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Recovery Dynamics of Skeletal Muscle Oxygen Uptake during the Exercise Off-Transient

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Abstract

The time course of muscle $\dot{V}_{O_2}$ recovery from contractions (i.e., muscle $\dot{V}_{O_2}$ off-kinetics), measured directly at the site of O_2 exchange i.e., in the microcirculation, is unknown. Whereas biochemical models based upon creatine kinase flux rates predict slower $\dot{V}_{O_2}$ off- than on-transients (Kushmerick, 1998) whole muscle $\dot{V}_{O_2}$ data (Krustrup et al., 2009) suggest on-off symmetry. Purpose: We tested the hypothesis that the slowed recovery blood flow (Q_m) kinetics profile in the spinotrapezius muscle (Ferreira et al. *J. Physiol.* 2006) was associated with a slowed muscle $\dot{V}_{O_2}$ recovery compared with that seen at the onset of contractions (time constant, $\tau \sim 23$ s, Behnke et al. *Resp. Physiol.* 2002), i.e., on-off asymmetry. Methods: Measurements of capillary red blood cell flux and microvascular pressure of O_2 (P_{O_2mv}) were combined to resolve the temporal profile of muscle $\dot{V}_{O_2}$ across the moderate intensity contractions-to-rest transition. Results: Muscle $\dot{V}_{O_2}$ decreased from an end-contracting value of 7.7 ± 0.2 to 1.7 ± 0.1 (ml/100 g/min) at the end of the 3 min recovery period, which was not different from pre-stimulation $\dot{V}_{O_2}$. Contrary to our hypothesis, muscle $\dot{V}_{O_2}$ in recovery began to decrease immediately (i.e., time delay < 2 s) and demonstrated rapid first order-kinetics (τ , 25.5 ± 2.6 s) not different (i.e., symmetrical to) to those during the on-transient. This resulted in a systematic increase in microvascular P_{O_2} during the recovery from contractions. Conclusions: The slowed Q_m kinetics in recovery serves to elevate the $Q_m/\dot{V}_{O_2}$ ratio and thus microvascular P_{O_2} . Whether this Q_m response is obligatory to the rapid muscle $\dot{V}_{O_2}$ kinetics and hence speeds the repletion of highenergy phosphates by maximizing conductive and diffusive O_2 flux is an important question that awaits resolution.

1. Introduction

Skeletal muscle possesses a prodigious ability to augment blood flow rapidly from rest to exercise (Armstrong and Laughlin, 1985; Buckwalter, et al., 1998; Clifford, et al., 2006; Grassi, et al., 1996; Kindig, et al., 2002; Naik, et al., 1999; Radegran and Saltin, 1998; Shoemaker, et al., 1997; Tschakovsky and Sheriff, 2004). Furthermore, the dynamics of muscle blood flow (Q_m) across the exercise on-transient are either faster than (Behnke, et al., 2002a; Behnke, et

al., 2003; Grassi, et al., 1996; Koga, et al., 2005) or similar to (Harper, et al., 2008) those of muscle oxygen uptake ($\dot{V}_{O_2}m$). During the recovery from exercise, however, much less is known regarding the kinetics of microcirculatory Qm and $\dot{V}_{O_2}m$. Given the modulating effect of O_2 on intracellular energetics (Haseler, et al., 2004; Hogan, et al., 1992; Wilson, et al., 1977), it is important to quantify the dynamics of $\dot{V}_{O_2}m$ and its relationship to O_2 availability (i.e., microvascular P_{O_2} ; $P_{O_2}mv$) during recovery.

McDonough et al. (McDonough, et al., 2001) have demonstrated that, in healthy muscle during recovery from contractions, $P_{O_2}mv$ (index of the local Qm/ $\dot{V}_{O_2}m$ relationship) does not fall below end-exercising values. This indicates that the Qm/ $\dot{V}_{O_2}m$ ratio does not decrease below the contracting value during the exercise off-transient; thus effectively preserving O_2 availability and the driving force (i.e., pressure) for blood-myocyte O_2 diffusion. Recently, Ferreira et al. (Ferreira, et al., 2006b) have resolved the temporal profile of capillary hemodynamics during the recovery from contractions and demonstrated that the dynamics of red blood cell flux (index of O_2 delivery) are significantly slower during recovery compared to the onset (Kindig, et al., 2002) of contractions. Despite the quantification of $P_{O_2}mv$ and capillary Qm kinetics, the dynamics of $\dot{V}_{O_2}m$ during the recovery period, at the level of blood-myocyte O_2 flux, have not yet been determined.

There are consistent reports of exercise on-off asymmetry in the temporal responses of cardiac output (Yoshida and Whipp, 1994) and Qm (Ferreira, et al., 2006b; Kindig, et al., 2002).

