A validated model of oxygen uptake and circulatory dynamic interactions at exercise onset in humans

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Benson AP, Grassi B, Rossiter HB. A validated model of oxygen uptake and circulatory dynamic interactions at exercise onset in humans. J Appl Physiol 115: 743–755, 2013. First published June 13, 2013; doi:10.1152/japplphysiol.00184.2013.—At the onset of muscular exercise, the kinetics of pulmonary O2 uptake (V˙O2P) reflect the integrated dynamic responses of the ventilatory, circulatory, and neuromuscular systems for O2 transport and utilization. Muscle O2 uptake (V˙O2m) kinetics, however, are dissociated from V˙O2P kinetics by intervening O2 capacitances and the dynamics of the circulation and ventilation. We developed a multicompartment computational model (MCM) to investigate these dynamic interactions and optimized and validated the MCM using previously published, simultaneously measured V˙O2m, alveolar O2 uptake (V˙O2A), and muscle blood flow (Q˙m) in healthy young men during cycle ergometry. The model was used to show that 1) the kinetics of V˙O2m during exercise transients are very sensitive to preexercise blood flow distribution and the absolute value of Q˙m, 2) a low preexercise Q˙m exaggerates the magnitude of the transient fall in venous O2 concentration for any given V˙O2m kinetics, necessitating a tighter coupling of Q˙m/V˙O2m (or a reduction in the available work rate range) during the exercise transient to avoid limits to O2 extraction, and 3) information regarding exercise-related alterations in O2 uptake and blood flow in nonexercising tissues and their effects on mixed venous O2 concentration is required to accurately predict V˙O2A kinetics from knowledge of V˙O2m and Q˙m dynamics. Importantly, these data clearly demonstrate that V˙O2A kinetics are nonexponential, nonlinear distortions of V˙O2m kinetics that can be explained in a MCM by interactions among circulatory and cellular respiratory control processes before and during exercise.

AT THE ONSET OF MUSCULAR EXERCISE, the kinetics of pulmonary O2 uptake (V˙O2P) reflect the integrated dynamic responses of the ventilatory, circulatory, and neuromuscular systems for O2 transport and utilization (42, 46). As such, V˙O2P kinetics are strongly related to state of health [V˙O2P kinetics are slowed in chronic heart failure (CHF) and chronic obstructive pulmonary disease (40, 51)], fitness [V˙O2P kinetics are accelerated in endurance-trained athletes and slowed in the elderly (1, 29)], and exercise tolerance (38). In addition, V˙O2P kinetics in CHF disease (40, 51), fitness (V˙O2P kinetics are accelerated in chronic heart failure (CHF) and chronic obstructive pulmonary disease (40, 51)), and exercise tolerance (38), and subsequently, muscle O2 uptake (V˙O2m) is slow compared with other bioenergetic reactions and is determined by a control process that is close to first order in vivo (2, 47; cf. 56). V˙O2m kinetics [described by a time constant (τ)], however, are dissociated from V˙O2P by intervening O2 capacitances and the dynamics of the circulation and ventilation. While algorithms exist to account for dynamic changes in pulmonary O2 stores and calculate alveolar O2 uptake (V˙O2A) from V˙O2P (6, 11), circulatory dynamics distort the profiles of myocyte O2 extraction in transit to the lung. The result is a biphasic V˙O2A response (52) that contains a nonlinearly altered variant of the original V˙O2m dynamic (24).

Computational models integrating circulatory and respiratory dynamics (3, 5, 15, 24, 32, 33, 57–59) have proven extremely useful in elucidating the mechanisms underlying these O2 uptake (V˙O2) kinetic distortions. Barstow et al. (3) developed a relatively simple, but highly effective, three-compartment model composed of the pulmonary system, the exercising muscle, and a lumped circulation for the rest of the body linked by arterial and venous circulations (Fig. 1A) to examine the effects of the circulatory system dynamics on V˙O2A. This model demonstrated how circulatory and respiratory dynamics can interact to generate the phase I (“cardiodynamic”) and phase II (“fundamental”) V˙O2A kinetic profiles in humans (52). It also demonstrated, and contrary to suggestions at the time (12, 26), that phase II τV˙O2A closely reflected τV˙O2m (to within ±2 s) under conditions where venous volume (Vv), cardiac output (Qa) dynamics, muscle blood flow (Qm), and V˙O2m dynamics were set to values expected for healthy young subjects. While direct measurements of V˙O2m and V˙O2A during cycling (21), or V˙O2m and V˙O2P during knee extensor exercise (28, 31), support this theory on average, 60% of the observations from individual subjects found that V˙O2m and V˙O2A (or V˙O2P) were kinetically dissociated—phase II V˙O2A (or V˙O2P) kinetics being >10% faster or slower than V˙O2m kinetics in vivo (46). Indeed, recent reports suggest kinetic distortions between muscle and lung of ∼25–35% on average (20, 24).

This study therefore aimed to identify the physiological process(es) required to bring about these kinetic dissociations. We used an optimized computational model, based on the original model of Barstow et al. (3), to probe the roles of 1) the dynamics of exercise-induced changes in V˙O2 and blood flow (Q) in the nonexercising tissues (V˙O2b and Qb) (2), 2) the V˙O2m and Q˙m dynamics of the model (15, 3) changes in the skeletal muscle gas exchange; oxygen uptake kinetics; blood flow; computational modeling; skeletal muscle

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Fig. 1. A: schematic of the single-compartment model (SCM) of Barstow et al. (3) that links muscle and rest-of-body compartments via a single venous volume (Vv) to the pulmonary circulation. Muscle and body venous effluents are mixed in a flow-weighted manner instantaneously on leaving their respective compartments before traveling through a “mixed” Vv to the lung. Flow in this mixed Vv (Vv,m) is determined by cardiac output (Qm). B: schematic of the multicompartment model (MCM), where muscle and body venous effluents travel down separate Vv (Vv,m and Vv,b, respectively) before flow-weighted mixing occurs. The MCM was developed and optimized using experimental data of Grassi et al. (21). (Default parameter values for the SCM and MCM are given in Table 1.) See Glossary for definition of abbreviations.

**Glossary**
- **Cao2**: Arterial O2 concentration
- **Cvo2**: Venous O2 concentration
- **Cvo2m**: Venous O2 concentration in the blood draining the muscle compartment
- **Cvo2b**: Venous O2 concentration in the blood draining the body compartment
- **CvO2**: Mixed venous O2 concentration
- **Q**: Blood flow
- **Qb**: Blood flow in nonexercising tissue
- **Qm**: Blood flow in muscle
- **Qout**: Cardiac output
- **f**: Time
- **TD**: Time delay
- **TDAI**: Phase I duration
- **Vo2**: O2 uptake
- **Vo2A**: Alveolar O2 uptake
- **Vo2b**: O2 uptake in nonexercising tissue
- **Vo2m**: O2 uptake in muscle
- **Vo2p**: Pulmonary O2 uptake
- **Vb**: Blood volume
- **Vv**: Venous volume
- **Vvm**: Mixed venous volume
- **Vv,b**: Venous volume in nonexercising tissue
- **Vv,m**: Venous volume in muscle
- **W**: Work rate
- **ΔI**: Phase I amplitude
- **τ**: Time constant
- **ΦI**: Phase I
- **ΦII**: Phase II

