Gløersen, Ø. N., Colosio, A. L., Boone, J., Dysthe, D. K., Malthe-Sørenssen, A., Capelli, C., Pogliaghi, S. (2022). Modeling V̇o2 on-kinetics based on intensity-dependent delayed adjustment and loss of efficiency (DALE). *Journal of applied physiology, 132*(6), 1480-1488. http://dx.doi.org/10.1152/japplphysiol.00570.2021

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**Title:**

# Modeling $VO_2$ on-kinetics based on intensity-dependent Delayed Adjustment and Loss of Efficiency (DALE)

Running title: Time to revise the 3-phase model for $VO_2$ on-kinetics?

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**Abstract**

This study presents and evaluates a new mathematical model of $\dot{V}O_2$ on-kinetics, with the following properties: (*i*) a progressively slower primary phase following the size-principle of motor unit recruitment, explaining the delayed $\dot{V}O_2$ steady state seen in the heavy exercise intensity domain, and (*ii*) a severe-domain slow component modelled as a time-dependent decrease in efficiency. Breath-by-breath $\dot{V}O_2$ measurements from eight subjects performing step cycling transitions, in the moderate, heavy and severe exercise domains, were fitted to the conventional 3-phase model and the new model. Model performance was evaluated with a residual analysis and by comparing Bayesian (BIC) and corrected Akaike (AICc) information criteria. The residual analysis showed no systematic deviations, except perhaps for the initial part of the primary phase. BIC favored the new model, being 9.3 (SD 7.1) lower than the conventional model while AICc was similar between models. Compared to the conventional 3-phase model, the proposed model distinguishes between the kinetic adaptations in the heavy and severe domains by predicting a delayed steady state $\dot{V}O_2$ in the heavy and no steady state $\dot{V}O_2$ in the severe domain. This allows to determine when stable oxygen costs of exercise are attainable and it also represents a first step in defining time-dependent oxygen costs when stable energy conversion efficiency is not attainable.

*Keywords:*
Oxidative metabolism, VO2 kinetics, Primary component, Slow component, Modelling, Loss of efficiency, Work economy

## New & Noteworthy

We propose and assess a new minimalistic integrated model for the VO2 on-kinetics, inspired by the currently available best evidence of the underlying mechanisms. We show that the model provides a similar fit as the conventionally used 3-phase model, even though a stricter data fitting method is used for the proposed model. The proposed model clarifies misconceptions related to the VO2 slow component's behaviour, by clearly predicting that steady-state VO2 is attainable in the moderate and heavy exercise intensity domains. Furthermore, the model opens new possibilities for assessing oxygen cost during severe intensity exercise without the fallible assumption of time-constant energy-conversion efficiency.

## Introduction

The current model for the oxygen uptake ($\dot{V}O_2$) kinetics to a step increase in energy demand, termed the 3-phase model, predicts that $\dot{V}O_2$ measured at the mouth adjusts to increased external work rate in three phases. The first phase, termed the cardio-pulmonary phase, is attributed to increased blood flow through the lungs caused by increased heart rate and increased venous return due to the muscle pump (1-3). The second phase, termed the primary phase, is attributed to increased $\dot{V}O_2$ in the working muscles. Because of the blood's transit time through the venous system, the onset of this phase is delayed by 15-30 s when measured at the level of the mouth, i.e. the time delay (1, 2). During the primary phase, $\dot{V}O_2$ follows a first order exponential pattern. The third phase is dependent on exercise intensity: for moderate intensity exercise, it is the attainment of a steady-state $\dot{V}O_2$; for heavy intensity exercise, the third phase includes an additional, delayed increase in $\dot{V}O_2$ before steady state is attained; for severe intensity exercise, $\dot{V}O_2$ will continue to increase until it reaches $\dot{V}O_{2\,max}$ and/or the subject reaches exhaustion (4). Despite the difference in behavior between the heavy and severe exercise intensity domains, the third phase is commonly modelled with a single delayed exponential function (Although there is a lack of consensus on how this phase should be quantified (5)). Compared to the primary phase, the onset delay of the third phase is minutes rather than seconds (1–3 min), and the time constant is substantially larger (6). Accordingly, this phase is termed the $\dot{V}O_2$ slow component (5).

In the past 30 years, the 3-phase modeling of $\dot{V}O_2$ kinetics during a step response has offered an invaluable non-invasive means to evaluate the dynamic behavior of $\dot{V}O_2$, which again has facilitated characterization of the limiting factors of $O_2$ delivery and utilization (3, 7).

However, the connection between the 3-phase model's mathematical form and the underlying physiological mechanisms is in fact not obvious (8). For the primary component – considered to reflect $\dot{V}O_2$ within the working muscles – the first order exponential model is underpinned by observations at the whole muscle level (8). However, there is evidence that the single first order exponential behavior observed at the whole muscle level arises from a sum of non-uniform responses in the muscle cells it is comprised of (8-11). Specifically, fast-twitch glycolytic fibers exhibit slower $\dot{V}O_2$ kinetics and lower energy conversion efficiency than slow-twitch fibers (9). It follows from Henneman's recruitment principle (12) that one should expect to see a slowing (and possibly an increased amplitude) of the whole-muscle $\dot{V}O_2$ kinetics as recruitment of fast-twitch fibers becomes significant, which occurs at an exercise intensity of 50–60% of $\dot{V}O_{2\,max}$ (13). Indeed, these theoretical predictions align well with data from studies comparing $\dot{V}O_2$ kinetics in the moderate and heavy exercise intensity domains (14). Within the 3-phase model, the above-described behavior is typically accounted for by the $\dot{V}O_2$ slow component. However, if slowing of the time constant and the increase in overall gain from the moderate to the heavy domain are in fact the results of an increased contribution of glycolytic fibers with increasing work rate, it would be more appropriate to call this phenomenon a "delayed steady state" and to ascribe it to the primary phase of $\dot{V}O_2$ kinetics. The reason for this is that it represents the same physiological mechanism, i.e. the working muscles' inertia to attain a steady rate of oxidative phosphorylation (15).

In contrast, the failure to reach a steady-state $\dot{V}O_2$ observed in the severe exercise intensity domain cannot be explained by the mechanism outlined above only. The mechanisms underlying this inability to attain steady-state $\dot{V}O_2$ are still debated, however, it appears that the majority (about 85%) of the increase in $\dot{V}O_2$ observed over time arises from the working muscles (16, 17). This behavior only appears when the subject exceeds a critical work rate (4), and is accompanied by the inability to maintain a stable intra-cellular biochemical environment in the working muscles (16). These changes in the biochemical environment lead to a gradual reduction in the energy-conversion efficiency of the myocytes, resulting in the inability to attain steady-state $\dot{V}O_2$ even if the work rate is constant. As such, this loss of efficiency developing over time may be distinct and independent from the "delayed steady state" described earlier (15). It would therefore be preferable if the term "$\dot{V}O_2$ slow component" was reserved for the behavior outlined in this paragraph, which is normally only observed in the severe exercise intensity domain.

