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# Multi-Scale Modeling of Respiration: Linking External to Cellular Respiration during Exercise

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## Abstract

In human studies investigating factors that control cellular respiration in working skeletal muscle, pulmonary $VO_2$ dynamics ($VO_{2p}$) measured at the mouth by indirect calorimetry is typically used to represent muscle $O_2$ consumption ($UO_{2m}$). Furthermore, measurement of muscle oxygenation using near-infrared spectroscopy has provided information on the dynamic balance between oxygen delivery and oxygen consumption at the microvascular level. To relate these measurements and gain quantitative understanding of the regulation of $VO_2$ at the cellular, tissue and whole-body level, a multiscale computational model of oxygen transport and metabolism during exercise was developed. The model incorporates mechanisms of oxygen transport from the airway opening to working muscle and other-organs cells, as well as the phosphagenic and oxidative pathways of ATP synthesis in these tissue cells. Model simulations of external ($VO_{2p}$) and cellular ($UO_{2m}$) respiration show that, during moderate exercise, their characteristic mean response times are similar even when a transit delay exists between tissue cells and the external environment for normal subjects.

## Introduction

To distinguish mechanisms of impaired muscle oxygen delivery and oxidative metabolism in response to exercise, we need to evaluate how these factors affect muscle oxygen utilization ($UO_{2m}$), which represents cellular respiration. During human or animal exercise experiments, direct *in vivo* measurement of $UO_{2m}$ is not feasible. Instead, pulmonary oxygen uptake ($VO_{2p}$), which represents external respiration, is measured non-invasively at the mouth as an indirect indicator of metabolic processes that control cellular respiration in the working skeletal muscles. Factors that contribute to the differences between the dynamic responses of $UO_{2m}$ and $VO_{2p}$ are circulatory dynamics[14], ventilation, oxygen stores in blood and muscle[7], and oxygen exchange across membranes. Therefore, using $VO_{2p}$ as an indicator of metabolic processes may be misleading in the presence of various disease states. In chronic obstructive pulmonary disease[21], diabetes[3,12], or chronic heart failure[20], the dynamic response of $VO_{2p}$ to exercise is abnormally slow. In type 2 diabetes, low muscle blood flow may impair oxygen delivery to working muscle. Clinically, these diseases also may impair the mitochondrial oxidative metabolism[8].

In general, muscle power output and ATP utilization rate change in less than a second after the onset of exercise, but the $VO_{2p}$ response is much slower. Typically, the $VO_{2p}$ response

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has two phases whose slopes are discontinuous: a short (~20s) cardiac-dependent rise characterized by a circulatory transit time delay (Phase I) followed by a longer exponential-type increase to a plateau (Phase II)[25]. The relationship between $VO_{2p}$ and $UO_{2m}$ dynamics has been studied under a variety of conditions[1,2,9,15]. From dynamic measurements of arterial and femoral venous blood and leg blood flow, Grassi et al. [9] evaluated muscle oxygen uptake ($VO_{2m}$) dynamics, under the assumption its dynamics represents those of $UO_{2m}$, and observed that during the transition from light to moderate intensity exercise, the dynamics of $VO_{2p}$ and $VO_{2m}$ did not differ significantly.

Barstow et al. [1,2] performed model simulations of $VO_{2p}$ in response to a moderate step increase in muscle work. Assuming no effects from muscle and pulmonary oxygen stores, simulated $VO_{2m}$ followed a monoexponential increase towards a steady state. Consistent with experimental findings of Grassi et al.[9], simulated $VO_{2p}$ dynamics during Phase II were similar to $VO_{2m}$ dynamics regardless of the Phase I dynamics. However, if oxygen stores are considered in a more general mathematical model of oxygen transport and utilization, then simulated exercise responses of $VO_{2p}$ in Phase II and $VO_{2m}$ may be different. Indeed, Lai et al. [15,17] used such a model to simulate $VO_{2m}$, and $UO_{2m}$ dynamics in response to exercise. They estimated $UO_{2m}$ dynamics from muscle oxygen saturation ($StO_{2m}$) measurements performed via near-infrared spectroscopy (NIRS). The $UO_{2m}$ and $VO_{2m}$ mean response times were much smaller than that of experimental $VO_{2p}$. The dynamics of $UO_{2m}$ and $VO_{2m}$ are different during transient in exercise considering the $O_2$ store in muscle tissue [16].

The Phase II characteristics of the $VO_{2p}$ exercise response depend on multiple factors, e.g., training status and cardiopulmonary disease. An overshoot may occur, as Koppo et al. [13] observed in the $VO_{2p}$ Phase II response of trained cyclists exercising at moderate intensity. Using $VO_{2p}$ as a proxy measurement for $UO_{2m}$, these authors suggested that this phenomenon may be attributed to a higher ATP demand at the beginning of exercise in trained cyclists. Also, voluntary hyperventilation has been shown to slow the $VO_{2p}$ Phase II response to moderate intensity exercise[11].

Experiments conducted at a specific scale have showed that a perturbation in $O_2$ transport can have different effects on oxygen uptake dynamics, viz, $VO_{2p}$ and $VO_{2m}$. For instance, during moderate exercise, an increase in oxygen delivery due to an abrupt increase in heart rate –controlled by a cardiac pacemaker– resulted in a slower Phase II $VO_{2p}$ dynamic response than that obtained with the heart rate fixed [2]. In contrast, in an isolated dog muscle preparation, a faster $O_2$ delivery due to a step increase in blood flow just before the onset of contraction did not affect $VO_{2m}$ significantly[10]. However, when these data were analyzed using a mathematical model, Lai et al.[18] found that increasing the rate of $O_2$ delivery to contracting muscle did not change the dynamics of $UO_{2m}$, but instead predicted a lag in $VO_{2m}$ response. From these and other experiments investigating the $VO_2$ kinetic responses at various scales and characterizing them empirically using a linear combination of exponential functions, it can be inferred that the model parameters are not independent from each other and thus straightforward comparisons may not be possible. In general, the relationship between external and cellular respiration as indicated by $VO_{2p}$ and $UO_{2m}$ (or $VO_{2m}$) depends on physiological processes and interconnections of oxygen uptake dynamics between whole body and local cellular-tissue responses to exercise. To gain quantitative understanding of the impact of oxygen transport limitations on the regulation of oxygen consumption at the cellular level, a multiscale computational model is needed that links $O_2$ transport processes between the lungs and skeletal muscle cells and oxidative phosphorylation in skeletal muscle cells.