**METHODS**

**Experimental data.** The computational model developed here was validated and optimized against the only existing experimental data where both VO2m and VO2A kinetics were determined during cycle ergometry (21). Briefly, six healthy male competitive or amateur bicycle racers (means ± SD: 22.8 ± 4.4 yr of age, 1.81.0 ± 4.2 cm, 73.7 ± 6.1 kg body wt, and 4.35 ± 0.46 l/min or 59.1 ± 5.3 ml·kg⁻¹·min⁻¹ maximum VO2) performed five identical exercise transitions from unloaded pedaling (for 4–6 min) to moderate-intensity constant power output (for 5 min) on a cycle ergometer (Monark, Sweden). The power output was 183 ± 20 W, which corresponded to ~50 W less than each individual’s estimated lactate threshold determined from a previous incremental test to the limit of tolerance. Each moderate-intensity repetition was separated by ≥30 min of rest to reestablish baseline conditions. During all tests, VO2A was calculated breath-by-breath using an OUS system (Consentius Technologies, Sandy, UT), with the inspired and expired flows measured by a pneumotachograph (Fleisch no. 3) and gas concentrations measured by a mass spectrometer (model MGA 1100, Perkin-Elmer, Waltham, MA). During three of the constant-power tests, Qm was determined by thermodilution in the femoral vein of one leg over discrete 3-s time intervals throughout the transient. During the other two constant-power tests, 3- to 4-ml samples of arterial (radial artery) and venous (femoral vein) blood were drawn anaerobically at rest and approximately every 5–8 s during the transient for measurement of PO2, PCO2, pH, O2 saturation, and Hb concentration by a gas analyzer and CO oximeter (models IL1306 and IL282, Instrumentation Laboratories). VO2 of one leg was then calculated from the Fick principle at discrete time intervals corresponding to the timing of the blood samples and doubled for the VO2m of two legs. Data for each subject were time-aligned and averaged over the repetitions. All equipment, calibrations, and measurements are described in detail by Grassi et al. (21).

**Fitting the experimental data.** The original presentation of Grassi et al. (21) did not report the individual values for VO2A phase I amplitude (ΔIφI), phase I duration (TDφI), and phase II τ, which are required for the model optimization procedures (see below). Therefore, all VO2A responses were refitted to estimate these parameter values for each participant. To ensure consistency between variables, the Qm and VO2m responses were also refitted using the same method. The fitting procedure involved use of the Levenberg-Marquardt algorithm to minimize the sum of squares between the fitting function and the
Experimental data (44). VO_{2m} and Q_{m} data during the exercise step were fit with a monoeponential function of the form

\[ y(t) = y_0 + \Delta y[1 - e^{-\tau t}] \]  

where \( y(t) \) is the variable of interest, \( t \) is time, \( y_0 \) is the value of \( y \) at \( t = 0 \) s (i.e., the baseline value), \( \Delta y \) is the steady-state increase in the variable above baseline during the exercise step, and \( \tau \) is a time constant. Baseline values were determined during the final minute of unloaded pedaling (21), and steady-state exercise values were calculated from the mean of each measurement beginning at four time constants after the start of exercise (or after the phase I-to-phase II transition for VO_{2m} data) until the end of exercise. The direct Fick method for VO_{2m} calculation at exercise onset in humans results in a small time delay (TD) between the onset of exercise and the initial increase in VO_{2m} (21). This may be due to the presence of a “true” TD because of non-first-order behavior in oxidative phosphorylation (56) and/or the influence of transit delays between muscle capillaries and the blood sampling site (2). In the present study, therefore, VO_{2m} or Q_{m} data that did not increase immediately at exercise onset were omitted for the purposes of fitting, and the start of exercise ( \( t = 0 \) s) was taken as the time when the variable began to increase. For four subjects this corresponded to the first data point after exercise onset, and for two subjects two data points were removed. The effect is to assume that VO_{2m} kinetics were first order and to ignore a negligible component (<2%) of the total venous blood capacitance between the muscle capillary and the blood sampling site in the femoral vein.

For VO_{2A} data from phase I were removed (54) and phase II was fit with an equation of the form

\[ y(t) = y_0 + \Delta y[1 - e^{-(t - \delta)}] \]  

where \( \delta \) is a TD. Note that this TD is not the VO_{2A} phase I duration but, rather, the extrapolation of the exponential back to the baseline value. To determine VO_{2A} phase I amplitude and duration, Eq. 1 was fit to the isolated phase I data and the intercept of the phase I and II fits was taken as the end of phase I, with the amplitude of phase II reported as a percentage of the overall change in steady-state values (\( \Delta y \)).

Q and VO_{2} in the rest of the body, Q_{tot} was not measured in the original experiments (21); therefore, the proportion of Q_{tot} directed to the rest of the body (Q_{b}) at unloaded pedaling was extrapolated using the following assumptions. The steady-state Q_{tot}-VO_{2A} relationship has a linear slope (\( \Delta Q_{tot}/\Delta VO_{2A} \)) with a positive intercept on the Q_{tot} axis (19, 55). \( \Delta Q_{tot}/\Delta VO_{2A} \) was assumed to be equal to \( \Delta Q_{tot}/\Delta VO_{2m} \), which was directly measured in each individual. The Q_{tot}/VO_{2A} intercept was then extrapolated from resting Q_{tot} and VO_{2A} estimates (13, 14): 

\[ Q_{tot,b} = 2.78 \times BSA \] 

and VO_{2A,R} = 0.149 \times BSA, where the subscript R denotes rest, BSA is body surface area (m²) calculated by 0.00714 \times BM^{0.425} \times H^{0.725}, BM is body mass (kg), and H is height (cm). These assumptions allowed steady-state Q_{tot} to be derived from measured VO_{2A} at unloaded pedaling and exercise; steady-state Q_{b} was then determined by subtraction of measured Q_{m} from estimated Q_{tot}, with the kinetics of Q_{b} assumed to be identical to those of Q_{tot}; i.e., \( \tau Q_b = \tau Q_{tot} \). Steady-state VO_{2m} (i.e., in nonleg muscles and all other tissues) at unloaded pedaling and exercise was calculated by subtraction of VO_{2m} from VO_{2A}. Similar to Q_{b}, the kinetics of VO_{2m} were assumed to be the same as those for VO_{2m}; i.e., \( \tau VO_{2m} = \tau VO_{2m} \).

Computational model. Computations were constructed starting from the original model of Barstow et al. (3), which we termed the single-compartment model (SCM) because of its single Vv (Fig. 1A). Briefly, the SCM is split into three compartments representing the lungs, the exercising muscle, and a lumped compartment representing the rest of the body, with a single Vv connecting the compartments on the venous side. Resting Q_{tot} was assigned, with a fraction going to the muscle and the remainder to the rest of the body. Similarly, resting VO_{2A} was assigned, with a fraction in the muscle and the remainder in the body.

During the simulated exercise step, Q_{tot} and VO_{2m} increased exponentially, according to Eq. 1, toward their work rate-dependent steady-state values. All values in the SCM during the exercise step were calculated with a temporal resolution of 0.1 s. Note that Q_{b} (5.31 l/min), VO_{2m} (0.21 l/min), and arterial O₂ concentration (CaO₂, 0.20 ml O₂/ml blood) in the SCM were constant throughout. (Q_{m} and VO_{2m} were time-varying in the models developed in the current experiments.) O₂ concentration in the blood draining the muscle (CvO₂, b) and body compartments (CvO₂, m) were calculated from the Fick equation

\[ C_{vO_2,m}(t) = C_{vO_2}(t)/Q_{m}(t) \]  

where the subscript \( s \) represents either muscle or body. These two venous effluents were then mixed in a flow-weighted manner to give a mixed “muscle and body” venous O₂ concentration

\[ C_{vO_2,m}(t) = C_{vO_2,m}(Q_{m}/Q_{tot}) + C_{vO_2,m}(Q_{b}/Q_{tot}) \]  

where all variables are functions of time. Blood with this O₂ concentration then transited down the length of the single Vv to the lung, the variable flow in Vv being determined by Q_{tot}. This resulted in a muscle-to-lung transit delay that was dependent on Q_{v}, Q_{tot}, and \( \tau \). The transit delay (TD) for the venous effluents being mixed at any given time was calculated by integrating Q_{tot} from \( t \) until the integral was equal to Q_{v}, such that

\[ V_{v} = \int_{t}^{t + TD} Q_{tot}(t) \, dt \]  

