(t_0 - t)/\tau_{Q_{\text{m}}}] \end{aligned}, \quad (12)$$

where $UO_{2\text{m}}^{\text{W}}$ and Q_{m}^{W} are the time-averaged warm-up steady state values known from measurements; $\Delta UO_{2\text{m}}$ and ΔQ_{m} are the differences in steady state values between warm-up and the target work rate; $\tau_{UO_{2\text{m}}}$ and $\tau_{Q_{\text{m}}}$ are the time constants of the muscle oxygen utilization and muscle blood flow responses to exercise. The parameters ΔQ_{m} and $\tau_{UO_{2\text{m}}}$ for each exercise intensity were estimated by fitting model to data (see [Parameter estimation](#)).

To simulate the oxygen concentration dynamics of skeletal muscle to a step change in work rate from warm-up, we must specify the initial conditions:

$$C_{\text{cap}}^{\text{F}}(t_0) = C_{\text{cap}}^{\text{F,W}} \quad \text{and} \quad C_{\text{tis}}^{\text{F}}(t_0) = C_{\text{tis}}^{\text{F,W}}, \quad (13)$$

where $C_{\text{cap}}^{\text{F,W}}$ and $C_{\text{tis}}^{\text{F,W}}$ are the warm-up steady state values obtained from Eqs. 8 and 10 at steady state conditions. To simulate responses to exercise, the differential equations were solved numerically using a robust algorithm for stiff ordinary differential equation (ODE) problems (DLSODE, <http://www.netlib.org/odepack/>, Hindmarsh 1983).

For comparison of oxygen responses to exercise between model simulations and experimental data, we computed muscle oxygen saturation, $\text{StO}_{2\text{m}}$, as a composite volume-averaged value of concentrations:

$$\text{StO}_{2\text{m}} = \frac{C_{\text{cap}}^{\text{B}} V_{\text{cap}} + C_{\text{tis}}^{\text{B}} V_{\text{tis}}}{C_{\text{rbc,Hb}} \text{Hct } V_{\text{cap}} + C_{\text{mc,Mb}} W_{\text{mc}} V_{\text{tis}}} \quad (14)$$

in which the variables $C_{\text{cap}}^{\text{B}}(t)$ and $C_{\text{tis}}^{\text{B}}(t)$ are functions of $C_{\text{cap}}^{\text{F}}(t)$ and $C_{\text{tis}}^{\text{F}}(t)$ according to Eqs. 6 and 7, respectively.

Characteristics of measured dynamic responses

The dynamics responses of the heart rate (HR) of each subject to square-wave changes in work rate were characterized assuming an exponential behavior:

$$\text{HR}(t) = \text{HR}^{\text{W}} + \Delta \text{HR} [1 - \exp(t_0 - t)/\tau_{\text{HR}}], \quad (15)$$

where HR^{W} is the time average of the HR data at warm-up steady state conditions. The time constant τ_{HR} was computed using data from the first minute of exercise. The same value is assumed for the time constant of the muscle blood flow $\tau_{Q_{\text{m}}}$.

For step changes from warm-up to moderate, heavy, and very heavy exercise intensities, the model-simulated responses of oxygen consumption $UO_{2\text{m}}$ (Eq. 12) and muscle oxygen uptake:

$$VO_{2\text{m}} = Q_{\text{m}}(t) (C_{\text{art}}^{\text{T}} - C_{\text{cap}}^{\text{T}}(t)) \quad (16)$$

are compared to the measured responses of pulmonary oxygen uptake $VO_{2\text{p}}$.

These response dynamics were characterized in terms of mean response times as:

$$\tau_A = \frac{\int_{t_0}^{t_{\text{ex}}} t \cdot (A_{\text{ss}} - A(t)) dt}{\int_{t_0}^{t_{\text{ex}}} (A_{\text{ss}} - A(t)) dt}, \quad (17)$$

where $A(t)$ represents the dynamic response of $VO_{2\text{p}}$, $VO_{2\text{m}}$ or $UO_{2\text{m}}$; A_{ss} is the steady state value observed for a specific exercise intensity; and (t_{ex}, t_0) is time interval of the exercise response.

The mean response time is one characteristic of the dynamic response, which in general requires calculation of higher moments of the response (e.g., the variance) for a more complete representation (Varma and Morbidelli 1997). This is a technique that is used to characterize responses of many biomedical systems (Audi et al. 1998; Jaquez 1985). It avoids the bias associated with choosing an arbitrary parametric model (e.g., a single or double exponential function). When $A_{\text{ss}} - A(t)$ is a mono-exponential function, the mean response time is identical to the time constant, for example, as determined from $UO_{2\text{m}}(t)$.

For a step change in work rate, the ‘‘oxygen deficit’’ is defined as the difference between the oxygen requirement, based on the steady state value of $VO_{2\text{p}}$, and total

amount of oxygen taken up, based on the actual dynamic response, $A(t)$, as follows:

$$OD_A = \int_{t_0}^{t_{ex}} (A_{ss} - A(t)) \cdot dt. \quad (18)$$

The oxygen requirement $\Delta VO_{2p}(t_{ex} - t_0)$ is the same for all the three dynamic responses VO_{2p} , VO_{2m} and UO_{2m} .

Parameter estimation

To quantify the relationship between pulmonary oxygen uptake and muscle oxygen utilization in response to different exercise intensities, we must evaluate characteristic parameters. The values of some model parameters can be obtained from previous studies available directly from literature (Tables 1, 2). A second set of parameters can be approximated empirically from a combination of experimental data in this study and relationships developed previously in the literature. A third set of parameters can be estimated by fitting model outputs to measured variables.

