Constructing quasi-linear \( \dot{V}O_2 \) responses from nonlinear parameters

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Running Head:
Linear \( \dot{V}O_2 \) Response from Non-Linear Parameters

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Abstract

Oxygen uptake (\(\dot{V}O_2\)) kinetics have been shown to be governed by a nonlinear control system across a range of work rates. However, the linearity of the \(\dot{V}O_2\) response to ramp incremental exercise would appear to be the result of a linear control system. This apparent contradiction could represent a balancing of changing \(\dot{V}O_2\) kinetics parameter values across a range of work rates. To test this, six healthy men completed bouts of ramp incremental exercise at 15, 30, and 60 W∙min\(^{-1}\) (15R, 30R, 60R, respectively) and four bouts of an extended-step incremental exercise. \(\dot{V}O_2\) parameter values were derived from the step exercise using two mono-exponential models: one starting at time zero and encompassing the entire stage (MONO), the other truncated to the first five minutes and allowing a time delay (5TD). The resulting parameter values were applied to an integrative model to estimate the ramp responses. As work rate increased, gain values increased (\(p<0.001\) for MONO and 5TD), as did mean response time (or time constant) values (MONO: \(p<0.001\); 5TD: \(p=0.003\)). Up to \(\dot{V}O_{2\text{MAX}}\), the gains of the estimated ramp responses from both models were not different from the gains of the actual observed \(\dot{V}O_2\) responses for 15R and 30R (15R: 11.3±1.2, 11.7±0.7, 10.9±0.3; 30R: 10.5±0.8, 11.0±0.5, 10.7±0.3 ml \(O_2\)∙min\(^{-1}\)∙W\(^{-1}\), for actual, MONO, 5TD, respectively) but were significantly greater for 60R (8.7±1.0, 9.9±0.4, 10.3±0.3 ml \(O_2\)∙min\(^{-1}\)∙W\(^{-1}\) for actual, MONO, 5TD, respectively). Up to 80%\(\dot{V}O_{2\text{MAX}}\) gain values were not significantly different for any ramp rate (\(p>0.05\) for all).

We conclude that the apparently linearity of the \(\dot{V}O_2\) response to ramp incremental exercise is consequent to a balancing of increasing time constant and gain parameter values.
Keywords \( \dot{V}O_2 \) Kinetics Linear Ramp
Introduction

Pulmonary (and by implication muscle) oxygen uptake has previously been described as being determined by a linear control system modulated predominantly by work rate. This conclusion was based on the observed \( \dot{V}O_2 \) responses to step increases in work rate from an unloaded or very light work rate baseline to intensities at least up to the gas exchange threshold (GET), in which the rate of adjustment of \( \dot{V}O_2 \) (as a time constant \( \tau \) or mean response time MRT) and amplitude of change (as gain \( \Delta \dot{V}O_2 \Delta \text{work rate}^{-1} \)) were constant and independent of the magnitude of the change in work rate (1, 10). This implied that the increase in oxygen uptake (\( \dot{V}O_2 \)) responses adhered to the principle of superposition, which states that a given input (change in work rate) will always produce an identical output (change in \( \dot{V}O_2 \)) (33, 42).

In response to ramp exercise, \( \dot{V}O_2 \) increases linearly after an initial time delay. As the ramp-incremental work rate protocol is the integral of the step work rate protocol, the \( \dot{V}O_2 \) response to ramp exercise appeared to be the integral of the \( \dot{V}O_2 \) response to step exercise (50), reinforcing the notion that \( \dot{V}O_2 \) was in fact governed by a linear control system. Further, the fundamental parameters used to describe the response to step changes in work rate (gain and MRT or \( \tau \)) (1, 10, 52) were appropriate to describe the response of \( \dot{V}O_2 \) to ramp incremental exercise (16, 21).

However, many studies have provided indisputable evidence that the \( \dot{V}O_2 \) control system is nonlinear and is determined by more factors than work rate. First, the slow component of \( \dot{V}O_2 \) (\( \dot{V}O_{250} \)) imparts an additional \( \dot{V}O_2 \) increase during exercise above a moderate intensity (3, 10, 24, 34, 39, 49, 52). Second, the MRT of the \( \dot{V}O_2 \) response has...
been shown to be different when the work rate was increased or decreased by the same magnitude (11, 37, 38). Finally, elevated baseline work rate studies show that the gain and MRT of the \( \dot{V}O_2 \) response to a given change in work rate depends on the initial work rate (or \( \dot{V}O_2 \)) (15, 17-19, 27, 54, 55). Importantly, these elevated baseline studies showed differences not only for higher intensities, but within the moderate intensity as well (6, 8, 35, 47, 57). It is thus well documented that \( \dot{V}O_2 \) is controlled by a non-linear system, despite the apparent linearity of the \( \dot{V}O_2 \) response to a ramp protocol.