Integration was carried out using the trapezoidal rule (44). Mixed CvO₂ (CvO₂, b) at the lung at time \( t + TD \) was then given by CvO₂, b at time \( t \), with CvO₂ remaining at its unloaded pedaling value for \( t < TD_{\text{iso}} \) (i.e., the initial muscle-to-lung time delay). VO_{2A} at each time \( t \) was then solved using the Fick principle

\[ VO_{2A}(t) = Q_{tot}(t)[C_{vO_2} - C_{vO_2}(t)] \]  

The default parameter values from Barstow et al. (3) for the SCM are given in Table 1. New parameter values derived from the experimental data were gradually incorporated into the model, with an

### Table 1. Default parameter values for the SCM and for the MCM following optimization

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SCM</th>
<th>MCM</th>
</tr>
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<tbody>
<tr>
<td>CaO₂, ml/100 ml</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Venous volumes, liters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Body</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>3.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Unloaded pedaling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO_{2A}, l/min</td>
<td>0.54</td>
<td>0.87</td>
</tr>
<tr>
<td>Fraction from muscle</td>
<td>0.62</td>
<td>0.57</td>
</tr>
<tr>
<td>Fraction from body</td>
<td>0.38</td>
<td>0.43</td>
</tr>
<tr>
<td>Q_{tot,b}, l/min</td>
<td>7.70</td>
<td>8.89</td>
</tr>
<tr>
<td>Fraction to muscle</td>
<td>0.31</td>
<td>0.57</td>
</tr>
<tr>
<td>Fraction to body</td>
<td>0.69</td>
<td>0.43</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \Delta VO_{2A}/\Delta W ), ml·min⁻¹·W⁻¹</td>
<td>10.0</td>
<td>9.5</td>
</tr>
<tr>
<td>( \Delta VO_{2m}/\Delta W ), ml·min⁻¹·W⁻¹</td>
<td>10.0</td>
<td>11.0</td>
</tr>
<tr>
<td>( \Delta VO_{2m}/\Delta W ), ml·min⁻¹·W⁻¹</td>
<td>10.0</td>
<td>11.0</td>
</tr>
<tr>
<td>( \Delta Q/\Delta VO_{2} )</td>
<td>5.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Q/VO_{2} intercept, l/min</td>
<td>5.0</td>
<td>3.6</td>
</tr>
<tr>
<td>( \tau Q_{m} ), s</td>
<td>15.0</td>
<td>24.0</td>
</tr>
<tr>
<td>( \tau VO_{2m} ), s</td>
<td>30.0</td>
<td>22.0</td>
</tr>
</tbody>
</table>

*External work during unloaded pedaling in the single-compartment model (SCM) (Ref. 3) was assumed to be 4 W. MCM, multicompartiment model (present study). See Glossary for definition of abbreviations.*
examination at each stage of the effects of incorporating each new parameter value. These changes necessitated the development of a modified version of the SCM that contained multiple venous compartments, termed the multicompartment model (MCM). These compartments represent Vv associated with the muscle, the body, and the mixed venous vasculature (Fig. 1B). Using the experimentally measured and derived data as inputs to the model (default SCM parameter values are given in Table 1), the MCM was then optimized by varying the sizes of the three Vv, so that simulated VO2A kinetics gave the best match to experimental VO2A kinetics, thereby solving for the remaining model unknowns. A copy of the optimized MCM is available from the BioModels Database.

**Optimizing the MCM.** The kinetics of VO2A are determined by the kinetics of VO2m, the variable muscle-to-lung TD (which is determined by Qtot and the intervening Vv; Eq. 5), and the changes in CvO2 (incorporating flow-weighted mixing of CvO2m and CvO2b). Of these, the experimental data gave all but the Vv; therefore, the MCM was optimized for each individual subject by varying the sizes of Vv,m, Vv,b, and Vv, such that the simulated VO2A kinetics gave the best match to experimental VO2A kinetics. To keep total Vv (i.e., Vv,m + Vv,b + Vv) within an anatomically appropriate range, we estimated total blood volume (Vb) for each subject using Vb = 2.56 × BSA (17), assumed that Vv was between 55% and 75% of Vb (7), and calculated these extremes for each subject. We then took the minimum and maximum of all calculated values to set bounds on model Vv. This procedure yielded bounds for Vv of 2.5 and 4.0 liters.

The kinetic optimization was made by comparing several key kinetic components of the resultant model VO2A with their experimental equivalents, namely, ΔφI, TDΔI, and τVO2A. Note that TDΔI in the model is the initial muscle-to-lung TD, given by Eq. 5 at t = 0. The optimal MCM was that with the three Vv giving the smallest “kinetic error” between the experimental data and the model output. This error was given by

\[
\text{error} = 0.25 \left( \frac{\Delta \phi_{I,e} - \Delta \phi_{I,c}}{\text{SD}_{\Delta}} \right) + 0.25 \left( \frac{\text{TD}_{\Delta I,e} - \text{TD}_{\Delta I,c}}{\text{SD}_{\text{TD}}} \right) + 0.5 \left( \frac{\tau_{VO2A,e} - \tau_{VO2A,c}}{\text{SD}_{\tau}} \right)
\]

(7)

where the subscripts e and c denote experimental and computed values, respectively, the pairs of vertical bars indicate the absolute value of the term between them, and SD is the standard deviation of the model errors over all permutations of the model (i.e., all combinations of Vv) from the measured “population” (i.e., SDΔ = 6.59%, SDTD = 5.17 s, and SDτ = 1.58 s). Weighting factors were chosen to equalize the error contributions from phase I (ΔφI and TDΔI errors) and phase II (τVO2A error) to the optimization process. Note that each of the summed terms in Eq. 7 is analogous to a z score. Here, however, the numerator gives the difference of the model output from the experimentally recorded value (rather than the difference from the population mean), thus taking into account situations where the mean of the model result is not identical to the experimentally recorded value.

**Statistical analyses.** Values are means ± SD for all six subjects, unless otherwise stated. Significant differences between data were tested using two-sample (paired or unpaired) or one-sample t-tests, Wilcoxon’s signed-ranked tests, one-way ANOVA, or repeated-measures ANOVA with Tukey’s post hoc tests, as appropriate. Significance level was set at P < 0.05.

**RESULTS AND DISCUSSION**

**Experimental data.** Figure 2 shows fits to experimentally recorded Qm, VO2m, and VO2A for one representative subject; these fits are summarized for all subjects in Table 2. Note the comparatively slow Qm and VO2m kinetics compared with the phase II VO2A kinetics for all subjects, but particularly for subject 6. We found that the solution required to resolve VO2A from VO2m kinetics for subject 6 was different from that for all other participants (see discussion in Ref. 21 regarding the outlying response of subject 6). Therefore, we excluded subject 6 for the purposes of summarizing the group kinetics and return to the solutions for subject 6 below. The mean τ values for Qm, VO2m, and phase II VO2A in subjects 1–5 were 23.9 ± 2.3, 22.4 ± 2.9, and 18.5 ± 4.8 s, respectively. τVO2A was significantly less than τVO2m (~18% absolute difference) and τQm (P < 0.05, by repeated-measures ANOVA, n = 5; Table 2). In addition, τQm was not different from τVO2m (P = 0.06; Table 2). However, the experimentally measured τ values for Qm and VO2m were significantly different from their respective default values in the SCM model (P < 0.05, by 1-sample t-tests; Table 1).