To solve Eqs. 8 and 10 for the oxygen concentrations, we estimated the parameters PS_{cap} , V_{cap} , V_{tis} , and C_{art}^T . The product PS_{cap} was arbitrarily chosen large enough to ensure enough oxygen supply to muscle tissue to match the demand at different intensity of exercise. Capillary and tissue volumes were computed according to the volume fraction and body mass of each subject (Tables 1 and 2). We assumed that C_{art}^T remained constant during exercise and is calculated by Eqs. 4 and 6 from values of Table 2.

At rest, muscle oxygen consumption (UO_{2m}^R) is about 20% of pulmonary oxygen uptake (VO_{2p}^R) and muscle blood flow (Q_m^R) is about 15% of cardiac output (Q_p^R) (Rowell 1993). This gives the following estimates:

$$UO_{2m}^R = 0.2 \cdot VO_{2p}^R; \quad Q_m^R = 0.15 \cdot Q_p^R \quad (19)$$

Cardiac output is related to heart rate and stroke volume:

$$Q_p^R = SV^R \cdot HR^R \quad (20)$$

At rest, the stroke volume is empirically related to body height (de Simone et al. 1997).

$$SV^R = 26.5 \cdot H_{body}^{1.78} \quad (21)$$

Cardiac output, at warm-up steady-state condition, can be approximated (Miyamoto et al. 1982; Rosenthal and Bush 1998; Rowland et al. 1997; Vanyushin and Sittikov 2001):

$$Q_p^W = 1.25 \cdot SV^R \cdot HR^W. \quad (22)$$

To obtain the warm-up, steady-state values of oxygen utilization and blood flow, we used steady-state relationships between skeletal muscle and lungs:

Table 2 Model parameters values

Notation	Value	Reference
K_{Hb} (mM) ⁻ⁿ	7800.7	Dash and Bassingthwaighe (2004)
K_{Mb} (mM) ⁻¹	308.6	Dash and Bassingthwaighe (2004)
C_{art}^T (mM)	0.135*	Dash and Bassingthwaighe (2006)
C_{Hb} (g l ⁻¹)	150**	Dash and Bassingthwaighe (2006)
$C_{rbc,Hb}$ (mM)	5.18	Dash and Bassingthwaighe (2006)
$C_{mc,Mb}$ (mM)	0.5	Dash and Bassingthwaighe (2006)
Hct (-)	0.45	Dash and Bassingthwaighe (2006)
n (-)	2.7	Dash and Bassingthwaighe (2006)
W_{mc} (-)	0.75	Dash and Bassingthwaighe (2006)
V_{cap} (l)	7% of V_{mus}	Dash and Bassingthwaighe (2006)
V_{tis} (l)	93% of V_{mus}	Dash and Bassingthwaighe (2006)
V_{mus} (l)	49% of M_{body}	Rowell (1993)
PS_{cap} (l min ⁻¹)	20,000	Arbitrary

*3 ml O₂ l⁻¹, **MW_{Hb} = 64,500

$$UO_{2m}^W = UO_{2m}^R + (VO_{2p}^W - VO_{2p}^R); \quad (23)$$

$$Q_m^W = Q_m^R + (Q_p^W - Q_p^R).$$

These assume that changes between the resting and warm-up steady states do not affect other system tissues (Clausen 1976; Delp and O'Leary 2004). Finally, combining these relationships, we obtain

$$UO_{2m}^W = VO_{2p}^W - 0.8 \cdot VO_{2p}^R, \quad (24)$$

$$Q_m^W = 26.5 \cdot H_{body}^{1.78} \cdot (1.25 \cdot HR^W - 0.85 \cdot HR^R),$$

where VO_{2p}^W , VO_{2p}^R , HR^W and HR^R are the pulmonary oxygen uptake and heart rate values measured at rest and warm-up steady-states.

Let us consider changes between the steady state at warm-up and a higher exercise intensity. The change in muscle oxygen utilization equals the change in measured pulmonary oxygen uptake:

$$\Delta UO_{2m} = \Delta VO_{2p} \quad (25)$$

The time constant of muscle blood flow is assumed to be equal to that of heart rate (DeLorey et al. 2004; Miyamoto et al. 1982), which is estimated for each subject at moderate, heavy, and very heavy exercise intensities:

$$\tau_{Q_m} = \tau_{HR}. \quad (26)$$

The parameters ΔQ_m and $\tau_{UO_{2m}}$ for each subject at each exercise intensity are estimated as the value that yield the best fit of the model output to the experimental data. Specifically, for each subject at each exercise intensity, we minimize a least-squares objective function:

$$\Gamma(\tau_{UO_{2m}}, \Delta Q_m) = \frac{1}{2} \sum_{i=1}^N \left[\left(\frac{StO_{2m}(t_i) - StO_{2m}^W}{StO_{2m}^W} \right)_{exp} - \left(\frac{StO_{2m}(t_i) - StO_{2m}^W}{StO_{2m}^W} \right)_{mod} \right]^2, \quad (27)$$

where N is the number of data points. The optimal estimates of the parameters are the values that minimize the objective function, i.e., the difference between the model output and experimental data. These estimates were obtained by iterating the numerical solution of the model oxygen concentrations and output relationships with numerical optimization using an adaptive, nonlinear algorithm (DN2FB, Dennis et al. 1981, <http://www.netlib.org>).