However, estimates of pulmonary $\dot{V}_{O_2}$ on-off symmetry remain equivocal. Specifically, for moderate intensity exercise pulmonary $\dot{V}_{O_2}$ kinetics both dynamic symmetry (Langsetmo and Poole, 1999; Yoshida and Whipp, 1994) or asymmetry (Lai, et al., 2008; Rossiter, et al., 2002) have been found. Most recently, Krstrup et al. (Krstrup, et al., 2009) demonstrated on-off symmetry in both pulmonary and leg $\dot{V}_{O_2}$ measured simultaneously. This finding is inconsistent with the elegant modeling studies of Kushmerick (Kushmerick, 1998) where a slower reverse (i.e., PCr recovery) versus forward (i.e., PCr degradation) flux of creatine kinase was predicted. Therefore, assuming linearity between PCr and $\dot{V}_{O_2}$ (Meyer, 1988), a slower off-versus on-transient $\dot{V}_{O_2}$ kinetics would be expected from these biochemical models. This issue has yet to be addressed at the muscle microvascular level i.e., the site of blood-muscle O_2 flux.

In summary, in recovery the slowed capillary Qm (Ferreira, et al., 2006b) and $P_{O_2}mv$ (McDonough, et al., 2001) kinetics, close correspondence between estimated $\dot{V}_{O_2}m$ and capillary Qm (Harper, et al., 2008) and biochemical models that suggest less rapid PCr kinetics (Kushmerick, 1998) all support an on-off $\dot{V}_{O_2}$ asymmetry. It was the purpose of the present investigation to test the hypothesis, at the microcirculatory level, that $\dot{V}_{O_2}m$ recovery kinetics would be slower compared with that seen at the onset of contractions (i.e., $\tau \sim 23$ s (Behnke, et al., 2002a)).

2. Methods

Six month old male Sprague-Dawley rats ($n = 7$; 279 ± 8 g) were used in this investigation. All procedures were approved by the Kansas State University Institutional Animal Care and Use Committee. Resolution of muscle $\dot{V}_{O_2}$ kinetics required combination of two data sets obtained using different techniques. Specifically, intravital microscopy was utilized to measure capillary hemodynamics (Ferreira, et al., 2006b) and this data was combined with that collected from

phosphorescence quenching (i.e., P_{O_2mv}) in the current study to calculate $\dot{V}_{O_2}m$. This approach was utilized to avoid: 1) Light contamination from intravital microscopy that would have interfered with the phosphorescence quenching measurements and 2) The potential confounding effects of prior contractions on muscle O_2 exchange (Behnke, et al., 2002c). We have demonstrated previously that the surgeries required for intravital microscopy and phosphorescence quenching do not alter spinotrapezius hemodynamics (Bailey, et al., 2000), and it should be noted that all physical (i.e., weight, strain, age) and electrical stimulation parameters were identical among independent experiments. All measures were then rigorously time-aligned to construct the $\dot{V}_{O_2}m$ responses and resolve the temporal profiles of $\dot{V}_{O_2}m$.

2.1 Microvascular P_{O_2}

Animals were anaesthetized (pentobarbital sodium 40 mg/kg i.p., to effect) and their right carotid artery was isolated and cannulated with a fluid-filled catheter (PE-50). This fluid-filled catheter was used for the administration of additional anesthesia and for the infusion of phosphorescent probe (R2). Rectal temperature was monitored and maintained at 37 °C with a heating pad.

The left spinotrapezius was exposed as described previously (Bailey, et al., 2000; Diederich, et al., 2002). Briefly, the skin and fascia were carefully removed from the caudal portion of the dorsal aspect of the muscle. Stainless steel electrodes were used to stimulate the muscle. The cathode was placed in close proximity to the motor point (0.5–1.0 cm caudal to the scapula), while the anode was sutured in place at the caudal edge of the muscle, near the fourth thoracic vertebrae. Stimulation parameters (i.e., voltage and placement of electrodes) were invariant among all animals. The phosphor, palladium meso-tetra-(4-carboxyphenyl)-porphyrin dendrimer (R2; Oxygen Enterprises Ltd., Philadelphia, PA), was infused at a dose of 15 mg/kg through the arterial cannula ~15 min prior to each experiment.

The muscle was kept moist using a Krebs-Henseleit bicarbonate-buffered solution equilibrated with 5% CO_2 /95% N_2 at 37 °C during a 10-minute stabilization period following exposure and throughout the subsequent experiment. The muscle was stimulated to contract at 1 Hz (~4–6 V, 2.0 ms pulse duration, twitch contractions) for 3 min with a Grass S88 stimulator. P_{O_2mv} measurements were recorded every 2 s throughout rest, exercise, and for 3 min of recovery. Upon completion of the experiment, each rat was euthanized with an overdose of anesthesia (pentobarbital sodium, 50 mg/kg, i.a.).