We therefore explored the notion that we could account for circulatory distortions between τVO2m and τVO2A by using knowledge of alveolar O2 exchange alone. Because phase I VO2A reflects predominantly changes in Qtot, we investigated whether accounting for phase I and II kinetics simultaneously would effectively deconvolute τVO2m from the entire VO2A response [similar to the suggestion by Barstow and Molé for heavy exercise (4)]. This approach is based on the notion that allowing the phase I fit to project beyond TDΔI would account for the influence of ongoing Qbot kinetics on phase II τVO2A.
of $\dot{Q}_{\text{tot}}$ delivered to the muscle compartment was significantly less in the SCM than in the experiment (31 vs. 57 ml·min⁻¹·W⁻¹). Furthermore, the percentage $\dot{Q}_{\text{tot}}$ and $\dot{V}_{O2}$ between the muscle and body compartments at steady-state unloaded pedaling (Table 3).

Because the magnitude of the $\Delta y$ responses is dependent on $W$, they are reported in a normalized form in Table 3 as $\Delta V_{O2}/\Delta W$, along with the slope and intercept of the $Q_{\text{tot}}$-$\dot{V}_{O2A}$ relationships. For all subjects, $\dot{V}_{O2A}$ decreased during exercise, resulting in an average reduction in $\Delta V_{O2}/\Delta W$ of $1.57 ± 1.10$ ml·min⁻¹·W⁻¹. As a consequence, muscle $\Delta V_{O2m}/\Delta W$ was significantly greater than whole body $\Delta V_{O2}/\Delta W$ during exercise ($P < 0.05$, by paired $t$-test; Table 3). As a group, there were no significant differences in the fractional distributions of $Q_{\text{tot}}$ and $V_{O2}$ between the muscle and body compartments at steady-state unloaded pedaling (Table 3).

$\Delta V_{O2}$ and $\dot{V}_{O2}$ at unloaded pedaling. Figure 3A compares the distributions of $Q_{\text{tot}}$ and $V_{O2}$ between the muscle and body compartments of the SCM and the experimental data during unloaded pedaling. Assumed $Q_{\text{tot}}$ during unloaded pedaling was significantly less in the SCM than in the experimental data (7.7 vs. 8.9 ± 0.44 l/min, $P < 0.05$, by 1-sample $t$-tests for all SCM vs. experimental analyses). Furthermore, the percentage of $Q_{\text{tot}}$ delivered to the muscle compartment was significantly less in the SCM than in the experiment (31 vs. 57 ± 8%, $P < 0.05$). Unloaded $V_{O2A}$ was also less in the SCM than in the experiment (0.54 vs. 0.87 ± 0.08 l/min, $P < 0.05$), although the percent contributions of the muscle compartments to total $V_{O2}$ were similar (62 vs. 57 ± 11%). $CaO_2$ was not significantly different between the SCM and the experimental data (20.0 and 19.64 ± 1.06 ml·100 ml⁻¹; Fig. 3B). These differences between the SCM and the experimental data resulted in a hypoperfusion (low $Q_{m}$: 2.39 vs. 5.09 ± 0.84 l/min, $P < 0.05$) and low $O_2$ delivery relative to $V_{O2m}$ (0.34 vs. 0.50 ± 0.12 l/min, $P < 0.05$) in the original SCM. Thus, in the muscle compartment, $Q_{m}$ was 53% less and $V_{O2m}$ was 33% less in the SCM than in the experimental data, which caused a low $CvO_2m$ during unloaded pedaling in the original SCM (5.97 vs. 10.07 ± 2.85 ml·100 ml⁻¹, $P < 0.05$; Fig. 3B).

It is important to recognize that the difference in unloaded $Q_{m}/V_{O2m}$ proportional distributions between the default parameters of the SCM and the experimental data affect the unloaded $CvO_2m$ steady state and its subsequent exercise dynamics, even under conditions where $\tau Q_m$ and $\tau V_{O2m}$ are constant. This is because, where $CaO_2$ is constant, the $CvO_2m$ profile is determined by the absolute ratio of the $Q_{m}/V_{O2m}$ relationship (Eq. 3), which has a positive $Q_{m}$ intercept (17, 52). Figure 3C illustrates the effect of a 100-W step increment in power output from unloaded pedaling with use of the SCM default parameters and the experimentally determined values. For both simulations, $\tau Q_m$ was 45 s and $\tau V_{O2m}$ was 30 s.

With use of this example, the influence of slow $Q_{m}$ kinetics (relative to $V_{O2m}$) is for $CvO_2m$ to overshoot the steady-state value during the transient (3, 18). When the default parameter values are used (Table 1), Fig. 3C illustrates that the $CvO_2m$ overshoot is 50% greater than the steady-state change when

Table 2. *Fitted kinetic parameter values for the experimentally collected $\dot{Q}_{m}$, $\dot{V}_{O2m}$, and $\dot{V}_{O2A}$

<table>
<thead>
<tr>
<th>Subj No.</th>
<th>Work Rate, W</th>
<th>$Q_{m}$, l/min</th>
<th>$\dot{V}_{O2m}$, l/min·W⁻¹</th>
<th>$\dot{V}_{O2A}$, l/min·W⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>220</td>
<td>6.14</td>
<td>12.16</td>
<td>27.1</td>
</tr>
<tr>
<td>2</td>
<td>180</td>
<td>4.80</td>
<td>10.64</td>
<td>21.9</td>
</tr>
<tr>
<td>3</td>
<td>180</td>
<td>3.77</td>
<td>12.87</td>
<td>24.6</td>
</tr>
<tr>
<td>4</td>
<td>180</td>
<td>5.47</td>
<td>10.11</td>
<td>21.4</td>
</tr>
<tr>
<td>5</td>
<td>160</td>
<td>5.64</td>
<td>11.94</td>
<td>24.6</td>
</tr>
<tr>
<td>6</td>
<td>180</td>
<td>4.72</td>
<td>12.33</td>
<td>37.0</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>5.09</td>
<td>11.83</td>
<td>29.4*</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>0.84</td>
<td>1.23</td>
<td>13.7</td>
</tr>
</tbody>
</table>

* $P < 0.05$ vs. phase II $\tau V_{O2A}$; † $P = 0.06$ vs. $\tau Q_m$ (by repeated-measures ANOVA with subjs 1–5).

Table 3. Functional gain ($\Delta V_{O2}/\Delta W$), the $Q_{m}/V_{O2A}$ relationship, and unloaded pedaling $Q_{\text{tot}}$ and $V_{O2A}$ fractional distributions determined from fits to experimental data