Statistical analysis

All data are expressed as means \pm SD. Comparison of mean response time and oxygen deficit at moderate, heavy, and very heavy intensities was performed using a one-way analysis of variance. Pairwise comparisons within the same exercise intensity domain were done using paired t -tests. A P -value < 0.05 was considered to be statistically significant.

Results

Typical step responses of oxygen saturation in skeletal muscle StO_{2m} for moderate (M), heavy (H), and very heavy (V) exercise relative to a warm-up steady state StO_{2m}^W are shown in Fig. 2a. The model-simulated responses corresponded closely to experimental data. Step responses of pulmonary oxygen uptake $\dot{V}O_{2p}$ for moderate, heavy, and very heavy exercise from a warm-up steady state $\dot{V}O_{2p}^W$ are shown in Fig. 2b. The corresponding model simulations for skeletal muscle oxygen consumption, UO_{2m} show faster responses than experimental data for $\dot{V}O_{2p}$.

Measured values of steady-state pulmonary oxygen uptake $\dot{V}O_{2p}$ and heart rate HR obtained at rest (R) and warm-up (W) from seven human subjects have a coefficient of variation less than 15% (Table 3). The average amplitude of the responses, $\Delta\dot{V}O_{2p}$, at moderate, heavy, and very heavy intensities, represented a 1.8-, 2.8-, and 3.9-fold, increase, respectively from warm-up values, $\dot{V}O_{2p}^W$ (Table 4). Also, an increase occurs in the average change in steady state blood flow ΔQ_m as estimated using model simulations (Table 5). A quantitative comparison of the mean response times of the step responses for oxygen utilization $\tau_{UO_{2m}}$, muscle oxygen uptake $\tau_{\dot{V}O_{2m}}$, and pulmonary oxygen uptake $\tau_{\dot{V}O_{2p}}$ is shown in Fig. 3. The mean response times determined from model simulations, $\tau_{UO_{2m}}$ and $\tau_{\dot{V}O_{2m}}$, changed relatively little with exercise intensity ($P > 0.05$); however, the mean response time determined directly from experimental data $\tau_{\dot{V}O_{2p}}$ increased significantly from moderate to heavy ($P < 0.001$) and from moderate to very heavy ($P < 0.01$) intensity exercise. Nevertheless, $\tau_{\dot{V}O_{2p}}$ was greater during heavy intensity exercise than during very heavy intensity exercise because a steady state was not attained in the latter condition.

The dynamic responses of $\dot{V}O_{2m}$ and UO_{2m} from model simulations and $\dot{V}O_{2p}$ from experimental measurements were used in Eq. 18 to estimate their respective oxygen deficits, i.e., $OD_{\dot{V}O_{2m}}$, $OD_{UO_{2m}}$ and $OD_{\dot{V}O_{2p}}$ at each intensity of exercise. Oxygen deficit increased significantly ($P < 0.01$) with exercise intensity regardless whether $\dot{V}O_{2p}$, $\dot{V}O_{2m}$, or UO_{2m} was used in its calculation. In addition, $OD_{UO_{2m}}$ was smaller ($P < 0.001$) than $OD_{\dot{V}O_{2m}}$, with the latter being significantly smaller ($P < 0.005$) than $OD_{\dot{V}O_{2p}}$ (Fig. 4).

Finally, model simulations show that muscle oxygen uptake, $Q_m (C_{art}^T - C_{cap}^T)$, is not equal to the rate of oxygen consumption, UO_{2m} , during the transition from warm-up to exercise (Fig. 5).

Discussion

A mathematical model was developed to describe the dynamics of oxygen transport and utilization in contracting skeletal muscle at various exercise intensities. With this model, we quantified the dynamic relationships between model-simulated muscle oxygen consumption and measured pulmonary oxygen uptake during moderate, heavy, and very heavy intensity exercise. During the transition from warm-up to exercise, we quantified the significant differences in the time profiles of pulmonary oxygen uptake and muscle oxygen consumption. The main finding of this work was that for the same individual and at a given work rate, the muscle oxygen consumption dynamic response—derived from measurements of muscle oxygenation using NIRS—was always significantly faster than that of pulmonary oxygen uptake.

Pulmonary and muscle oxygen dynamics

The tissue oxygenation dynamic response to exercise showed a rapid drop in StO_{2m} indicating a greater rate of oxygen consumption than that of oxygen delivery at the onset of exercise. The simulated dynamic changes in muscle oxygen saturation closely matched those from experimental data (Fig. 2a). Model results (Fig. 5) described the dynamic interplay of oxygen delivery (convective and permeation) and oxygen utilization in skeletal muscle during exercise demonstrating differences in the kinetic responses of estimated UO_{2m} and measured $\dot{V}O_{2p}$ (Fig. 2b). As a consequence, significance differences were found between their corresponding response times, $\tau_{\dot{V}O_{2p}}$ and $\tau_{UO_{2m}}$, at each exercise intensity (Fig. 3).