The apparent linearity of a \( \dot{V}O_2 \) response to ramp exercise thus indicates a dynamic balancing of variable gain and MRT parameters. An increasing gain would increase the \( \dot{V}O_2 \) at a given work rate (or time for a ramp protocol). An increasing MRT would delay the attainment of \( \dot{V}O_2 \), which would appear to decrease the \( \dot{V}O_2 \) at a given time (or work rate). These two effects could balance each other to maintain the apparent linearity of the ramp \( \dot{V}O_2 \) response. How exactly these parameters may balance each other has not yet been determined. An attempt has been made to combine the concepts of increasing MRT and decreasing efficiency (i.e. increasing gain) to produce a quasi-linear response (for review, see (43)), but this pursuit has not been verified empirically.

The purpose of this study, therefore, was to investigate the dynamic relationship between the gain and MRT parameters throughout a range of work rate transitions. Through the use of an extended-step protocol, values for gain and MRT can be determined for a series of work rates to test if the \( \dot{V}O_2 \) response adhered to the principle of superposition regarding constant output amplitude and kinetics irrespective of starting baseline. As a ramp protocol will escalate through these same work rates, we sought to
determine if the $\dot{V}O_2$ response to the ramp protocol is controlled by the same or similar
progression of gain and MRT values (i.e., principle of superposition regarding constant
output amplitude and kinetics irrespective of input forcing function). We hypothesized that
1) gain and MRT for a series of progressively increasing step work rate transitions would
increase with work rate, 2) an integrative model incorporating these step-protocol derived
parameter values for gain and MRT would accurately estimate the ramp response and, 3) a
more sophisticated model (i.e., including a time delay with the exponential response)
would improve the estimation of the model.

**Methods**

Participants

Six healthy men [(mean ± SD) age: 23.5 ± 2.4 years; height: 178.2 ± 5.7 cm; weight:
77.6 ± 9.2 kg] participated in this study. All participants were nonsmokers and free of
known cardiovascular, respiratory, and metabolic diseases as indicated by medical
questionnaire, which was distributed before testing. All participants gave written, informed
consent for the study as approved by the Kansas State University Institutional Review
Board. All participants were instructed to not consume caffeine or food for at least two
hours before each test and to avoid strenuous exercise and alcohol consumption for the 24
hours before each test.

Measurements

Breath-by-breath gas exchange was measured using an open circuit metabolic
system (Ultima CardiO2, Medical Graphics, St. Paul, MN, USA). The system measured
pulmonary $\dot{V}O_2$, carbon dioxide production, and minute ventilation. Before each testing
session, the flow transducer was calibrated using a 3 liter syringe and gas sensors were calibrated using precision-analyzed gases.

Exercise Protocol

All participants adjusted the seat height and handlebars on the cycle ergometer (Lode Excalibur Sport, Groningen, the Netherlands) to their own specifications. The handlebar and seat positions were then recorded and reset to the same values for every test. Each participant completed seven bouts of exercise to volitional exhaustion over a period of three to four weeks. There were at least 48 hours between each exercise bout.

The first three bouts were ramp-incremental exercise of varying ramp rates and the last four bouts were extended step-incremental exercise. Participants were instructed to maintain a pedal cadence between 70 and 75 rpm. Ramp rates of 15 W·min⁻¹ (15R), 30 W·min⁻¹ (30R), and 60 W·min⁻¹ (60R) were completed in a randomized order. Each ramp test began with five minutes of pedaling at a baseline work rate of 25 W. The initiation of the ramp was not indicated to the participant and the ramp increase in work rate continued until the participant failed to maintain 70 rpm for five s despite vigorous verbal encouragement. The work rate was then reduced to 25 W for five minutes of recovery.

The gas exchange data from the ramp incremental tests provided the $\dot{V}O_2$ at baseline ($\dot{V}O_{2BL}$), maximal oxygen uptake ($\dot{V}O_{2MAX}$), and the gas exchange threshold (GET). $\dot{V}O_{2MAX}$ was determined as the highest 15 s bin-averaged value across the three ramp protocols and validated, as similar $\dot{V}O_2$ values (<150 ml O₂/min difference) were reached at the end of both the 15R and 30R conditions. From the 30R data, GET was determined via V-slope method (4) in combination with examination of ventilatory equivalents and end-tidal
pressures of O₂ and CO₂ and the respiratory exchange ratio (32). These parameters were then used to establish the work rates for the extended-step incremental protocol. Each step incremental test began with five minutes of cycling at 25 W. The work rates for the next five steps were based on $\dot{V}O_{2BL}$, GET and $\dot{V}O_{2MAX}$ values for each subject. Each target $\dot{V}O_2$ value (described below) was paired to the closest five-breath mean value from the 30R. 20 W was then subtracted from the time-paired work rate to account for a 40 s MRT (27). Using that procedure, the target $\dot{V}O_2$ values for each of the five steps were: 1) 45% of the difference between $\dot{V}O_{2BL}$ and GET (S1), 2) 90% of the difference between $\dot{V}O_{2BL}$ and GET (S2), 3) 20% of the difference between GET and $\dot{V}O_{2MAX}$ (S3), 4) 40% of the difference between GET and $\dot{V}O_{2MAX}$ (S4), and 60% of the difference between GET and $\dot{V}O_{2MAX}$ (S5). Each step below GET lasted five minutes, while each step above GET lasted 15 minutes or until volitional exhaustion. Steps above GET were held for 15 minutes to allow the $\dot{V}O_{2SC}$ to fully develop so that $\dot{V}O_2$ would reach a steady state (if possible). Four repetitions of this extended step-incremental protocol were performed by each participant on separate days.