## Methods

Simulation of oxygen uptake ($VO_2$), at the tissue and whole-body levels and utilization ($UO_2$) at the cellular level, in response to exercise can be accomplished with a multiscale model that incorporates a multi-organ, whole-body model [27] and a skeletal muscle model[17,18] of oxygen transport and metabolism. The output of this multiscale model can be combined with experimental measurements during exercise to evaluate the dynamic responses of muscle oxygenation ($StO_{2m}$) and pulmonary oxygen uptake ($VO_{2p}$). Such a multi-organ, whole-body model (Fig.1) distinguishes lungs, muscle, and other organ compartments, which are connected by the circulatory system (artery, vein, and capillaries).

### Tissue transport and cellular metabolism

The blood $O_2$ concentration in muscle, $C_{mb}(v,t)$, changes with position in the capillary bed as indicated by cumulative volume ($v$)from the arterial input

$$\frac{\partial C_{mb}}{\partial t} = -Q_m(t)\frac{\partial C_{mb}}{\partial v} + D\frac{\partial^2 C_{mb}}{\partial v^2} + J_m(v,t); 0 < v < V_{mb} \quad (1)$$

where $V_{mb}$ is the muscle capillary blood volume; $J_m$ is the $O_2$ transport rate between capillary blood and muscle tissue; and $D$ is the $O_2$ dispersion coefficient. The muscle blood flow in response to exercise is

$$Q_m(t) = Q_{m0} + \Delta Q_m[1 - e^{(t_0 - t)/\tau_Q}] \quad (2)$$

where $\Delta Q_m$ is the muscle blood flow increase; $t_0$ is the time at the onset of exercise; and $\tau_Q$ is the time constant of the blood flow response. The rate of muscle oxygen uptake is

$$VO_{2m}(t) = Q_m(t)[C_{art,m}(t) - C_{ven,m}(t)] \quad (3)$$

where $C_{art,m}(t) = C_{mb}(t,0)$ and $C_{ven,m}(t) = C_{mb}(t, V_{mb})$ are the input and output $O_2$ concentrations of the of muscle capillary bed.

The metabolic response of working skeletal muscle is described by bioenergetic systems associated with $O_2$, ATP and phosphocreatine (PCr) metabolism (Fig.1). The change in tissue $O_2$ concentration, $C_{tis}(v,t)$ depends on mass transfer across the blood-tissue membrane and reaction processes (oxidative phosphorylation):

$$\frac{\partial C_{tis}}{\partial t} = -\phi_{OxPhos} + \frac{J_m}{f_b}; 0 < v < V_{tis} \quad (4)$$

where $f_b = V_{tis}/V_{mb}$ is the volume ratio of muscle tissue to muscle capillary blood and $\varphi_{OxPhos}$ is the oxidative phosphorylation rate:

$$\phi_{OxPhos}(v,t) = V_{\max}\left[\frac{C_{ADP}}{K_{ADP} + C_{ADP}}\right]\frac{C_{tis}^F}{K_m + C_{tis}^F} \quad (5)$$

where $V_{\max}$ is the maximal flux of oxidative phosphorylation, $C_{ADP}$ is the ADP concentration and $C_{tis}^F$ is the free $O_2$ concentration in muscle cells. The energy demand

imposed by exercise is represented by the rate of ATP utilization, which is balanced by ATP production from oxidative phosphorylation and phosphocreatine (PCr) hydrolysis. [17] The P:O ratio in oxidative phosphorylation is assumed as 3. The reaction fluxes of creatine kinase are nonlinearly related to the coupled concentration of Cr, PCr, ADP and ATP, which must satisfies the conservation of adenosine and creatine [17] The contribution of glycolysis to ATP synthesis, however, is negligible when the imposed work rate is of moderate intensity. [22] The rate of oxygen utilization at the cellular level can be estimated as:

$$UO_{2m}(t)=\int_0^{V_{tis}}\phi_{OxPhos}(v,t)\,dv \quad (6)$$

## External respiration

In the lung compartment, we consider the alveolar gas as well-mixed with a constant breath-averaged volume. From the net input-output of oxygen in the alveolar gas[25], the rate of pulmonary oxygen uptake is computed as:

$$VO_{2p}(t)=V_A(t)[C_IO_2 - C_AO_2(t)] \quad (7)$$

where $C_IO_2$ is the constant inspiratory $O_2$ concentration and $C_AO_2(t)$ is the alveolar $O_2$ concentration. The alveolar ventilatory response, which is estimated from the ventilatory measurement during moderate exercise, is represented by an exponential function:

$$V_A(t)=V_{A0}+\Delta V_A[1 - e^{(t_0-t)/\tau_V}] \quad (8)$$

where $V_{A0}$ is the ventilation at a warm-up steady state; $\Delta V_A$ is the ventilatory increase in response to exercise; and $\tau_V$ is the time constant of the ventilatory response.