The values of $\tau_{\dot{V}O_{2p}}$ are large compared to those in the literature because of the method for calculating $\dot{V}O_{2p}$. This volume rate of pulmonary oxygen uptake at the mouth differs from the volume exchange rate at the alveolar-capillary level. To provide a more precise dynamic description related to the alveolar gas exchange, a

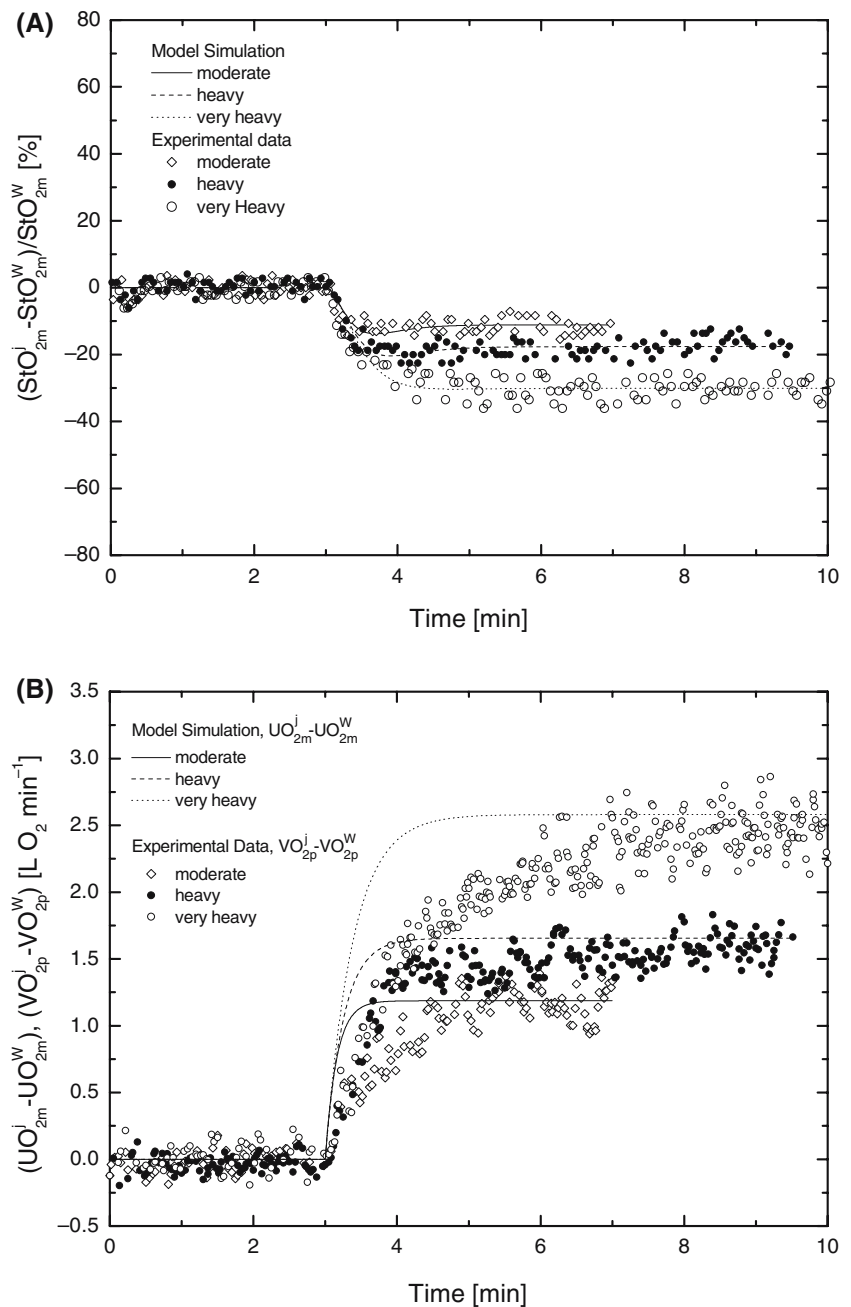
different algorithm could be used (Capelli et al. 2001; Cautero et al. 2005). However, even if the response times $\tau_{VO_{2p}}$ were overestimated by 30% (Cautero et al. 2003), the differences of the dynamic responses among VO_{2p} , VO_{2m} and UO_{2m} during exercise would still be significant.

Small but significant differences ($P < 0.01$) between $\tau_{UO_{2m}}$ and $\tau_{VO_{2m}}$ at each exercise intensity indicate a tight coupling between oxygen diffusion across the capillary membrane and utilization within skeletal muscle. This is consistent with a large value of the permeability-surface area. The response times of simulated dynamics of muscle oxygen consumption in the present study are similar to those of deoxygenated

hemoglobin in other studies (Chuang et al. 2002; DeLorey et al. 2003, 2004; Grassi et al. 2003). Furthermore, the response times for pulmonary VO_2 and the time constant of heart rate obtained experimentally in our study are consistent with published data (Miyamoto et al. 1982).

The relative response times at exercise onset (viz., $\tau_{VO_{2p}} > \tau_{VO_{2m}} > \tau_{UO_{2m}}$) from this study seem in agreement with findings of other investigators (di Prampero 1981; Cerretelli and di Prampero 1987; Kemp 2005). Grassi et al. (1996), however, found no significant differences between $\tau_{VO_{2m}}$ and $\tau_{VO_{2p}}$ from experiments in the transition from light to moderate intensity exercise (Grassi et al. 1996).

Fig. 2 Human subject (M7) responses to step changes from a steady state warm-up (W) condition to a steady state during moderate, heavy, and very heavy ($j = M, H, V$) exercise: **a** Relative oxygen saturation in muscle, StO_{2m} : model output compared with experimental data. **b** Pulmonary oxygen uptake, VO_{2p} experimental data compared to muscle oxygen consumption simulated, UO_{2m}



This difference can be attributed to the methodology for measuring $\dot{V}O_{2m}$ dynamics, which relies on lumped measurements of oxygen content in the femoral vein and bulk measurements of femoral blood flow. This measurement does not account for heterogeneity of blood flow to the active muscles. In contrast, the sampled muscle region with our NIRS technique represents just a small portion of the total muscle involved. We assume, however, that this sample is representative of overall muscle recruitment where most of the oxygen consumption takes place. This may limit the reliability of our method in estimating the dynamics of muscle oxygen consumption at exercise onset.