Data Processing

Offline, all gas exchange data were corrected for spurious breaths. Spurious breaths were defined as those outside three standard-deviations of the middle-five-of-seven breaths of a rolling seven breath average. These values were then replaced with the mean value of those same middle-five-of-seven breaths. These breath-by-breath data were then interpolated to second-by-second values. The ramp data were then averaged into 30 s bins, while the step-incremental data were separated into each work rate step. The second-by-second data for the four bouts of each step were time-aligned and averaged together. These
data were then averaged into 5 s bins. The average $\dot{V}O_2$ value from the final 30 s of the
previous step was used as the baseline value for the next step.

These averaged steps were then fit using non-linear regression with minimization of
the residual sum of squared errors (SigmaPlot 12.5, Systat Software, San Jose, CA, U.S.A.) to
each of two monoexponential models:

1) full stage with no time delay (MONO):

$$\dot{V}O_2 = \dot{V}O_{2BL} + \dot{V}O_{2SS} \cdot (1 - e^{-t/MRT}),$$

2) first five minutes of each stage with a time delay (5TD):

$$\dot{V}O_2 = \dot{V}O_{2BL} + \dot{V}O_{2SS} \cdot (1 - e^{-(t-\delta)/\tau})$$

where $\dot{V}O_{2BL}$ is the baseline $\dot{V}O_2$, $\dot{V}O_{2SS}$ is the steady state $\dot{V}O_2$, $t$ is time, MRT is the mean
response time, $\delta$ is the time delay, and $\tau$ is the time constant. These two models were
selected to span a range of complexity of previously published models. The first one was a
simple monoexponential model with no time delay (MONO), where the resulting kinetics (as
MRT) have been used to estimate the overall rate of change in $\dot{V}O_2$ (1, 10, 52). The second one
included a time delay to account for the circulatory delay between the contracting muscles and
the lungs (5TD). For this second model, the kinetics as tau would be closer to the kinetics of $\dot{V}O_2$
at the muscle level (2, 51). Post-hoc examination of the $\dot{V}O_2$ responses for the step transitions
above the GET failed to identify a slowly increasing $\dot{V}O_2$ past 3-4 minutes (slow component),
suggesting modeling the responses with a more complex double exponential function was not
warranted.
The parameter values for gain (as $\Delta \dot{V}_{O_2} / \Delta \text{work rate}^{-1}$) and either MRT or $(\tau + \delta)$ (depending on model) determined for each of these steps were then assigned to the work rate halfway between the previous and current steps. Values between adjacent steps were determined by linear interpolation. The parameter values for the first step of the extended-step protocol (S1) were used to describe the ramp responses between baseline (25 W) and the first work rate. In a similar manner, the parameter values from the highest completed step of the extended-step protocol (usually S4, as subjects typically fatigued before adequate data were attained for S5) were used to describe the responses from that step up to the peak work rate for each ramp. Parameter values were thus available for the range of work rates encountered during each ramp test.

These parameters were then used in integrative models to estimate $\dot{V}_{O_2}$ responses to each ramp test. There were two models used, corresponding to the fitting models described above (viz. MONO and 5TD). The integrative models were designed to emulate the actual ramp tests already performed. Therefore, each test began with a 25 W baseline. As a ramp work rate protocol is the integral of a step work rate protocol, every 30 s a new monoexponential component commenced with parameters set by the corresponding work rate. For every 30 s, all active monoexponential components were summed and added to the $\dot{V}_{O_2BL}$ value determined by the average $\dot{V}_{O_2}$ over the last 30 s of the 25 W baseline from the corresponding actual ramp test (Figure 1). This method provided an estimated value every 30 s which could then be compared to the actual 30 s values from each ramp style (Figure 2).
Each estimated model and the corresponding actual ramp responses were then graphed as functions of time with data points every 30 s. The gain for each response was calculated by first determining the slope of $\dot{V}O_2$ vs time by linear regression, excluding the nonlinear data from approximately the first minute (i.e., within the MRT). Gain was then calculated from the following equation:

$$gain = \frac{\text{slope}}{\text{ramp rate}} \cdot 1000$$

where slope is given in $l\,O_2\cdot min^{-1}\cdot s^{-1}$ and ramp rate is given in $W\cdot s^{-1}$ to ultimately give gain in units of $ml\,O_2\cdot min^{-1}\cdot W^{-1}$. MRT (s) was calculated, as previously described (45, 48), as the time at which the slope of $\dot{V}O_2$ vs time, determined while excluding the first minute of data and any data $> GET$, intersected the baseline $\dot{V}O_2$.

