A Validated and Optimised Model Linking Muscle and Pulmonary Oxygen Uptake Kinetics

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Introduction

The dynamics of pulmonary oxygen uptake ($\dot{V}O_2$) at the start of exercise (i.e. the rate with which $\dot{V}O_2$ achieves a new steady-state value) reflect the combined response of the ventilatory, circulatory and neuromuscular systems to transport and utilise oxygen. These dynamics therefore provide a powerful non-invasive tool for monitoring the effectiveness of physiological systems integration in health and disease [1,2].

Muscle $\dot{V}O_2$ ($\dot{V}O_{2m}$) increases approximately mono-exponentially (described by a time-constant, τ) to a step change in energy demand (i.e. external power output). However, $\dot{V}O_{2m}$ kinetics are dissociated from those measured at the lung (alveolar $\dot{V}O_2$; $\dot{V}O_{2A}$) due to the intervening capacitances and dynamics of the circulation, resulting in biphasic $\dot{V}O_{2A}$ response kinetics [3] – see figure 1a. Nevertheless, a simple computational model [4] and direct measurements [5,6] describing the effects of the circulatory system on $\dot{V}O_{2m}$ and $\dot{V}O_{2A}$ dissociation suggest that, in health, phase II $\tau\dot{V}O_{2A}$ provides a reasonable estimate of $\tau\dot{V}O_{2m}$ (to within ~10%). This assumption, however, may not be true for subjects with congestive heart failure or chronic obstructive pulmonary disease [7]. We were therefore interested in updating, validating and optimising a computational model [4] that determines the influence of the circulatory structure on these parameters, to better understand the coupling, or not, of $\tau\dot{V}O_{2A}$ to $\tau\dot{V}O_{2m}$.

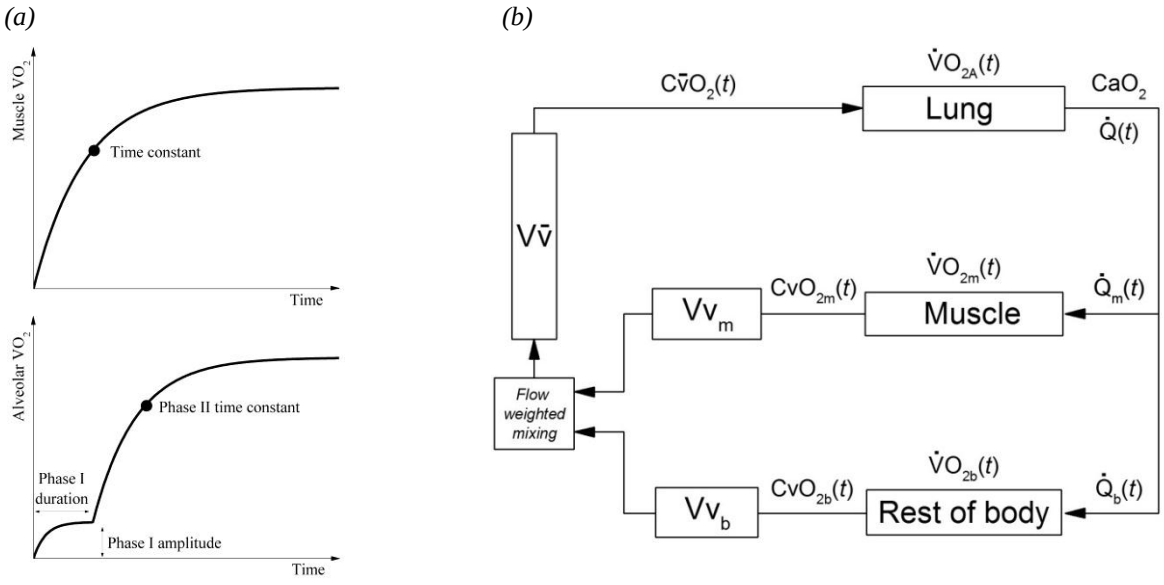

Figure 1. *(a)* Representations of $\dot{V}O_{2m}$ (top) and $\dot{V}O_{2A}$ (bottom) in response to a step increase in work rate. $\dot{V}O_{2m}$ has a mono-exponential response described by a single time constant, while the circulatory system causes the resultant $\dot{V}O_{2A}$ to have a biphasic response described by a phase I duration and amplitude and a phase II time constant. *(b)* Schematic of the multi compartment model (MCM). See [4] and Methods for details. CaO_2 and CvO_2, arterial and venous oxygen concentrations; Vv, venous volume; subscript 'b', body compartment; other abbreviations as described in text.