The probe of a PMOD 1000 Frequency Domain Phosphorimeter (Oxygen Enterprises Ltd., Philadelphia, PA) was positioned ~2 mm above the spinotrapezius, as described by Bailey et al. (Bailey, et al., 2000). A light guide contained within the probe focuses excitation light (524 nm) on the medial region of the exposed spinotrapezius (~2.0 mm diameter, to ~500 μ m deep). The PMOD 1000 uses a sinusoidal modulation of the excitation light (524 nm) at frequencies between 100 Hz and 20 kHz, which allows phosphorescence lifetime measurements from 10 μ s to ~2.5 ms. In the single frequency mode, a series of 10 scans (100 ms) were used to acquire the resultant lifetime of the phosphorescence at 700 nm and this series was repeated every 2 seconds (for review of technique see (Vinogradov, 2001)). The phosphorescence lifetime was obtained computationally based on the decomposition of data vectors to a linearly independent set of exponentials (Vinogradov and Wilson, 1994).

The Stern-Volmer relationship allows the calculation of P_{O_2mv} from a measured phosphorescence lifetime using the following equation (Rumsey, et al., 1988):

$$P_{O_2mv} = [(t^\circ/t) - 1] / (k_Q * t^\circ) \quad \text{Eq.1}$$

where k_Q is the quenching constant (mmHg/s) and t^* and t are the phosphorescence lifetimes in the absence of O_2 and at the ambient O_2 concentration, respectively. For R2, in *in vitro* conditions similar to those found in the blood, k_Q is 409 mmHg/s and t^* is 601 μ s (Lo, et al., 1997). Since the R2 is tightly bound to albumin in the plasma and is negatively charged, in combination with the extremely high albumin reflection coefficients in skeletal muscle (for review see (Renkin and Tucker, 1998)), the P_{O_2} measurements are ensured to result from signals within the microvasculature, rather than the surrounding muscle tissue (Poole, et al., 2004). The phosphorescence lifetime is insensitive to probe concentration, excitation light intensity, and absorbance by other chromophores in the tissue (Rumsey, et al., 1988). The effects of pH and temperature are negligible within the normal physiological range which was maintained herein (Lo, et al., 1997; Pawlowski and Wilson, 1992).

For the $P_{O_2}mv$ data, curve fitting was accomplished using KaleidaGraph software (version 4; Synergy Software, Reading, PA, USA) and was performed on the off-transient using a two-component model described previously (McDonough, et al., 2001) as follows:

$$P_{O_2}mv(t) = P_{O_2}mv_{(ss)} + \Delta_1 * \left[1 - e^{-(t-TD1)/\tau_1} \right] + \Delta_2 * \left[1 - e^{-(t-TD2)/\tau_2} \right] \quad \text{Eq.2}$$

where $P_{O_2}mv(t)$ is the $P_{O_2}mv$ at any time t , $P_{O_2}mv_{(ss)}$ is the $P_{O_2}mv$ immediately preceding the cessation of contractions, Δ_1 and Δ_2 are the amplitudes of the fast and slow recovery components, TD_1 and TD_2 are the time delays and τ_1 and τ_2 are the time constants for each component.

2.2 Muscle Oxygen Consumption

Muscle oxygen consumption ($\dot{V}_{O_2}m$) was estimated from data collected on capillary red blood cell (RBC) flux (Ferreira, et al., 2006b), muscle blood flow (Behnke, et al., 2001) and $P_{O_2}mv$ dynamics (current study) in the spinotrapezius muscle across the recovery transition after the cessation of contractions, with data sets being obtained under identical conditions.

Through the Fick equation (i.e., mass balance) $\dot{V}_{O_2}m$ was calculated using $P_{O_2}mv$ as an analog of venous P_{O_2} (Behnke, et al., 2002a; Roca, et al., 1992; Wagner, 1991), as the direction and temporal profile of P_{O_2} tracks that of venous O_2 pressure (P_{vO_2} ; (McDonough, et al., 2001)). Microvascular blood O_2 content (C_{mvO_2}) was calculated from the rat O_2 dissociation curve (Altman and Dittmer, 1974) using $P_{O_2}mv$ data collected every 2 s after the cessation of contractions. Considering no change was observed in muscle temperature or blood pH, and the relatively light workload performed by the muscle, no significant Bohr shift in the O_2 dissociation curve would be expected.