Statistics

One-way repeated measures ANOVAs were used to compare the peak $\dot{V}O_2$ values from the three ramp tests. Paired t-tests were used to compare the target and actual $\dot{V}O_2$ values from each stage of the extended-step protocol. To evaluate whether gain and MRT increased over the range of work rates used in the step protocol, a Friedman repeated-measures ANOVA on ranks was completed for each fitting strategy. This test was used instead of a one-way repeated-measures ANOVA because the intervals between work rates were not evenly spaced and the data were thus ordinal. Post-hoc Student-Newman-Keuls tests were used to compare parameter values between work rates. To evaluate the accuracy of each model's estimation, the actual $\dot{V}O_2$ ramp responses were compared to the estimated $\dot{V}O_2$ ramp via linear regression up to $\dot{V}O_{2\text{MAX}}$. Ramp $\dot{V}O_2$ responses were also evaluated by a two-way repeated measures ANOVA (ramp rate x model), which was run for
each parameter (i.e. gain and MRT) determined from the linear regression of the ramp responses. As we did not obtain parameter values for work rates all the way up to \( \bar{VO}_{2\text{MAX}} \), we also compared the models only up to 80\% \( \bar{VO}_{2\text{MAX}} \) to evaluate the models over a range of work rates for which we did have parameter values.

A linear regression was used to investigate the relationship between the change in gain and MRT for the range of work rates. Statistical significance was determined at the \( \alpha=0.05 \) level. However, we include any p-value below 0.10 for the consideration of the reader.

**Results**

**Ramp Protocols**

For the group, GET was 2.13±0.26 l·min\(^{-1}\). Peak \( \bar{VO}_2 \) values were determined for each ramp rate and were not significantly different between the 15R and 30R ramp rates (15R: 3.98±0.40, 30R: 3.90±0.41 l·min\(^{-1}\)) nor between 30R and 60R (60R: 3.75±0.55 l·min\(^{-1}\)). This confirmed that the peak \( \bar{VO}_2 \) value was indeed the \( \bar{VO}_{2\text{MAX}} \). However, peak \( \bar{VO}_2 \) values for 15R were significantly greater than for 60R (p=0.037) (Figure 3).

**Extended-Step Protocol**

The end step \( \bar{VO}_2 \) from the highest stage at which \( \bar{VO}_2 \) parameters were measureable (S4; 3.47±0.27 l·min\(^{-1}\)) was significantly less than \( \bar{VO}_{2\text{MAX}} \) (p=0.018). However, the peak \( \bar{VO}_2 \) from the extended-step protocol (3.88±0.34 l·min\(^{-1}\)) was not significantly different from the \( \bar{VO}_{2\text{MAX}} \).
For both data-fitting strategies (MONO and 5TD), the gains of the extended-step protocol transitions significantly increased with work rate (p<0.001 for both MONO and 5TD) (Table 1). For MONO, the gain for each step was significantly greater than all lower steps (p<0.05 for all). For 5TD, the gain for each step was significantly greater than all lower steps (p<0.05 for all) except for S4 compared to S3.

For both data-fitting strategies, the MRT or τ of the extended-step protocol steps was significantly greater with higher work rates (p<0.001 and p=0.003 for MONO and 5TD, respectively) (Table 1). For MONO, the MRT of each steps was significantly greater than all lower steps (p<0.05 for all). For 5TD, the τ for S1 was significantly less than all greater steps (p<0.05 for all). However, the τ of the three higher steps were not significantly different from each other.

Accuracy of MRT Estimations

As a main effect, the MRT estimations from the models were not significantly different from the actual ramp (ACT) (Table 2). For the MONO model, the estimated MRT was significantly different from ACT for 15R (p=0.019), but not for 30R nor for 60R. For the 5TD model, the estimated MRTs were not significantly different from ACT for any ramp rate (p=0.096 for 15R). As MRT is calculated using only the data after one minute and up to GET, these values will be the same for the VO2MAX, and 80%VO2MAX data subsets.

Accuracy of Gain Estimations Up to VO2MAX

Within ACT, the gain was not significantly different between 15R and 30R (Table 2). However, the gain of 60R was a significantly less than both 15R (p<0.001) and 30R (p=0.009). There were no significant differences between the gains estimated by either
model and ACT for 15R or 30R. However, for 60R the gains predicted by both models were significantly greater than ACT (p=0.004 and p<0.001 for MONO and 5TD, respectively). The gains predicted by the two models were significantly different from each other for 15R (p=0.028) but not for 30R or 60R.

Accuracy of Gain Estimations Up to 80%VO₂MAX

Up to 80%VO₂MAX, the gain for ACT 60R was significantly less than 15R and 30R (p<0.001 and p=0.001, respectively), whereas 15R and 30R were not significantly different (Table 2). The gain estimates from both models were not significantly different from the ACT gain nor from each other for any ramp rate.