The framework described above is corroborated by recent findings from our group (15, 18) and others (19), suggesting that, in the heavy domain, a contribution of fast twitch fibers may suffice to explain the observed slowing of the $\dot{V}O_2$ kinetics and, possibly, a concomitant increase in gain, without the need for increased recruitment over time as an explanatory mechanism. Moreover, in the heavy domain, the so-called $\dot{V}O_2$ slow component may not be the result of a loss of efficiency manifesting over time; rather, it may be the result of a slower up-regulation of the activity of rate-limiting enzymes and provision of adequate substrates. In the severe domain of exercise, however, the bioenergetic approach proposed by Colosio et al. (15, 18) verified the existence of a true slow component of $\dot{V}O_2$ (i.e. a loss of efficiency over time), which develops in unison with increased muscle activation. Accordingly, characterization of the $\dot{V}O_2$ response in this domain should include a delayed onset term, similar to the third phase of the traditional 3-phase modeling of $\dot{V}O_2$ kinetics.

In summary, the traditional successive delayed exponential modeling of the $\dot{V}O_2$-on kinetics is being questioned (15, 20-22) on the grounds of recent evidence that supports a domain-dependent modeling of the primary component, and modeling of the slow component as a gradually developing change in energy conversion efficiency. A critical re-visitation of the current fitting strategies may contribute to further our understanding of the possibly distinct physiological determinants of the adjustment of oxidative metabolism at exercise onset in the different domains of exercise. Accordingly, the aim of this study is to propose and to test the performance of a new minimal model for the on-kinetics of the primary and slow components of $\dot{V}O_2$ kinetics. Specifically, the model should satisfy two key points. First, the progressively slower $\dot{V}O_2$ kinetics at the mouth should be explained by recruitment of muscle fiber populations with different first order kinetics, whilst the kinetics of each fiber population remain unchanged across intensity domains. Second, the slow component should represent an inability to maintain stable energy conversion efficiency in the severe exercise intensity domain. We will test the model, termed Delayed adjustment and Loss of Efficiency (DALE), on step responses into the moderate, heavy and severe exercise intensity domains, and compare the model's performance to the conventional 3-phase model.

## Methods

### Mathematical model

*Fiber-type dependency of $\dot{V}O_2$ kinetics in the working muscles*

The DALE model assumes two fiber populations, corresponding to slow twitch (st) and fast twitch (ft) fibers. Both fiber populations follow first order kinetics, but with different time constants ($\tau_{st}$ and $\tau_{ft}$). Furthermore, the model assumes that the two fiber populations are activated in a strictly sequential manner, with no fast twitch activation prior to full activation of the slow twitch population. Hence, the exercise intensity corresponding to full activation of slow twitch fibers marks the point where $\dot{V}O_2$ kinetics in the working muscles will start to become progressively slower. In the current study, this threshold (known to occur at intensities 50–60% of $\dot{V}O_{2\,max}$ (13)). is termed $\dot{V}O_{2st,max}$. Following Henneman's size principle for motor unit recruitment (12), no further activation of slow twitch fibers can occur at exercise intensities above $\dot{V}O_{2,st,max}$, and any additional increase in intensity will lead to activation of the ft-fiber population. Letting $A_{st}$ and $A_{ft}$ represent the attractor for $\dot{V}O_2$ (after subtracting baseline $\dot{V}O_2$) in each fiber population, this is described by the two differential equations

$$\tau_{st} \cdot \ddot{V}O_{2,st} = A_{st} - \dot{V}O_{2,st}, \quad (1)$$

$$\tau_{ft} \cdot \ddot{V}O_{2,ft} = A_{ft} - \dot{V}O_{2,ft}, \quad (2)$$

where $\ddot{V}O_2$ is the time derivative of $\dot{V}O_2$, $A_{st}$ is bounded upwards to $\dot{V}O_{2,st,max}$, and $A_{ft}$ is zero if $\dot{V}O_2 \leq \dot{V}O_{2,st,max}$.

*Time dependent energy conversion efficiency during constant work rate exercise*

To accommodate the gradual loss of energy conversion efficiency (16) observed during constant work rate exercise in the severe (4) and (possibly) heavy exercise intensity domains, $A_{ft}$ is allowed to be time dependent in these domains. Specifically, the model allows for a time delayed linear increase in $A_{ft}$:

$$A_{ft}(t) = A_{0,ft} + \min\{0, \dot{A} \cdot (t - t_{d,sc})\}, \quad (3)$$

where $t_{d,sc}$ is the onset of the linear increase, and $\dot{A}$ is the rate of change ($mL \cdot min^{-2}$) in $A_{ft}(t)$ for $t \geq t_{d,sc}$.

*Analytical solution during a step-increase in work rate*

In the case of a step increase in work rate, Eqs. (1) and (2) are linear inhomogeneous differential equations with closed form analytical solutions. Due to the delayed onset of the linear increase term in Eq (3), Eq. (2) must be solved using $A_{ft}(t) = A_{0,ft}$ for $t < t_{d,sc}$ and $A_{ft}(t) =$

$A_{0,ft} + \dot{A}(t\text{-}t_{d,sc})$ for $t \geq t_{d,sc}$, and the two solutions are stitched together by requiring continuity at $t = t_{d,sc}$. Furthermore, we include a delayed onset ($t_{d,p}$) of the primary phase due to the venous transport time, by setting the initial conditions to be $\dot{V}O_{2,st}(t = t_{d,p}) = \dot{V}O_{2,ft}(t = t_{d,p}) = 0$. In this case, the differential equations have solutions:

$$\dot{V}O_{2,st}(t) = A_{st}\left(1 - e^{-\frac{t-t_{d,p}}{\tau_{st}}}\right), \tag{4}$$

$$\dot{V}O_{2,ft}(t) = A_{0,ft}\left(1 - e^{-\frac{t-t_{d,p}}{\tau_{ft}}}\right) + \begin{cases} 0, & \text{if } t < t_{d,sc} \\ \dot{A}\left(t - t_{d,sc} - \tau_{ft}\left(e^{-\frac{t-t_{d,sc}}{\tau_{ft}}} - 1\right)\right), & \text{if } t \geq t_{d,sc}. \end{cases} \tag{5}$$

Finally, $\dot{V}O_2$ measured at the mouth is given by

$$\dot{V}O_2(t) = \dot{V}O_{2,st}(t) + \dot{V}O_{2,ft}(t) + \dot{V}O_{2,baseline}, \tag{6}$$

where $\dot{V}O_{2,baseline}$ is the oxygen uptake directly prior to the step increase.