<table>
<thead>
<tr>
<th>Subj No.</th>
<th>Whole body, l/min·W⁻¹</th>
<th>Muscle, l/min·W⁻¹</th>
<th>Rest of body, l/min·W⁻¹</th>
<th>$\dot{Q}<em>{\text{tot}}/\dot{V}</em>{O2A}$</th>
<th>$Q_{\text{tot}}/\dot{V}_{O2A}$ Distribution</th>
<th>Unloaded $Q_{\text{tot}}$ Distribution</th>
<th>Unloaded $V_{O2A}$ Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta V_{O2}/\Delta W$</td>
<td>Slope</td>
<td>Intercept</td>
<td>$\Delta Q_{m}/\Delta W$</td>
<td>Muscle</td>
<td>Rest of body</td>
<td>Muscle</td>
</tr>
<tr>
<td>1</td>
<td>8.47</td>
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<td>4.02</td>
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<td>0.64</td>
<td>0.52</td>
<td>0.48</td>
</tr>
<tr>
<td>2</td>
<td>8.59</td>
<td>5.74</td>
<td>3.73</td>
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<td>0.56</td>
<td>0.69</td>
<td>0.51</td>
</tr>
<tr>
<td>3</td>
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<td>6.98</td>
<td>3.40</td>
<td>0.44</td>
<td>0.44</td>
<td>0.69</td>
<td>0.51</td>
</tr>
<tr>
<td>4</td>
<td>10.06</td>
<td>5.69</td>
<td>3.73</td>
<td>0.60</td>
<td>0.60</td>
<td>0.98</td>
<td>0.60</td>
</tr>
<tr>
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<td>10.03</td>
<td>5.70</td>
<td>3.64</td>
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<tr>
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<td>0.52</td>
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<td>0.56</td>
<td>0.44</td>
</tr>
<tr>
<td>Mean</td>
<td>9.47</td>
<td>6.03</td>
<td>3.64</td>
<td>0.57</td>
<td>0.57</td>
<td>0.57</td>
<td>0.43</td>
</tr>
<tr>
<td>SD</td>
<td>0.85</td>
<td>0.53</td>
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<td>0.08</td>
<td>0.08</td>
<td>0.11</td>
<td>0.11</td>
</tr>
</tbody>
</table>

* $P < 0.05$ (by paired $t$-test) vs. whole body $\Delta V_{O2}/\Delta W$; † $P < 0.05$ (by 1-sample $t$-test) vs. no change in $\Delta V_{O2}/\Delta W$. NS, no significant difference between $Q_{\text{tot}}$ and $V_{O2A}$ fractional distributions during unloaded pedaling (by paired $t$-tests).
SCM defaults are used (6.08 ml/100 ml) compared with a 14% overshoot when the experimental data are used (5.72 ml/100 ml). This causes the SCM defaults to result in a complete draining of the muscle venous O2 [it is recognized that CVO2m = 0 ml/ml is a theoretical artifact of the model not possible under physiological conditions but is used here to delimit a mathematical boundary for O2 extraction (53); see also Fig. 3A in Ref. 3]. Note that the only differences between the two simulations are the absolute value of Qm and VO2m values at unloaded pedaling; all other parameters in the two simulations, including ΔVO2/ΔW, ΔQiso/ΔVO2A, and Qm and VO2m kinetics, are the same. Yet the CVO2m dynamics (time course, overshoot magnitude, and steady-state amplitudes) are not simply transposed vertically depending on the initial conditions. A CVO2m overshoot is more pronounced under conditions where the muscle is poorly perfused at rest or in unloaded pedaling, risking the attainment of a critical capillary PO2 (43).

Therefore, muscles or muscle regions composed of different fiber types or in which resting O2 delivery differs would also be expected to express different CVO2m kinetics, even where ΔQm/ΔVO2m during exercise was similar. This notion is supported by the data of McDonough et al. (36) and Ferreira et al. (18), where predominantly fast-twitch rat muscles are relatively hypoperfused at rest and have a greater CVO2m overshoot during exercise than slow-twitch muscles, despite similar ΔQm/ΔVO2m. Together, these results highlight the importance of the resting conditions in the subsequent O2 extraction dynamics. This impact of initial conditions on kinetics during the exercise step might help explain the significant inverse correlation ($r^2 = 0.51, P < 0.05$) between resting muscle oxygenation and phase II $\tau$VO2A in patients with CHF (9).

Because the baseline Qm/VO2m influences subsequent CVO2m exercise dynamics, we examined the effect of altered Qm/VO2m during unloaded cycling on transient muscle venous O2 depletion during exercise. That is, we mapped the theoretical combinations of Qm/VO2m that would return mathematical CVO2m values of ≤0 ml/100 ml and the kinetic relationships between VO2m and VO2A (i.e., the difference between $\tau$VO2m and $\tau$VO2A) over a wide range of muscle Qm and VO2m kinetics. Figure 4 shows the results of simulations using the default unloaded pedaling values from the SCM or the experimental data. In Fig. 4, the degree of muscle-to-lung kinetic uncoupling for each combination of $\tau$Qm and $\tau$VO2m is color-coded. Negative values are blue and indicate faster VO2A than VO2m kinetics. Positive values are red and show slower VO2A than VO2m kinetics. The white area shows the $\tau$Qm and $\tau$VO2m combinations that result in CVO2m ≤0 at some point during the exercise transient (e.g., as in Fig. 3C). Regions of blue/green show where the value of pulmonary phase II $\tau$VO2A is close to the muscle $\tau$VO2m, and the kinetic combinations that lay outside ±2 s are bounded by the solid black lines. The dashed boxes show the bounds of the $\tau$Qm and $\tau$VO2m values (means ± 2 SDs) measured in the experimental data.

Using the SCM defaults, only 66% of the 2,500 $\tau$Qm and $\tau$VO2m combinations between 1 and 50 s resulted in viable conditions to maintain aerobic energy transfer (nonwhite areas in Fig. 4A), and some of the experimentally measured $\tau$Qm and $\tau$VO2m combinations resulted in predicted CVO2m ≤0 (dashed boxes in Fig. 4A). Indeed, the SCM default settings use Qm kinetics that are substantially faster than VO2m, unlike the measured values, where $\tau$Qm and $\tau$VO2m are similar. The narrow scope for viable kinetic combinations of muscle O2 delivery and utilization reflects the relative hypoperfusion during unloaded pedaling of the default SCM parameter values (Fig. 4A). This scope, however, was dramatically increased (to 90%) when the experimentally measured parameter values for unloaded pedaling were used (Fig. 4B). Altering the unloaded Qm/VO2m values also causes a change in the predicted phase II VO2A kinetics, with a tendency toward more positive kinetic uncoupling; i.e., VO2A kinetics became slower as the muscle perfusion was increased during unloaded pedaling. Mean kinetic uncoupling within the bounds of the experimental data (dashed boxes in Fig. 4) was significantly different between the two models: $-4.8 \pm 1.1$ s for the SCM defaults (values where CVO2m ≤0 ml/100 ml were ignored) and $-3.8 \pm 1.5$ s when experimental unloaded defaults were used ($P < 0.05$, by ANOVA).

Fig. 3. Distributions of blood flow (Q) and O2 uptake (VO2) between muscle and body compartments during unloaded pedaling for the SCM and experimental data (Exp). A: Qtot and VO2A, and percent distributions between muscle and body compartments. B: muscle compartment CaO2, Qm, VO2m, and CVO2m from the SCM and experimental data. Values are normalized to the mean of the experimental data. C: simulated CVO2m profiles for a 100-W step change in work rate from unloaded pedaling (ULP) with use of default SCM parameter values or experimentally measured values. *P < 0.05 vs. Exp (by 1-sample t-test).
The comparison of the SCM model with default and measured values for unloaded pedaling highlights the significance of preexercise perfusion on subsequent phase II \( V_{O2A} \). Pathological conditions where resting perfusion is compromised, such as CHF (43), result in a nonlinear reduction in a range of viable dynamic combinations during exercise, such that the stability of the dynamic system would require a tighter coupling of muscle perfusion to metabolism to avoid limitations to \( Q_{m}/V_{O2m} \) values for unloaded pedaling. It is well known that instantaneous muscle \( Q_{m}/V_{O2m} \) is heterogeneous, with a broad distribution that may become wider during the transient (22, 27). Therefore, the large reduction of viable kinetic combinations in a system that transits from a hypoperfused baseline (Fig. 4A) increases the scope for transient capillary-to-myocyte diffusion limitation within some, or all, of the recruited muscles. The necessity for tight dynamic control mechanism(s) between instantaneous \( Q_{m}/V_{O2m} \) is dramatically ameliorated by an increase in the relative perfusion at rest or unloaded pedaling but is accompanied, seemingly paradoxically, by slightly slower phase II \( V_{O2A} \) kinetics on average (dashed box in Fig. 4B). This raises the possibility that solely raising the muscle perfusion during unloaded pedaling would result in phase II \( V_{O2A} \) kinetics that were slowed to a small degree. It is intriguing to speculate whether similar phase II \( \tau V_{O2p} \) values measured before and after “warm-up” exercise that increases unloaded perfusion (8, 10, 16, 48) actually reflect a speeding of \( \tau V_{O2m} \) (23), which is then slowed in its pulmonary manifestation as phase II \( \tau V_{O2p} \).

