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NON-INVASIVE ESTIMATION OF METABOLIC FLUX AND BLOOD FLOW IN WORKING MUSCLE: EFFECT OF BLOOD-TISSUE DISTRIBUTION

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Abstract

Muscle oxygenation measurements by near infrared spectroscopy (NIRS) are frequently obtained in humans to make inferences about mechanisms of metabolic control of respiration in working skeletal muscle. However, these measurements have technical limitations that can mislead the evaluation of tissue processes. In particular, NIRS measurements of working muscle represent oxygenation of a mix of fibers with heterogeneous activation, perfusion and architecture. Specifically, the relative volume distribution of capillaries, small arteries, and venules may affect NIRS data. To determine the effect of spatial volume distribution of components of working muscle on oxygen utilization dynamics and blood flow changes, a mathematical model of oxygen transport and utilization was developed. The model includes blood volume distribution within skeletal muscle and accounts for convective, diffusive, and reactive processes of oxygen transport and metabolism in working muscle. Inputs to the model are arterial O_2 concentration, cardiac output and ATP demand. Model simulations were compared to exercise data from human subjects during a rest-to-work transition. Relationships between muscle oxygen consumption, blood flow, and the rate coefficient of capillary-tissue transport are analyzed. Blood volume distribution in muscle has noticeable effects on the optimal estimates of metabolic flux and blood flow in response to an exercise stimulus.

1. INTRODUCTION

For analysis of regulation mechanisms of oxygen homeostasis during exercise, dynamic measurements of pulmonary oxygen uptake (VO_2) by indirect calorimetry and of muscle oxygenation by NIRS are performed simultaneously.[1,2,3] These measurements have intrinsic limitations that can cause inaccurate evaluation of underlying tissue processes.[4] Specifically, estimates of metabolic flux and blood flow in response to exercise depend on factors that are not precisely known such as the local microvascular volume distribution and the oxygenated hemoglobin and myoglobin concentrations. To evaluate the effects of extra-vascular volume and blood volume distribution during exercise, a mathematical model was applied to quantify how these factors affect oxygen transport and utilization.[5,6,7] The mathematical model presented here is used to examine the effect of local muscle blood-tissue volume

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distribution on the responses of muscle oxygen saturation during exercise. Together with NIRS data, optimal estimates can be obtained of maximal metabolic flux (V_{max}) and blood flow increase (ΔQ) during exercise.[7] This model accounts for spatial and temporal distribution of oxygen concentration in tissue and between arterioles, capillaries and venules. Model simulations of the dynamic response of muscle oxygenation are compared with NIRS measurements of StO_2 from the vastus lateralis muscle during bicycle exercise in human subjects.[6]

2. METHODS

Model Development

The metabolic response of skeletal muscle to an exercise stimulus can be described by transport and metabolic processes associated with Oxygen, ATP, and PCr.[6,7] The processes of oxygen transport and utilization in muscle can be modeled as spatially distributed in blood and tissue.[7] The total muscle volume, $V_{mus}=V_{bl}+V_{tis}$, consists of (artery, capillary and venous) blood volume (V_{bl}) and extra-vascular muscle cells of tissue (V_{tis}). Total oxygen concentration ($C^T_{O_2,x}$) in blood (x=b) and in tissue cells (x=c) within the muscle is the sum of the free ($C^F_{O_2,x}$) and bound oxygen ($C^B_{O_2,x}$) concentrations, which are related by local equilibrium.[7] Total oxygen concentrations in the capillary blood, and in muscle cells vary with time (t) and tissue location as indicated by the cumulative muscle volume (v) from the arterial input v=0 to the venous output $v=V_{mus}$:

$$\frac{\partial C^T_{O_2,b}}{\partial t}=-\frac{Q}{f_{cap}}\frac{\partial C^T_{O_2,b}}{\partial v}+D_b\frac{\partial^2 C^T_{O_2,b}}{\partial v^2}-\frac{PS}{f_{cap}}(C^F_{O_2,b}-C^F_{O_2,c})\,0<v<V_{mus} \quad (1)$$