Methods

$\dot{V}O_{2m}$ (by direct Fick) and muscle blood flow ($\dot{Q}_m$; by thermodilution) were measured on transition from unloaded to 183 ± 20 W cycle ergometry (published in [5]). Baselines and time constants obtained from exponential fits to these data were used as inputs for a model with a single 3 l venous volume (SCM; see [4] for details) and an optimised multi-compartment model (MCM; see figure 1b). Model output was a predicted

$\dot{V}O_{2A}$. We introduced into the MCM: (i) venous volumes draining the exercising muscle and the rest of the body, and one carrying mixed-venous blood to the lung, with total venous volume constrained to be between 2.5 and 4.0 L; (ii) exercise-induced dynamic alterations in $\dot{V}O_2$ and $\dot{Q}$ in the body compartment; (iii) arterial O_2 concentration, $\Delta\dot{V}O_2/\Delta W$ and the $\dot{Q}/\dot{V}O_2$ relationship derived from experimental data, rather than from estimates; and (iv) a biphasic time course for $\dot{Q}_m$ [8] where this improved the model output.

Optimisation of the MCM was carried out by varying the sizes of the three venous volumes (with total venous volume constrained to be between 2.5 and 4.0 l), on a subject-by-subject basis, until the "kinetic error" between model-predicted and experimental breath-by-breath $\dot{V}O_{2A}$ was minimised. This error was calculated as the weighted sum of the normalised absolute differences in phase I duration ($TD_{\phi I}$), phase I amplitude ($\Delta_{\phi I}$, as a percentage of the overall $\dot{V}O_{2A}$ response) and the phase II time constant ($\tau_{\phi II}$):

$$\text{Kinetic Error} = 0.25\left(\frac{|TD_{\phi I,mod} - TD_{\phi I,exp}|}{SD_{TD}}\right) + 0.25\left(\frac{|\Delta_{\phi I,mod} - \Delta_{\phi I,exp}|}{SD_{\Delta}}\right) + 0.5\left(\frac{|\tau_{\phi II,mod} - \tau_{\phi II,exp}|}{SD_{\tau}}\right), \quad (1)$$

where the subscripts 'mod' and 'exp' signify model and experimental results respectively, and SD is the standard deviation of the model-experiment difference across all venous volume permutations of the model.

Results

Experimental $\dot{V}O_{2A}$ kinetics were (mean ± SD): $TD_{\phi I}$ = 17.5 ± 1.8 s, $\Delta_{\phi I}$ = 24.7 ± 5.7 % and $\tau_{\phi II}$ = 18.4 ± 4.3 s. The SCM-predicted $\dot{V}O_{2A}$ kinetics did not quite match experimental values; although $\Delta_{\phi I}$ (26.4 ± 5.3%) and $\tau_{\phi II}$ (22.0 ± 12.7 s) were not significantly different from experiment, the $TD_{\phi I}$ (15.3 ± 1.5 s) was significantly different (paired *t*-tests, p = 0.41, 0.51 and 0.004 respectively). The mean SCM kinetic error was 2.19 ± 3.47.

The optimised MCM (including a biphasic $\dot{Q}$ response for subject 6) with separate muscle, body and mixed-venous volumes of 0.6 ± 1.5, 0.1 ± 0.2 and 2.3 ± 1.1 l respectively (a total venous volume of 3.1 ± 0.6 l) significantly reduced kinetic error in all subjects to 1.41 ± 2.27 (Wilcoxon signed-rank test, p = 0.04) – see figure 2. All MCM kinetic parameters matched experimental values, with $TD_{\phi I}$ = 17.2 ± 6.3 s, $\Delta_{\phi I}$ = 25.9 ± 3.8 % and $\tau_{\phi II}$ = 20.5 ± 7.9 s (paired *t*-tests, p = 0.90, 0.41 and 0.51 respectively), thus validating our updated and optimised model.