\( Q \) and \( V_{O2} \) changes during exercise. The effects of altering the magnitude of the exercise hyperemia (the \( \Delta Q_{m}/\Delta V_{O2m} \) slope) were examined in Fig. 4C. The whole body functional gain \( \Delta V_{O2A}/\Delta W \) determines the magnitude of the \( V_{O2A} \) change for any given work rate change and was similar between the SCM defaults and the experimental data (10.0 and 9.47 ± 0.85 ml·min\(^{-1}·W\)^{-1}, respectively). However, \( \Delta Q_{m}/\Delta V_{O2m} \) (which links the \( Q_{tot} \) and \( V_{O2m} \) changes during exercise) was significantly lower in the SCM than the experimental data (5.0 vs. 6.03 ± 0.53, \( P < 0.05 \)). Figure 4C shows the effects of increasing the exercise perfusion on the viable combinations of \( \tau Q_{m} \) and \( \tau V_{O2m} \) (all other model parameters are the same as in Fig. 4B). Interestingly, the effects of this ~2 l/min increase in \( Q_{m} \) during exercise are limited: viable kinetic combinations increase to 92% (from 90% in Fig. 4B). Contrast this with the effects of a 1 l/min increase in \( Q_{m} \) during unloaded pedaling, i.e., the difference between 66% viability in Fig. 4A and 90% viability in Fig. 4B. These analyses demonstrate that attainment of transient limiting conditions within the muscle during exercise may be more sensitive to small changes during the preexercise unloaded phase (or at rest) than during the exercise itself.

The mean kinetic uncoupling of \( V_{O2m} \) and \( V_{O2A} \) dynamics (dashed box in Fig. 4C) did not significantly change when the experimental \( \Delta Q_{m}/\Delta V_{O2m} \) values were incorporated: \(-3.7 ± 2.0\) vs. \(-3.8 ± 1.5\) s in Fig. 4B \( (P ≠ \) not significant, by ANOVA). However, over the entire kinetic range (1–50 s), there were widespread regional changes in the kinetic uncoupling map, with a greater mismatching between the \( \tau V_{O2A} \) and \( \tau V_{O2m} \) overall by use of the experimental parameter values (Table 1). Note that areas of red and blue in Fig. 4C are larger and that the ±2-s isolines are closer together than in Fig. 4, A and B.

Validating the SCM. We then examined whether the SCM was sufficiently detailed to predict the experimentally measured \( V_{O2A} \) from knowledge of the measured \( Q_{m} \) and \( V_{O2m} \) responses. We therefore incorporated the unloaded and exercising experimental measurements into the SCM (see Table 1 for the SCM parameter list and Tables 2 and 3 for experimental values) and ran simulations on a subject-by-subject basis to compare model \( V_{O2A} \) outputs with the individual’s experimental \( V_{O2A} \) response. The SCM (with experimental parameter sets) was able to produce outputs that were qualitatively similar to the experimental \( V_{O2A} \) response (3), yet the modeled parameters were broadly distributed on an individual basis. While \( \Delta dq \) (26.4 ± 5.3 vs. 24.7 ± 5.7% for SCM and experimental data, respectively) and phase II \( \tau V_{O2A} \) (22.0 ± 12.7 vs. 18.4 ± 4.3 s) values were similar between SCM and measured data, TDq values were significantly different (15.3 ± 1.5 vs. 17.5 ± 1.8 s, \( P < 0.05 \), by paired t-tests). These statistics, however, obscured an ~19% absolute difference in \( \tau V_{O2A} \) (some values

![Fig. 4](http://jappl.physiology.org/11011-J Appl Physiol • Benson AP et al.)

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were larger and some were smaller), where the SCM (with experimental parameter sets) was not well able to reproduce the phase II \( \dot{V}O_2A \) kinetic profiles on an individual basis. Additionally, the phase II \( \dot{V}O_2A \) dynamics were then displaced temporally because of the shorter TD in the SCM. We therefore increased the complexity of the SCM guided by the experimentally measured data to investigate whether additional model components could minimize these model-experiment kinetic differences.

Development of the MCM. A key difference between the model and the measurements was the contraction of \( \dot{V}O_2b \) during the exercise transient, which is expressed as a change in \( \Delta \dot{V}O_2/\Delta W \) among compartments (Fig. 5). This means that the flow-weighted mixing of \( O_2 \) concentrations draining the body and muscle compartments to generate \( CvO_2 \) is not solely dependent on exercise-induced changes in the muscle compartment (Table 1), but also relies on small (~15%), but significant, changes in \( Q_v/\dot{V}O_2b \) in nonexercising tissues. The SCM is unable to appropriately account for changes in \( Q_v/\dot{V}O_2b \) because it does not contain a venous volume \( V_v \) draining the body compartment (\( V_v,b \)). We therefore aimed to optimize the SCM to determine whether accounting for dynamic changes in \( Q_v/\dot{V}O_2b \) and \( Q_m/\dot{V}o2m \) could allow accurate prediction of \( \dot{V}O_2A \) kinetics.

Introduction of body compartment dynamics and functional gains into the SCM is not straightforward. \( CvO_2m \) and \( Q_b \) change dynamically during the transient. Therefore, the venous capacitance of this compartment must also be taken into account, because altering venous capacitance affects the amplitude and duration of the phase I \( \dot{V}O_2A \) (3) and the subsequent kinetic coupling (Fig. 4). We therefore incorporated three separate \( V_v \) into the model, one each draining venous effluent from the muscle and body compartments and another carrying mixed venous blood to the lungs (Fig. 1B). This model is termed the MCM. Note that each \( V_v \) in the MCM has its own time-dependent TD (Eq. 5) and that the TDs for the muscle and body venous compartment have to be taken into account before \( CvO_{2m,v} \) (Eq. 4) is calculated.

Optimizing the MCM. As previously discussed, dynamic responses of \( \dot{V}O_2A \) are nonlinear variants of \( \dot{V}O_2m \), with the distortions dependent on resting and exercising \( O_2 \) delivery relative to \( \dot{V}O_2 \), and \( V_v \) in the body tissue compartments. Of these, all but \( V_v \) were directly measured or derived from the experimental data. We therefore optimized the MCM for each individual participant by solving for the three \( V_v \) levels that resulted in the minimum kinetic error between model output and experimental data (Eq. 7).

The kinetic errors for all 9,416 combinations of the \( V_v \) values, ranked from smallest error to largest, are shown for a representative subject in Fig. 6A. The kinetic error rises sharply as rank increases from 1, indicating that the smallest error arises as a consequence of a unique combination of the three \( V_v \) values. Qualitatively similar results were found for all subjects. For the whole group, the mean optimized values were \( 0.67 \pm 1.63 \) liters for \( V_{v,m} \), \( 0.10 \pm 0.17 \) liter for \( V_{v,b} \), and...
2.30 ± 1.17 liters for mixed volume, to give a mean total \( V_v \) of 3.07 ± 0.61 liters. A Wilcoxon’s signed-rank test (to account for the outlying values of subject 6) showed that the MCM significantly reduced kinetic error by 39 ± 28% compared with the SCM (Fig. 6B).