The profile of change in muscle blood flow (Q_m) was measured directly from capillary RBC flux (via intravital microscopy; (Ferreira, et al., 2006b)) across the recovery transition from contractions. RBC flux, and thus Q_m , decreased rapidly following the cessation from exercise (i.e., 25% reduction within 5 s (Ferreira, et al., 2006b)), demonstrating a near-exponential profile (half-time of ~ 26 s) to the resting steady-state. From data collected on arterial blood samples (17.8 ml O_2 /100 ml blood) and $P_{O_2}mv$ measurements (from 8 muscles) in concert with individual Q_m responses ($n=5$), $\dot{V}_{O_2}m$ was calculated using:

$$\dot{V}_{O_2}m(t) = Q_m(t) \times (Ca_{O_2} - C_{mvO_2}) \quad \text{Eq.3}$$

where $\dot{V}_{O_2}m$ oxygen uptake at the muscle at time t , Q_m is muscle blood flow at time t , and Ca_{O_2} and C_{mvO_2} are the oxygen contents of the arterial and microvascular blood, respectively.

Forty individual $\dot{V}_{O_2}m$ profiles were calculated by temporally aligning the individual $P_{O_2}mv$ recovery profiles ($n=8$) measured herein with the individual capillary RBC recovery profiles ($n=5$), i.e., 8 $P_{O_2}mv$ profiles $\times$ 5 Qm responses.

The calculated $\dot{V}_{O_2}m$ was then curve fit (KaleidaGraph, version 4) as a single exponential with no time delay using the following function:

$$\dot{V}_{O_2}m(t) = \dot{V}_{O_2}m_{ss} - \Delta\dot{V}_{O_2}m \times \left[1 - e^{\left(-t/\tau\dot{V}_{O_2}\right)} \right] \quad \text{Eq. 4}$$

where $\dot{V}_{O_2}m_{ss}$ is the steady-state muscle $\dot{V}_{O_2}$ immediately preceding the cessation of contractions, $\Delta\dot{V}_{O_2}m$ is the difference between the steady-state contracting and end-recovery $\dot{V}_{O_2}m$, and $\tau\dot{V}_{O_2}$ is the time constant for the change in $\dot{V}_{O_2}m$. Goodness of fit was determined by two criteria: 1) the sum of the squared residuals; and 2) the coefficient of determination (i.e., r^2).

2.3 Computer Simulations

Several series of simulations (via SigmaPlot V. 9 software) were performed by specifying measured steady-state contracting and end-recovery values for Qm and $\dot{V}_{O_2}m$. A number of different temporal responses (i.e., by varying TD and τ) for $\dot{V}_{O_2}m$ and Qm were simulated to generate various Cmv_{O_2} (and thus $P_{O_2}mv$ from the O_2 dissociation curve) profiles. Ca_{O_2} was set at 17.8 ml O_2 /100 ml blood from values obtained in our laboratory for the anesthetized rat.

For the purpose of our model, a homogeneous spatial distribution of Qm and $\dot{V}_{O_2}$ within the muscle compartment was assumed for simulation of exercise.

2.4 Statistics

A one-way analysis of variance was used to compare pre-stimulation, steady-state contracting and end-recovery $\dot{V}_{O_2}m$ and $P_{O_2}mv$, as well as for kinetic variables for the off-transition versus those reported for the on-transition (Behnke, et al., 2002a). A Student-Newman-Keuls test was used for post-hoc analysis. Significance was accepted at $P < 0.05$. All data are reported as mean $\pm$ SE.

3. Results

3.1 Microvascular P_{O_2} ($P_{O_2}mv$) Profile

The $P_{O_2}mv$ during the last 30 seconds of contractions averaged 21.4 ± 1.1 mmHg and after the cessation of contractions the $P_{O_2}mv$ increased to pre-stimulation values (Table 1). The recovery profile of $P_{O_2}mv$ after 3 minutes of contractions for a representative animal is shown in Figure 1 and the mean response in Figure 2a. The $P_{O_2}mv$ recovery profile was fit best with a two component model as demonstrated by McDonough et al. (McDonough, et al., 2001). After the cessation of contractions there was a short-delay (TD_1 , 5.5 ± 1.1 s; range 3–9 s) followed by a fast exponential increase (τ_1 , 26.2 ± 5.9 s; range 15–38 s) with an amplitude (Δ_1) of 10.6 ± 2.6 mmHg. The second component of the $P_{O_2}mv$ recovery profile began 88.6 ± 22.9 s after the end of contractions with a time constant (τ_2) of 38.0 ± 10.6 s and an amplitude (Δ_2) of 2.6 ± 0.7 mmHg.

