

# “LINEAR” VERSUS “NONLINEAR” $\dot{V}O_2$ RESPONSES TO EXERCISE: RESHAPING TRADITIONAL BELIEFS

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A number of basic tenets in traditional exercise physiology have been formulated on the assumption that pulmonary oxygen uptake ( $\dot{V}O_2$ ) adapts to changes in metabolic rate with linear, first-order response kinetics. However, questions regarding this premise have been raised for over half a century and clear contradictions have been reported. Specifically, Boltzmann's principle of superposition that defines linearity is violated for exercise transitions of different magnitudes, and the symmetry between on- and off-responses that first-order kinetics implies is not always present. Furthermore, a single exponential model does not adequately describe the  $\dot{V}O_2$  response to high-intensity exercise because a supplementary response compartment of delayed onset is manifest. Collectively, these findings reflect a range of nonlinear behaviors that indicate greater complexity of the  $\dot{V}O_2$  response, and it is imperative that these deviations be universally recognized, both to reshape our interpretation of the acute metabolic adaptation to exercise and also to provide clues regarding cellular mechanisms of respiratory control. [*J Exerc Sci Fit* • Vol 7 • No 2 • 67–84 • 2009]

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## Introduction

The purpose of this article is to review the history of oxygen uptake kinetics research with specific emphasis on discoveries of departures from first-order dynamic system linearity during both the on- and off-transition responses of pulmonary oxygen uptake ( $\dot{V}O_2$ ). Unfortunately, in a number of cases, this research has gone unrecognized by the exercise physiology community, which has, instead, shaped important tenets based on the flawed assumption that linear, first-order kinetics is consistently present. We will outline some of these unsupported premises and, specifically, how they should be modified to account for the observed departures

from linearity. Furthermore, we will consider potential mechanisms that might underpin nonlinear  $\dot{V}O_2$  behaviors and, finally, how deviations from dynamic response linearity can provide clues to help with the identification of potential mechanism(s) of  $\dot{V}O_2$  and, by extension, cellular respiratory control.

## Energy Transfer in Exercising Humans

Every time American swimmer Michael Phelps exploded off the starting block at the 2008 Olympic Games in Beijing, energy was utilized by his contracting muscles. Energy is defined as the capacity of a physical system to do work, and bringing home eight gold medals attests to the fact that Phelps performed a considerable amount of muscular work in the pool. However, muscular work is also done whenever we blink an eye or take a breath, so it is safe to say that energy is the essence of our very existence. The first law of thermodynamics states that energy can neither be created nor destroyed. However, it can be converted



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from one form to another, and Phelps' ability to do so was surely one of the key elements responsible for his success. There are three systems capable of converting the energy contained in the foods we eat into adenosine triphosphate (ATP), the substrate required to energize muscular contractions. The predominant one involves ATP synthesis (phosphorylation) via oxidation (the transfer of electrons from one molecule to another).

### ***Oxidative phosphorylation and O<sub>2</sub> consumption***

Oxidative phosphorylation takes place in mitochondria with molecular O<sub>2</sub> serving as the final electron acceptor. Consequently, this system of energy transfer mandates delivery of O<sub>2</sub> from the atmosphere to contracting muscle fibers where it will be consumed. The process of O<sub>2</sub> delivery/consumption is multifaceted; for example, convective O<sub>2</sub> transport alone depends upon pulmonary ventilation, arterial oxygenation, hemoglobin concentration, cardiac output, muscle blood flow and the spatial distribution of that blood flow to active muscle fibers. Furthermore, once O<sub>2</sub> is delivered, its diffusion into and utilization by mitochondria is determined by mitochondrial density, oxidative enzyme activity, metabolic substrate supply, muscle capillarity and the O<sub>2</sub> gradient that exists between capillary and mitochondria. Skeletal muscle O<sub>2</sub> consumption can, therefore, be influenced by many factors along this "O<sub>2</sub> cascade" route. As a discipline, O<sub>2</sub> uptake kinetics involves assessment of the rapidity with which O<sub>2</sub> consumption in contracting skeletal muscle adapts in response to a change in metabolic demand and the factor(s) along the O<sub>2</sub> transport/utilization route that might modulate this response.

### ***Pulmonary O<sub>2</sub> uptake ( $\dot{V}O_2$ )***

Ideally, O<sub>2</sub> uptake kinetics researchers would analyze O<sub>2</sub> consumption in the contracting muscles of exercising humans by directly measuring mitochondrial O<sub>2</sub> uptake. Unfortunately, technical limitations currently prevent this evaluation. Using the Fick principle, O<sub>2</sub> consumed across an exercising limb can be measured *in vivo* by simultaneously determining muscle blood flow in conjunction with blood O<sub>2</sub> content at arterial and venous sampling sites. However, while the findings from studies that have utilized this technology have been very insightful, the type of exercise that can be performed and the invasive nature of this procedure prevent its use during "normal" exercise conditions. Similarly, the measurement of O<sub>2</sub> consumption in surgically isolated single muscle groups, muscles and even muscle fibers has also proved vital for furthering our

understanding of the oxidative response in muscle. However, intrinsic factors critical to the process *in vivo* (e.g. the adaptation of blood flow/O<sub>2</sub> delivery and muscle fiber recruitment via nervous innervation) are artificially manipulated in these preparations; therefore, some ecological validity is compromised. With appropriate caveats, whole body O<sub>2</sub> consumption measured at the mouth (i.e. pulmonary O<sub>2</sub> uptake;  $\dot{V}O_2$ ) has been shown to closely reflect the kinetics of O<sub>2</sub> consumption in active muscles (Krustrup et al. 2009; Grassi et al. 1996; Barstow et al. 1990) and, therefore, provides a noninvasive alternative for measuring mitochondrial O<sub>2</sub> consumption in intact human muscle during conventional exercise activities.

## **The $\dot{V}O_2$ Response to Exercise**

### ***$\dot{V}O_2$ increase at exercise onset***

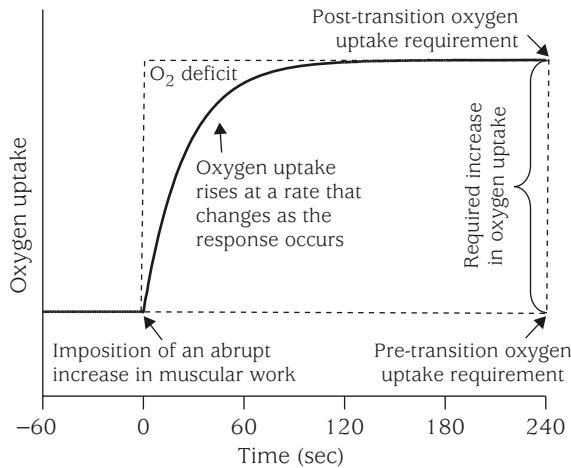
When muscular work is increased,  $\dot{V}O_2$  must also rise as a result of increased oxidative phosphorylation in active muscle mitochondria to support the ATP demands of contraction. It is well-established that  $\dot{V}O_2$  can increase quite rapidly at the onset of increased contractile activity, especially in endurance-trained athletes; however, regardless of conditioning level or the magnitude of the increase that is required, it is never instantaneous (i.e. the requisite or "steady state" level of O<sub>2</sub> consumption cannot be attained immediately). Rather, some degree of inertia is present and the instantaneous rate of the response (i.e.  $dy/dt$ , where  $y = \dot{V}O_2$  and  $t = \text{time}$ ) changes depending on how far the response is from fruition (e.g. see Figure 1). This response profile appears to be of an exponential nature which, if confirmed, would indicate that first-order kinetics is in operation.

### ***First-order kinetics***

A reaction conforms to first-order kinetics when its response rate depends exclusively on the concentration of one of its reactants. First-order kinetics indicates that the reaction rate at any point during the response will be dictated by the ever-changing error signal (i.e. the difference between the critical reactant's concentration at that point in time and what is required). This is exemplified in Figure 2A, which depicts the  $\dot{V}O_2$  response that might be expected during a square-wave transition from 0- to 150-W leg cycling. (Note: The block arrows indicate the error signal at three discrete time points: 1, upon initiation of the response, and 2 and 3, after 40 and 80 seconds of response time have elapsed, respectively. It is important to realize, however,

that an infinite number of error signal delineations could be made.) As is apparent, the instantaneous rate of the response ( $dy/dt$ ) is reduced as the error signal decreases.