**Modeling \( \dot{V}O_{2A} \) kinetics using the MCM.** All three \( \dot{V}O_{2A} \) kinetic parameters obtained from the optimized MCM were not significantly different from the experimental values (paired \( t \)-tests): \( \Delta_{\phi I} \) was 26.8 ± 2.8% (MCM) vs. 24.7 ± 5.7% (experiment), \( TD_{\phi I} \) was 17.4 ± 6.8 vs. 17.5 ± 1.8 s, and \( \tau_{\dot{V}O_{2A}} \) was 21.3 ± 9.6 vs. 18.4 ± 4.3 s. The \( \dot{V}O_{2A} \) outputs from the optimized MCM for each subject are shown superimposed on the experimental \( \dot{V}O_{2A} \) measurements in Fig. 7, and the parameter values for the optimized MCM are given in Table 1. These results demonstrate the striking ability of the MCM to predict the entire kinetic profile of \( \dot{V}O_{2A} \) based on knowledge of respiratory and circulatory dynamics at the onset of exercise. The MCM (Fig. 1B, Table 1) accounts for \( V_{v,b} \), a small central compartment, and the ~15% exercise-induced change in \( Q_b/V_{\dot{O}2b} \). Although each of these effects is relatively small, they exert a significant influence on the kinetics of \( \dot{V}O_{2A} \) (Fig. 8A). In the optimized MCM, 91% of the kinetic combinations were viable (compared with 66% for the SCM, as in Fig. 4A), and the mean kinetic uncoupling within the experimental bounds was ~5.2 ± 2.2 s (dashed box in Fig. 8A), such that the kinetic uncoupling in the MCM was slightly wider than that predicted by the SCM (~4.8 ± 1.1 s; Fig. 4A). Over the entire range of \( \tau_{Q_m} \) and \( \tau_{\dot{V}O_{2m}} \) investigated, there were fewer combinations where phase II \( \tau_{\dot{V}O_{2A}} \) was within ±2 s \( \tau_{\dot{V}O_{2m}} \) and the kinetic uncoupling was more widely distributed in the MCM than the SCM. This is consistent with our hypothesis that dynamic circulatory-respiratory interactions could account for the broad range of dissociation between \( \dot{V}O_{2m} \) and \( \dot{V}O_{2A} \) kinetics (20, 24).

Therefore, by accounting for the effects of vascular volumes, blood flows, and flow-weighted mixing of venous \( \dot{O}2 \) concentrations, the MCM is able to very closely predict phase I and phase II \( \dot{V}O_{2A} \) kinetics during moderate-intensity cycling exercise in healthy young men.

An important feature of the MCM is that it predicts that phase II \( \dot{V}O_{2A} \) kinetics are not strictly exponential. Isolation and fitting of phase II \( \dot{V}O_{2A} \) (or \( \dot{V}O_{2P} \)) kinetics in vivo are suggested to provide a window on the control of muscle cellular metabolism (21, 28, 31). It is not surprising that phase II \( \dot{V}O_{2A} \) is typically well characterized by a monoexponential function, because \( \dot{V}O_{2m} \) is thought to be controlled by a first-order rate reaction (35, 37, 47, 56). However, the MCM demonstrates that \( CV_{\dot{O}2} \) kinetics (a key component of \( \dot{V}O_{2A} \) kinetics; Eq. 6) do not simply rely on \( Q_m/V_{\dot{O}2m} \) during the exercise transient, but also on \( Q_b/V_{\dot{O}2b} \), and capacitances, and flow-weighted mixing of \( CV_{\dot{O}2} \) from different vascular compartments. The result is that \( CV_{\dot{O}2} \) kinetics are distorted variants of \( CV_{\dot{O}2m} \) and that phase II \( \dot{V}O_{2A} \) kinetics are “compressed” in time relative to muscle (the actual rate of change is steeper at

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**Fig. 7.** Optimized MCM \( \dot{V}O_{2A} \) output (lines) and measured experimental \( \dot{V}O_{2A} \) (○) during transition to moderate-intensity cycling in 6 healthy young men.

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the beginning and shallower at the end of the transient than in the case of the fitted exponential). This is shown by the mean absolute residuals between the MCM phase II $V_O^{2A}$ and the best exponential fit, plotted for multiple $\tau_{Q_m}$ and $\tau_{V_O^{2m}}$ combinations in Fig. 8B. Not a single $\tau_{Q_m}$ and $\tau_{V_O^{2m}}$ combination resulted in a phase II $V_O^{2A}$ that was a pure exponential, i.e., with a mean absolute residual of zero, because of the intervening vascular capacitances and circulatory dynamics. Although these effects can be rather subtle (the default MCM parameter values from Table 1 give a mean absolute residual of 15.4 ml/min; Fig. 8C), there is an important cautionary outcome, also highlighted by Hughson (25): the fitted phase II $\tau_{V_O^{2A}}$ is not constant throughout the transient. In measured $V_O^{2A}$ and $V_O^{2P}$ data, the breath-to-breath fluctuations (34) will likely obscure this underlying subtile deviation from the exponential fit, but the “compression” effect places an increased onus on accurate identification of the phase I-to-phase II transition as an appropriate point from which to begin kinetic characterization. Typical approaches to fit phase II $\tau_{V_O^{2A}}$ use the suggestion that “at least” 20 s be eliminated from exercise onset to avoid phase I contamination of $\tau_{V_O^{2A}}$ (54). However, by erring on the side of caution, phase II data may also be excluded, which is predicted by the MCM to slow the resulting $V_O^{2A}$ parameter estimates (cf. Ref. 39). This emphasizes the need to establish robust methods for phase I-II identification to standardize approaches to $V_O^{2A}$ kinetic fitting.

The MCM may provide the opportunity to better account for the kinetic distortions to $\tau_{V_O^{2m}}$ by use of noninvasive measurement of $V_O^{2A}$ and $Q_{tot}$ kinetics. With use of the work rate, the measured $\Delta V_O^{2A}/\Delta W$ in the steady-state, and the measured $\tau_{V_O^{2A}}$ and $\tau_{Q_{tot}}$ (or a surrogate, such as heart rate kinetics) as inputs to the model and with the other variables fixed at the MCM defaults, the MCM may be set to search $\tau_{V_O^{2m}}$ parameter space to identify the $\tau_{V_O^{2m}}$ value that results in the closest match between model and experimental $\tau_{V_O^{2A}}$. (A copy of this algorithm is available from the BioModels Database.) For subjects 1–5, this procedure yields values for $\tau_{V_O^{2m}}$ of 26.9, 19.1, 22.7, 21.4, and 28.2 s, respectively, which are not significantly different from the measured $\tau_{V_O^{2m}}$ (~7% absolute difference; cf. Table 2) but are significantly different from experimentally measured phase II $\tau_{V_O^{2A}}$ derived from isolated or simultaneous fitting approaches (4, 47, 52) ($P < 0.05$, by repeated-measures ANOVA; see Experimental data). Therefore, the MCM may be used to backcalculate muscle $V_O^{2}$ kinetics (in young healthy subjects during cycling, for which the MCM defaults were defined) and provides a more accurate representation of muscle gas exchange kinetics than that obtained by inferring these kinetics directly from phase II $V_O^{2A}$. A similar solution to this backcalculation problem is provided by Hoffmann et al. (24), who used a pseudorandom binary sequence to collect gas exchange and cardiovascular (heart rate and stroke volume) response dynamics with high kinetic fidelity. The time series analysis applied to these data also provided $\tau_{V_O^{2m}}$ prediction to within 7% across a wide range of $\tau_{V_O^{2A}}$, and $\tau_{Q_{tot}}$ combinations (24): as with the MCM backcalculation method, this return is superior to that of the method that relies on phase II $\tau_{V_O^{2A}}$ alone. These approaches appear promising and, therefore, deserve further attention to assess their accuracy and validity. While each improves $\tau_{V_O^{2m}}$ estimation compared with current techniques, it is nevertheless clear that an accurate noninvasive determination of $\tau_{V_O^{2m}}$ using accessible methods in the wider population (a population that is not well represented by the young healthy individuals in the present study or in Ref. 24) is not a trivial task and remains to be resolved.