3.2 $\dot{V}_{O_2}m$ Recovery Dynamics

Based on eq. 3 and the $P_{O_2}mv$ (Figure 2a) and Q_m (Figure 2b) data obtained from muscle *in situ* (Ferreira, et al., 2006b), $\dot{V}_{O_2}m$ decreased in an exponential fashion (τ , 25.5 ± 2.6 s) following the cessation of stimulation with no apparent delay (Figure 2c). The $\dot{V}_{O_2}m$ at the end of the recovery period was not different than resting, pre-stimulation $\dot{V}_{O_2}m$ (Table 1). There was no significant difference in the time constant of $\dot{V}_{O_2}m$ recovery versus that of the exercise on-transient (Figure 3). These kinetics values are similar to those reported for the human quadriceps during moderate intensity exercise (Krustrup, et al., 2009). The ratio of the time constants for Q_m and $\dot{V}_{O_2}m$ was typically less than 1.0 across the on-transient and greater than 1.0 during the off-transient (Figure 4).

3.3 Simulated $P_{O_2}mv$ Profiles

Figure 5 demonstrates the effects of changing the speed of the Q_m response, with the $\dot{V}_{O_2}m$ time constant set to that reported herein ($\tau = 25$ s), on the $P_{O_2}mv$ recovery profile. When the Q_m time constant is set at 140 or 160% of the $\dot{V}_{O_2}m$ time constant (i.e., τ_{Q_m} of 35 and 40 s, respectively), $P_{O_2}mv$ follows a qualitatively similar time course as that observed in the current study (Figures 1 and 5). However, when the Q_m time constant is set at 60 or 40% of the $\dot{V}_{O_2}m$ time constant (i.e., τ_{Q_m} of 15 and 10 s, respectively), there is precipitous decline in $P_{O_2}mv$ followed by a subsequent increase to the steady-state value.

4. Discussion

To our knowledge, this is the first study to resolve the temporal response of $\dot{V}_{O_2}$ after the cessation of rhythmic contractions at the level of the intact skeletal muscle microcirculation. As such, we believe that this study complements and extends the work of Krustrup et al. (Krustrup, et al., 2009) measured across the whole quadriceps muscle in humans. The present investigation has demonstrated that muscle $\dot{V}_{O_2}$ ($\dot{V}_{O_2}m$) during the exercise off-transient recovers at a substantially faster rate than muscle capillary blood flow (Q_m) (Figure 2b, c & Figure 4). In contrast to our hypothesis, however, $\dot{V}_{O_2}m$ during recovery from contractions followed a similar temporal profile (i.e., dynamic symmetry) to that observed during the on-transient (Figure 3). As $P_{O_2}mv$ and tissue oxygenation is dependent crucially upon the $Q_m/\dot{V}_{O_2}m$ ratio, the faster onset and slower offset dynamics of muscle O_2 delivery versus $\dot{V}_{O_2}$ (Figure 4) allows $P_{O_2}mv$ to remain higher than otherwise possible thereby facilitating diffusional blood-myocyte O_2 flux. This observation provides further evidence that, under normal healthy conditions, muscle O_2 delivery is unlikely to limit $\dot{V}_{O_2}$ kinetics during the exercise on- or off-transients.

4.1 Symmetry of On-Off $\dot{V}_{O_2}$ Kinetics

In the current study, $\dot{V}_{O_2}m$ began to decrease immediately (i.e., < 2 s) after the cessation of contractions and was apparently well characterized by a first-order model (Figure 2c).

Furthermore, $\dot{V}_{O_2}m$ kinetics parameters did not differ between the exercise on- versus off-transients (Figure 3), which apparently is inconsistent with the biochemical modeling of Kushmerick (Kushmerick, 1998) that predicts slower off- versus on-transient PCr kinetics. In this regard, the intransigent *in vivo* $\dot{V}_{O_2}m$ on- versus off-contractions kinetics found herein is characteristic of a linear control system (Lamarra, 1990). As discussed by Whipp & Mahler