In the pulmonary capillary bed, $O_2$ concentration in the blood from the arterial to venous sides is simulated by a one-dimensional convection-dispersion model with transport flux between blood and alveolar space[27]. The rate of oxygen uptake in alveolar blood is

$$VO_{2A}(t)=Q(t)\,[C_{art}(t) - C_{ven}(t)] \quad (9)$$

where the dynamic response of cardiac output $Q(t)$ has a similar form as Eq. 2. The increase in cardiac output and muscle blood flow in response to exercise are assumed to be the same.[28] The arterial-venous blood $O_2$ concentration difference is given in the brackets. To simulate $O_2$ transport between muscle and lungs, the $O_2$ concentration in large blood vessels is represented by a one-dimensional convection-dispersion model[27]. The blood flow and oxygen uptake of the other organs compartment are assumed constant.

## Model simulations for comparison with experimental data

Using this model, we can simulate and compare the quantitative relationship between cellular, tissue, alveolar blood and whole-body $O_2$ uptake responses to moderate exercise indicated by $UO_{2m}$, $VO_{2m}$, $VO_{2A}$, $VO_{2p}$, respectively. We then characterize the dynamic responses of these outputs by the mean response time, MRT. Between the initial time, $t_0$, and the time to reach the maximum response, $t_1$, simulated step-up responses can be compared using the mean response time:

$$MRT=\frac{\int_{t_0}^{t_1} t\Delta y(t)\,dt}{\int_{t_0}^{t_1}\Delta y(t)\,dt} \quad (10)$$

where $\Delta y=y_{max}-y(t)$ represents the amplitude of the dynamic response of $VO_{2p}$,$VO_{2A}$, $VO_{2m}$, or $UO_{2m}$.

For comparison of model outputs to experimental data, we relate model variables to measurable variables at the muscle level. From the model, we evaluate muscle oxygenation as:

$$StO_{2m}=\frac{4f_{bl}C_{Hb}S_{Hb}+f_{tis}C_{Mb}S_{Mb}}{4f_{bl}C_{Hb}+f_{tis}C_{Mb}} \quad (11)$$

$StO_{2m}$ is intended to reflect the volume averaged signal from both hemoglobin in blood and myoglobin in tissue. The volume fractions of blood and tissue are $f_{bl}=1/(1+f_b)=7\%$ and $f_{tis}=f_b/(1+f_b)=93\%$. The concentrations of hemoglobin in blood and myoglobin in tissue are $C_{Hb}$ and $C_{Mb}$. The averaged oxy-hemoglobin saturation is a weighted combination of hemoglobin in muscle arterioles, capillaries, and venules:

$$S_{Hb}=S_{art,m}\omega_{art}+\langle S_{cap,m}\rangle\,\omega_{cap}+S_{ven,m}\omega_{ven} \quad (12)$$

where $\omega_{art}$ (=20%), $\omega_{cap}$ (=15%), and $\omega_{ven}$ (=65%) are blood volume fractions in muscle. The averaged oxy-myoglobin saturation in muscle tissue is $S_{Mb}=\langle S_{tis}\rangle$. The spatially averaged saturations $S_{cap,m}\rangle$and $\langle S_{tis}\rangle$.are defined as:

$$\langle S_X\rangle=\frac{\int_0^{V_X} S_X\,dv}{V_X}(X=cap, mor\ tis) \quad (13)$$

The oxy-hemoglobin and oxy-myoglobin saturations are related to free $O_2$ concentrations in blood and tissue $S_{cap,m}(C_{mb}^F), S_{tis}(C_{tis}^F)$[15].

## Experimental data from a step change in work rate

Seven male African-American adolescents performed moderate intensity exercise (90% VT) on an electromagnetically-braked cycle ergometer. 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. Local muscle oxygen saturation time profiles, $StO_{2m}(t)$, of the right quadriceps vastus lateralis muscle were obtained with near infrared spectrometry (NIRS). Minute ventilation $V_E$ and pulmonary oxygen uptake $VO_{2p}$ were continuously monitored with a commercially available metabolic cart system [17]. Values of most model parameters and exercise variables have been determined and published previously[17,27]. $V_{A0}$, $\Delta V_A$ and $\tau_V$ were estimated by least-squares fitting of $V_A(t)$from the measured ventilatory response. Parameters $V_{max}$ and $\Delta Q_m$ for each subject were estimated by least-squares fitting of model output ($StO_{2m}(t)$) to its corresponding experimental measurement. The time constant of the muscle blood flow $\tau_Q$ was computed using data from the first minute of heart rate response to exercise. Using the estimated parameters, the multiscale model was validated by comparing its $VO_{2p}$ simulation with experimental data. Model simulations are intended to show the effect of changing

parameter values (e.g., $V_{max}$) on oxygen uptake and utilization at various scales, i.e., $UO_{2m}$, $VO_{2m}$, $VO_{2A}$, and $VO_{2p}$.

## Results

Simulations of the dynamic responses of $StO_{2m}$ and $VO_{2p}$ to a change in work rate (moderate intensity) from baseline are compared to experimental responses obtained in a typical normal human subject (Fig.2). For the same subject, model simulations of the dynamic responses of oxygen uptake ($VO_{2p}$, $VO_{2A}$, and $VO_{2m}$) and oxygen utilization rate ($UO_{2m}$) are compared (Fig. 3A). The dynamic responses of $UO_{2m}$ and $VO_{2m}$, which represent the processes at the cellular-tissue level, are nearly the same. These responses at the tissue-cells level differ from the responses of $VO_{2A}$ and $VO_{2p}$ that represent processes at the whole-body level. The whole-body responses displayed two phases: Phase I reflects oxygen transport from muscle to lungs, whereas Phase II reflects cellular metabolism of exercising skeletal muscle. The biphasic behaviors are more evident in the derivatives of their dynamic responses (Fig. 3B). The area under the derivative curve represents the amplitude of the dynamics response. A comparison of the derivative responses shows that the amplitude and dynamics of the two phases of $VO_{2p}$ are different to those of $VO_{2A}$. The model-predicted a ∼40% decrease in phosphocreatine concentration, while ATP concentration remained constant (Fig. 3C).