Experimental data

The model was tested on a dataset from a recently published study (15), which comprised three step-increases in power output during ergometer cycling. The dataset included eight active males (age 25 years (SD 2), body mass 74 kg (SD 10), height 181 cm (SD 5), $\dot{V}O_{2,peak}$ 49 ml·min$^{-1}$·kg$^{-1}$ (SD 3)), and the data collection was approved by the University of Verona Ethics Committee for Research on Human Subjects. The detailed description of the experimental protocol can be found in the original paper (15). In brief, work rate during the three different step-increases were set individually for each participant to ensure that they corresponded to moderate, heavy and severe exercise intensities (4). The moderate-, heavy- and severe-domain boundaries were established from a ramp incremental exercise test to exhaustion, with the metabolic intensity at the gas exchange threshold (GET) defining the boundary between moderate and heavy, and the respiratory compensation point (RCP) defining the boundary between heavy and severe (23).

The constant work rate steps were defined to be 80% of GET, midpoint between GET and RCP, and 60% Δ between GET and $\dot{V}O_{2,peak}$ for moderate, heavy and severe, respectively. These metabolic intensities were translated into constant external loads by left-shifting the $\dot{V}O_2$/W relationship from the incremental test, to account for the mean response time. In turn, the mean response time was determined based on $\dot{V}O_2$ data as a function of time from the ramp incremental exercise, as the intersection point of the line fitting the baseline $\dot{V}O_2$ data and the line fitting the incremental portion of the $\dot{V}O_2$ up to GET (24). The step increases in

work rate followed three minutes of 20 W cycling, and the step was repeated three times with durations 3, 6 and 9 minutes (i.e. a total of 9 step responses for each participant, 3 to each domain). Pulmonary gas exchange and ventilation were measured breath-by-breath throughout each constant load trial using a metabolic cart (Jaeger Oxycon Pro, Viasys Healthcare GmbH, Höchberg, Germany). Gas exchange measurements that were aberrant were removed using a 3 SD cutoff from the local mean, before the measurements were linearly resampled to 1 s intervals and then decimated to 5 s averages. $\dot{V}O_2$ during the constant load trials was averaged over the three trials (3, 6 and 9 minutes) in each intensity domain. GET and RCP were determined with ventilator technique based on inspection of the fractional concentration of end-tidal $O_2$ and $CO_2$ and the ventilatory equivalents for $O_2$ and $CO_2$ during the ramp trial (25), and was assessed by three blinded expert reviewers.

Data fitting

In line with the assumption that $\tau$ is constant for each fiber population, measurements of $\dot{V}O_2$ during the constant load trials were fitted to Eqs (4) and (5) using least squares optimization to all trials (moderate, heavy, severe) simultaneously. Specifically, the optimization variables $\tau_{st}$ and $\tau_{ft}$ were constants across all three exercise intensity domains, while the remaining variables ($t_{d,p}$, $t_{d,sc}$, $\dot{A}$ and $A$) were domain-specific (i.e. these parameters could take different values in different domains). This resulted in 12 optimization variables for the DALE model, since $t_{d,sc}$ and $\dot{A}$ are not included in the moderate domain. $\dot{V}O_{2,st,max}$ was set a priori to $\dot{V}O_2$ at GET. The data fitting was accomplished using the Trust Region algorithm implemented in Matlab's Curve fitting toolbox, using initial values and bounds as specified in Table 1. The conventional 3-phase model was fitted to the data using the same optimization algorithm (Trust Region algorithm, initial values and bounds specified in Table 1). In line with previous studies in the field (7, 26, 27), all optimization variables were free to vary between intensity domains. This resulted in 15 optimization variables for the conventional model (three in moderate, six in heavy and severe).

*** Table 1

Table 1: Initial values (IV) and bounds (LB: lower bound, UB: upper bound) for the model parameters used in the data fitting procedure. $A_{3\text{-}5}$ represents average $\dot{V}O_2$ measured from 3-5 minutes during the step that the model was fitted to. The Trust-region algorithm was used, with a tolerance on the function value of $10^{-9}$.

| | Parameter | Unit | IV | LB | UB |
|---|---|---|---|---|---|
| DALE model | $t_{d,p}$ | s | 10 | 0 | 20 |
| | $\tau_{st}$ | s | 20 | 10 | 40 |
| | $\tau_{ft}$ | s | 45 | 20 | 90 |
| | $t_{d,sc}$ | s | 90 | 0 | 180 |
| | $\dot{A}$ | $mL \cdot min^{-2}$ | 0 | -60 | 150 |
| | $A$ | $L \cdot min^{-1}$ | $A_{3\text{-}5}$ | $0.8 \cdot A_{3\text{-}5}$ | $1.2 \cdot A_{3\text{-}5}$ |
| Conventional model | $t_{d,p}$ | s | 10 | 0 | 20 |
| | $\tau_{p}$ | s | 25 | 5 | 90 |
| | $A_{p}$ | $L \cdot min^{-1}$ | $A_{3\text{-}5}$ | $0.5 \cdot A_{3\text{-}5}$ | $1.5 \cdot A_{3\text{-}5}$ |
| | $t_{d,sc}$ | s | 90 | 0 | 180 |
| | $\tau_{sc}$ | s | 100 | 50 | 1000 |
| | $A_{sc}$ | $L \cdot min^{-1}$ | 0 | 0 | $0.5 \cdot A_{3\text{-}5}$ |

*** End table 1

Statistics

Plots of model residuals versus time were prepared to check if there were periods where the model did not provide a good fit. The residuals at each time point were averaged over all participants and displayed with 95 % confidence intervals (CI). The hypothesis that the slow component exists only in the severe intensity domains was assessed by checking if the model parameter $\dot{A}$ was non-zero in the severe domain, but not different from zero in the heavy domain, using two one-sample *t*-tests. Significance level was $\alpha = 0.05$.

Finally, the DALE model's overall performance compared to the 3-phase model was evaluated using the corrected Akaike information criterion (AICc, that allows to select the model that minimizes information loss) and the Bayesian information criterion (BIC, that allows to select the model that generated the observed data) (28). Differences in AICc and BIC were reported as mean (SD) across all participants. Furthermore, differences in AICc were interpreted using Akaike weight (29), which represents the probability that either model minimizes information loss, and differences in BIC were interpreted using the recommendations of Kass and Raftery (30) (<2: Not worth more than a bare mention, 2-6: Positive, 6-10: Strong, >10: Very strong).