First-order kinetics is based on the assumption of a linear model, i.e. a response profile described by a first-order differential equation (an equation that contains a first derivative, but none of higher order) with constant coefficients. The linear aspect of this model is apparent



**Fig. 1** When muscular work is abruptly increased (i.e. when an immediate transition from a lower to higher level of ATP turnover takes place), the corresponding increase in  $\dot{V}O_2$  does not follow a similar “square-wave” profile. Instead, the instantaneous rate of the response changes depending on how far the response is from fruition. This creates an “O<sub>2</sub> deficit” at exercise onset.

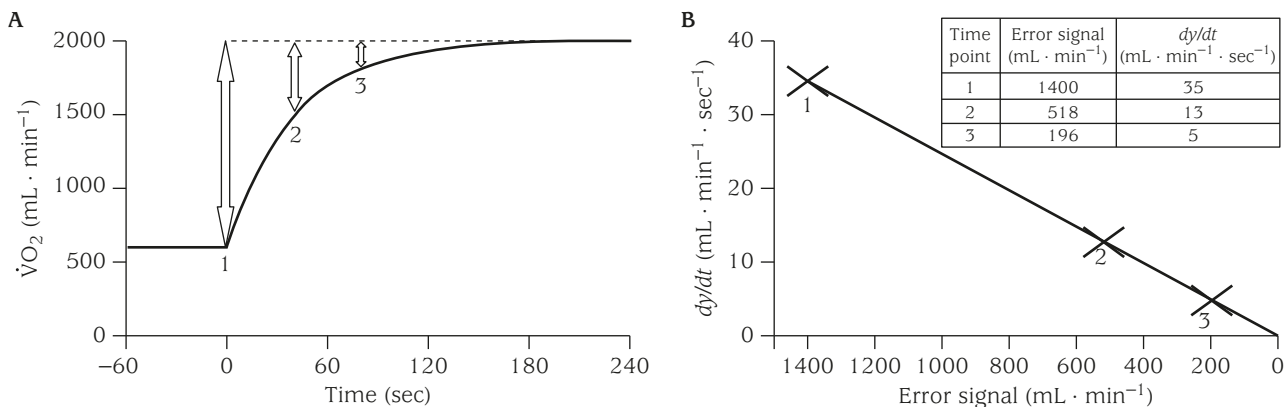
when the instantaneous response rate characterizing the exponential is graphed against the ever-changing error signal. For example, Figure 2B depicts a plot of these parameters for the response depicted in Figure 2A. (Note: The three error signals specifically highlighted in Figure 2A are also indicated on Figure 2B.) The depicted linearity means that there is a proportional relationship between the instantaneous rate of change of  $\dot{V}O_2$  ( $dy/dt$ ) and the error signal—i.e. the difference between the  $\dot{V}O_2$  value at steady state ( $y_{ss}$ ) and the  $\dot{V}O_2$  value at any point in time ( $y_t$ )—that can be described by a proportionality constant ( $k$ ) in accordance with the following equation:

$$dy/dt = k \cdot (y_{ss} - y_t)$$

The inverse of the proportionality constant is the time constant; therefore, the product of the instantaneous rate of change of  $\dot{V}O_2$  and the time constant determines the value of the  $\dot{V}O_2$  error signal at any point during a response that increases exponentially. From a practical standpoint, the time constant ( $\tau$ ) indicates the degree of curvature of the response curve and is the parameter typically used by oxygen uptake kinetics researchers to characterize the time course of  $\dot{V}O_2$  kinetics.

**Dynamic system linearity and Boltzmann’s principle of superposition**

Dynamic system linearity ensures that a number of important response characteristics will be present. Boltzmann’s principle of superposition forms the basis for defining linearity (Riggs 1976; Fujihara et al. 1973a;



**Fig. 2** (A) First-order  $\dot{V}O_2$  kinetics characterized by a monoexponential response profile where the instantaneous reaction rate at any point during the response (i.e.  $dy/dt$ ) is dictated by the ever-changing error signal (i.e.  $y_{ss} - y_t$ ). The block arrows indicate the error signal at three discrete time points during such a response: 1, upon initiation, and 2 and 3, after 40 and 80 seconds have elapsed, respectively. (B) The linear aspect of this model becomes apparent when the instantaneous response rate is plotted against the error signal. To exemplify this construct, the three error signals specifically highlighted in panel A are also indicated both graphically and in the inserted table in panel B.

Milsum 1966) and this principle states that the response of a linear system to two separate inputs is additive (i.e. the sum of the responses elicited by each input as if the other were not present). This means that if the  $\dot{V}O_2$  response to increased contractile activity conforms to the principle of superposition, the parameters describing the response would be independent of the baseline work rate from which the response is elicited and also of the amplitude and frequency of the forcing function that elicits the response (i.e. the specific sequence of stimulation that precipitates the contractile activity). First-order kinetics also mandates on-off symmetry, which means that the change in  $\dot{V}O_2$  that occurs when the contractile activity is ceased must be a mirror image of that which occurred when it was commenced (Rossiter et al. 2005).

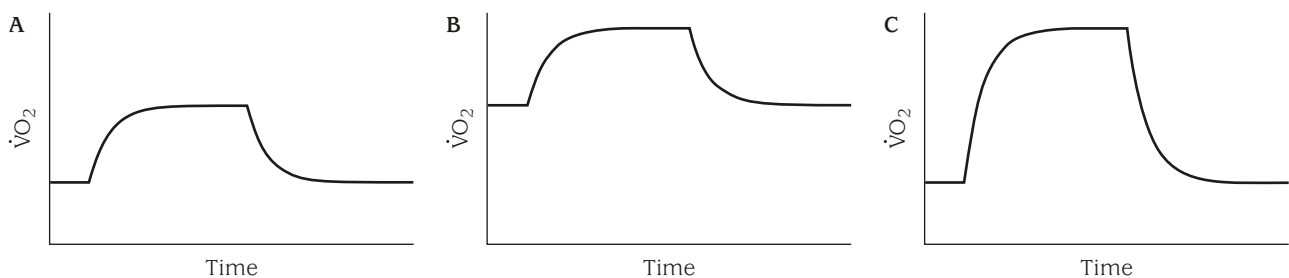
Figure 3 illustrates what would be expected if dynamically linear, first-order  $\dot{V}O_2$  kinetics was present across three separate square-wave on-/off-transitions elicited by changes in contractile activity (e.g. from Panel A to C, step changes from low to mid-range back to low work rate, step changes of the same magnitude from mid-range to high back to mid-range work rate, and a singular transition where both of the aforementioned are combined, i.e. a step change from low to high back to low work rate). Regardless of the magnitude of the  $\dot{V}O_2$  response (which depends on the change in work rate),  $\tau$  describing the on-transition curve is invariant and exactly equal to  $\tau$  describing the off-transition curve. Furthermore, the functional “gain” (G) of the response (i.e.  $\Delta\dot{V}O_2/\Delta\text{work rate}$ ) would be invariant during all transitions. These response characteristics would also be present if stimulatory patterns other than those of a square-wave nature (e.g. sinusoidal, impulse or pseudorandom binary sequence functions) were used to force the  $\dot{V}O_2$  response (Rossiter et al. 2005; Hughson et al. 1988; Casaburi et al. 1977).

A first-order  $\dot{V}O_2$  response model provides important inferences regarding metabolic control. Consequently, a number of well-established tenets and practices in traditional exercise physiology are directly based on the assumption of oxidative system linearity. However, questions regarding this assumption date all the way back to the mid-20<sup>th</sup> Century and in the ensuing years,  $O_2$  uptake kinetics researchers have devoted a great deal of investigative effort to assess whether the  $\dot{V}O_2$  response does, in fact, conform to this model. In the following section, we will review this research and how it has shaped our current level of understanding.