The first term on the right side represents convective transport of oxygen in the direction of blood flow Q in which f_{cap} is the ratio of capillary blood volume to total muscle volume; the second term represents axial dispersion characterized by an effective dispersion coefficient D_b; the third term represents transport between capillary blood and extra-vascular tissue, which depends on the permeability-surface area, PS. The dynamic, spatial distribution of total oxygen concentration in muscle cells of extravascular tissue is

$$\frac{\partial C^T_{O_2,c}}{\partial t}=D_c\frac{\partial^2 C^T_{O_2,c}}{\partial v^2}+\frac{PS}{f_{tis}}(C^F_{O_2,b}-C^F_{O_2,c})-\frac{uO_{2m}}{f_{tis}}\,0<v<V_{mus} \quad (2)$$

where D_c is an effective dispersion coefficient in muscle tissue; f_{tis} is the ratio of extra-vascular muscle tissue volume to total muscle volume. The oxygen utilization rate per unit volume of total muscle volume is proportional to the oxidative phosphorylation flux, $uO_{2m}=f_{tis}\,\varphi_{OxPhos}$. The metabolic reaction processes that involve oxidative phosphorylation are associated with the concentration dynamics of ATP and PCr. These cellular concentrations depend implicitly on spatially distributed oxygen transport flux between blood and muscle cells. The dynamic mass balances of cellular concentrations are related to metabolic fluxes:

$$\frac{\partial C_{ATP}}{\partial t}=-\phi_{ATPase}+\beta\phi_{OxPhos}+\Delta\phi_{CK};\frac{\partial C_{PCr}}{\partial t}=-\Delta\phi_{CK} \quad (3,4)$$

where φ_{ATPase} is the ATP utilization flux,β is the stoichiometric coefficient that relates oxidative phosphorylation to ATP production, and $\Delta\varphi_{CK}$ is the net forward flux of the creatine kinase reaction.

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The metabolic fluxes are functions of O_2, ADP, ATP, PCr, and Cr. However, the concentration pairs ATP-ADP and PCr-Cr are related by mass conservation of adenosine and creatine, respectively, whose total concentrations are constant: $C_A^T = C_{ADP} + C_{ATP}$ and $C_C^T = C_{Cr} + C_{PCr}$.

In response to a step increase in work rate from rest, the dynamic response of blood flow Q at exercise is assumed to be exponential:[7]

$$Q(t) = Q_0 + \Delta Q \left[1 - exp[-(t - t_0)/\tau_Q]\right] (t > t_0) \quad (5)$$

where Q_0 is the steady-state flow before exercise, $\Delta Q = Q_{SS} - Q_0$ is the increase in blood flow between steady states, τ_Q is the time constant of muscle blood flow, and t_0 is the time at the onset of exercise. Also, associated with blood flow increase in response to exercise, there is an effective increase in the rate coefficient of capillary-tissue transport:

$$PS(t) = PS_0 + \Delta PS\,[1 - exp[-(Q - Q_0)/q_C]]\,(Q > Q_0) \quad (6)$$

where PS_0 is the steady-state rate coefficient before exercise, ΔPS is the increase in the rate coefficient, Q_0 is the steady-state blood flow, and q_C is an arbitrary parameter.[6]

For comparison of oxygen responses to exercise from model simulations and experimental data, the simulated muscle oxygen saturation, StO_2, is intended to reflect the muscle volume distribution in the region of the NIRS measurement (Fig. 1a)

$$StO_2 = \frac{f_{bl} C_{HbO_2} + C_{MbO_2} f_{tis}}{C_{Hb} f_{bl} + C_{Mb} f_{tis}} \quad (7)$$

where f_{bl}, f_{tis} are the volume fractions of blood and extravascular (cells and interstitial fluid) in muscle ($f_{bl}+f_{tis}=1$); C_{Hb}, C_{Mb} are the total concentrations of hemoglobin in blood and myoglobin in tissue. The total composite oxyhemoglobin in blood and oxymyoglobin concentrations in tissue is defined as:

$$C_{HbO_2} = C_{art}^B W_{art} + \langle C_{cap}^B \rangle W_{cap} + C_{ven}^B W_{ven}, C_{MbO_2} = \langle C_{tis}^B \rangle W_{tis} \quad (8,9)$$

where C_{art}^B and C_{ven}^B are oxyhemoglobin concentrations in red blood cells of arteries and veins; $\langle C_{cap}^B \rangle$ and $\langle C_{tis}^B \rangle$ are volume-averaged capillary and tissue concentrations. Since these concentrations are defined with respect to different domain volumes, volume weighting fractions (W_{art},W_{ven},W_{cap},W_{tis}) are introduced. W_{tis} is the ratio of myocyte volume to total tissue volume. In domain X (art,cap,ven) the fraction W_X is the ratio of blood cell volume to total blood volume so that $W_{art}+W_{ven}+W_{cap}=Hct$. Furthermore, we can scale these ratios so that $\omega_{ar} + \omega_{cap} + \omega_{ven} = 1$, where $\omega_X = W_X/Hct$.