## Results

The absolute intensity at which the constant-load trials were conducted was 129 W (SD 27), 209 W (SD 29) and 267 W (SD 38) for the moderate, heavy and severe domain respectively. An example of the individual fitting results in all three exercise intensity domains is shown in Figure 1. This participant had a $\tau_{ft}$ that was 38 s longer than $\tau_{st}$; a distinct linear increase in $\dot{V}O_2$ ($\dot{A}$ = 126 mL·min$^{-2}$) in the severe trial, and a relatively small linear increase in $\dot{V}O_2$ ($\dot{A}$ = 24 mL·min$^{-2}$) in the heavy trial. The model coefficients for all participants, for both the DALE and conventional models, are shown in Table 2. As seen from the table, $\tau_{ft}$ was 19 s (SD 26) longer than $\tau_{st}$. The parameter $\dot{A}$ was 16 mL·min$^{-2}$ (SD 29) during the heavy trial, which was not different from zero ($P$ = 0.17). However, two of the participants did show a linearly increasing $\dot{V}O_2$ in the heavy domain. In contrast, $\dot{A}$ was 88 mL·min$^{-2}$ (SD 42) during the severe trial ($P$ < 0.001), and all participants showed a distinct increase in $\dot{V}O_2$ following the primary phase.

*** Table 2

Table 2: Model coefficients for the DALE-model and the conventional 3-phase model. All values are presented as mean (SD). Entries marked *clamped* indicates that the value was fixed to the value in the column to the left of the entry, according to the sequential fitting strategy. NA: parameter not applicable to this domain. Parameter definitions in footnote.

| | | Unit | Moderate | Heavy | Severe |
|---|---|---|---|---|---|
| DALE model | $t_{d,p}$ | [s] | 11.5 (3.0) | 13.8 (1.7) | 12.4 (1.9) |
| | $A_0$ | [L·min$^{-1}$] | 1.30 (0.27) | 2.08 (0.41) | 2.55 (0.34) |
| | $\tau_{st}$ | [s] | | 28 (8) | |
| | $\tau_{ft}$ | [s] | | 47 (24) | |
| | $\dot{A}$ | [mL·min$^{-2}$] | NA | 16 (29) | 88 (42) |
| | $t_{d,sc}$ | [s] | NA | 72 (72) | 118 (43) |
| Conventional model | $t_{d,p}$ | [s] | 12.7 (3.0) | 13.0 (2.2) | 13.2 (1.0) |
| | $\tau_p$ | [s] | 26 (9) | 30 (7) | 29 (5) |
| | $A_p$ | [L·min$^{-1}$] | 1.30 (0.27) | 2.04 (0.42) | 2.47 (0.35) |
| | $t_{d,sc}$ | [s] | NA | 144 (32) | 137 (38) |
| | $\tau_{sc}$ | [s] | NA | 455 (449) | 306 (260) |

| | | | | |
|---|---|---|---|---|
| $A_{sc}$ | [L·min$^{-1}$] | NA | 0.38 (0.37) | 0.74 (0.35) |
| $\dot{V}O_{2,baseline}$ | [L·min$^{-1}$] | 0.68 (0.04) | 0.71 (0.07) | 0.70 (0.05) |

**Parameters common for both models**: $t_{d,p}$ = time delay of primary phase, $t_{d,sc}$ = time delay of slow component. **Parameters in DALE model**: $A_0$ = initial $\dot{V}O_2$ amplitude (at $t$ = 0), $\tau_{st}$ = time constant of slow twitch fiber population, $\tau_{ft}$ = time constant of fast twitch fiber population, $\dot{A}$ = change in $\dot{V}O_2$ amplitude with time, **Parameters in conventional model**: $\tau_p$ = time constant of primary phase, $A_p$ = amplitude of primary phase, $\tau_{sc}$ = time constant of slow component phase, $A_{sc}$ = amplitude of slow component phase

*** End table 2

*Residual analysis and comparison to the 3-phase model*

The model residuals averaged over participants are shown in Figure 2. By visual inspection, the residuals appear randomly distributed with constant variance, except perhaps for the initial ~90 s. In this region, corresponding to the primary phase, both the DALE model and the conventional 3-phase model showed signs of small systematic deviations. For the between-model comparisons: AICc was similar for both models, being 1.8 (SD 7.1) lower for the conventional model. The Akaike weights were 0.36 for DALE and 0.64 for the conventional model, meaning that there was no clear evidence in favor of either model in minimizing information loss. BIC favored the DALE model, being 9.3 (SD 7.1) lower than the 3-phase model, which is considered "strong" evidence in favor of DALE being the model that generated the experimental data (30).

## Discussion

The aim of this study was to propose and assess a model for the on-kinetics of the primary and slow components of $\dot{V}O_2$, with the following two requirements: (*i*) a progressively slower primary phase (or delayed $\dot{V}O_2$ adjustment) attributed to the size-principle of motor unit recruitment, and (*ii*) a "true" slow component attributed to a gradually decreasing energy conversion efficiency with time. For the first point, we found that $\tau_{st}$ and $\tau_{ft}$ were 28 and 47 s, respectively, which adheres well with the difference in $\tau$ between fast and slow twitch fibers observed during in-vivo experiments on humans (9). For the latter point, the proposed (DALE) model showed no systematic deviations from experimental data and provided a similar fit as the conventional delayed exponential formulation.

The DALE model is an important alternative to the conventional 3-phase model because it establishes a clear distinction between the delayed steady-state $\dot{V}O_2$ typically observed in the

heavy domain, which we argue should be ascribed to the primary component (15), and the inability to achieve a steady state $\dot{V}O_2$ typically seen in the severe domain (16). Although the mechanisms underlying the proposed model have been previously reported in the literature and other studies have presented models that accommodate them in part (10, 14, 31), this is the first comprehensive model tested on experimental data in the moderate, heavy and severe exercise intensity domains. The results of the experimental evaluation, which was conducted using a fitting strategy that is stricter than the conventionally used fitting strategy where all variables are free to vary, largely support the proposed model. Importantly, systematic deviations between model and experimental data were observed only during the primary phase and were also present when using the conventional 3-phase model. These deviations are most likely modulations of pulmonary $\dot{V}O_2$ by circulatory and ventilatory dynamics (32), which suggests that model refinements of the early portion of the $\dot{V}O_2$ adjustment might be appropriate.