## **O<sub>2</sub> Uptake Kinetics**

### ***Discovery of O<sub>2</sub> and biological oxidation***

It is difficult to pinpoint a definitive event that signaled the dawning of  $O_2$  uptake kinetics as a field of scientific investigation. In fact, it can be argued that the birth of the discipline dates back to the very discovery of  $O_2$  itself! In the late 1700s, Joseph Priestly and Carl Wilhelm Scheele independently discovered a gas that we now know comprises 20.93% of ambient air (Sprigge 2002). Upon learning of their discoveries, Antoine Laurent Lavoisier named this “eminently respirable” gas oxygene (Jones & Poole 2005) and used a piece of apparatus he created to determine that the quantity in a chamber decreased when a living animal was sealed within (Brooks et al. 2000). Lavoisier’s innovative device also revealed that when  $O_2$  was consumed by the animal, a “chalky aeroform acid” ( $CO_2$ ) left the animal’s body in an approximately equal volume (Jones & Poole 2005). This was the earliest form of indirect calorimetry, the measurement of  $O_2$  consumption and  $CO_2$  production to estimate body heat production and, by extension, metabolic rate. Lavoisier concluded that



**Fig. 3** Dynamically linear, first-order  $\dot{V}O_2$  kinetics across three separate square-wave on-/off-transitions elicited by changes in contractile activity. Note that regardless of baseline or forcing function amplitude, the on-transition response time course (i.e. the value of  $\tau$  describing the exponential curve) is invariant and a mirror image of what occurs upon cessation. These responses are also additive (i.e. the system response to two separate inputs reflects the sum of each input as if the other were not present). See text for further explanation.

the rusting of metals and animal metabolism were similar processes that involved oxidation. However, before he could discover how and where oxidation took place (the prevailing belief was that it occurred in the lungs), he was tragically guillotined during the French Revolution (Sprigge 2002).

### **Human gas exchange analysis**

Lavoisier's calorimeter is an example of a spirometer (a piece of equipment that measures the volume and flow of inspired and expired air at the mouth). Specifically, it was a closed-circuit version because the animal breathed air within a sealed system. Open-circuit spirometry involves inhalation of ambient air and is the method typically used to measure pulmonary  $\text{O}_2$  consumption ( $\dot{V}\text{O}_2$ ) and  $\text{CO}_2$  production ( $\dot{V}\text{CO}_2$ ) during exercise. This process involves determination of the quantity of air ventilated and the change in gas concentration that occurs when ventilated air crosses the lungs.

Soon after Lavoisier's death, English scientist Humphry Davy became the first person to use open-circuit spirometry to perform human gas exchange analysis. Davy read Lavoisier's textbook (*Traite Elementaire de Chimie*) and correctly concluded that biological oxidation occurred in tissues where energy was released (Sprigge 2002). He then performed the first estimates of human  $\text{O}_2$  consumption and  $\text{CO}_2$  production by collecting expired air in silk bags and subsequently determining their  $\text{O}_2$  and  $\text{CO}_2$  content in a mercurial gasometer. By measuring and comparing the concentrations in the captured air with what was present in the air he inhaled, Davy estimated his own resting  $\dot{V}\text{O}_2$  ( $484 \text{ mL} \cdot \text{min}^{-1}$ ) and  $\dot{V}\text{CO}_2$  ( $447 \text{ mL} \cdot \text{min}^{-1}$ ) from a series of 20 experiments (Sprigge 2002).

Gas exchange analysis advanced to a new level in 1911 when British scientist Claude Douglas and three colleagues from Oxford and Yale ascended Pikes Peak in Colorado to study the acute effects of altitude exposure on ventilation and respiration (Cunningham 1964). During the expedition, Douglas used a bag-collection method he developed to measure  $\dot{V}\text{O}_2$  and  $\dot{V}\text{CO}_2$  at rest and during muscular work. Douglas was influenced to collect gases in this manner by childhood memories of magic lantern shows that involved storage of requisite gases (hydrogen and oxygen) in rubberized canvas bags. During his storied career, Douglas used similar bags to perform human gas exchange analysis with extraordinary speed and accuracy, thereby establishing a methodology that is practiced to this day. In fact, so powerful was his influence that this technique still bears his name (the Douglas bag method).

Douglas bag gas exchange analysis is considered the gold standard against which other methods are compared. This form of open-circuit spirometry requires the test subject to expire through a mouthpiece connected to a high-flow, low-resistance valve into a large plastic bag. After collection for specific time periods (e.g. 30 seconds), bags are sealed and a small sample from each bag is analyzed for  $\text{O}_2$  and  $\text{CO}_2$  concentrations. Bags are subsequently emptied into a gas meter to measure total volume ventilated (with account made for factors that affect gas volume, e.g. temperature and barometric pressure), and  $\dot{V}\text{O}_2$  and  $\dot{V}\text{CO}_2$  are determined from these measurements.

### **Gas exchange analysis during the non-steady state**

Douglas and partner J.S. Haldane were not the only research team to analyze human gas exchange during the early portion of the 20<sup>th</sup> Century. In 1913, Danish physiologists August Krogh and Johannes Lindhard published a groundbreaking study detailing the changes in circulation and respiration that took place in humans during the first few minutes of work (Krogh and Lindhard 1913). Unlike prior researchers dating all the way back to Lavoisier, these were the first to characterize  $\dot{V}\text{O}_2$  in the non-steady state (i.e. during the transition phase before a match between oxidative energy provision and energetic demand is achieved). Krogh and Lindhard measured gas exchange during rest-to-exercise transitions on a cycle ergometer and discovered that the increase in  $\dot{V}\text{O}_2$  upon initiation of work was rapid but, importantly, not instantaneous. They also identified a latent period of "a couple of seconds" prior to the response during which they speculated rapid chronotropic adaptation with inadequate venous supply (and, therefore, diminished systolic output) and suggested that for at least the first 6–10 seconds, the increase in  $\text{O}_2$  consumption by active tissue would be accompanied by a "nearly proportional" increase in circulation (i.e. tissue  $\text{O}_2$  consumption would increase, but the  $\text{O}_2$  tension of venous blood returning to the lungs would remain constant). Finally, they attributed the "considerable increase in  $\text{O}_2$  absorption" that followed to an additional (although smaller) increase in circulation, but suggested greater complexity by recognizing that oxygen extraction would also be increasing during this stage.

Bag collection of expired gases provides a viable way to determine  $\dot{V}\text{O}_2$  and  $\dot{V}\text{CO}_2$  during steady state conditions where volumes remain constant for extended periods and even during shorter measurement intervals, but not with the temporal resolution necessary to

precisely characterize a rapidly changing response. For example, while Krogh and Lindhard correctly determined that  $\dot{V}O_2$  does not immediately reach the requisite value when muscular work is initiated, the response characterization they provided was understandably vague (Krogh and Lindhard 1913). Their initial measurement consisted of air collected over the first ~12 seconds of work and two more collections were made during the first minute. In conjunction with  $\dot{V}O_2$  estimates they obtained in prior investigations where subjects performed single expiratory efforts of different durations to residual volume both before and after the initiation of work (to provide data that would presumably represent what occurred during the first few seconds of the response), these data allowed for the general response description they provide.

The third decade of the 20<sup>th</sup> Century saw the next important advance in our understanding of the  $\dot{V}O_2$  response following the onset of exercise. After being awarded the Nobel Prize for his work on contracting skeletal muscle and associated heat production in 1922, Hill and colleagues set forth to link observations they made on frog muscle isolated *in vitro* with observations made in exercising man (Hill et al. 1924). To do so, they used a portable Douglas bag gas exchange collection system to measure  $\dot{V}O_2$  and  $\dot{V}CO_2$  as subjects walked and ran on an open-air track. Importantly, this system also included a series of taps that provided the ability to instantaneously switch between multiple collection bags. These were used during the transitions to and from exercise to obtain a rapid succession of samples, thereby providing data with greater temporal resolution during transient response phases. The main purpose of this research was to determine how the  $O_2$  that was consumed during exercise compared to the volume that was actually required.