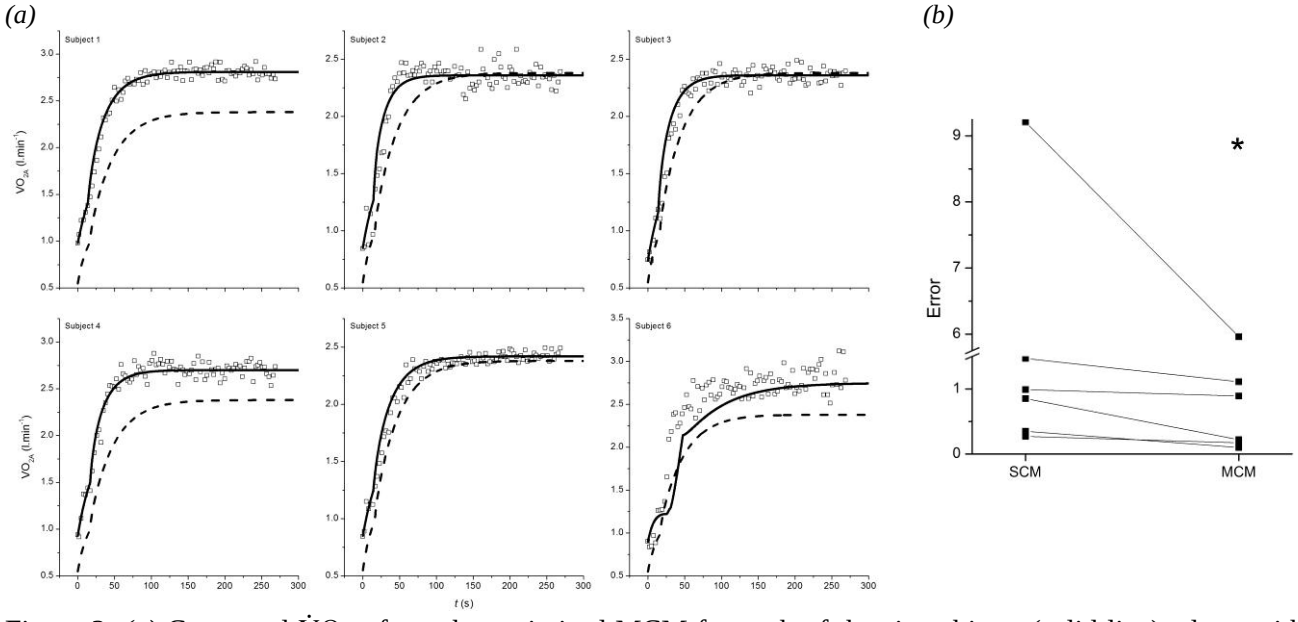

Figure 2. *(a)* Computed $\dot{V}O_{2A}$ from the optimised MCM for each of the six subjects (solid line), along with experimentally-measured breath-by-breath $\dot{V}O_{2A}$ (squares) and $\dot{V}O_{2A}$ from the original SCM as published in [4] for a 183 W work rate step (dashed lines). *(b)* Error is significantly reduced for all subjects in the updated and optimised MCM. * = $p < 0.05$ vs. SCM.

Conclusions

These data update, optimise and validate, against experimental measurements, a computational model linking the kinetics of $\dot{V}O_{2m}$ and $\dot{V}O_{2A}$. Distributing blood between three venous vascular compartments and allowing $\dot{Q}$ and $\dot{V}O_2$ to change in the body compartment improved the accuracy with which the model was able to reproduce experimentally-determined $\dot{V}O_{2A}$ kinetics – particularly in those subjects with divergent muscle and lung $\dot{V}O_2$ kinetics. This suggests that both the structure and dynamics of the circulation should be accounted for when interpreting the alveolar expression of $\dot{V}O_{2m}$ dynamics.

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