Model simulation and parameter estimation

Numerical solution of the partial differential equations is based on the method of lines. The spatial derivatives are discretized so that the model consists of a set of ordinary differential-difference equations. Parameter values of ΔQ and V_{max} were estimated by comparing simulations of StO_2 evaluated by Eq. 7 with experimental measurement of using a least-squares (Φ) objective function.[6] The data, obtained from an experiment with a normal human subject, are typical of responses measured by NIRS for a step response to moderate intensity exercise from a warm-up steady state.[5,6] The transport processes (Eqs. 1 and 2) depend on the muscle blood composition and distribution (f_{bl},ω_{cap}) in which $f_{cap}=f_{bl}\omega_{cap}$

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and (f_{tis}=1-f_{bl}). In these equations that relate to the whole muscle, the same parameter values for muscle composition (Table 1) were used for all simulations. NIRS measurements for StO_2 depend on blood composition and distribution parameters (f_{bl}, ω_{art}, ω_{cap}, ω_{ven}) might have a range of values associated with the working muscle (e.g., Table 1). Simulations with these parameter values affect the oxygen saturation model (Eq. 7). Values of all other model parameters were the same as those determined previously.[5,6,7]

3. RESULTS

Muscle blood volume distribution and ΔPS affect optimal estimates of V_{max} and ΔQ from model simulations of StO_2 data (Fig. 1a). This was quantified by the minimum objective function (Φ), i.e., sum of square differences, which varied by less than 1% for the range of parameter values in Table 1. The StO_2 response depends on the relative contributions of oxyhemoglobin C_{HbO2} and oxymyoglobin C_{MbO2}. In these simulations, the absolute concentration of C_{HbO2} at steady-state warm up was 4 times greater than that of C_{MbO2}. From warm up to exercise steady states, the C_{HbO2} decreases 7 times more than C_{MbO2}. Blood composition and distribution (f_{bl}, ω_{cap}, ω_{ven}) in working muscle affected the optimal estimates of V_{max} (Fig. 1b) and ΔQ. When f_{bl} increased from 2% to the reference level of 7%, the estimated values of V_{max} decreased by 14% while ΔQ increased by 25%. When f_{bl} increased from 7 to 15% the estimated values of V_{max} decreased by 7% while ΔQ increased by 20%. Over the entire range of blood distribution parameters (ω_{ven}, ω_{ven}) in Table 1, estimates of V_{max} and ΔQ changed less than 4%.

4. DISCUSSION

Non-invasive, simultaneous measurements[1,2,3] of pulmonary oxygen uptake by indirect calorimetry and of muscle oxygenation by NIRS provide the database for analyzing regulation mechanisms of oxygen homeostasis during exercise. These measurements combined with biophysically based mathematical models can be used to estimate parameters that are essential in quantifying various factors that affect oxygen transport and utilization during exercise.[5,6,7]

The optimal estimation of key muscle parameters requires comparison of model simulations to measured NIRS signals, which depend on blood volume fraction and its distribution in the muscle region. Several confounding aspects must be addressed to interpret the NIRS signal including (a) Hb absorbance within the blood (arterial, capillary, and venous) is a summed signal; (b) Oxygenation concentration in blood changes continuously with location with the capillary bed from arterial to venous blood. (c) The concentrations of bound oxygen (C_{HbO2}, C_{MbO2}) have different values and responses to exercise depending on the rates of oxygen transport (convection and diffusion) and utilization.

Analysis of several confounding aspects of the data requires a mathematical model that describes the spatial variation of oxygen transport in muscle in which (arterial, capillary, venous) blood and tissue are distinguished and the related dynamics of cellular metabolism. Furthermore, the model must be able to simulate the dynamic response to exercise, which requires incorporation of muscle blood flow dynamics, $Q(t)$, and the flow dependence of capillary-tissue O_2 transport, $PS(Q)$. Finally, the model must simulate the dependence of StO_2 on the relative concentrations of (C_{HbO2}, C_{MbO2}) and volume fraction of blood in muscle (f_{bl}). With a variety of model parameter values, simulations of StO_2 agree closely with data (e.g., Fig. 1a). To determine how well V_{max} and ΔQ can be estimated from such sparse data with many unknown parameters, a sensitivity analysis was performed in which the effect of blood tissue composition on these estimates was investigated. The responses of C_{HbO2} and C_{MbO2} to exercise depend on blood composition and distribution (f_{bl}, ω_{cap}, ω_{ven}).