Hill et al. (1924) believed that the anaerobic energy production that satisfied the  $O_2$  deficit at exercise onset (the difference between what is required and what can be consumed, e.g. see Figure 1) was directly responsible for the increased  $O_2$  that was consumed once exercise was ceased. Their estimates of the  $O_2$  cost of running were, therefore, based on assumed symmetry between the on and off response, and were determined by adding the measured consumption during a bout to the volume consumed above resting levels afterwards. Using this methodology, Hill et al. determined that despite the initial response lag, subjects eventually (i.e. after “2 or 3 minutes”) achieved an  $O_2$  consumption that was equal to the requirement (i.e. steady state  $\dot{V}O_2$ ) at submaximal intensities, but that did not reach

the requisite value and was unable to be exceeded (i.e.  $\dot{V}O_{2max}$ ) at the highest speeds. They also published diagrams of their results that revealed an oxidative response profile characterized by a decreasing rate of change as progression to the eventual plateau took place (e.g. see Hill et al. 1924; pg. 167). However, these researchers were only concerned with analyzing the post-exercise response and made no attempt to mathematically characterize the rise they discovered at exercise onset. Surprisingly, almost 30 years would pass before any others did!

## Dynamic System Linearity of $\dot{V}O_2$ Kinetics

### *Henry's model of $\dot{V}O_2$ control*

In 1951, Henry suggested that during muscular work supported by sufficient  $O_2$  delivery (e.g. during exercise at steady state),  $O_2$  intake is determined by the availability of oxidizable metabolic substrate (e.g. Krebs cycle intermediates) and proposed a model by which the rate of accumulation of this provision would increase in an exponential manner during the transition to constant-load work (Henry 1951). By extension, Henry hypothesized that the rate of  $O_2$  consumption during a transition could be calculated as:

$$dy/dt = a_o \cdot (1 - e^{-kt})$$

where  $a_o$  is the steady state rate of  $O_2$  consumption (the response amplitude once equilibrium is reached between the accumulation and oxidation of the controlling substrate) and  $k$  is a velocity constant that would be entirely independent of (i.e. mathematically uncorrelated with) both  $a_o$  and the work rate that elicited the response. With this system of feedback control,  $a_o$  would increase linearly with work rate, at least up to the point where systemic limitations prevented a further rise. Henry tested his hypothesis by measuring  $\dot{V}O_2$  with subjects cycling at a variety of work rates and observed response curves that were satisfactorily described by the exponential model he proposed. However, it is important to note that subjects exercised at relatively light work rates that would have utilized only a small fraction of their metabolic reserve in this study.

### *Challenges to first-order $\dot{V}O_2$ kinetics*

The system proposed by Henry in 1951 suggests linear, first-order  $\dot{V}O_2$  control. However, in 1956, Henry and research partner J.C. DeMoor published findings that challenged this notion (Henry & DeMoor 1956).

Specifically, they demonstrated that the time to reach a steady state in  $\dot{V}O_2$  consumption increased with increasing work rates when subjects performed exercise of graded intensity. Consequently, they suggested that an equation with two exponential components was necessary to describe the rise of  $\dot{V}O_2$  during exercise.

During the 1960s, technological advancements dramatically changed open-circuit spirometry as computers and fast-responding  $O_2$  and  $CO_2$  analyzers were developed. This form of gas exchange analysis involves the measurement of flow volume at a mouthpiece through which inhalation and exhalation take place. Expired air is sampled for gas concentrations via an attached gas line and instantaneous calculations of  $O_2$  consumption and  $CO_2$  production are provided in an on-line manner. This new technology allowed for the measurement of pulmonary gas exchange on a breath-by-breath basis and when data collected by these systems were averaged over specific time periods, the  $\dot{V}O_2$  and  $\dot{V}CO_2$  estimates were similar to those indicated by Douglas bag collection. This confirmed the accuracy of the new technology and validated its use to more precisely characterize the time course of the  $\dot{V}O_2$  response to exercise.

Despite the enhanced temporal resolution offered by rapidly responding breath-by-breath gas analysis systems, definitive findings regarding the presence of linear, first-order  $\dot{V}O_2$  kinetics were still lacking in the late 1960s. For example, in 1967, Karlman Wasserman and colleagues had subjects perform constant-load cycle exercise at three different intensities determined relative to their individual capacity and compared the  $\dot{V}O_2$  responses they observed for each (Wasserman et al. 1967). Specifically, they used an incremental cycling test to exhaustion with 4-minute stages to identify the point at which the gas exchange ratio increased abruptly and subsequently had subjects perform a work rate just below this “anaerobic threshold”. They defined this as “moderate exercise”. Wasserman et al. (1967) also had subjects perform “heavy” and “very heavy” work (700 and 1,500 mL/min of  $O_2$  consumption above the moderate work rate, respectively) and found that achievement of a “true steady state” was delayed (not reached in less than 10 minutes compared to within 4 minutes during moderate exercise) or even unattainable during the more challenging bouts. This finding presented a significant challenge to the notion of linear, first-order  $\dot{V}O_2$  control.

Contrary to the findings of Wasserman et al. (1967), Di Prampero et al. (1970) measured the  $\dot{V}O_2$  half time to steady state ( $T_{50}$ ; time taken to achieve 50% of the

response or, for a monoexponential response profile,  $0.69 \cdot \tau$ ) during both stepping and cycling transitions from rest to a variety of arbitrarily determined work rates and observed invariant  $\dot{V}O_2$  kinetics ( $T_{50}$ , ~27–30 seconds) that were all adequately described by a monoexponential function (Di Prampero et al. 1970). Interestingly, these researchers also found that transitions from mild to heavier exercise were characterized by faster response kinetics ( $T_{50}$ , ~17 seconds) and suggested that the influence of the utilization of body  $O_2$  stores that would normally dissociate pulmonary from muscle  $O_2$  consumption during full transitions was absent during transitions initiated from an elevated baseline metabolic rate.

### **Confirmation of nonlinear $\dot{V}O_2$ kinetics**

In 1972, Wasserman and Brian Whipp published research that proved beyond doubt that departures from first-order linearity are present during the  $\dot{V}O_2$  response to exercise, at least under some circumstances (Whipp & Wasserman 1972). Breath-by-breath  $\dot{V}O_2$  measurements made as subjects cycled at six different constant work rates revealed that a steady state rate of  $O_2$  consumption was, in fact, progressively delayed (or even not yet attained by exercise cessation at minute 6) at higher work rates and, indeed, so pronounced was this slowing that the hypothesis forwarded by Henry some 15 years prior seemed to be confirmed (i.e. at least for exercise at higher work rates, the response appeared to comprise two exponential components with the second describing all changes occurring after approximately 3 minutes of the initial response). The authors cited the late emergence of this additional response compartment to explain why prior investigators (e.g. Di Prampero et al. 1970; Margaria et al. 1965) found an invariant  $\dot{V}O_2$  time course that conformed to a monoexponential model throughout a wide range of work intensities. In these studies, Whipp and Wasserman suggested that exercise bouts were not continued long enough for the “ $\dot{V}O_2$  slow component” they discovered to be discerned.