Discussion

Consistent with our first hypothesis, MRT and gain were found to increase with work rate during the progressive step incremental protocol. Up to VO₂MAX the integrative models produced accurate estimates of the actual VO₂ response to a ramp incremental protocol for both 15R and 30R, but not 60R. However, when the models were run up to work rates for which actual parameter values were available (i.e. 80%VO₂MAX), the models were accurate for all three ramp slopes, consistent with hypothesis two. However, in contrast to hypothesis three, the inclusion of a time delay and limiting the influence of the VO₂SC (5TD) did not produce a more accurate estimate than a simple monoexponential model (MONO).

Gain and τ or MRT Related to Work rate
Our data demonstrate that with an increase in work rate, both gain and MRT (or $\tau$) increase. These findings agree with previous research which shows that the end-exercise gain increases with work rate (8, 37, 38, 44, 46, 47, 54). Furthermore, below GET several studies have shown that the gain of the primary phase increases with increases in baseline work rate (6, 8, 35, 46, 47). Above GET, the gain of the primary phase has been shown to decrease as $\hat{V}O_{2\text{MAX}}$ is approached (45), yet the overall end-exercise gain continues to increase (9, 41, 44, 54). This occurs primarily as a result of the increasing $O_2$ cost mediated by the $\hat{V}O_{2\text{SC}}$ (44, 54). Thus, for a simple monoexponential response, as modelled in this study, the (end-exercise) gain has been shown to increase with work rate (1).

Previous research has also shown that an increasing work rate produces longer $\tau$ or MRT values. Below GET, $\tau$ of the primary response has been shown to be longer for higher baseline work rates (6, 8, 27, 35, 47). Studies have also shown a greater $\tau$ of the primary response with exercise above GET compared to exercise below GET (19, 29, 31, 38, 55, 56) although some studies suggest that $\tau$ remains constant (30, 37, 44). To help clarify these mixed results, Jones and Poole combined the mean results of 25 studies and found that the $\tau$ of the primary response was typically about 20% longer for exercise above GET (28).

The mechanism(s) behind an increase in $\tau$ with increasing work rate are still under debate. Two mechanisms have received the most attention: 1) muscle fiber recruitment patterns (8, 46) and 2) muscle blood flow kinetics (7, 20, 25, 35). As exercise intensity increases, myofibers with progressively slower $\tau$ and lower efficiencies are recruited (12-14, 22). The responses of these active fibers will then be summed to provide a pulmonary (or muscle) $\hat{V}O_2$ response which will appear to be simply a mono- or double exponential
response, but with slower $\dot{V}O_2$ kinetics (8, 53, 54). Muscle blood flow kinetics were purported to slow $\dot{V}O_2$ by limiting $O_2$ availability at the muscle (27, 35). However, recent evidence suggests that these two mechanisms are not the only mediators of the increase in $\tau$ (57). This latter study used a canine gastrocnemius preparation in which a pump controlled blood flow and the sciatic nerve was activated maximally. Blood flow kinetics and muscle unit activation were both controlled and yet the slowing of $\tau$ persisted.

In the current study, both S3 and S4 were above GET, thus the $\dot{V}O_{2SC}$ should be present and would be expected to increase both $\tau$ or MRT and gain as compared to S1 and S2, which were below GET (37, 38, 40). The MONO model showed significant increases in both MRT and gain across all steps, consistent with this expectation. The 5TD model, however, did not result in consistent differences between the gain and MRTs above versus below GET. Much of this is likely due to an attenuation of the effect of the $\dot{V}O_{2SC}$, as the final 10 minutes of the stages above GET were removed from fitting for this model. This could reflect a diminishing rate of increase in the amplitude of the primary component of $\dot{V}O_2$ as a function of work rate. As noted above, this would fall against the weight of observations, but the point is debatable. Due to the low signal-to-noise ratio inherent in small increases in work rate, we were unable to reliably fit a more complex model, which would have allowed us to more directly analyze the contributions and behaviors of the primary and slow-components of $\dot{V}O_2$. Regardless of the statistical analysis of the data, the models utilized parameter values based on the empirically derived parameter values precisely determined for each subject, which did increase with work rate.

Estimated Versus Actual Results
When the data up to $\dot{V}O_{2\text{MAX}}$ were compared, both models produced estimates whose parameter values were not significantly different from the ACT responses except for gain in the 60R condition and MRT in the 15R condition (only MONO).

Because of the variability and unreliability of the calculation of MRT, especially in the 15R condition, we do not believe this difference in MRT for 15R alone indicates a shortcoming of the MONO model. This considerable variability in MRT is primarily due to the imprecision in calculating MRT using linear regression, especially from single ramp incremental responses (26, 36, 48). Much of this imprecision is due to the leveraging of data during linear regression where small changes in gain can result in extreme changes in MRT (26). Furthermore, differences in $\dot{V}O_{2BL}$ values can provide another source of imprecision. All ramps and extended step protocols were started from a baseline work rate of 25 W and a notable intrasubject variability in $\dot{V}O_{2BL}$ was observed (mean range of $\dot{V}O_{2BL}$ values from all tests was 128 ml O$_2$ · min$^{-1}$). Considering a typical gain of 10 ml O$_2$·min$^{-1}$·W$^{-1}$, that discrepancy in $\dot{V}O_{2BL}$ alone could explain 13 s of variability in the MRT for the 15R. Moreover, these discrepancies will be magnified within the 15R condition where, due to the expansion of the scale of the abscissa, small differences in the calculation of gain or $\dot{V}O_{2BL}$ would result in larger differences in time. Due to these factors, we believe the inaccuracy of the MONO estimated MRT value for 15R does not reflect a failure of the model but rather an imprecise method for parameter estimation.