To characterize the metabolic dynamic response to exercise corresponding to seven human subjects, mean response times (MRT) of simulated oxygen uptake responses are compared in Table 1. The mean response times characterizing the pulmonary and alveolar oxygen uptake rates ($VO_{2p}$, $VO_{2A}$) were not significantly different ($P>0.05$). For $VO_{2p}$ and $VO_{2A}$, the MRT was also computed for Phase II alone to eliminate the effect of the circulatory transport delay. These mean response times –calculated without including Phase I of the response– were consistently reduced by ∼10%, with their values not been significantly different from those characterizing the $VO_{2m}$ and $UO_{2m}$ dynamic responses ($P>0.05$).

Model simulations show that different values of $V_{max}$, the maximal flux rate of oxidative phosphorylation, affect the dynamic exercise responses of $VO_{2p}$ and $VO_{2m}$ (Fig.4). With high $V_{max}$, an evident overshoot occurs in the $VO_{2p}$ response (Fig. 4A), but not in the $VO_{2m}$ response. Phase I does not change with $V_{max}$ . The effects of $V_{max}$ on MRT values for oxygen utilization and uptake responses are given in Table 2. With a higher $V_{max}$, the MRT values are lower.

## Discussion

A mathematical multiscale model that couples pulmonary gas exchange[27] in a multi-organ whole-body model to a whole body-tissue model of $O_2$ transport and cellular metabolism in skeletal muscle[15,17] was developed to study responses of oxygen uptake and cellular consumption to exercise. The corresponding energy demand due to exercise is represented by a step increase in ATP utilization. Cellular ATP homeostasis is maintained through oxidative phosphorylation and the reactions of $ATP_{ase}$ and CK. The model also includes explicit relationships between free and bound forms of $O_2$ that incorporate effects of hemoglobin and myoglobin in blood and skeletal muscle. To simulate experimental responses of human subjects, the maximal flux rate of oxidative phosphorylation $V_{max}$ and the blood flow increase $\Delta Q_m$ were estimated from measurements of muscle oxygenation during exercise[17]. The increase in cardiac output are assumed the same as $\Delta Q_m$ as Calbet et al.[28] showed that cardiac output and leg blood flow increased in parallel during incremental cycling exercise. Simulations with this model show the relationships between

$VO_{2p}$, $VO_{2A}$, $VO_{2m}$ and $UO_{2m}$ and the effect of $V_{max}$ on oxygen uptake/utilization dynamics.

The cellular respiration is regulated by feedback control from ADP and tissue oxygen concentrations. In the literature, several feedback control models have been proposed for the regulation of cellular respiration: (1) feedback control using a Michaelis-Menten relationship between oxidative phosphorylation and [ADP][29]; (2) higher-order feedback control from [ADP][30,31]; (3) dependence of oxidative phosphorylation on the free energy of ATP hydrolysis.[32] However, the experimental data available in the present study are not sufficient to address this issue. In the measurement range of Ref. [30] ([ADP] from 0.018 to 0.084 mM), the experimental data were equally well described by the Michaelis-Menten relationship and higher-order model. Therefore, we chose the approach that was successfully applied previously to *in vivo* study obtained by NMR spectroscopy.[29]

Parameters estimates, especially for $V_{max}$, are highly dependent on the type of compartmental model (lumped vs. distributed) used and on the value selected for working muscle volume. Lai et al. [17] used a lumped model and 49% of the whole body weight as the working skeletal muscle volume during cycling exercise. MRI measurements of body volumes show that the leg muscle volume is around 20% of the whole body weight[23]. In this study, we used a distributed model and a working muscle volume of 20% of the whole body weight. As a consequence, the estimated $V_{max}$ value in this study is 18.3±4 mM/min, which is much lower than the previously estimated value of 45±15 mM/min [17]. Model simulations of $StO_{2m}$ response to exercise corresponds closely with experimental data (Fig. 2A), but the predicted $VO_{2p}$ has a faster dynamics than the experimental data (Fig. 2B). The simulated $VO_{2p}$ response (Fig. 2B) indicates the presence of two phases, which are also evident for $VO_{2A}$ (Fig. 3B). Phase I reflects the effect of the circulatory transit time delay from skeletal muscle to lungs. The duration of Phase I in $VO_{2p}$ and $VO_{2A}$ simulations is similar to that (19±3 s) typically observed experimentally [25]. During moderate-intensity exercise, the simulated PCr concentration decreased 14mM, which agrees well with the [PCr] decrease of 30% obtained experimentally by McCreary et al [19].

Since direct measurement of $UO_{2m}$ is not readily available, it was estimated by simulation with our model that includes the main elements of cellular metabolism and energetics. The $UO_{2m}$ and $VO_{2m}$ kinetic responses to exercise displayed a monophasic behavior without any delay after exercise onset; in contrast, the $VO_{2p}$ and $VO_{2A}$ kinetic responses displayed a biphasic behavior that includes a transport lag. When the effect of this circulatory transit time delay (Phase I) was eliminated from the responses of $VO_{2p}$ and $VO_{2A}$, as is commonly done for the empirical analysis of the $VO_2$ kinetic response to exercise[25], the MRTs of $VO_{2p}$ and $VO_{2A}$ during Phase II were only 3s smaller than the MRTs computed from the entire kinetic response (Table 1). However, even though these results are, in this case, consistent with previous experimental studies demonstrating that $VO_{2m}$ and $VO_{2A}$ have similar dynamic responses to moderate exercise [9], our predicted $VO_{2p}$ has a faster dynamics comparing to the experimental data (Fig. 2B). This discrepancy may due to the limitation in our NIRS or $VO_{2p}$ measurements. Firstly, considering the heterogeneity in structure and perfusion in the working skeletal muscle, using the NIRS signal obtained from a local region with an uncertain volume to represent the $O_2$ saturation in the whole working muscle may be misleading. Secondly, our model assumed a constant volume of the alveolar space and didn't consider its change during exercise. But the $VO_{2p}$ experimental measurement included the alveolar gas store change due to the variation in its volume, which would slow down the $VO_{2p}$ dynamic response to exercise[5]. Finally, in this model, the permeability surface area coefficient (PS) in the working skeletal muscle was considered as a function of muscle blood flow[15]. PS coefficient was set to sufficiently high values to ensure enough oxygen supply to the working muscle. If the dynamics of PS change limits