### **Nonlinear $\dot{V}O_2$ behavior: the $\dot{V}O_2$ slow component**

Once it was confirmed that attainment of a steady state  $\dot{V}O_2$  was delayed for work intensities above the anaerobic threshold, the slow component responsible for this departure from first-order kinetics was studied extensively. In 1988, an important investigation greatly improved our understanding of both the potential mechanistic bases of the slow component and also how it affected exercise tolerance. David Poole and

associates at the UCLA Medical Center in Torrance, California, studied high-intensity cycle exercise both at and slightly above the power output defined by the asymptote of the power/time-to-fatigue hyperbola and found that this demarcation point (the point typically termed the “critical power” or CP; e.g. see Moritani et al. 1981, Monod & Scherrer 1965) also separates intensity regions characterized by markedly different  $\dot{V}O_2$  responses (Poole et al. 1988). These researchers found that constant-load cycle exercise at CP could be maintained for 24 minutes (the requisite duration as per methodological design) by all subjects, whereas cycling at a power output 5% above it (15 W above it, on average) could only be sustained for ~18 minutes. Additionally, a steady state  $\dot{V}O_2$  was delayed, but attainable (i.e. reached within 12–20 minutes) when cycling at CP; however, above it,  $\dot{V}O_2$  continued to rise until attaining a value at exhaustion that was not different from the subject’s  $\dot{V}O_{2max}$  as determined from an incremental ramp test. The authors concluded that exercise characterized by the presence of a  $\dot{V}O_2$  slow component (i.e. above the anaerobic threshold) encompasses two distinctly different intensity domains—one where  $\dot{V}O_2$  attains a delayed steady state below  $\dot{V}O_{2max}$  (referred to as the heavy domain) and one comprised of a range of different intensity/time-to-exhaustion combinations where, in each case, steady state is unattainable and  $\dot{V}O_2$  rises inexorably to its maximal value (severe exercise).

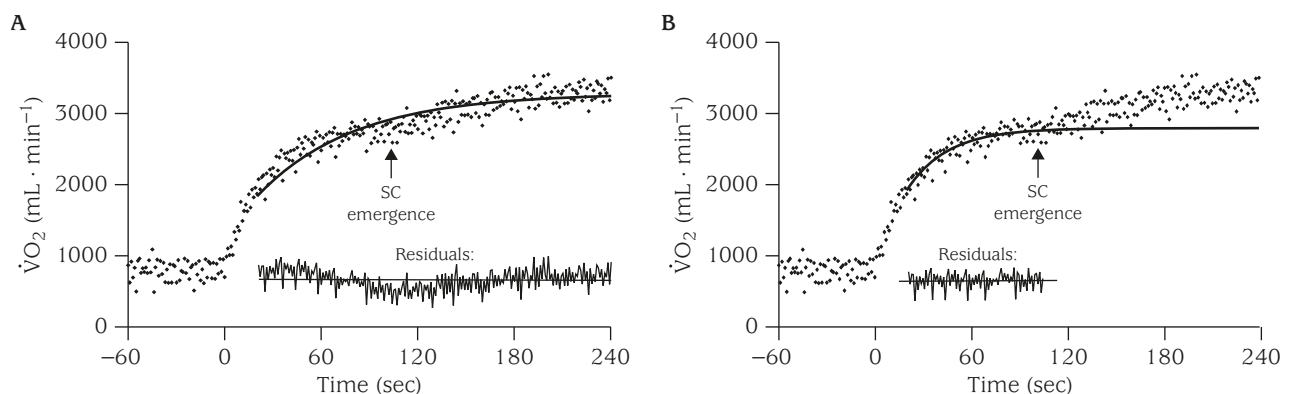
The presence of a  $\dot{V}O_2$  slow component during exercise transitions to intensities above the anaerobic threshold (or, given our current level of understanding, what is better referred to as the lactate threshold [LT]) elevates  $\dot{V}O_2$  above that which would be predicted from

the  $\dot{V}O_2$  response to moderate exercise (i.e. the eventual response G at steady state for heavy exercise or at exhaustion for severe exercise will be greater than the G for moderate exercise where no slow component is present). Consequently, this behavior violates Boltzmann’s principle of superposition (i.e. represents a departure from linearity) because a parameter describing the response (G) is not independent of the amplitude of the function that forces it (Rossiter et al. 2005).

During transitions to work rates above the LT, the  $\dot{V}O_2$  slow component distorts the monoexponential response profile that characterizes transitions in the moderate-intensity domain. Consequently, if the entire  $\dot{V}O_2$  response to heavy-/severe-intensity exercise is modeled with a monoexponential function, the fit will be poor (i.e. residuals will be biased; e.g. see Figure 4A). However, if the fit is constrained to the point where the slow component appears (i.e. becomes discernible), residuals throughout the initial response region indicate that a monoexponential profile is still in effect (Figure 4B). It is interesting to consider whether first-order linearity is at least maintained throughout this “primary” phase of the  $\dot{V}O_2$  response.

#### **Nonlinear behavior of primary phase $\dot{V}O_2$ kinetics**

Barstow and Molé (1991) were perhaps the first to compare the time course of primary phase  $\dot{V}O_2$  kinetics above LT with overall  $\dot{V}O_2$  kinetics below it and found that primary  $\tau$  ( $\tau_p$ ) exhibited no significant change as work rate was increased. These researchers concluded that even though the overall  $\dot{V}O_2$  response displayed nonlinear characteristics above LT, the primary component of the  $\dot{V}O_2$  response did not. This conclusion was based on a small sample size ( $n=4$ ) and,



**Fig. 4**  $\dot{V}O_2$  response profile with characteristic slow component (SC) that is present above the lactate threshold. This additional response compartment that appears to be of delayed onset distorts first-order kinetics. Consequently, fitting the entire response with a monoexponential function will result in biased residuals (A). However, if the fit is constrained to the point where the SC emerges, residuals throughout the primary region indicate that first-order kinetics is preserved (B).

although supported by some future findings, was refuted by others. For example, Özyener et al. (2001) had subjects perform moderate, heavy and severe cycle ergometer exercise and found an invariant  $\tau_p$  (~32–34 seconds) throughout the range of intensities studied. Conversely, Paterson and Whipp (1991) compared sub- and supra-LT  $\dot{V}O_2$  kinetics and found that  $\tau_p$  was significantly longer above LT (~40 seconds vs. ~31 seconds). In an attempt to reconcile this discrepancy, Poole and Jones (2005) summarized the results of 17 studies (combined  $n=127$ ) that involved measurement of  $\tau_p$  during both moderate and heavy/severe cycle exercise and found a strong trend for  $\tau_p$  to become longer for supra-LT transitions. The authors cited this as evidence that the primary component  $\dot{V}O_2$  kinetics is also not under linear control throughout the continuum of submaximal exercise.

Barstow and Molé (1991) also reported that when modeled, the slow component was better described by a function with an independent time delay, suggesting that the break from first-order kinetics occurs at some point after exercise onset (e.g. according to their data, after ~105 seconds). This justified the use of a monoexponential model in conjunction with a constrained fitting window to characterize the primary phase (e.g. as in Figure 4B). Furthermore, they found that the primary amplitude of the  $\dot{V}O_2$  response increased in a linear manner for the four work rates they examined (i.e.  $G$  for moderate exercise and  $G_p$  for supra-LT exercise were not significantly different). Once again, this suggested that linearity was at least maintained throughout the primary phase. However, future research would also call this finding into question. For example, citing a number of previous findings that suggested  $G_p$  was significantly lower during high- compared to moderate-intensity exercise (e.g. Pringle et al. 2003a, 2003b; Scheuermann & Barstow 2003; Jones et al. 2002), Wilkerson et al. (2004) performed a comprehensive study involving cycle exercise at seven discrete intensities and found that  $G_p$  did, in fact, fail to achieve the anticipated value (i.e. the moderate  $G$ ) during severe-intensity exercise. They also determined that during exercise so intense that sustainable duration did not allow for the achievement of  $\dot{V}O_{2max}$  (i.e. “extreme” exercise),  $G_p$  as indicated by the primary response asymptote also fell short. However,  $G_p$  for heavy exercise was not significantly different compared to moderate exercise. This suggests that for  $G_p$ , Boltzmann’s principle of superposition is obeyed for the primary phase in the heavy domain; however, for exercise above CP, nonlinear behavior in this phase is present.