Oxygen deficit

The oxygen deficits $OD_{\dot{V}O_{2p}}$, $OD_{\dot{V}O_{2m}}$ and $OD_{UO_{2m}}$ calculated from the dynamic responses of $\dot{V}O_{2p}$, $\dot{V}O_{2m}$ and UO_{2m} , respectively, increased significantly from moderate to very heavy exercise (Fig. 4). The differences between the oxygen deficit values associated with $\dot{V}O_{2p}$ and UO_{2m} are consistent with those previously reported (Cerretelli and di Prampero 1987), which also take into account the oxygen stores contributions. If oxygen deficit is considered to be the sum of the oxygen equivalents for phosphocreatine breakdown, lactate production, and body oxygen stores, then model results would indicate that the oxygen deficit associated with muscle oxygen consumption is smaller than that associated with pulmonary oxygen uptake. To determine the “true oxygen deficit” incurred by contracting muscle from measurements of $\dot{V}O_{2p}$ dynamics, it is necessary to take into account the kinetics of oxygen stores in blood and tissue changes (di Prampero et al. 1983). This is evident by comparing the model-simulated oxygen transport and utilization rate processes in skeletal muscle (Fig. 5).

In this investigation, the difference between $OD_{\dot{V}O_{2p}}$ and $OD_{\dot{V}O_{2m}}$ is very large, while the difference between $OD_{\dot{V}O_{2m}}$ and $OD_{UO_{2m}}$ is small. These results may be a consequence of several factors: First, pulmonary oxygen uptake measured at the mouth responds more slowly than alveolar oxygen uptake. Secondly, muscle oxygen uptake and oxygen consumption are estimated from muscle oxygen saturation, which responds rapidly. The latter seems to mirror the dynamics of phosphocreatine (PCr) breakdown as reported by Rossiter et al. (1999), who proposed that PCr changes reflect phase II of the $\dot{V}O_{2p}$ dynamic response. This implies that UO_{2m} and $\dot{V}O_{2p}$ have similar dynamic responses.

The oxygen deficit associated with PCr breakdown can be estimated from the product of $\tau_{PCr} \cong \tau_{UO_{2m}}$ (at moderate intensity) and $\Delta\dot{V}O_{2p}$ ($j = M, H, V$) (di Prampero and Margaria 1968; Piiper et al. 1968). In fact, these estimates were close (M: $0.211 \text{ L} \pm 0.116$, H: $0.338 \text{ L} \pm 0.160$, V: $0.459 \text{ L} \pm 0.171$) to $OD_{UO_{2m}}$ computed based on the estimated UO_{2m} (Fig. 4). Moreover, the dynamics of $\dot{V}O_{2m}$ are different from UO_{2m} because of the oxygen stores in muscle

(di Prampero et al. 1970) as indicated by the difference between $OD_{\dot{V}O_{2m}}$ and $OD_{UO_{2m}}$. As reported by Cerretelli and di Prampero (1987), the contribution of oxygen stores increases with work intensity (Fig. 4). This is consistent with the concept that a decrease in venous oxygen stores causes a dissociation between pulmonary oxygen uptake and muscle oxygen consumption. With a greater work rate increment, dissociation is more pronounced.

The fast dynamic response of $\dot{V}O_{2m}$ is associated with the rapid change of C_{cap}^T (Eq. 3) that matches the decrease of muscle oxygen saturation (Eq. 27). These simulated model results appear to contradict the slower response of muscle oxygen uptake reported by Grassi et al. (1996), who found that dynamic changes of the femoral venous oxygen concentration are slower than the dynamic responses of the oxygenated and de-oxygenated hemoglobin measured by NIRS. This difference might be attributed to model assumptions of a homogeneous blood flow distribution, uniform oxygen consumption in muscle, and perfect mixing within all muscle during exercise.

The large $OD_{\dot{V}O_{2p}}$ observed in this study may be due to the low fitness level of the subjects recruited. Indeed, the ventilatory threshold and the maximum oxygen uptake (23.3 ± 3.4 and $45.3 \pm 6.8 \text{ ml O}_2 \text{ kg}^{-1} \text{ min}^{-1}$, respectively) of the adolescents who participated in this study were lower than corresponding predicted normal values (27 ± 6 and $50 \pm 8 \text{ ml O}_2 \text{ kg}^{-1} \text{ min}^{-1}$, Cooper et al. 1984). Potentially, lactate production could have also contributed significantly to $OD_{\dot{V}O_{2p}}$ in these subjects, especially during heavy and very heavy exercise (Cerretelli et al. 1977). Finally, a possible improvement for estimating $OD_{\dot{V}O_{2p}}$, which should lead to smaller values of oxygen deficit, involves a different basis for calculating the oxygen requirement at high exercise intensities (Whipp and Rossiter 2005).