**Influence of biphasic $Q_m$ kinetics on $V_O^{2A}$ kinetics.** It was clear that the kinetic error for subject 6 was large compared with that for the other subjects, even when the optimized MCM was used (Figs. 6B and 7). This is because of slow $V_O^{2m}$, but relatively normal $V_O^{2A}$, kinetics in this subject (Table 2). Despite significant narrowing of the difference between the modeled and measured $V_O^{2A}$ response obtained using the MCM, a large kinetic uncoupling of 33.8 s remained between muscle and lung. Interestingly, the biphasic $Q_m$ response at exercise onset was more pronounced in subject 6 than in the
other participants (Fig. 9A). This “phase I” \( \dot{Q}_m \) response is likely mediated by muscle pump and a rapid-onset vasodilation, with the slower “phase II” increase determined by local vasodilatory feedback mechanisms linked to metabolic demand (50). Use of this biphasic \( Q_m \) response in the optimized MCM further improved the kinetic error in this subject by 22%. (\( \dot{V}_{v,m}, \dot{V}_{v,b}, \) and \( \dot{V}_v \) with monoexponential \( Q_m \) were 4.0, 0.0, and 0.0 liters, respectively; therefore becoming closer to the group means of 3.6, 0.2, and 0.2 liters, respectively.)

Improvements in the predictive power of the MCM in subject 6 were mainly the result of increased \( Q_m \) in the initial seconds of the exercise step, forcing \( V_{O2A} \) to rise rapidly at the start of phase II (Fig. 9B). A monoexponential fit to the presumed phase II region of the MCM-predicted \( V_{O2A} \) gave \( \tau = 34.3 \) s (compared with 39.3 s with the monoexponential \( Q_m \)), which is closer to the experimental data (17.9 s). However, while a biphasic \( Q_m \) response could not completely account for the kinetic uncoupling in subject 6, it resulted in a rapid and biphasic \( V_{O2A} \) within the region typically characterized by phase II. The kinetically slow \( V_{O2b} \) in this subject (51.7 s) was not manifest in \( V_{O2A} \) until almost 1 min after exercise onset and, again, highlights the concern for estimating \( \tau V_{O2m} \) from the phase II region of \( \tau V_{O2A} \) that is presumed to begin after ~20 s (20, 24). In addition, the effect of rapid early \( Q_m \) kinetics can be extreme and contribute to \( V_{O2A} \) overshoot/oscillations during the steady state early in the transient and uncoupling muscle and lung kinetics (see subjects 2 and 6 in Fig. 7 and red/yellow regions in Fig. 8) (30). These data suggest that a biphasic profile in \( Q_m \) (or \( Q_{tot} \)) on transition to exercise may result in a large degree (>30 s) of \( O_2 \) kinetic uncoupling between muscle and lung.

Limitations. The limitations underlying collection of the experimental data are discussed in detail elsewhere (21). Here we discuss three aspects of the experimental data that relate to our modeling study.

First, the changes in \( V_{O2b} \) and \( Q_b \) were only measured in the steady state, and we had no experimental information of \( V_{O2b} \) and \( Q_b \) kinetics. Therefore, the latter were assumed to be identical to their respective values in the muscle compartment. We performed a sensitivity analysis by increasing/decreasing \( \tau V_{O2b} \) and \( \tau Q_b \) by 50% from their default values, either in isolation or in combination, which resulted in a 1.4 ± 0.7 s absolute change in \( \tau V_{O2A} \) (range -2.4 to +2.1 s). Although the dynamic changes introduced into the MCM body compartment were necessary features that influence \( V_{O2A} \) and enable the MCM to accurately reproduce the experimental measures, the sensitivity analysis suggests that this influence is small enough that any inaccuracies in the parameterization of \( \tau V_{O2b} \) and \( \tau Q_b \) would have a negligible effect on the overall conclusions of the study.

Second, as there are no experimental data for \( Q_{tot} \), we made assumptions about the \( Q_{tot} \) steady-state values in the model on the basis of the muscle \( \Delta Q/\Delta V_{O2} \) and equations from the literature for estimating resting \( Q_{tot} \). Despite this approach, these assumptions resulted in physically sensible values for all subjects.

Third, the time resolution of the thermodilution technique is limited in relation to \( Q_m \) kinetics, potentially masking complex \( Q_m \) responses. This may explain some of the remaining discrepancy between the \( V_{O2A} \) kinetics predicted by the MCM and those observed in the measured data. It is worth noting here that the MCM was developed on the basis of experimental data recorded during a transition from unloaded pedaling. Biphasic, or complex, \( \dot{Q} \) kinetics may be exaggerated in transitions from complete rest (increasing kinetic uncoupling between muscle and lung, similar to that in subject 6; Fig. 9) or ameliorated during transitions from an active baseline (52).

All models are, by definition, simplifications of more complex systems. Although our developed MCM is a more complex version of the SCM of Barstow et al. (3), it is salient to emphasize that it is still a relatively simple model with lumped “exercising muscle,” “nonexercising muscle,” and “lung” compartments. Spatial and/or temporal heterogeneities within these compartments, e.g., fiber types that differ in \( Q_m/V_{O2m} \) (18) or ventilation-perfusion distributions in the lung (54), would be expected to influence the model predictions. Inclusion of these heterogeneities will likely be an important step in accounting for the residual differences between the model and the physiological response kinetics.

Summary. The data presented here provide an optimization and increased complexity to the computational model presented by Barstow et al. (3). These optimizations allowed \( V_{O2A} \) kinetics to be accurately predicted from knowledge of circula-
ory and respiratory dynamic interactions at the onset of exercise. Changes in the default parameters in our model are highlighted in Table 1 and include the separation of V̇E into multiple compartments, increased resting Q̇ and V̇O2 and an alteration in their distribution, dynamic changes in “rest-of-body” Q̇ and V̇O2 during exercise, and similar time constants for Q̇m and V̇O2m. The validated MCM shows that 1) the kinetics of V̇O2A during an exercise transient are very sensitive to preexercise conditions, such as resting or unloaded exercise blood flow distributions, 2) a low preexercise Q̇m exaggerates the magnitude of the transient fall in Cvo2 for any given V̇O2m kinetics, necessitating a tighter coupling of Q̇m/V̇O2m (or a reduction in the available work rate range) during the exercise transient to avoid O2 extraction limitation, and 3) information regarding exercise-related alterations in V̇O2 and Q in the nonexercising muscles and their effects on CVO2 is required to accurately predict V̇O2A kinetics from knowledge of V̇O2m and Q̇m dynamics. Use of the MCM with default values established in this study, together with measured values of V̇O2A and τQ̇, significantly improved V̇O2A and τQ̇ prediction compared with use of the phase II V̇O2A as a proxy. Importantly, these data clearly demonstrate that V̇O2A kinetics are nonexponential, nonlinear distortions of V̇O2m kinetics, which can be explained in a MCM by interactions among circulatory and cellular respiratory control processes before and during exercise.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.P.B. and H.B.R. conceived and designed the study; A.P.B. and H.B.R. interpreted the results of the experiments/simulations; A.P.B. prepared the figures and the first draft of the manuscript; A.P.B., B.G., and H.B.R. edited and approved the final version of the manuscript.

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