(Whipp and Mahler, 1980), beyond a creatine change of a few millimoles the relationship between creatine and $\dot{V}_{O_2}$ becomes markedly nonlinear. Without concurrent measures of muscle PCr dynamics a dissociation of $\dot{V}_{O_2}$ and PCr cannot be ruled out. It should be noted, however, that PCr demonstrates apparent first-order behavior in rat skeletal muscle during submaximal workloads (Meyer, 1988). For moderate intensity exercise, measurements of pulmonary $\dot{V}_{O_2}$ kinetics have demonstrated on-off symmetry (Linnarsson, 1974; Paterson and Whipp, 1991; Yoshida and Whipp, 1994) or asymmetry (Rossiter, et al., 2002), although the difference in the latter study was less than 10%. More recently, Harper and colleagues (Harper, et al., 2008) (using pulmonary $\dot{V}_{O_2}$ as an analog of $\dot{V}_{O_2}$ m) and Krstrup et al. (Krstrup, et al., 2009) found no differences in $\dot{V}_{O_2}$ m kinetics following exercise onset and during recovery from moderate intensity exercise. Thus, the lack of difference in the time course of recovery $\dot{V}_{O_2}$ m (current study, Figure 2c) from that found during the on-transient (Behnke, et al., 2002a) is consistent with the majority of pulmonary $\dot{V}_{O_2}$ measures demonstrating on-off symmetry for moderate intensity exercise. These findings provide further evidence that pulmonary $\dot{V}_{O_2}$ reflects closely $\dot{V}_{O_2}$ m kinetics across the exercise on- (see also (Grassi, et al., 1996)) and off-transitions under healthy conditions. It should be noted, however, that when circulatory transit delays were accounted for Krstrup et al. (Krstrup, et al., 2009) did not find a relationship between pulmonary and muscle $\dot{V}_{O_2}$ during exercise recovery.

4.2 Relation between O_2 delivery and $P_{O_2}mv$

Hill and Lupton (Hill and Lupton, 1923) were the first, to our knowledge, to postulate that “the oxidative process of recovery is intimately dependent on the pressure of oxygen, increasing rapidly in speed as the latter is raised”. Indeed, phosphocreatine (PCr) resynthesis occurs predominately via oxidative processes (Kemp, et al., 1993) and follows a monoexponential time course after moderate intensity exercise (Forbes, et al., 2009; Haseler, et al., 1999). Furthermore, consistent with a putative phosphate-linked controller of oxidative metabolism (Meyer, 1988), the breakdown and resynthesis of PCr demonstrate similar kinetics to that of $\dot{V}_{O_2}$ (Meyer & Foley, 1996; Rossiter et al., 1999). Under healthy conditions, the rate constant of PCr resynthesis is directly proportional to muscle oxidative capacity (Paganini, et al., 1997), although, both the amplitude and dynamics of PCr recovery are affected acutely by O_2 availability (Haseler, et al., 1999). During the recovery from moderate intensity exercise the time constants of (Δ) cardiac output (Yoshida and Whipp, 1994) and Q_m (Ferreira, et al., 2005) are appreciably longer than for $\dot{V}_{O_2}$ (see (Harper, et al., 2008) for exception). Presumably, the slower recovery dynamics of blood flow versus $\dot{V}_{O_2}$ will ensure a higher $P_{O_2}mv$ and thus sufficient O_2 flux to the muscle for high energy phosphate replenishment at its maximal rate for the presiding muscle oxidative capacity (see (McDonough, et al., 2001) for discussion), although this remains to be determined.

The precise mechanisms regulating arterial tone and skeletal muscle hyperemia during the exercise on- and off-transients are multifactorial and the proportional contribution of each has not been resolved (see (Ferreira, et al., 2006b) for discussion). However, it is informative, from a mechanistic perspective, to consider the effect of altering global Q_m recovery kinetics on the temporal profile of $P_{O_2}mv$ (and thus capillary-to-myocyte O_2 driving pressure). Through simulations, the effect of either speeding or slowing the recovery dynamics of Q_m (at the $\dot{V}_{O_2}$ m τ set at that from the current study), on $P_{O_2}mv$ kinetics is demonstrated in Figure 5. Whereas there is minimal impact on the $P_{O_2}mv$ profile with slowing Q_m dynamics from 35 to 40 seconds, considerable differences become apparent when Q_m dynamics are speeded.

Specifically, if the time constant of Q_m during the off-transient is set at that measured during the on-transient (~ 15 s; (Kindig, et al., 2002)), there is a temporary reduction in $P_{O_2}mv$ below that found during contractions followed by a slow increase as metabolic rate is compromised. In pathologically-induced conditions such as peripheral arterial disease (increased circulating endothelin-1 with exercise (Mangiafico, et al., 2000)) or chronic heart failure (elevated sympathetic tone (Zelis and Flaim, 1982)), there may be a rapid reduction in muscle blood flow post-exercise due to enhanced vasomotor tone. Faster Q_m recovery dynamics under such conditions would result in a precipitous decline in $P_{O_2}mv$ (Figure 5, solid line) to extremely low levels. In addition, an increased $\dot{V}_{O_2}m$ concomitant with normal Q_m dynamics, would result in a similar decline in $P_{O_2}mv$ during recovery. The simulation under this condition may be misleading as a P_{O_2} of zero (i.e., 100% extraction) in the microcirculation is not physiologically possible due to the finite diffusing capacity of the tissue. Nonetheless, in accordance with Fick's law, the low O_2 driving pressure (due to a reduced $Q_m/\dot{V}_{O_2}m$ ratio) would impair the speed with which muscle can recover energetically (see below). Indeed, the rate of PCr recovery after exercise is over 3 times slower in patients with peripheral arterial disease versus healthy controls (Kramer, 2007). Whether the blunted PCr recovery in this patient population is due, in part, to faster recovery dynamics of Q_m which, in turn, lowers $P_{O_2}mv$ and thus $\dot{V}_{O_2}m$ remains to be determined.