The objective of the models was to accurately estimate the changing $\dot{V}O_2$ over a ramp incremental protocol given increasing parameter values. The gain describes exactly this change in $\dot{V}O_2$ over a change in work rate without specific regard for the $\dot{V}O_{2BL}$ value.
When the data up to $\dot{V}O_{2\text{MAX}}$ were compared, the gain was not significantly different between either model and ACT for 15R and 30R, but for 60R, both models over-estimated the gain compared to the ACT response (Figure 4).

This over-estimation could be due to the model using parameters that were not obtained at the highest $\dot{V}O_2$ values. Although the protocol included S5 (at 60%Δ), four of the six subjects fatigued before sufficient data were collected for fitting of the $\dot{V}O_2$ response. Therefore, the highest step for which we obtained parameter values was S4 (40%Δ). However, the $\dot{V}O_2$ value at the end of S4 was significantly lower than $\dot{V}O_{2\text{MAX}}$ (only 86.5±5.0% of $\dot{V}O_{2\text{MAX}}$). As a work rate, S4 was lower than the peak work rate from each ramp (86.0±3.5%, 74.3±3.6%, and 65.2±2.9% for 15R, 30R, and 60R, respectively). In this model, for work rates above S4 the parameter values were kept constant. Thus, for the 60R, the models estimated $\dot{V}O_2$ for the highest 35% of work rates based on constant values for gain and MRT.

Previous studies have shown that at work rates associated with peri-maximal $\dot{V}O_2$, MRT stays relatively constant while gain decreases (44, 54). These values were obtained using multiple step transitions from a single, lower baseline work rate. A step at these highest work rates was not possible with this extended-step protocol as task-failure occurred at stages with a lower work rate. However, a decreasing gain at higher work rates would decrease the estimated $\dot{V}O_2$ value at the highest work rates and thus ameliorate the over-estimations of the models. As we did not have exact work rate values at which this decline should begin, nor a reliable factor by which to decrease the gain from our S4 values, we were unable to directly apply this concept in our model.
To better understand the accuracy of the model for work rates at which we had empirically derived parameter values, we ran the models up to only 80% VO2MAX. Although the r² values decreased, removing the values from the top 20% of VO₂ resulted in more accurate estimations of the data (Figure 5). The decrease in r² values in this case is not a reflection of more disparate estimated values, but instead is a result of the decrease in the ranges of values. Using these datasets, the gain was not significantly different between either model and ACT for any ramp rate (Table 2). As MRT is calculated by truncating the dataset to only include values up to GET, the MRT values did not change by cutting the dataset down to 80% VO2MAX. However, as stated earlier, we do not believe that the discrepancy between the models’ and ACT values for MRT in 15R alone evinces a failure of the model.

Reliability Across Ramp Rates

Previous studies have shown that both the MRT (5, 45, 48) and gain (5, 21, 45, 48) decrease with increasing ramp rate (although see (16) for contrary results). The current data support those findings as gain decreased significantly with increasing ramp rate. However, in the current study, MRT was found to be significantly shorter for 15R than for 30R and 60R (as may be seen in the ACT data in Table 2). This shorter MRT in the 15R condition is heavily weighted by two trials which resulted in negative values. The MRT was determined from only data below GET and the first minute was excluded, however if the response had not yet reached its “linear” portion, a shorter MRT would be calculated. We removed the first 120 s of data, but some values were still negative. This reflects the
unreliability of MRT calculations from single ramp responses that has been previously reported (26, 36, 48).

Relationship Between MRT or \( \tau \) and Gain

The quasi-linear \( \dot{V}O_2 \) response to ramp incremental exercise appears to be due to the interactions between the nonlinear natures of gain and MRT or \( \tau \). Both the end-exercise gain and MRT were seen to increase with work rate. An increase in MRT means that the system is taking longer to exhibit a given increase in \( \dot{V}O_2 \). As the increase in \( \dot{V}O_2 \) is slowed, the \( \dot{V}O_2 \) at a given time is less than it would be if MRT was constant. This would appear as a progressive slowing of the rise in the \( \dot{V}O_2 \) response to ramp incremental exercise. This is counteracted by an increase in gain, which means that the subject is becoming less efficient, i.e. using more \( O_2 \) per minute per W. By itself, this would result in a growing upward shift in the \( \dot{V}O_2 \) response to ramp incremental exercise (Figure 6). Therefore, as both parameters increase, the downward shift caused by the increasing MRT is balanced by an upward shift due to an increasing gain, resulting in the appearance of a quasi-linear response.