the blood-tissue $O_2$ diffusion process at the onset of exercise, we would get a smaller $V_{max}$ estimated from the $StO_{2m}$ measurement. Specific experiments are needed to perform to quantify the muscle permeability surface area change during exercise. The advantage of our approach is that it provides a more general and mechanistic approach to investigating the dynamics of oxygen uptake at different biological scales. As a consequence, our mechanistic multiscale model –in contrast to empirical exponential fits– can be applied to many conditions under which the dissociation between pulmonary and muscle oxygen uptake may be significantly greater. For instance, when there is an oxygen transport limitation in the lungs compartment due to a less increase in alveolar permeability during exercise, which cause a decrease of the arterial $O_2$ partial pressure to 65 to 70 mmHg, the dynamics of the simulated $VO_{2p}$ and $VO_{2A}$ can be slowed down with a 10s increase in their MRT but no significant changes occur in the simulated dynamics of $VO_{2m}$ and $UO_{2m}$.

Model simulations quantify the relative changes of the oxygen uptake and utilization dynamic responses to exercise produced with different values of the maximal oxidative phosphorylation flux $V_{max}$ (Table 2). A 50% decrease in $V_{max}$, which represents the disease condition with mitochondria dysfunction, both the cellular and external respirations have been slowed down even with sufficient ventilation and perfusion. An 100% increase in $V_{max}$, which represents the fitness level of a subject, generates faster responses (i.e., MRT decreases) in $VO_{2p}$, $VO_{2A}$, $VO_{2m}$ and $UO_{2m}$ (Table 2). This is consistent with experimental studies that found trained subjects to have faster $VO_{2p}$ responses than untrained subjects during constant-load exercise[26]. Korzeniewski et al.[33,34] also proposed that an increase in the amount of mitochondrial proteins and an intensification of the parallel activation of ATP usage and ATP supply accelerate the oxygen-uptake kinetics at the onset of exercise. With higher $V_{max}$, a Phase II overshoot can occur in the oxygen uptake response, which is most prominent for $VO_{2p}$ and least prominent for $VO_{2m}$. No overshoot occurs in the $UO_{2m}$ response. Even with overshoot of the oxygen uptake response, the MRTs of $VO_{2p}$ and $VO_{2A}$ during Phase II are close to that of $VO_{2m}$. Experimentally, Koppo et al.[13] reported an overshoot in the $VO_{2p}$ response to moderate-intensity cycle exercise. This overshoot was interpreted as an indication of a variable ATP demand that is higher at the beginning of exercise. From model simulations, however, this overshoot can occur in the oxygen uptake responses even with a constant ATP demand which is imposed by the ATP turnover rate through $ATP_{ase}$ in the model. But the ATP turnover rate is very difficult to experimentally measure *in vivo*. When $V_{max}$ is increased, a temporary arterial hypoxemia happens at the onset of exercise with $\tau_Q$ and $\tau_V$ unchanged. The corresponding simulated alveolar $PO_2$ is normal (>90 mmHg). If both $\tau_Q$ and $\tau_V$ decreased by 50%, the overshoot in the $VO_{2p}$ disappeared. Powers et al. found that highly trained subjects could have exercise-induced hypoxemia.[35] A further experiment for the arterial $PO_2$ measurement is needed to indentify the origination of the overshoot signal (pulmonary vs. cellular level).

## Conclusion

A multiscale mathematical model was developed to distinguish responses of external and cellular respiration to exercise of moderate intensity. Simulation shows that the characteristic response times (MRT) of external and cellular respiration are similar even when a transit delay exists between tissue cells and the lungs. The results of our model shows that the $O_2$ transport processes from lungs to muscle are tightly coupled to provide enough $O_2$ for working skeletal muscle during exercise in normal subjects. Under abnormal conditions, the effect of $O_2$ transport limitation- occurring at different scale of the body - on internal to external respirations can be examined. Such results can be used for comparative quantitative analysis of the regulation of respiration in subjects suffering from abnormal function associated with disease states (e.g., chronic obstructive pulmonary disease, diabetes and congenital heart disease).