### **Nonlinear $\dot{V}O_2$ behavior: on-off asymmetry**

The existence of a  $\dot{V}O_2$  slow component during supra-LT exercise indicates that parameters describing the overall  $\dot{V}O_2$  response are not independent of the amplitude of the function that forces it. A longer  $\tau_p$  above LT and a decreased  $G_p$  above CP indicate similar response deviations within the primary phase. This means that Boltzmann’s principle of superposition is violated during both the primary and overall phases of the  $\dot{V}O_2$  response to high-intensity exercise. Another key response characteristic that accompanies first-order, linear behavior is on-off symmetry (Rossiter et al. 2005). Consequently, a number of  $O_2$  uptake kinetics investigations have been undertaken to compare the on- and off-transition characteristics of the  $\dot{V}O_2$  response. For example, in 1991, Paterson and Whipp found that both  $\tau$  and  $G$  were similar for the on- and off-transition during moderate exercise; however, for exercise above LT, the off-transition response profile was either monoexponential or had a slow component that was appreciably smaller than the on-transition one (Paterson & Whipp 1991). This suggested that first-order kinetics might be maintained during the supra-LT off-transition despite the deviation (i.e. the  $\dot{V}O_2$  slow component) that occurs during the on-transition. However, the authors also noted that this “relative speeding” of the off- compared to on-transition might only operate within a restricted range above LT compared to at higher work rates where a significant slow phase of the off-kinetics appeared to become more prominent.

Özyener et al. (2001) extended the findings of Paterson and Whipp (1991) by comparing on- and off-transitions for moderate exercise with supra-LT transitions specifically differentiated as either heavy or severe. Similar to the prior findings, these authors found on/off response symmetry for moderate exercise (i.e. an off-transition response profile that was monoexponential and characterized by a  $\tau$  and  $G$  not significantly different from the on-transition values) and first-order linearity that was maintained during the off-transition of heavy exercise, even though the expected deviation from this behavior (i.e. a  $\dot{V}O_2$  slow component) was a feature of the on-transition response. However, a monoexponential model did not adequately describe the off-transition response to severe exercise, which confirmed the suggestion advanced by Paterson and Whipp 10 years prior (Paterson & Whipp 1991). Therefore, the departure from first-order kinetics that occurs above LT during the on-transition is not mirrored by a similar departure in the off-transition until CP is surpassed. Interestingly, Özyener et al. (2001)

also found an invariant primary phase off-transition  $\tau$  and  $G$  across all three exercise intensities with values that were not significantly different from the corresponding on-transient ones during moderate and severe exercise. This indicates that at least one of the requirements of dynamic response linearity (on/off symmetry) is obeyed for the primary response phase throughout exercise in these two domains. However, only six subjects took part in this investigation and there was considerable intersubject variability for these parameters.

Another interesting finding from Özyener et al. (2001) was that for the highest intensities within the severe domain, on-transient  $\dot{V}O_2$  kinetics reverted back to a monoexponential profile. Specifically, this occurred for exercise at work rates requiring a steady state  $\dot{V}O_2$  in excess of  $\dot{V}O_{2max}$ ; consequently, this was likely a function of tolerable duration being too short to allow for a slow component to be discerned. However, a slow component was still evident during the off-transition from exercise at these intensities.

#### ***Nonlinear $\dot{V}O_2$ behavior below LT***

Collectively, the findings outlined above indicate clear departures from linearity for the high-intensity (in some cases, for all work rates above LT and in others, for those above CP) primary and overall  $\dot{V}O_2$  responses to exercise. However, first-order kinetics, response parameters independent of the amplitude of the function that forces them and on-off symmetry were all present for sub-LT transitions. This led to the belief that linearity is at least maintained in the moderate-intensity region. However, when another of the mandates of the principle of superposition was tested for discrete transitions exclusive to this domain, a clear departure from linearity was observed. Specifically, while full transitions from rest or “unloaded” cycling are typically examined in  $\dot{V}O_2$  kinetics investigations, partial transitions from an elevated baseline (i.e. work-to-work transitions) have also been studied and parameters describing the  $\dot{V}O_2$  response to moderate exercise have been shown to be not independent of the baseline work rate from which the response is elicited.

In 2001, Brittain et al. determined the on- and off-transition  $\dot{V}O_2$  responses to full cycling transitions within the moderate-intensity domain (i.e. from 20-W cycling to 90% LT to 20-W cycling) and compared them to the responses observed when the same transition was divided into a lower and upper step (i.e. 20-W cycling to 45% LT to 90% LT to 45% LT to 20-W cycling) (Brittain et al. 2001). Citing previous equivocal findings

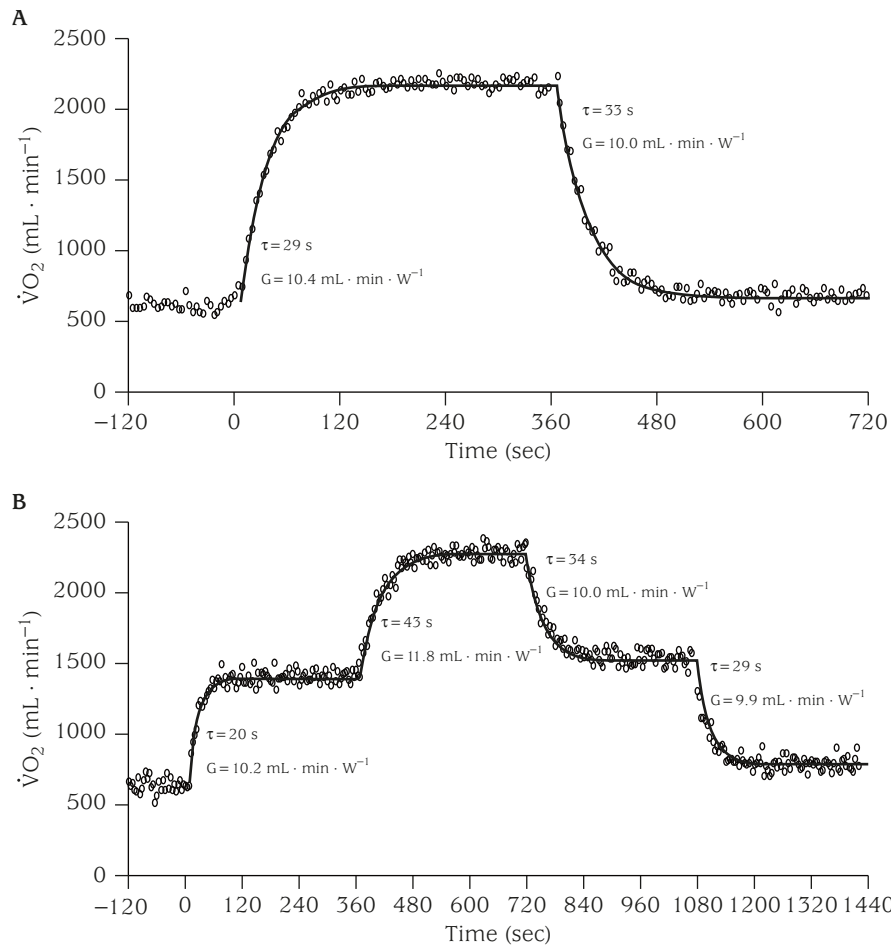
that found either faster (Davies et al. 1972; Di Prampero et al. 1970), slower (Hughson et al. 1988; Hughson & Morrissey 1983, 1982) or unchanged (Casaburi et al. 1977; Diamond et al. 1977)  $\dot{V}O_2$  kinetics during work-to-work transitions, these researchers capitalized on advanced technology, used breath-by breath analysis of multiple like-transitions to improve confidence in parameter estimation, and employed more progressive modeling procedures to confirm that on-transient  $\dot{V}O_2$  kinetics are slower in the upper compared to lower moderate region ( $\dot{V}O_2$   $\tau$ , ~40 and 25 seconds, respectively). Brittain et al. (2001) also reported a further departure from linearity as  $\tau$  was significantly different from both (~32 seconds) when the increment was made in one full step. However, off-transition  $\tau$  values did not vary between transitions (~37, 39 and 31 seconds for lower, upper and full step, respectively). This constancy indicates that on-off symmetry was not universally present. Nonlinear behavior was also expressed in the on-transition  $G$ , which was significantly different for all three transitions (lowest for the lower step, highest for the upper step and intermediate for the full step). Off-transition  $G$  values showed no such variability, which again suggests asymmetry between the on and off response. The authors concluded that their findings did not support a model of a dynamically linear system of  $\dot{V}O_2$  in the moderate-intensity domain and, therefore, suggest that the system is more complex than usually considered. Figure 5 depicts the characteristic  $\dot{V}O_2$  response to moderate exercise that is transitioned to/from in either one full (Figure 5A) or two symmetrical half (Figure 5B) steps.