*Dependency of primary phase kinetics on muscle fiber type*

The values for $\tau_{st}$ and $\tau_{ft}$ (28 and 47 s, respectively) found in this study adhere well with studies on the muscle level (33 and 55 s, Krustrup et al. (9)). They are also close to the results from studies investigating the primary time constant during steps from elevated baselines. Specifically, Wilkerson and Jones (11) reported $\tau_p$ = 26 s and 46 s following a step increase in workload from unloaded to moderate and heavy intensities, respectively. In consonance with the model proposed in the current study, they interpreted this blunting of the primary phase kinetics as resulting from a shift from recruitment of primarily slow twitch fibers to primarily fast twitch fibers. Further, Pringle et al. (33) investigated the relationship between muscle fiber type distribution and $\dot{V}O_2$ pulmonary kinetics in a diverse group of subjects. When comparing groups with different fiber composition, they found differences in $\tau_p$ during steps to the heavy and severe domains, where the group with primarily slow twitch fibers showed faster kinetics (shorter $\tau_p$) than the group with primarily fast twitch fibers. They also found a tendency for the primary phase time constant to lengthen more in subjects with a low fraction of slow twitch fibers. Interestingly, there was no relationship between fiber type distribution and $\tau_p$ in steps to the moderate domain. All these findings agree with the DALE model, with the latter finding depending on the model assumption of no fast twitch fiber activation in the moderate intensity domain. This assumption, however, is challenged by the findings of Brittain et al. (34), who tested different steps within the moderate intensity domain (from 20 W to 50% of the lactate threshold and from 50 to 90% of the lactate threshold). They reported

an increase in the primary time constant in the higher compared to lower ranges of the moderate domain. In contrast, Spencer at al. (35), did not find differences in the primary time constant within the moderate domain during steps of different amplitude but from the same baseline. However, if the findings of Brittain et al. (34) are representative, this could imply that the DALE model's assumption of no fast twitch activation within the moderate domain (and consequently, unchanged $\tau_p$) is too simplistic. Alternatively, it can imply that fibers activated by motor units higher in the recruitment hierarchy have systematically slower kinetics, even if they are slow twitch fibers. Assessing fiber type activation directly is experimentally challenging, however, studies on glycogen depletion in different fiber types indicate a predominant, but not exclusive, activation of slow twitch fibers within the moderate domain (36). Taken together, these findings indicate that there is a shift in activation from slow twitch to fast twitch fibers at the boundary between moderate and heavy exercise intensity, but that the shift is probably not wholly abrupt. The DALE model can be modified to accommodate a gradual shift in fiber type recruitment, but this comes at the cost of increased model complexity (at least one additional model parameter). The importance of including a gradual shift in the model depends on how abrupt the shift in recruitment is: if the shift occurs over a small fraction of aerobically sustained workloads (say, 90-110% of GET), then modifying the model will have trivial consequences. However, the modification will be significant if the shift in recruitment progresses over a relatively large fraction of aerobically sustained workloads. Further studies on the relationship between muscle fiber type activation and the threshold separating moderate from heavy exercise would be useful to understand if, and how, the model should be modified. If the shift is close to abrupt, we maintain that the DALE model is appropriate as an idealized representation of the underlying mechanisms.

The assumption of homogenous kinetics within each muscle fiber population (slow- or fast twitch) should also be critically evaluated. Within-population heterogeneity undoubtably exists, and the assumption of homogeneity is a simplification. The important question is if it is a reasonable simplification. This can be taken to mean that $\tau_{st}$ and $\tau_{ft}$ determined by fitting the DALE model closely resembles the average $\tau$ of each population. On the grounds of numerical simulations with models that include within-population heterogeneity (supplemental material S1, https://figshare.com/s/ffec74b9431ec5d35536), we contend that the assumption of homogeneity is likely to be appropriate. However, both above-mentioned assumptions (abrupt shift in recruitment and within-population homogeneity) would benefit from more investigations, both numerical and experimental.

*Fiber dependent energy conversion efficiency*

A topic that was not highlighted in the current study is the difference in energy conversion efficiency between slow- and fast twitch fibers. In vitro studies on muscle fibers with different myosin isoforms show that fast twitch fibers have a higher ATP cost of tension (37, 38), and probably also a higher mechanical efficiency at contraction velocities associated with ergometer cycling at ~80 rpm (39, 40). These findings, combined with several studies designed to investigate the relationship between muscle fiber type activation and $\dot{V}O_2$ kinetics (see review by Jones et al. (41)), have led to the conclusion that the $\dot{V}O_2$ slow component is intrinsically linked to recruitment of fast twitch fibers. The DALE model disagrees only as a matter of terminology. Specifically, in the heavy exercise intensity domain, the DALE model predicts a delayed steady state, and allows for an increased $\dot{V}O_2$ gain compared to the moderate domain. The difference from the conventional 3-phase model is that we consider these effects to originate from the shift from anaerobic to aerobic ATP production within each muscle fiber, which is slower in fast twitch than slow twitch fibers (9). On this basis, even if the steady state is delayed and the $\dot{V}O_2$ gain might be higher than in the moderate domain, we argue that this phenomenon should be considered a "delayed primary phase". A further development of the model could be to include fiber-specific gains, where the slow twitch fiber gain is determined from steps to the moderate exercise intensity domain, and the fast twitch fiber gain is determined during steps from an elevated baseline at the transition between moderate and heavy. According to most studies in the literature, one should expect a higher gain for the fast twitch compared to slow twitch model component (16). The findings of Spencer et al. (35) indicate that a higher gain might be apparent already within the moderate domain. This finding can suggest fast twitch activation within the moderate domain, which would violate one of our model assumptions.

*Slow component as a delayed, gradual change in energy conversion efficiency*

We observed no systematic deviations from the prediction of a linearly increasing $\dot{V}O_2$ after 120 s in the severe domain. However, there were no systematic deviations using the conventional delayed exponential representation either. Hence, the residual analysis alone does not give a decisive answer for which of the models is more appropriate. The delayed exponential formulation was originally based on the presumption of a progressive recruitment of fast twitch muscle fibers (4, 6, 17, 42, 43). However, the $\dot{V}O_2$ slow component has been shown to emerge without progressive muscle fiber recruitment (44-46), which erodes the

argument of a causal relationship between progressive recruitment of fast twitch fibers and the $\dot{V}O_2$ slow component. Rather, the evidence points towards a gradual loss of energy conversion efficiency that is mainly attributed to an increased cost of ATP per force generation (13, 16, 47, 48) in the active muscle fibers. Consequently, it is more likely that the progressive iEMG activation seen during severe intensity constant load exercise is an effect of a gradually declining energy conversion efficiency in active muscle fibers – requiring additional neural stimulation to maintain a stable work rate – and not the cause of the $\dot{V}O_2$ slow component per se (48). Therefore, we contend that a linearly increasing gain with time is more appropriate than a delayed exponential function as a mechanistically based, minimalistic, integrated model for the $\dot{V}O_2$ slow component in the severe intensity domain.