4.3 $P_{O_2}mv$ and $\dot{V}_{O_2}m$ Kinetics

If the $Q_m/\dot{V}_{O_2}m$ ratio is significantly reduced due to heavy exercise or a pathologically induced diminution of Q_m , the greater fractional extraction would result in an exceedingly low P_{O_2} in the microcirculation (i.e., $P_{O_2}mv$). There are several conditions that oblige a low $P_{O_2}mv$ with contractions, including 1) chronic heart failure (Behnke, et al., 2004; Ferreira, et al., 2006a), 2) type I (Behnke, et al., 2002b) and type II (Padilla, et al., 2007) diabetes, 3) hypotension (Behnke, et al., 2006), and 4) heavy exercise (McDonough, et al., 2005). For example, in rats with chronic heart failure at the end of spinotrapezius contractions $P_{O_2}mv$ ranges from ~ 10 – 15 mmHg (Diederich, et al., 2002; McDonough, et al., 2004). Furthermore, during the recovery from contractions in rats with CHF $P_{O_2}mv$ may be transiently reduced (Figure 6; Behnke, Poole, Musch unpublished observations) or exhibit extremely slow $P_{O_2}mv$ kinetics (McDonough, et al., 2004). Whereas the low $P_{O_2}mv$ at the end of contractions with CHF is due, in part, to diminished exercise hyperemia (Richardson, et al., 2003), the transient decline in $P_{O_2}mv$ after the cessation of contractions from Figure 6 occurs when the recovery dynamics of Q_m are faster than $\dot{V}_{O_2}m$ (dashed line Figure 5).

As posited by Hill & Lupton (Hill & Lupton, 1923) and discussed above, intracellular bioenergetics are modulated by O_2 availability (Haseler, et al., 1999; Hogan, et al., 1992). Therefore, at the exceptionally low $P_{O_2}mv$'s present in disease (or possibly heavy intensity exercise), even though mitochondrial P_{O_2} may be above the P_{50} (apparent K_m) for cytochrome oxidase, there would likely be compensatory changes in cellular metabolites, i.e., decrease in $[ATP]/[ADP][Pi]$ and/or $[NAD^+]/[NADH]$, which are necessary to maintain a given $\dot{V}_{O_2}$ (Wilson, et al., 1977). As discussed by Meyer (Meyer, 1988), the consequences of a transient change in redox state (resulting from reduced O_2 availability in this case), could be that PCr and $\dot{V}_{O_2}$ no longer conform to first order kinetics. This scenario would result in a slower and more complex recovery profile of PCr and $\dot{V}_{O_2}$, i.e., not well fit by a single exponential. Indeed, the pulmonary $\dot{V}_{O_2}$ profile during recovery from both maximal (Cohen-Solal, et al., 1995; Nanas, et al., 2001) and submaximal (Belardinelli, et al., 1997; Nanas, et al., 2001) exercise is not always characterized best by a monoexponential model in CHF patients. Whether the

pulmonary $\dot{V}_{O_2}$ responses observed in patients with CHF are representative of muscle $\dot{V}_{O_2}$ kinetics remains to be determined, however, it is clear that the pathophysiology of CHF results in prolonged recovery of microvascular oxygenation (McDonough, et al., 2004) and phosphocreatine (Thompson, et al., 1995a; Thompson, et al., 1995b) after muscle contractions.

5. Conclusion

We have demonstrated that, after the cessation of muscular contractions, $\dot{V}_{O_2}$ m begins to decrease immediately exhibiting a kinetic profile not different from (i.e., symmetrical to) that found for the on-transient. To our knowledge, this is the first measurement of *in vivo* intramuscular $\dot{V}_{O_2}$ kinetics, versus those reported in isolated muscle (Mahler, 1978; Mahler, 1985) or across the whole muscle or leg (Krustrup, et al., 2009). In addition, the kinetics of blood flow during the off-transition are sluggish compared to those of $\dot{V}_{O_2}$, which serves to elevate the $Q_m/\dot{V}_{O_2}$ m ratio. This is in agreement with previous work showing no further increase in muscle O_2 extraction (fractional or total) after the cessation of exercise in healthy subjects (Krustrup, et al., 2009; McDonough, et al., 2001). The slower recovery of blood flow versus $\dot{V}_{O_2}$ m in recovery provides evidence that, under healthy conditions, O_2 delivery appears sufficient to meet metabolic demand.