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## References

1. Barstow TJ, Mole PA. Simulation of pulmonary $O_2$ uptake during exercise transients in humans. J Appl Physiol. 1987; 63:2253–2261. [PubMed: 3436861]
2. Barstow TJ, Lamarra N, Whipp BJ. Modulation of muscle and pulmonary $O_2$ uptakes by circulatory dynamics during exercise. J Appl Physiol. 1990; 68:979–989. [PubMed: 2341363]
3. Bauer TA, Levi M, Reusch JEB, Regensteiner JG. Skeletal muscle Deoxygenation after the onset of moderate exercise suggests slowed microvascular blood flow kinetics in type 2 diabetes. Diabetes care. 2007; 30:2880–2885. [PubMed: 17675540]
4. Beaver WL, Lamarra N, Wasserman K. Breath-by-breath measurement of true alveolar gas exchange. J Appl Physiol. 1981; 51:1662–1675. [PubMed: 6798003]
5. Casaburi R, Weissman ML, Huntsman DJ, Whipp BJ, Wasserman K. Determinants of gas exchange kinetics during exercise in the dog. J Appl Physiol. 1979; 46:1054–1060. [PubMed: 468623]
6. Casaburi R, Spitzer S, Haskell R, Wasserman K. Effect of altering heart rate on oxygen uptake at exercise onset. Chest. 1989; 95:6–12. [PubMed: 2491802]
7. Di Prampero PE, Boutellier U, Pietsch P. Oxygen deficit and stores at onset of muscular exercise in humans. J Appl Physiol. 1983; 55:146–153. [PubMed: 6885564]
8. Drexler H, Piede U, Munzel T, Konig H, Funke E, Just H. Alterations of skeletal muscle in chronic heart failure. Circulation. 1992; 85:1751–1759. [PubMed: 1315220]
9. Grassi B, Poole DC, Richardson RS, Knight DR, Erickson BK, Wagner PD. Muscle $O_2$ uptake kinetics in humans: implications for metabolic control. J Appl Physiol. 1996; 80:988–998. [PubMed: 8964765]
10. Grassi B, Gladden LB, Samaja M, Stary CM, Hogan MC. Faster adjustment of $O_2$ delivery does not affect VO2 on-kinetics in isolated in situ canine muscle. J Appl Physiol. 1998; 85:1394–1403. [PubMed: 9760333]
11. Hayashi N, Ishihara M, Tanaka A, Yoshida T. Impeding $O_2$ unloading in muscle delays oxygen uptake response to exercise onset in humans. Am J Physiol. 1999; 277:R1274–R1281. [PubMed: 10564197]
12. Kingwell BA, Bradley SJ, Formosa M, McConell GK, Muhlmann M. Type 2 diabetic individuals have impaired leg blood flow responses to exercise. Diabetes care. 2003; 26:899–904. [PubMed: 12610056]
13. Koppo K, Whipp BJ, Jones AM, Aeyels D, Bouckaert J. Overshoot in $VO_2$ following the onset of moderate-intensity cycle exercise in trained cyclists. Eur J Appl Physiol. 2004; 93:366–373. [PubMed: 15503122]
14. Lador F, zabji Kenfack M, Moia C, Cautero M, Morel DR, Capelli C, Ferretti G. Simultaneous determination of the kinetics of cardiac output, systemic $O_2$ delivery, and lung $O_2$ uptake at exercise onset in men. Am J Physiol. 2006; 290:R1071–R1079.
15. Lai N, Dash RK, Nasca MM, Saidel GM, Cabrera ME. Relating pulmonary oxygen uptake to muscle oxygen consumption at exercise onset: in vivo and in silico studies. Eur J Appl Physiol. 2006; 97:380–394. [PubMed: 16636861]
16. Lai N, Syed N, Saidel GM, Cabrera ME. Muscle oxygen uptake differs from consumption dynamics during transients in exercise. Advances in Experimental Medicine and Biology: ISOTT XXIX. 2006
17. Lai N, Camesasca M, Saidel GM, Dash RK, Cabrera ME. Linking Pulmonary Oxygen Uptake, Muscle Oxygen Utilization and Cellular Metabolism during Exercise. Ann Biomed Eng. 2007; 35:956–969. [PubMed: 17380394]

18. Lai N, Saidel GM, Grassi B, Gladden LB, Cabrera ME. Model of oxygen transport and metabolism predicts effect of hyperoxia on canine muscle oxygen uptake dynamics. J Appl Physiol. 2007; 103:1366–1378. [PubMed: 17600157]
19. McCreary CR, Chilibeck PD, Marsh GD, Paterson DH, Cunningham DA, Thompson RT. Kinetics of pulmonary oxygen uptake and muscle phosphates during moderate-intensity calfexercise. J Appl Phsiol. 1996; 81:1331–1338.
20. Mettauer B, Zhao Q, Epailly E, Charloux A, Lampert E, Heitz-Naegelen B, Piquard F, Di Prampero PE, Lonsdorfer J. $VO_2$ kinetics reveal a central limitation at the onset of subthreshold exercise in heart transplant recipients. J Appl Physiol. 2000; 88:1228–1238. [PubMed: 10749812]
21. Nery LE, Wasserman K, Andrews JD, Huntsman DJ, Hansen JE, Whipp BJ. Ventilatory and gas exchange kinetics during exercise in chronic airways obstruction. J Appl Physiol. 1982; 53:1594–1602. [PubMed: 6818216]
22. Piiper J, Di Prampero PE, Cerretelli P. Oxygen debt and high-energy phosphates in gastrocnemius muscle of the dog. Am J Physiol. 1968; 215:523–531. [PubMed: 5670989]
23. Tolfrey K, Barker A, Thom JM, Morse CI, Narici MV, Batterham AM. Scaling of maximal oxygen uptake by lower leg muscle volume in boys and men. J Appl Physiol. 2006; 100:1851–1856. [PubMed: 16484361]
24. Wasserman K. Coupling of external to cellular respiration during exercise: the wisdom of the body revisited. Am J Physiol. 1994; 266:E519–E539. [PubMed: 8178973]
25. Whipp BJ, Ward SA, Lamarra N, Davis JA, Wasserman K. Parameters of ventilatory and gas exchange dynamics during exercise. J Appl Physiol. 1982; 52:1506–1513. [PubMed: 6809716]
26. Zhang Y, Johnson MC, Chow N, Wasserman K. The role of fitness on $VO_2$ and $VCO_2$ kinetics in response to proportional step increases in work rate. Eur J Appl Physiol. 1991; 63:94–100.
27. Zhou H, Saidel GM, Cabrera ME. Multi-organ system model of $O_2$ and $CO_2$ transport during isocapnic and poikilocapnic hypoxia. Respir Physiol Neurobiol. 2007; 156:320–330. [PubMed: 17188027]
28. Calbet JA, Gonzalez-Alonso J, Helge JW, Søndergaard H, Munch-Andersen T, Boushel R, Saltin B. Cardiac output and leg and arm blood flow during incremental exercise to exhaustion on the cycle ergometer. J Appl Physiol. 2007; 103:969–978. [PubMed: 17600155]
29. Vicini P, Kushmerick MJ. Cellular energetic analysis by a mathematical model of energy balance: estimation of parameters in human skeletal muscle. Am J Physio Cell Physiol. 2000; 279:213–224.
30. Jeneson JA, Wisemant RW, Westerhoff HV, Kushmerick MJ. The signal transduction function for oxidative phosphorylation is at least second order in ADP. J Biol Chem. 1996; 271:27995–27998. [PubMed: 8910406]
31. Cieslar JH, Dobson GP. Free [ADP] and aerobic muscle work follow at least second order kinetics in rat gastrocnemius *in vivo*. J Biol Chem. 2000; 275:6129–6134. [PubMed: 10692403]
32. Jeneson JA, Westerhoff HV, Brown TR, Van Echteld CJ, Berger R. Quasi-linear relationship between Gibbs free energy of ATP hydrolysis and power output in human forearm muscle. Am J Physio Cell Physiol. 1995; 268:1474–1484.
33. Korzeniewski B, Zoladz JA. Factors determining the oxygen consumption rate ($VO_2$) on-kinetics in skeletal muscles. Biochem J. 2004; 379:703–710. [PubMed: 14744260]
34. Korzeniewski B, Zoladz JA. Training-induced adaptation of oxidative phosphorylation in skeletal muscles. Biochem J. 2003; 374:37–40. [PubMed: 12741955]
35. Powers SK, Dodd S, Lawler J, Landry G, Kirtley M, Mcknight T, Grinton S. Incidence of exercise induced hypoxemia in elite endurance athletes at sea level. Eur J Appl Physiol. 1988; 58:298–302.