Although most participants had kinetics consistent with our expectations (i.e. attaining a sub-maximal steady state $\dot{V}O_2$ in heavy and a gradually increasing $\dot{V}O_2$ in severe), a few individuals deviated from this behavior. Specifically, two participants did not reach steady state $\dot{V}O_2$ in heavy. Furthermore, although all participants showed a gradually increasing $\dot{V}O_2$ in severe, with six of eight subjects attaining $\dot{V}O_{2,max}$ at the end of the 9 minute trial, one individual only showed a slight increase in $\dot{V}O_2$ and ended just above his RCP at the end of the 9 minute trial. These deviations might be explained by inappropriate exercise intensity (i.e. prescribed power output) during the constant load trials, causing some participants to exercise close to the borders between moderate and heavy, and between heavy and severe. There are several studies showing that $\dot{V}O_2$ kinetics measured close to the heavy/severe border might not always be consistent with conventional expectations (49, 50), and that a gradual increase in $\dot{V}O_2$ might be observed even in the moderate domain if given enough time to develop (51). To summarize, even though most participants in the current study followed the expected behavior, we recognize that there is some dispute about the qualitative behavior of $\dot{V}O_2$ kinetics, particularly when exercising close to boundaries between intensity domains.

*Perspective*

Recent mechanistic evidence leads us to propose a revision of the conventional 3-phase mathematical modeling of the $\dot{V}O_2$ on-response. The revised model, termed DALE (Delayed Adjustment and Loss of Efficiency), was shown to be valid across exercise intensity domains, and had a fitting performance comparable to (or better than) that of the conventional delayed exponential representation. From a mechanistic perspective, the DALE model's distinction

between a delayed steady state and a true slow component may allow to clarify common misapprehensions and caveats when interpreting pulmonary $\dot{V}O_2$ kinetics. Specifically, the DALE model allows assessment of the overall metabolic energy cost of exercise/work economy in the moderate and heavy domains of exercise, where a steady state, though a delayed one, is attainable. Moreover, the time dependent gain included in the DALE model might be used to estimate the cost of severe intensity exercise.

In summary, the DALE model opens the possibility of assessing the function of different muscle fiber types, the domain-specific response to specific interventions (e.g. glycogen manipulations, fatigue, etc.) and it might also provide the first steps for a modeling framework were oxygen cost in all exercise domains can be accurately predicted.

**Supplemental material**

S1: "Effects of violating the DALE model's assumptions", available at https://figshare.com/s/ffec74b9431ec5d35536. Doi 10.6084/m9.figshare.19434983 is reserved but not active yet.

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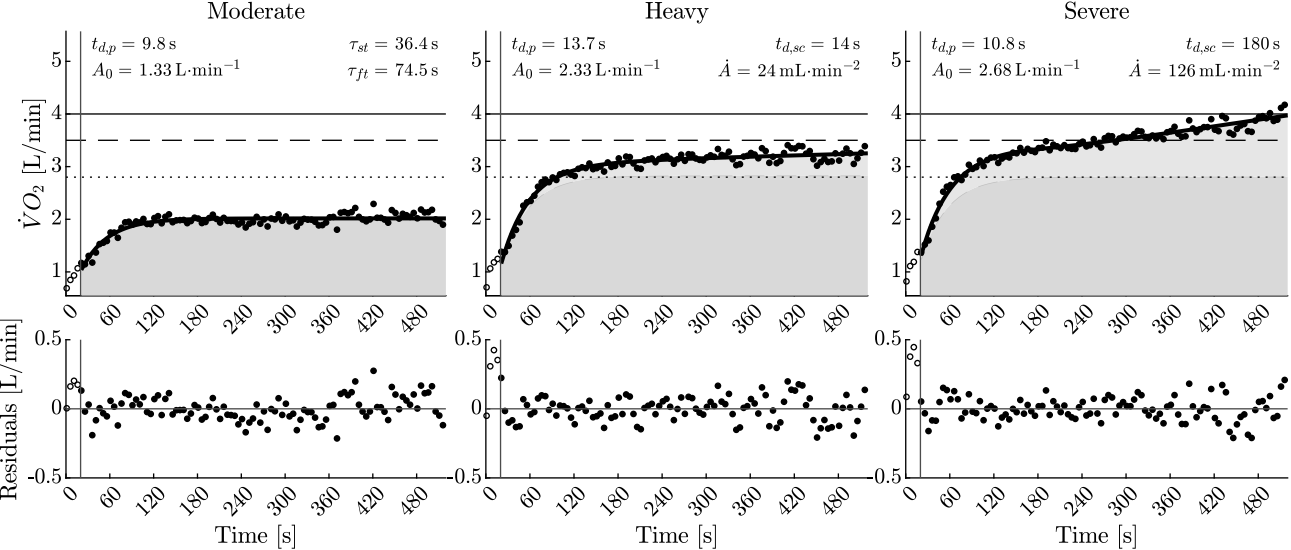
## Figure captions

Figure 1: Model fit in the moderate, heavy and severe domains for an example subject. Top row: $\dot{V}O_2$ vs time; bottom row: model residuals vs time. Measurements before 20 s are marked with open symbols and are not included in the analysis because they are confounded by the cardiopulmonary phase. The optimal parameters for each fit are shown in the upper left corner of each panel. Explanation of model parameters: $t_{d,p}$ = time delay of primary phase, $t_{d,sc}$ = time delay of slow component, $\tau_{st}$ = time constant of slow twitch fiber population, $\tau_{ft}$ = time constant of fast twitch fiber population, $A_0$ = initial $\dot{V}O_2$ amplitude (at $t = 0$), $\dot{A}$ = change in $\dot{V}O_2$ amplitude with time. The dotted, dashed and solid horizontal lines indicate GET, RCP and $\dot{V}O_{2\,max}$, respectively.

Figure 2: Residuals averaged over all participants at each time point, with 95% CI represented by the shaded areas. Blue lines represent the DALE model, red lines represent the conventional 3-phase model. The dashed horizontal lines indicate typical measurement variability, quantified as the standard deviation of $\dot{V}O_2$ measurements during the last minute of unloaded cycling (65 $mL \cdot min^{-1}$). It appears to be small systematic deviations during the primary phase (20 s < $t$ < 120 s), but no systematic deviations for $t \geq 120$ s. The vertical black line is at $t$ = 20 s and marks the presumed end of the cardiopulmonary phase. The root mean square (RMS) of the residuals is also reported within each panel.