Blood flow and oxygen uptake

Blood flow in skeletal muscle Q_m at different exercise intensities was estimated using our model. Simultaneous optimal estimates of ΔQ_m and $\tau_{UO_{2m}}$ provided a good fit of the model computed StO_{2m} dynamics to those of corresponding data for each subject at all intensities. Consequently, the estimation of Q_m by taking into account the dynamics of oxygen stores and muscle blood flow (Kemp 2005) is more accurate than that based on a Fick relationship (Barstow et al. 1990; Ferreira et al. 2005a, b), which is strictly valid only at steady state (Stringer et al. 2005). In our model, blood flow dynamics are approximated by a single exponential with time constant τ_{Q_m} similar to that of heart rate (τ_{HR}) determined from measurements of heart rate dynamics (DeLorey et al. 2004; Miyamoto et al. 1982). Typically heart rate, at the onset of exercise, has an initial abrupt rise starting with a negligible delay time followed by a gradual exponential rise. In spite of uncertainties in the

Table 3 Individual pulmonary oxygen uptake and heart rate at steady state rest and warm-up conditions

Parameter	Intensity	M1	M2	M3	M4	M5	M6	M7	Mean \pm SD	CV (%)
$\dot{V}O_{2p}^R$ (l O ₂ min ⁻¹)	Rest	0.2	0.22	0.25	0.26	0.21	0.22	0.215	0.22 \pm 0.021	10
$\dot{V}O_{2p}^W$ (l O ₂ min ⁻¹)	Warm-up	0.4	0.58	0.60	0.50	0.56	0.60	0.44	0.53 \pm 0.08	15
HR ^R (Beat min ⁻¹)	Rest	80.7	81.5	79.7	82.7	76.6	75.3	63.6	77.1 \pm 6.53	8
HR ^W (Beat min ⁻¹)	Warm-up	97.7	91.7	88.9	97.5	89.7	95.7	78.9	91.4 \pm 6.59	7

Table 4 Individual pulmonary oxygen uptakes and heart rate responses from warm-up to moderate, heavy, and very heavy exercise

Parameter	Intensity	M1	M2	M3	M4	M5	M6	M7	Mean \pm SD	CV (%)
$\Delta\dot{V}O_{2p}^M$ (l O ₂ min ⁻¹)	Moderate	0.47	1.22	1.44	0.46	0.79	1.14	1.18	0.96 \pm 0.38	40
$\Delta\dot{V}O_{2p}^H$ (l O ₂ min ⁻¹)	Heavy	1.03	1.96	1.99	1.24	1.32	1.46	1.65	1.52 \pm 0.36	24
$\Delta\dot{V}O_{2p}^V$ (l O ₂ min ⁻¹)	Very Heavy	1.62	2.39	2.28	1.97	1.87	1.99	2.58	2.10 \pm 0.33	15
$\tau_{\dot{V}O_{2p}}^M$ (s)	Moderate	65.5	61.0	64.0	76.0	69.8	66.5	50.3	64.7 \pm 6.94	12
$\tau_{\dot{V}O_{2p}}^H$ (s)	Heavy	78.1	77.2	140.2	127.2	97.4	85.7	100.4	100.9 \pm 24.3	24
$\tau_{\dot{V}O_{2p}}^V$ (s)	Very heavy	132.6	58.2	95.5	77.1	48.7	52.3	106.8	81.6 \pm 31.4	38
τ_{HR}^M (s)	Moderate	22.8	23.3	22.8	20.9	20.8	19.2	19.3	21.3 \pm 1.69	7
τ_{HR}^H (s)	Heavy	23.6	24.0	27.3	23.4	23.5	23.4	23.7	24.5 \pm 1.41	5
τ_{HR}^V (s)	Very Heavy	22.6	23.4	25.2	24.6	24.3	25.2	25.2	24.3 \pm 1.01	4

Table 5 Steady state changes of muscle blood flow rate and time constants of oxygen consumption rates estimated by fitting procedure at different intensity of exercise

Parameter	Intensity	M1	M2	M3	M4	M5	M6	M7	Mean \pm SD	CV (%)
ΔQ_m^M (l min ⁻¹)	Moderate	3.4	6.8	8.0	2.1	5.4	5.5	7.9	5.5 \pm 2.22	39
ΔQ_m^H (l min ⁻¹)	Heavy	6.1	8.4	10.4	4.8	7.7	5.9	9.3	7.5 \pm 2.01	26
ΔQ_m^V (l min ⁻¹)	Very Heavy	6.8	10.6	10.9	7.9	10.1	8.3	12.6	9.5 \pm 2.01	20
$\tau_{\dot{U}O_{2m}}^M$ (s)	Moderate	6.75	17.3	14.8	11.9	15.7	12.3	9.5	12.6 \pm 3.6	29
$\tau_{\dot{U}O_{2m}}^H$ (s)	Heavy	10.4	16.4	16.1	8.4	16.3	7.5	15.0	12.9 \pm 3.9	30
$\tau_{\dot{U}O_{2m}}^V$ (s)	Very Heavy	9.7	15.2	17.1	10.3	16.7	13.0	23.0	15.0 \pm 4.6	30

exact characterization of the cardiac output response to step changes in work rates (Shoemaker and Hughson 1999; Tschakovsky and Sheriff 2004), we chose to characterize the initial portion of the heart rate response at the onset of exercise with a single exponential. Model simulations were very sensitive to the time constant τ_{Q_m} because it affects oxygen delivery dynamics through blood flow changes and consequently, the estimation of the dynamic response of muscle oxygen consumption. However, irrespectively of the values used for τ_{Q_m} in our simulations, the dynamics of $\dot{V}O_{2p}$ were always significantly slower than those of $\dot{U}O_{2m}$.

The cardiac output response time to moderate exercise ($\tau_{Q_m} = 21$ s) was longer than that (13 s) from semi-invasive measurements at 100 w (Lador et al. 2006). Furthermore, we found that the dynamic responses of heart rate τ_{HR}^M and pulmonary oxygen uptake $\tau_{\dot{V}O_{2p}}^M$ (21 and 65 s, respectively) in our study were longer than those (~ 7 s and ~ 19 s) obtained by Lador et al. (2006). Nevertheless, this slower dynamic response of cardiac output is consistent with the slower dynamic response of $\dot{V}O_{2p}$ associated with the lower level of fitness of the population investigated.