Comparing the change in gain to the change in MRT reveals this balance (Figure 7). When the parameter values for all subjects from the extended step incremental are plotted against each other as a percent change from S1 values, it becomes apparent that although there is some intersubject variability, these parameters increase at a consistent proportion. The regression for the group data reveals that about 83\% of the variation in MRT can be explained by the variation in gain. Furthermore, for the group, a larger change in MRT is needed to balance a smaller change in gain in order to maintain apparent linearity. Therefore, a change in gain has a stronger relative influence on the \( \dot{V}O_2 \) response.
Limitations

The extended step incremental protocol was designed to segment the V̇O₂ response to specific regions. We believed that allowing each stage to reach a steady-state would more distinctly describe the V̇O₂ response to each increase in work rate. However, during that time, the milieu of the myofibers undoubtedly changes. Therefore, the state of the myofibers may be different from that at the same work rate during a ramp incremental test. We considered a protocol in which the subjects perform a single step each day to mitigate the effect of the prior work. However, for such a protocol to investigate the chosen stages with four trials and the three ramps would have required 23 visits to the lab. Further, since the previous work rate served as the baseline for each transition, there was no way to avoid any ‘contamination’ of the responses during the current work rate with any residual effect from the previous one. However, it should be noted that a similar contribution is likely occurring as work rate increases during the ramp test. Additionally, the extended-step protocol involved several smaller steps, which resulted in smaller increases in V̇O₂ responses (only a few hundred ml O₂). This resulted in a small signal to noise ratio for the fitting of the V̇O₂ responses. We took measures to decrease the noise such as correcting for spurious breaths, averaging four replicate transitions, and bin-averaging the data. Interestingly, the resulting V̇O₂ responses for S3 and S4 did not exhibit a discernible slow component. If V̇O₂ was measured even more precisely (requiring the averaging of many more step transitions), then a double-exponential (or monoexponential plus linear component) model may be applied and the presence and potential role of the V̇O₂SC could be determined. This would necessitate an additional component in the model, but could reveal important additional insights to the
control of oxygen uptake. Nonetheless, use of the simplest monoexponential function over
all the data permitted accurate prediction of the actual $\dot{V}O_2$ response in each subject.

Conclusions

We tested if an integrative model incorporating parameter values empirically
derived from constant work rate exercise could accurately estimate the $\dot{V}O_2$ response to
ramp incremental exercise. Both gain and MRT (or $\tau$) increased with work rate in an
extended-step incremental protocol. Through the range of work rates for which these
parameters were derived (80% $\dot{V}O_{2\text{MAX}}$), the models accurately estimated the actual $\dot{V}O_2$
response regardless of ramp rate. The addition of a time delay and a limiting of the impact
of the $\dot{V}O_{2\text{SC}}$ by only considering the first 5 min for S3 and S4 did not significantly improve
the ramp response estimates. Finally, increases in gain and MRT due to increases in work
rate showed a linear relationship. It therefore appears that the increasing gain and MRT
(or $\tau$) balance each other to produce the quasi-linear responses seen with ramp
incremental exercise.
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Conflicts of Interest

No conflicts of interest, financial, or otherwise, are declared by the authors.
Table 1: Parameter Values from Extended-Step Incremental Tests

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>MODEL</th>
<th>S1</th>
<th>S2</th>
<th>S3</th>
<th>S4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work Rate (W)</td>
<td>---</td>
<td>78.7±12.1</td>
<td>112.3±27.2</td>
<td>179.0±22.6</td>
<td>217.3±26.7</td>
</tr>
<tr>
<td>Gain (ml O₂·min⁻¹·W⁻¹)</td>
<td>MONO</td>
<td>10.0±0.9</td>
<td>11.6±1.1¹</td>
<td>13.1±1.3¹²</td>
<td>17.6±3.3¹²³</td>
</tr>
<tr>
<td></td>
<td>STD</td>
<td>9.8±0.9</td>
<td>11.5±1.1¹</td>
<td>12.5±1.5¹²</td>
<td>14.6±4.1¹²</td>
</tr>
<tr>
<td>MRT (s)</td>
<td>MONO</td>
<td>39.4±7.7</td>
<td>54.0±5.4¹</td>
<td>79.6±15.0¹²</td>
<td>180±56.2¹²³</td>
</tr>
<tr>
<td>τ (s)</td>
<td>STD</td>
<td>23.4±6.3</td>
<td>44.1±7.1¹</td>
<td>64.6±18.8¹</td>
<td>111.9±85.1¹</td>
</tr>
<tr>
<td>δ (s)</td>
<td></td>
<td>14.9±4.3</td>
<td>7.3±7.8</td>
<td>3.8±6.8</td>
<td>3.1±4.1</td>
</tr>
</tbody>
</table>

significantly different (p<0.05) than: ¹ S1, ² S2, ³ S3. As noted, parameter values from S5 were unavailable. However, the work rate for S5 was 250.7±30.4 W.
Table 2: Parameter Comparisons from Ramp Protocols