#### ***A summary of departures from linearity during the dynamic $\dot{V}O_2$ response***

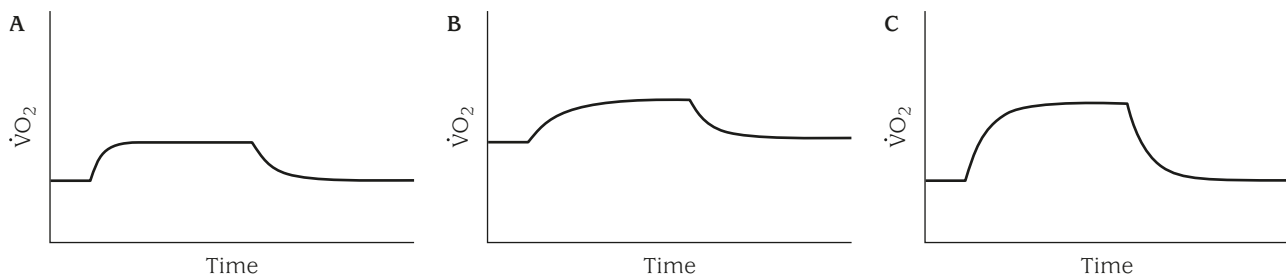
In summary, there is considerable evidence to indicate departures from first-order kinetics and dynamic system linearity throughout the range of metabolic capacity in exercising humans. Figures 6 and 7 depict how the theoretical model of dynamically linear, first-order  $\dot{V}O_2$  kinetics illustrated in Figure 3 is, in actuality, skewed for partial versus full moderate transitions (Figures 6A and 6B vs. 6C) and for heavy and severe versus moderate transitions (Figures 7B and 7C, respectively, vs. 7A). The existence of these deviations means that constant-load exercise intensity must be stated relative to domains within which different response characteristics should be expected. Tables 1 and 2 illustrate the domain system that is typically used, along with a summary of the response characteristics that are present during exercise specific to each. There is also

evidence to suggest that nonlinear behavior distorts the long-assumed linear relationship between  $\dot{V}O_2$  and work rate during incremental exercise. For example, confirming reports of a steeper  $\dot{V}O_2$ -power output slope in the latter compared to earlier stages of ramp incremental exercise by Hansen et al. (1988), Zoladz et al. (1995) found a linear relationship between  $\dot{V}O_2$  and power output during incremental exercise (30-W

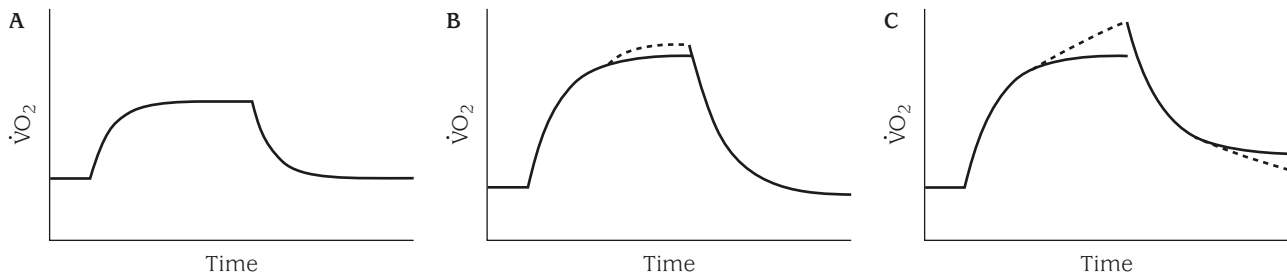
increase per 3-minute stage) below LT; however, once LT was surpassed, there was an additional increase in  $\dot{V}O_2$  above that predicted from extrapolation of the sub-LT  $\dot{V}O_2$ /work rate relationship (i.e. an upward curvilinear profile was present). It has been suggested that this “excess”  $\dot{V}O_2$  has similar mechanistic origins as the slow component that characterizes supra-LT constant-load work.



**Fig. 5** Characteristic  $\dot{V}O_2$  response to moderate exercise (e.g. cycle ergometer exercise at 150 W) that is transitioned to/from in either one full (A) or two symmetrical half (B) steps. Note the progressive lengthening of on-transition  $\tau$  and the progressive increase of on-transition G for the full- and upper-step transition that is not mirrored in off-transition variance. This indicates nonlinear behavior because the principle of superposition is violated for the on-transition and on-off symmetry is not universally present. See text for further explanation.



**Fig. 6** Unlike the dynamically linear, first-order constructs depicted in Figure 3, the response profiles reported for sub-lactate threshold (i.e. moderate) transitions from different baselines and of different magnitudes show clear departures from linear behavior during the on-transition, but not off-transition,  $\dot{V}O_2$  response. For example, note how the response profiles depicted in panels A and B differ from the one depicted in panel C and refer back to Figure 3 for comparison.



**Fig. 7** Unlike the dynamically linear, first-order constructs depicted in Figure 3, the response profiles reported for transitions of greater magnitude (i.e. supra-lactate threshold transitions) show clear departures from linear behavior during the on-transition  $\dot{V}O_2$  response. For example, note how the response profiles depicted in panels B and C (heavy and severe transitions, respectively) differ from the one depicted in panel A (a transition of lesser magnitude, i.e. a moderate transition) and refer back to Figure 3 for comparison. Furthermore, off-transition departures from linearity are also present for transitions above critical power (i.e. for severe exercise; see panel C).

## Tenets Based on the Assumption of Linear $\dot{V}O_2$ Kinetics

### *The O<sub>2</sub> debt hypothesis*

A system that displays dynamic linearity is highly predictable. Consequently, if there is evidence that appears to suggest the presence of first-order kinetics, it is attractive to assume linearity and establish related tenets accordingly. For example, as previously mentioned, Hill et al. (1924) predicted the total  $\dot{V}O_2$  requirement of an exercise bout in conjunction with the O<sub>2</sub> debt hypothesis, which presumes equivalence between the  $\dot{V}O_2$  shortfall at exercise onset (i.e. the O<sub>2</sub> deficit, see Figure 1) and the  $\dot{V}O_2$  excess upon cessation. This hypothesis is based on a characteristic of dynamic system linearity (i.e. on-off symmetry) that has since been refuted (see Table 1 and Figure 7). Appropriately, the term “O<sub>2</sub> debt” has been replaced by “excess post-exercise O<sub>2</sub> consumption” to dissociate these two phenomena.

### *The O<sub>2</sub> deficit*

Another way to calculate the O<sub>2</sub> deficit during constant-load exercise is to back-extrapolate the steady state  $\dot{V}O_2$  to  $t=0$ , integrate the area under the response curve above the baseline  $\dot{V}O_2$  requirement and subtract that value from the total area of the rectangle formed by the back extrapolation (i.e. the product of the steady-state  $\dot{V}O_2$  response amplitude and the total time of exercise; see the rectangle formed by the dashed lines in Figure 1). This is the traditional approach (e.g. see Hill 1926; Krogh & Lindhard 1913) and a routine procedure that exercise physiology students are taught during their preliminary laboratory exposures. However, it is important to recognize that this practice is not valid for exercise in the severe-intensity domain because no steady-state  $\dot{V}O_2$  will be attained (i.e. a value from

which to back-extrapolate cannot be determined). Furthermore, even though a steady state is achieved in the heavy domain, it includes a supplemental response phase (i.e. the  $\dot{V}O_2$  slow component) that complicates the aforementioned simple interpretation (Whipp & Rossiter 2005). For example, unless the slow component represents an O<sub>2</sub> requirement that is fully present at exercise onset, back extrapolation from the eventual steady state to  $t=0$  would not be justified. Furthermore, it would be equally inappropriate to add a second compartment to what might be considered a “primary O<sub>2</sub> deficit” (i.e. the region formed by back extrapolation of the primary asymptote to  $t=0$ ) because our current level of understanding would not allow for the determination of where that compartment’s initiation boundary would lie (i.e. there is no evidence to suggest that the  $\dot{V}O_2$  requirement satisfied by the slow component manifests completely at any precise moment including the one at which the break from exponentiality can initially be detected). Given this level of ambiguity, it is important to recognize that the method for determining the O<sub>2</sub> deficit by back extrapolation from steady state plateau to  $t=0$  is only applicable for exercise where first-order kinetics are in operation (i.e. during moderate-intensity exercise).