Differences in blood flow between steady states, ΔQ_m , estimated by fitting the model output to experimental data are proportionate to the change in work rate

imposed on each subject and in agreement with gain values reported in the literature despite experimental variability. Specifically, the mean value of $[\Delta Q_m/\Delta WR] = 5.7 \cdot 10^{-2} \pm 0.001$ (l min⁻¹W⁻¹) is close to the value (4.6×10^{-2} l min⁻¹W⁻¹) reported by others (Knight et al. 1992; Poole et al. 1992). The estimated work efficiency ($\eta = 0.28$) in the latter studies is based upon the functional gain $[\Delta\dot{V}O_{2p}/\Delta WR] = 10$ ml O₂ min⁻¹W⁻¹ and an energy equivalent for oxygen of 20.9 (Jml O₂⁻¹). In our study, the work efficiency ($\eta = 0.24$) is computed as the mean value of three exercise intensities based on $[\Delta\dot{V}O_{2p}/\Delta WR] = 12$ (ml O₂ min⁻¹ · W⁻¹).

Measurement limitations

To investigate the kinetics of muscle oxidative metabolism in response to exercise, we measured StO_{2m} using NIRS, $\dot{V}O_{2p}$ with indirect calorimetry, and HR with electrocardiography. Data from these studies are comparable to those of others (DeLorey et al. 2003; Grassi et al. 2003; MacPhee et al 2005). One of the limitations of using NIRS to evaluate StO_{2m} in skeletal muscle is that the sampling is not restricted to working muscle, but includes—in addition—skin, adipose tissue, capillaries, and small arterioles and venules. Therefore, the

absolute values may be misleading with respect to the rate of adjustment of oxidative metabolism. With less invasive and more accurate measures of muscle blood flow Q_m , the estimation of $\dot{V}O_{2m}$ and UO_{2m} can be more precise and reliable (Grassi et al. 1996; Lador et al. 2006; Poole et al. 1992; Tordi et al. 2004).

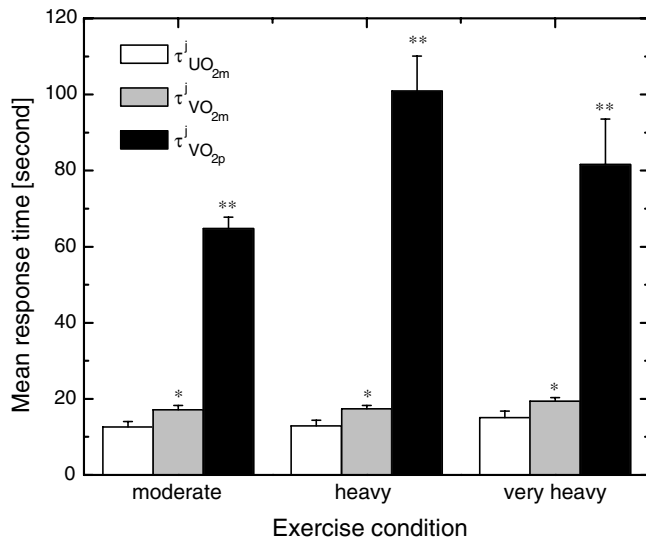


Fig. 3 Comparison of mean response times of pulmonary oxygen uptake ($\tau_{VO_{2p}}^j$), muscle oxygen uptake ($\tau_{VO_{2m}}^j$), and oxygen utilization ($\tau_{UO_{2m}}^j$) after a step change from warm-up to moderate, heavy, and very heavy exercise ($j = M, H, V$). Values are means \pm SE. * $P < 0.01$ versus corresponding value for $\tau_{UO_{2m}}^j$; ** $P < 0.02$ versus corresponding value for $\tau_{VO_{2m}}^j$.

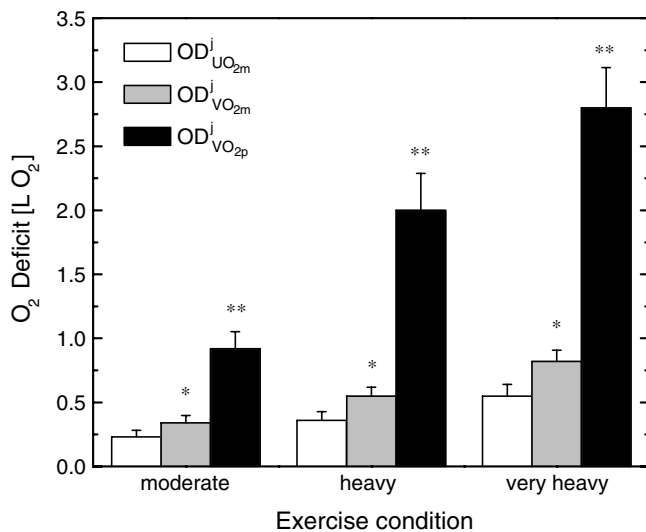


Fig. 4 Comparison of oxygen “deficits” $OD_{VO_{2p}}^j$, $OD_{VO_{2m}}^j$, and $OD_{UO_{2m}}^j$ associated with the dynamic responses of pulmonary oxygen uptake, muscle oxygen uptake, and oxygen consumption after a step change in exercise from warm-up to moderate, heavy, and very heavy exercise ($j = M, H, V$). Values are means \pm SE. * $P < 0.001$ versus corresponding value for $OD_{UO_{2m}}^j$, ** $P < 0.005$ versus corresponding value for $OD_{VO_{2m}}^j$.