Moderate
Heavy
Severe
$t_{d,p} = 9.8\,\mathrm{s}$
$\tau_{st} = 36.4\,\mathrm{s}$
$A_0 = 1.33\,\mathrm{L{\cdot}min^{-1}}$
$\tau_{ft} = 74.5\,\mathrm{s}$
$t_{d,p} = 13.7\,\mathrm{s}$
$t_{d,sc} = 14\,\mathrm{s}$
$A_0 = 2.33\,\mathrm{L{\cdot}min^{-1}}$
$\dot{A} = 24\,\mathrm{mL{\cdot}min^{-2}}$
$t_{d,p} = 10.8\,\mathrm{s}$
$t_{d,sc} = 180\,\mathrm{s}$
$A_0 = 2.68\,\mathrm{L{\cdot}min^{-1}}$
$\dot{A} = 126\,\mathrm{mL{\cdot}min^{-2}}$
$\dot{V}O_2$ [L/min]
Residuals [L/min]
Time [s]

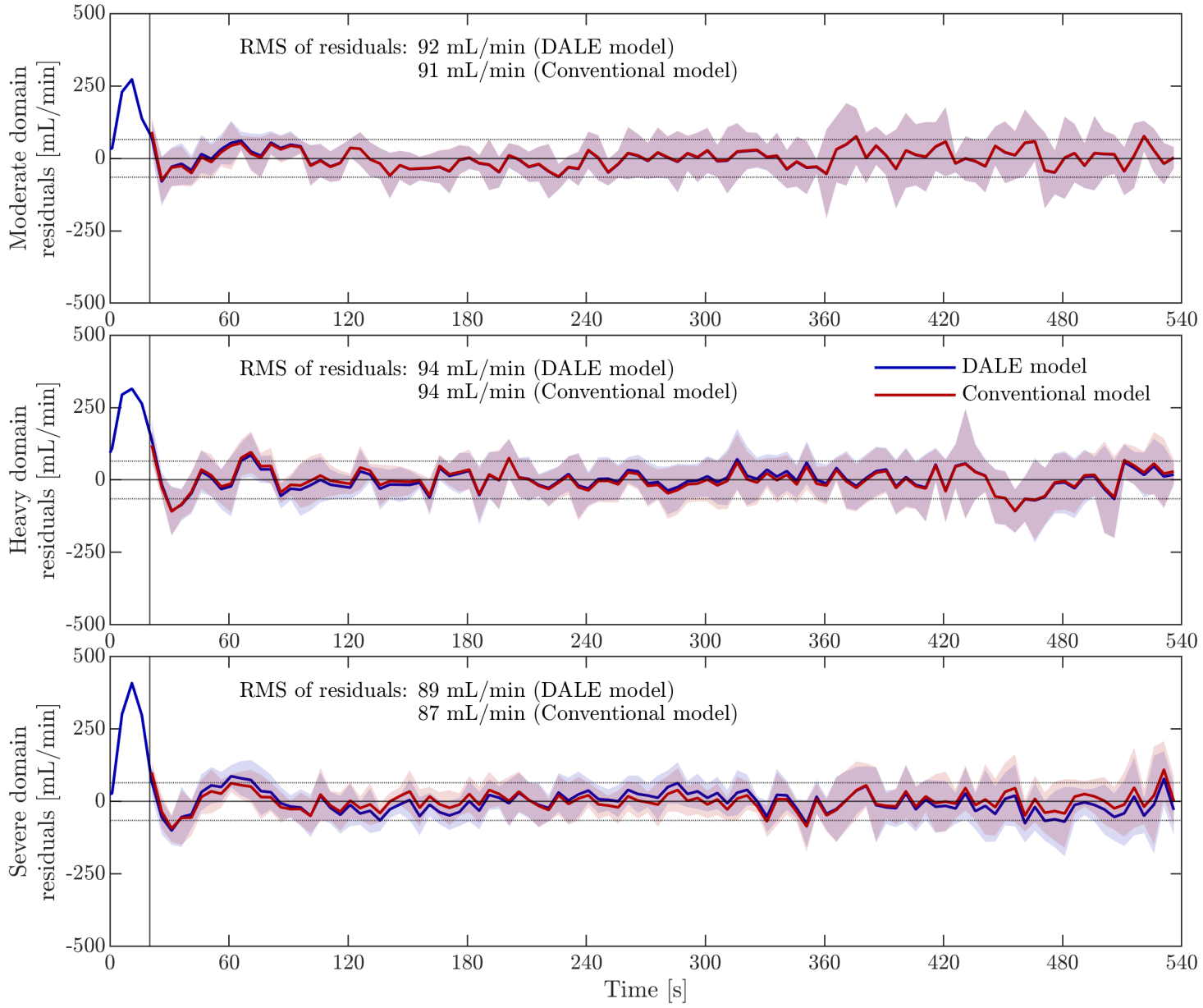

Moderate domain residuals [mL/min]
RMS of residuals: 92 mL/min (DALE model)
91 mL/min (Conventional model)
Heavy domain residuals [mL/min]
RMS of residuals: 94 mL/min (DALE model)
94 mL/min (Conventional model)
DALE model
Conventional model
Severe domain residuals [mL/min]
RMS of residuals: 89 mL/min (DALE model)
87 mL/min (Conventional model)
500
250
0
-250
-500
0
60
120
180
240
300
360
420
480
540
Time [s]

Table 1: Initial values (IV) and bounds (LB: lower bound, UB: upper bound) for the model parameters used in the data fitting procedure. $A_{3\text{-}5}$ represents average $\dot{V}O_2$ measured from 3-5 minutes during the step that the model was fitted to. The Trust-region algorithm was used, with a tolerance on the function value of $10^{-9}$.

| | **Parameter** | **Unit** | **IV** | **LB** | **UB** |
|---|---|---|---|---|---|
| DALE model | $t_{d,p}$ | s | 10 | 0 | 20 |
| | $\tau_{st}$ | s | 20 | 10 | 40 |
| | $\tau_{ft}$ | s | 45 | 20 | 90 |
| | $t_{d,sc}$ | s | 90 | 0 | 180 |
| | $\dot{A}$ | $mL \cdot min^{-2}$ | 0 | -60 | 150 |
| | $A$ | $L \cdot min^{-1}$ | $A_{3\text{-}5}$ | $0.8 \cdot A_{3\text{-}5}$ | $1.2 \cdot A_{3\text{-}5}$ |
| Conventional model | $t_{d,p}$ | s | 10 | 0 | 20 |
| | $\tau_p$ | s | 25 | 5 | 90 |
| | $A_p$ | $L \cdot min^{-1}$ | $A_{3\text{-}5}$ | $0.5 \cdot A_{3\text{-}5}$ | $1.5 \cdot A_{3\text{-}5}$ |
| | $t_{d,sc}$ | s | 90 | 0 | 180 |
| | $\tau_{sc}$ | s | 100 | 50 | 1000 |
| | $A_{sc}$ | $L \cdot min^{-1}$ | 0 | 0 | $0.5 \cdot A_{3\text{-}5}$ |

Table 1: Model coefficients for the DALE-model and the conventional 3-phase model. All values are presented as mean (SD). Entries marked *clamped* indicates that the value was fixed to the value in the column to the left of the entry, according to the sequential fitting strategy. NA: parameter not applicable to this domain. Parameter definitions in footnote.