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These affect StO_2 and estimation of V_{max} (Fig. 1b) and ΔQ. Associated with an increased f_{bl}, (a) StO_2 responded faster, (b) estimated V_{max} was lower, and (c) estimated ΔQ was higher. Changes of f_{bl} in the physiological range (7–15%) had a small effect on the estimation of V_{max} (7%) and a larger effect on ΔQ (20%).

The accuracy of model predictions is limited by uncertainties of blood tissue composition, blood flow, and permeability-surface area dynamics. Thus, future studies are needed to improve the estimation of structural and functional parameters affecting oxygen transport and metabolism during exercise. These studies require advances in NIRS technology in combination with optimal experimental design and mathematical modeling.[8,9] More detailed analysis of NIRS signals could lead to better absolute values of C_{HbO2} and C_{MbO2}[10,11] and blood volume distribution in working muscle. Although the mathematical model applied in this study incorporated the effects of blood volume distribution, the next level of investigation requires a model that distinguishes active and inactive muscle as well as heterogeneities of blood flow and O_2 utilization.[12] These developments are important for quantitative understanding of pathological alterations of oxygen transport and metabolism in subjects with diabetes and vascular disease.[13,14]

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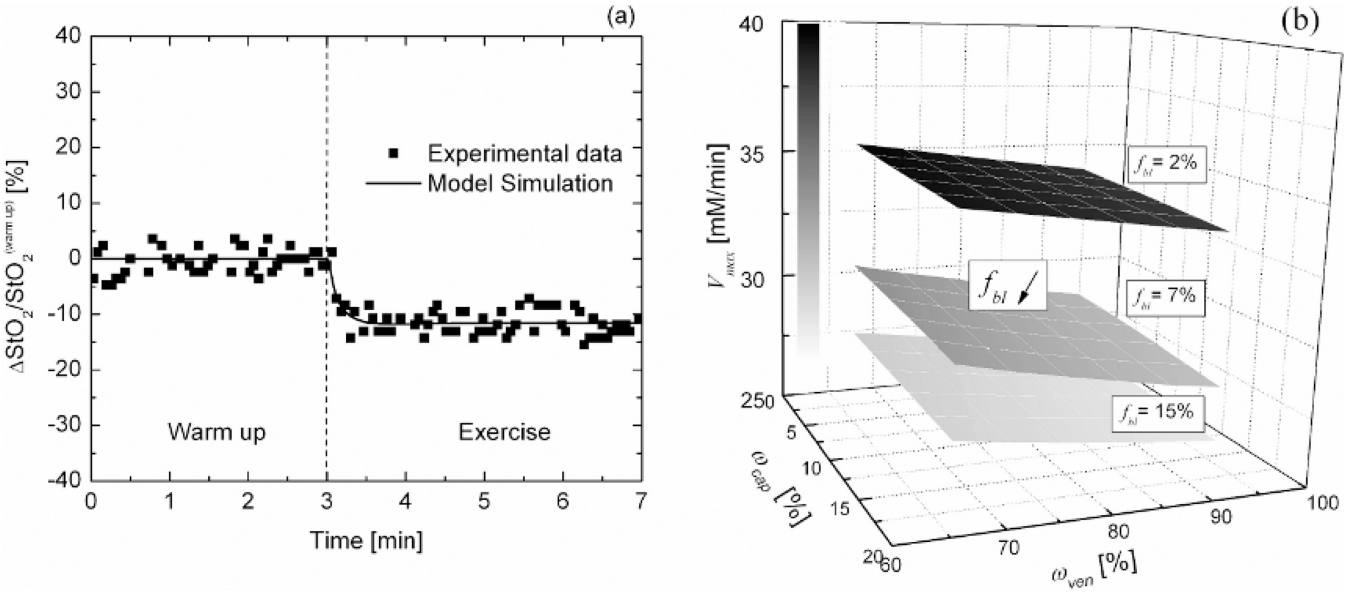

Figure 1.

(a) Dynamic response of StO_2 to a step change in work rate from warm up to moderate intensity exercise. Simulations of StO_2 are obtained assuming the NIRS muscle region volume composition to be the same as that of the whole muscle; (b) Effect of blood volume composition (f_{bl}) and its distribution within the muscle region investigated by NIRS (ω_{cap}, ω_{ven}) on parameter estimation of V_{max} (ΔPS=600 L L^{-1} min^{-1}).

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Table 1

Blood composition and distribution in the whole working muscle volume (V_m=10L) and within a local (NIRS) region.[3] Note that $\omega_{art}=1-\omega_{cap}-\omega_{ven}$.

Muscle Region	f_{bl}(%)	ω_{cap}(%)	ω_{ven}(%)
Whole muscle	7	15	75
Local (NIRS)	2–15	5–20	65–90