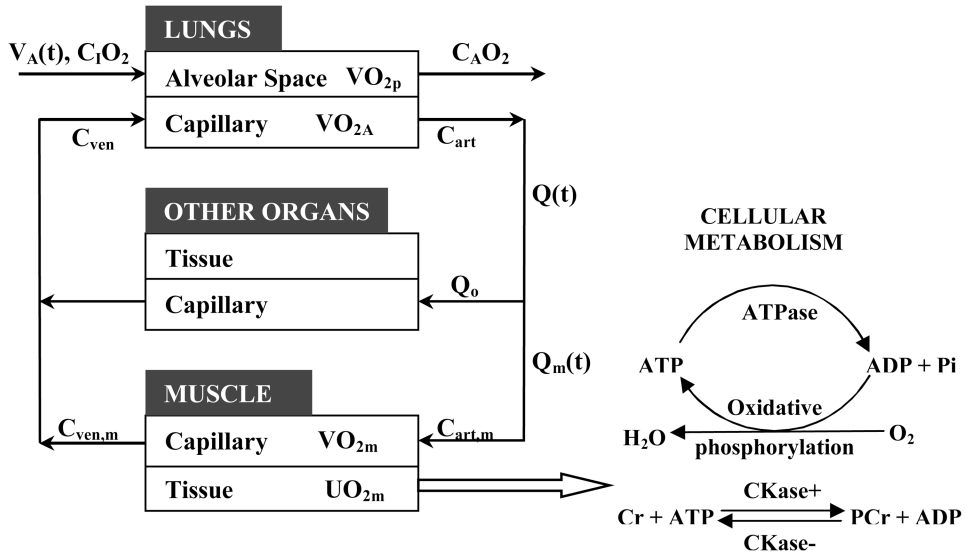


**Figure 1. Schematic representation of oxygen utilization in cell and transport between lungs and skeletal muscle**

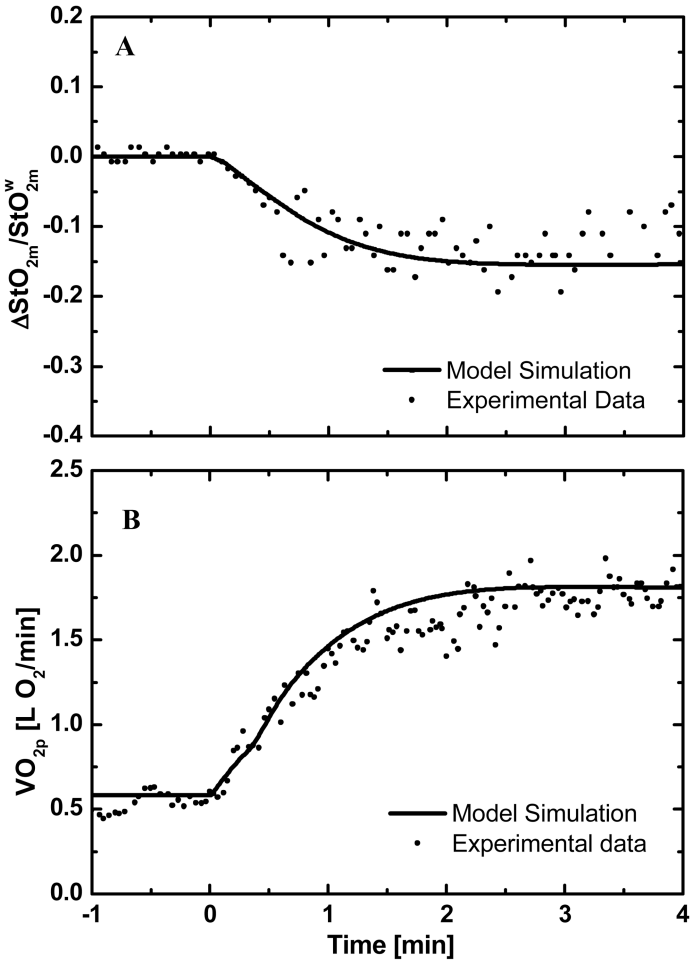


**Figure 2.**
Comparison of experimental and simulated responses of a representative subject from a warm-up steady-state to a moderate intensity exercise: (A) relative oxygen saturation in muscle and (B) pulmonary oxygen uptake.