<table>
<thead>
<tr>
<th></th>
<th>Model</th>
<th>15R</th>
<th>30R</th>
<th>60R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MRT (s)</strong></td>
<td>ACT</td>
<td>6.2 ± 28.4</td>
<td>25.0 ± 15.2 &lt;sup&gt;S&lt;/sup&gt;</td>
<td>35.7 ± 12.1 &lt;sup&gt;S&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>MONO</td>
<td>28.2 ± 8.1 *</td>
<td>23.1 ± 6.4</td>
<td>17.3 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>5TD</td>
<td>22.6 ± 8.0</td>
<td>21.2 ± 7.1</td>
<td>21.0 ± 5.4</td>
</tr>
<tr>
<td><strong>Gain (ml O&lt;sub&gt;2&lt;/sub&gt;·min&lt;sup&gt;-1&lt;/sup&gt;·W&lt;sup&gt;-1&lt;/sup&gt;)</strong></td>
<td>Up to V&lt;sub&gt;O&lt;/sub&gt;MAX</td>
<td>ACT</td>
<td>11.3 ± 1.2 &lt;sup&gt;R&lt;/sup&gt;</td>
<td>10.5 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>MONO</td>
<td>11.7 ± 0.7 &lt;sup&gt;R,#&lt;/sup&gt;</td>
<td>11.0 ± 0.5</td>
<td>9.9 ± 0.4 *&lt;sup&gt;S,R&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>5TD</td>
<td>10.9 ± 0.3</td>
<td>10.7 ± 0.3</td>
<td>10.3 ± 0.3 *</td>
</tr>
<tr>
<td></td>
<td>ACT</td>
<td>10.7 ± 1.1</td>
<td>10.2 ± 0.5</td>
<td>9.2 ± 1.0 &lt;sup&gt;S,R&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>MONO</td>
<td>11.0 ± 0.8 &lt;sup&gt;R&lt;/sup&gt;</td>
<td>10.3 ± 0.6</td>
<td>9.2 ± 0.5 &lt;sup&gt;S,R&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>5TD</td>
<td>10.4 ± 0.4</td>
<td>10.2 ± 0.3</td>
<td>9.8 ± 0.2 &lt;sup&gt;S&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Significantly different (p<0.05) than: *ACT, †5TD, 15R, R 30R,
Figure Captions

**Figure 1** Integral of 30 s responses
Using parameter values determined from extended-step incremental data, an exponential $\dot{V}O_2$ response is started every 30 s. Every 30 s all active exponential responses are summed and added to the baseline $\dot{V}O_2$. This summed response estimates the ramp response.

**Figure 2** Comparison of model and actual $\dot{V}O_2$ responses to various ramps
Comparison between model (MONO in solid shapes) and actual (open shapes) $\dot{V}O_2$ responses to the three ramp rates as a function of time in a representative subject. Note that the actual $\dot{V}O_2$ responses to 15R (circles), 30R (triangles), and 60R (squares) differed as a function of time and, furthermore, that the model estimates matched these differences.

**Figure 3** Mean responses to various ramp rates
Group average $\dot{V}O_2$ responses to the three ramp rates as a function of time (Panel A) and work rate (Panel B). Peak $\dot{V}O_2$ from 15R and 30R were not significantly different, although the 30R ended at a higher work rate, demonstrating a true $\dot{V}O_{2\text{MAX}}$. However, the 60R condition caused task-failure before $\dot{V}O_{2\text{MAX}}$ could be reached.

Figure 4 Actual versus estimated group $\dot{V}O_2$ responses up to $\dot{V}O_{2\text{MAX}}$
Estimated $\dot{V}O_2$ values versus actual $\dot{V}O_2$ data up to $\dot{V}O_{2\text{MAX}}$. MONO model on the left, 5TD on the right. 15R is top, 30R is middle, 60R is bottom. Line of identity is solid line. Linear regression is broken line.

**Figure 5** Actual versus estimated group $\dot{V}O_2$ responses up to 80%$\dot{V}O_{2\text{MAX}}$
Estimated $\dot{V}O_2$ values versus actual $\dot{V}O_2$ data up to 80%$\dot{V}O_{2\text{MAX}}$. MONO model on the left, 5TD on the right. 15R is top, 30R is middle, 60R is bottom. Line of identity is solid line. Linear regression is broken line.

**Figure 6** Effects of parameter changes
30 s $\dot{V}O_2$ data from ramp protocol from actual response (open circles) and MONO model allowing both gain and MRT to vary (grey circles). The MONO model was then applied where gain was kept constant (diamonds) or MRT was kept constant (triangles). Notice the opposing effects of an increase in gain or MRT.

**Figure 7** Comparison of changes in gain and MRT
Comparison of increases in parameter values from extended-step incremental values. Values are normalized as a percent of S1 value. Both gain and MRT increased as work rate increased. However, the scaling shows that MRT changes to a greater extent than gain. Linear regression is broken line.