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Figure 1.

Representative spinotrapezius $P_{O_2}mv$ response after the cessation of muscular contractions.

The dashed line reflects $P_{O_2}mv$ data collected every 2 s and the solid line is the two-component model fit to the $P_{O_2}mv$ data.

Figure 2.

Following the cessation of contractions (time zero) in the spinotrapezius muscle, average (a) microvascular P_{O_2} (with SE bars), (b) red blood cell flux (with SE bars; from (Ferreira, et al., 2006b)), and (c) calculated muscle $\dot{V}_{O_2}$ ($\dot{V}_{O_2m}$) with a one-component model (dashed line) fit to the $\dot{V}_{O_2m}$ data (solid line).

Figure 3.

Overlaying of reciprocal $\dot{V}O_2$ m response (normalized delta) after the onset of (open circles), and during recovery from (closed circles), muscle contractions. The $\dot{V}O_2$ m on-kinetics are modified from Behnke et al., (Behnke, et al., 2002a). Bars reflect the 95% confidence interval surrounding the estimation of the corresponding $\dot{V}O_2$ response.

Figure 4.

Ratio of the time constants for muscle blood flow ($\dot{Q}_m$) and $\dot{V}_{O_2}$ for the contracting on- and off-transients. For the spinotrapezius muscle, the time constant of $\dot{Q}_m$ is consistently faster than that of $\dot{V}_{O_2}$ across the on-transient and slower than $\dot{V}_{O_2}$ during the off-transient. The relative decrease in both $\dot{V}_{O_2}$ and $\dot{Q}_m$ during recovery is such that P_{O_2mv} increases systematically to the baseline, resting value. * $P < 0.05$ versus on-transient.

Figure 5.

Effects of altering the muscle blood flow (Q_m) time constant on P_{O_2mv} dynamics during the contractions off-transient. The computer model generates the microvascular O_2 concentration (C_{mvO_2} , see `Methods`) and P_{O_2mv} is determined from the O_2 dissociation curve. Time zero on these simulations represents when the model parameters begin (off-kinetics). The input parameters for $\dot{V}_{O_2m}$ reflect those calculated herein and remained consistent for all simulations. Q_m input parameters are based upon the measured blood flow (Behnke, et al., 2001) and time constants set at 35 and 40 s (from (Ferreira, et al., 2006b)), 15 s (that reported for the on-transient (Kindig, et al., 2002)), and 10 s (that which may occur due to heightened vasoconstriction; see text for explanation). *average Q_m response observed in the normal healthy condition.

Figure 6.

Representative microvascular P_{O_2} (P_{O_2mv}) profile after the cessation of contractions in normal, healthy animals (dotted line) and from an animal with chronic heart failure (CHF; solid line). The animal with CHF demonstrated severe heart failure i.e., right ventricular hypertrophy (right ventricle wt/body weight CHF = 1.02, control = 0.6 mg/g), lung congestion (lung wt/body weight CHF = 7.74, control = 4 mg/g) and increased left ventricular end-diastolic pressure (LVEDP CHF = 19, control = 3 mmHg). Dashed vertical line reflects the cessation of contractions.

Table 1Microvascular P_{O_2} and $\dot{V}_{O_2}$ m data.

$P_{O_2}mv$	
Pre-Stimulation $P_{O_2}mv$ (mmHg)	$35.6 \pm 2.1^*$
End-Contracting $P_{O_2}mv$ (mmHg)	21.4 ± 1.1
End-Recovery $P_{O_2}mv$ (mmHg)	$35.1 \pm 2.8^*$
Δ Off-Transient (fast; mmHg)	10.6 ± 2.6
TD_1 (s)	5.5 ± 1.1
τ_1 (s)	26.2 ± 5.9
Δ Off-Transient (slow; mmHg)	2.6 ± 0.7
TD_2 (s)	88.6 ± 22.9
τ_2 (s)	38.0 ± 10.6
$\dot{V}_{O_2}m$	
Pre-Stimulation $\dot{V}_{O_2}m$ (ml/100 g/min)	$1.6 \pm 0.1^*$
End-Contracting $\dot{V}_{O_2}m$ (ml/100 g/min)	7.7 ± 0.2
End-Recovery $\dot{V}_{O_2}m$ (ml/100 g/min)	$1.7 \pm 0.1^*$
τ (s)	25.5 ± 2.6

Values are means $\pm$ SE. Δ Off-Transient, amplitude of the fast and slow components of the $P_{O_2}mv$ response. TD, time delay; τ , time constant.

* $P < 0.05$ vs. end-contracting value.