Changes in vasodilatation and vasoconstriction, which in turn affect the concentrations of oxygenated and deoxygenated hemoglobin measured by NIRS, may cause variability in the evaluation of oxygen consumption (Binzoni et al. 2003; DeLorey et al. 2003). Other potential sources of uncertainty in the measurements with NIRS are the unknown region investigated that can be only estimated, interference of adipose tissue thickness (Niwayama et al. 2000), and relative contributions of Hb and Mb (Mancini et al. 1994; Tran et al. 1999). Most studies focus on Hb changes, since it has been reported that intracellular Mb accounts for less than 10% of the total NIRS signal (Grassi et al. 2003). Currently, available NIRS instrumentation cannot accurately determine the relative contribution of Mb to the total NIRS signal.

The tissue spectrometer used in the present study, is a single-distance continuous wave CW photometer, which cannot provide direct measurements of absolute concentration values. Therefore, the exercise responses were normalized with respect to those obtained during warm-up. Improvements in the analysis of pulmonary and muscle oxygen dynamics could be made by conducting experiments that simultaneously combine invasive and noninvasive techniques (Grassi et al. 1996, 2003; DeLorey et al. 2003; Knight et al. 1992) that measure venous oxygen content and muscle blood flow, as well as muscle oxygenation during exercise.

Limitations of mathematical models

The objective of this work was to relate a few noninvasive measurements of oxygen dynamics to intra-cellular

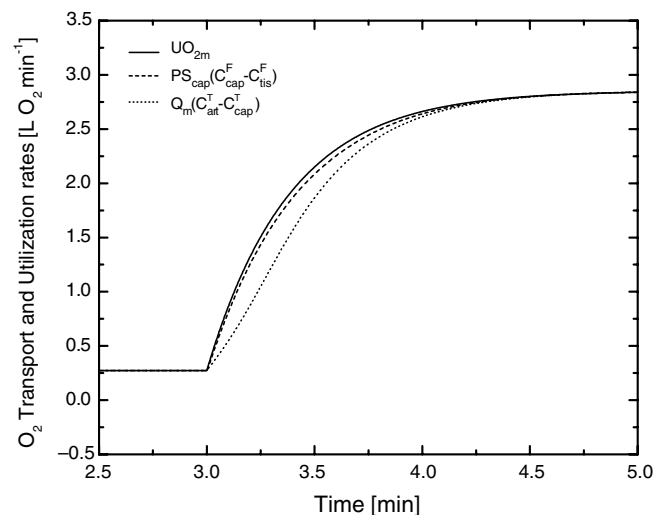


Fig. 5 Simulation of oxygen transport and utilization processes in skeletal muscle to a step response from a steady state warm-up condition during very heavy exercise (corresponding to Fig. 2). Rate of convective transport through the capillary bed $Q_m (C_{art}^T - C_{cap}^T)$. Rate of transport from capillary blood into tissue cells $PS_{cap} (C_{cap}^F - C_{tis}^F)$. Rate of utilization by tissue cells UO_{2m} .

oxygen consumption dynamics in skeletal muscle during exercise. Essential for this task is a minimal mathematical model of oxygen transport and metabolism. In this study, a simple exponential function was used to describe cellular oxygen consumption dynamics (Binzoni et al. 1999). More general and complex models (Beard et al. 2001; Beard 2003; Dash and Bassingthwaite 2006; Popel 1989) can be applied, but require even more assumptions about structure and function.

In our model, mass transport of oxygen between blood capillary and tissue is described by simple permeation characterized by a permeability-surface area coefficient PS_{cap} . This coefficient was set to a sufficiently high value to ensure enough oxygen supply to muscle tissue to match the demand at different intensities of exercise. During exercise, however, vascular conductance in active muscle can increase (Delp and O'Leary 2004), which effects the capillary surface area and can affect the oxygen transport rate and utilization. How blood flow is distributed in relationship to the rate of oxygen utilization depends on vascular and micro-vascular structure and associated hemodynamics (Poole et al. 2005). Furthermore, skeletal muscle blood flow rate is influenced by central cardiovascular and local vascular control mechanisms during exercise (Delp and O'Leary 2004).

If more appropriate and specific data from skeletal muscle were measured during exercise, then a more general computational model would be worth using. For example, if dynamic measurements using magnetic resonance spectroscopy were made, then the model could include other key metabolites controlling cellular respiration (Chung et al. 2005; Mader 2003). If dynamic measurements of O_2 , CO_2 , and pH were obtained in the venous blood perfusing the contracting muscle, then the mathematical model could include acid-base regulation (Dash and Bassingthwaite 2006) to investigate the control of respiration during heavy intensity exercise and/or hypoxia.

Conclusion

A mathematical model was developed that describes the dynamics of oxygen transport and utilization rates in contracting skeletal muscle at various exercise intensities. With this model, we quantified the dynamic relationships between model-simulated muscle oxygen consumption and measured pulmonary oxygen uptake in response to a change in work rate. During the transition from warm-up to exercise, the dynamics of pulmonary oxygen uptake were significantly slower than those of muscle oxygen consumption at all intensities (moderate, heavy, and very heavy). Thus, by taking into account the dynamics of oxygen stores in blood and tissue (Kemp 2005) in the determination of muscle oxygen consumption from muscle oxygenation measurements at exercise onset, this study demonstrates

significant temporal dissociation between UO_{2m} and VO_{2p} .

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