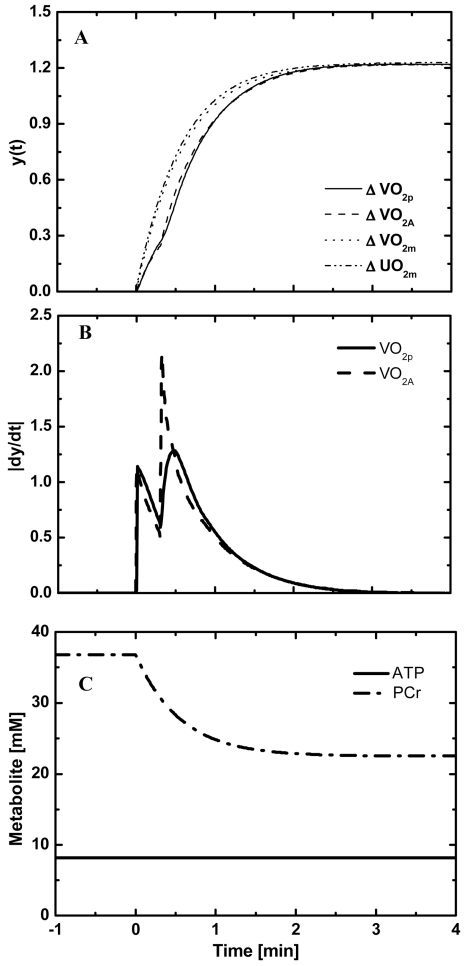


**Figure 3.**
(A) Comparison of oxygen uptakes at different scales of the body (B) Derivatives of pulmonary and alveolar blood oxygen uptakes, $VO_{2p}$ and $VO_{2A}$ (C) Simulation of PCr break down and ATP concentration of a representative subject from warm-up to moderate intensity exercise

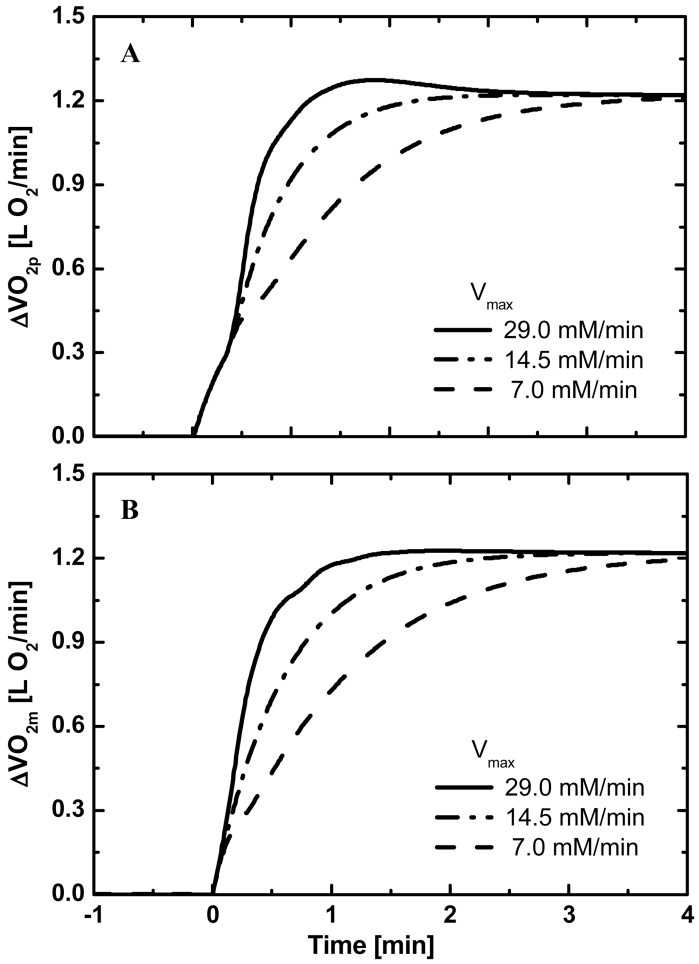


**Figure 4.**
Effects of the maximum oxidative phosphorylation flux rate $V_{max}$ on (A) Pulmonary oxygen uptake dynamics (B) Muscle oxygen uptake dynamics.

**Table 1**

Mean response time (MRT) of oxygen uptake and utilization responses to moderate exercise (n=7). The MRT within parentheses reflects Phase II only.

| MRT (s) | M1 | M2 | M3 | M4 | M5 | M6 | M7 | Mean±SD |
|---|---|---|---|---|---|---|---|---|
| $VO_{2p}$ | 25(19) | 34(31) | 27(23) | 28(23) | 27(23) | 33(29) | 24(19) | 28±3.8 (24±4.6) |
| $VO_{2A}$ | 24(19) | 35(33) | 28(25) | 29(25) | 28(26) | 34(31) | 24(20) | 29±4.3* (26±5.1) |
| $VO_{2m}$ | 20 | 34 | 26 | 25 | 26 | 33 | 24 | 27±4.6 |
| $UO_{2m}$ | 21 | 33 | 26 | 25 | 26 | 33 | 24 | 27±4.5 |

* Difference is significant at $P<0.05$ when comparing with muscle $O_2$ consumption ($UO_{2m}$) using paired t-test.

## Table 2

Effects of the maximum oxidative phosphorylation flux rate ($V_{max}$) on mean response time (MRT) of oxygen uptake and utilization responses to moderate exercise (M2). The MRT within parentheses reflects Phase II only.

| $V_{max}$ (mM/min) | MRT (s) | | | |
|---|---|---|---|---|
| | $VO_{2p}$ | $VO_{2A}$ | $VO_{2m}$ | $UO_{2m}$ |
| 7.0 | 60 (57) | 60 (57) | 57 | 55 |
| 14.5 | 34 (31) | 35 (33) | 34 | 33 |
| 29 | 23(17) | 22 (19) | 18 | 18 |