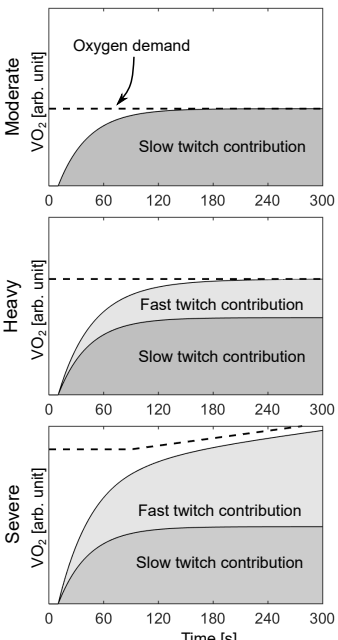
| | | Unit | Moderate | Heavy | Severe |
|---|---|---|---|---|---|
| DALE model | $t_{d,p}$ | [s] | 11.5 (3.0) | 13.8 (1.7) | 12.4 (1.9) |
| | $A_0$ | [L·min$^{-1}$] | 1.30 (0.27) | 2.08 (0.41) | 2.55 (0.34) |
| | $\tau_{st}$ | [s] | | 28 (8) | |
| | $\tau_{ft}$ | [s] | | 47 (24) | |
| | $\dot{A}$ | [mL·min$^{-2}$] | NA | 16 (29) | 88 (42) |
| | $t_{d,sc}$ | [s] | NA | 72 (72) | 118 (43) |
| Conventional model | $t_{d,p}$ | [s] | 12.7 (3.0) | 13.0 (2.2) | 13.2 (1.0) |
| | $\tau_p$ | [s] | 26 (9) | 30 (7) | 29 (5) |
| | $A_p$ | [L·min$^{-1}$] | 1.30 (0.27) | 2.04 (0.42) | 2.47 (0.35) |
| | $t_{d,sc}$ | [s] | NA | 144 (32) | 137 (38) |
| | $\tau_{sc}$ | [s] | NA | 455 (449) | 306 (260) |
| | $A_{sc}$ | [L·min$^{-1}$] | NA | 0.38 (0.37) | 0.74 (0.35) |
| | $\dot{V}O_{2,baseline}$ | [L·min$^{-1}$] | 0.68 (0.04) | 0.71 (0.07) | 0.70 (0.05) |

**Parameters common for both models**: $t_{d,p}$ = time delay of primary phase, $t_{d,sc}$ = time delay of slow component. **Parameters in DALE model**: $A_0$ = initial $\dot{V}O_2$ amplitude (at $t = 0$), $\tau_{st}$ = time constant of slow twitch fiber population, $\tau_{ft}$ = time constant of fast twitch fiber population, $\dot{A}$ = change in $\dot{V}O_2$ amplitude with time, **Parameters in conventional model**: $\tau_p$ = time constant of primary phase, $A_p$ = amplitude of primary phase, $\tau_{sc}$ = time constant of slow component phase, $A_{sc}$ = amplitude of slow component phase

# Modeling $VO_2$ on-kinetics based on intensity-dependent Delayed Adjustment and Loss of Efficiency (DALE)

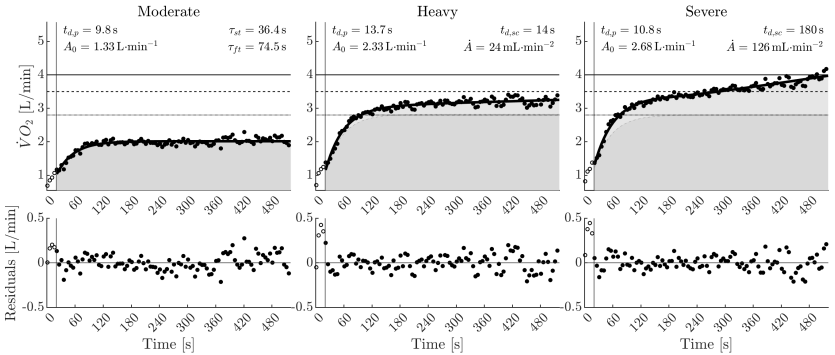
## Methods

Fitting a new mathematical model (DALE) to $VO_2$ step responses in the moderate, heavy and severe domains. Model properties:
1) Delayed steady-state $VO_2$ in heavy due to shift from slow- to fast-twitch muscle fibers.
2) No steady-state $VO_2$ in severe due to gradual loss of efficiency, leading to a time-dependent oxygen demand.

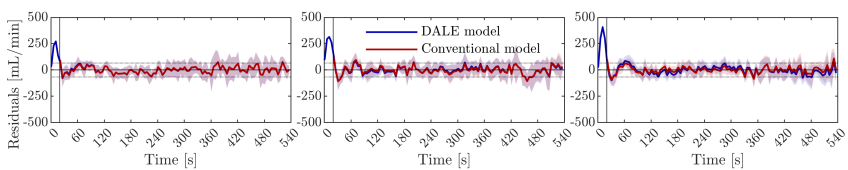



## Results

Model fit to an example participant:




Residuals averaged over all participants ($N$ = 8). Shaded areas show 95% confidence intervals.




There was no difference in RMS residuals between the DALE model and the conventional 3-phase model. The DALE model had a lower Bayesian Information Criterion, indicating that this is the preferred model.

## Conclusion

The DALE model is a viable alternative to the conventionally used 3-phase model of $VO_2$ kinetics because it is physiologically feasible, has fewer free parameters when fitted across intensity domains, while fitting equally well to experimental data as the conventional model. The model proposes a mechanistic distinction between the delayed steady state seen in the heavy domain and the continuous increase towards $VO_{2max}$ typically seen in the severe domain. This distinction has important consequences for interpretations of $VO_2$ reponses.