### *Assignment of exercise intensity as a percentage of $\dot{V}O_{2max}$*

Another conventional practice that is based on the flawed concept of dynamic  $\dot{V}O_2$  linearity is the assignment of exercise intensity as a percentage of  $\dot{V}O_{2max}$ . For example, in exercise research investigations, study participants are often asked to perform an incremental exercise test to exhaustion prior to the actual investigative testing so that the  $\dot{V}O_2$ /work rate relationship from that test can be used to calculate a work rate that

**Table 1.**  $\dot{V}O_2$  response characteristics and tests of linearity for moderate- and heavy-intensity exercise

	Moderate (work rate < LT)	Heavy (LT < work rate < CP)
On transient	<ul style="list-style-type: none"> <li>• Monoexponential response profile</li> <li>• Steady state attained</li> <li>• <math>\uparrow \tau</math> in upper region</li> <li>• <math>\uparrow G</math> in upper region</li> </ul>	<ul style="list-style-type: none"> <li>• Monoexponentiality distorted</li> <li>• Slow component <math>\rightarrow</math> delayed steady state</li> <li>• <math>\uparrow</math> end-exercise G</li> <li>• Monoexponential primary response</li> <li>• <math>\uparrow \tau_p</math></li> <li>• Unaltered <math>G_p</math></li> <li>• Monoexponential profile</li> </ul>
Off transient	<ul style="list-style-type: none"> <li>• Monoexponential response profile</li> <li>• Invariant <math>\tau</math> in upper vs. lower region</li> <li>• Invariant G in upper vs. lower region</li> </ul>	
On vs. off	<ul style="list-style-type: none"> <li>• Symmetry for full transitions</li> <li>• Possible asymmetry for smaller step transitions</li> </ul>	<ul style="list-style-type: none"> <li>• Asymmetry</li> </ul>

$\dot{V}O_2$ =pulmonary oxygen uptake; LT=lactate threshold; CP=critical power;  $\tau$ =time constant; G=functional gain of the response;  $\tau_p$ =primary  $\tau$ ;  $G_p$ =primary G.

**Table 2.**  $\dot{V}O_2$  response characteristics and tests of linearity for severe-intensity exercise

	Severe (work rate > CP)	
	Primary asymptote < $\dot{V}O_{2peak}$	Primary asymptote > $\dot{V}O_{2peak}$
On transient	<ul style="list-style-type: none"> <li>• Monoexponentiality distorted</li> <li>• No steady state attained</li> <li>• Slow component <math>\rightarrow \dot{V}O_{2peak}</math></li> <li>• <math>\uparrow</math> end-exercise G</li> <li>• Monoexponential primary response</li> <li>• <math>\uparrow \tau_p</math></li> <li>• <math>\downarrow G_p</math></li> </ul>	<ul style="list-style-type: none"> <li>• Monoexponential response profile</li> <li>• No steady state attained</li> <li>• <math>\uparrow \tau_p</math></li> <li>• <math>\downarrow G_p</math></li> </ul>
Off transient	<ul style="list-style-type: none"> <li>• Monoexponentiality distorted</li> <li>• Slow component present</li> </ul>	<ul style="list-style-type: none"> <li>• Monoexponentiality distorted</li> <li>• Slow component present</li> </ul>
On vs. off	<ul style="list-style-type: none"> <li>• Asymmetry</li> </ul>	<ul style="list-style-type: none"> <li>• Asymmetry</li> </ul>

$\dot{V}O_2$ =pulmonary oxygen uptake; CP=critical power;  $\dot{V}O_{2peak}$ =peak pulmonary oxygen uptake; G=functional gain of the response;  $\tau_p$ =primary time constant;  $G_p$ =primary G.

corresponds to a specific percentage of their  $\dot{V}O_{2max}$ . All subjects are then assigned this work rate for subsequent investigative testing under the assumption that each will be working at the same relative exercise intensity. However, this would only be the case if dynamic system linearity was present all the way up to  $\dot{V}O_{2max}$ , which is not the case. Consequently, intensity is not adequately controlled for during exercise testing that is designed in this manner.

To exemplify why exercise intensity should not be prescribed as a percentage of  $\dot{V}O_{2max}$ , consider a study design that requires subjects to perform exercise tests at 60% of their  $\dot{V}O_{2max}$ . Within this methodology, one subject might be exercising below LT, in which case their  $\dot{V}O_2$  will, in fact, rise with first-order kinetics and quite rapidly (e.g. within 2–3 minutes) achieve a steady state that is roughly equivalent to 60% of their maximal attainable  $\dot{V}O_2$ . Conversely, another subject might be exercising above LT, which means first-order linearity will be lost and a  $\dot{V}O_2$  slow component will be

present. If the work rate is below CP (i.e. in the heavy-intensity domain),  $\dot{V}O_2$  will eventually reach a steady state as it did for the other subject; however, this might not occur until 15–20 minutes have elapsed. Consequently, a shorter test might indicate that this subject is working at the requisite  $\dot{V}O_2$ ; however, this will not represent the “true”  $\dot{V}O_2$  requirement of the effort. Furthermore, even if the test is continued long enough for steady state to be reached, the percentage of  $\dot{V}O_{2max}$  that it will occur at will be greater than 60%. Regardless of the duration of the test, however, the important thing to recognize is that the metabolic stress encountered by this and the aforementioned subject will be quite different.

Assigning exercise intensity as a percentage of  $\dot{V}O_{2max}$  is equally dubious for efforts that fall within the severe-intensity domain. For all exercise above CP, no  $\dot{V}O_2$  steady state will be achieved regardless of the duration for which the bout is maintained; however, if exercise is continued for a long enough period of time,

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$\dot{V}O_{2max}$  will be reached (Poole et al. 1988). CP typically occurs approximately half way between LT (generally ~45–60% of  $\dot{V}O_{2max}$ ) and  $\dot{V}O_{2max}$  (Jones & Poole 2005; Poole et al. 1988); therefore, in general, a range of work rates from ~75% to 100%  $\dot{V}O_{2max}$  should all be considered “maximal” (i.e. 100%  $\dot{V}O_{2max}$ ). This will be the case despite the fact that numerous aspects of exercise at the lower end of this domain (e.g. sustainable duration, end-exercise blood lactate concentration, slow component amplitude, etc.) will be quite different compared to what will be observed for exercise in the upper region.

Deviations from  $\dot{V}O_2$  response linearity and, specifically, the need to quantify exercise relative to distinctly different intensity domains means that it is not appropriate to define a given work rate as a percentage of  $\dot{V}O_{2max}$ . However, linearity is maintained below LT, so moderate exercise can be stated as a percentage of LT (or, more often, the gas exchange threshold, which is used to approximate LT noninvasively). For exercise above LT,  $O_2$  uptake kinetics researchers typically quantify exercise intensity according to % $\Delta$  where  $\Delta$  is the difference between LT and  $\dot{V}O_{2max}$ . For example, if the work rate at LT during leg cycling is 120 W and the work rate at  $\dot{V}O_{2max}$  is 240 W, an exercise intensity designated as 50% $\Delta$  would mandate a work rate of 180 W. This method is superior to % $\dot{V}O_{2max}$  because it ensures subjects will experience similar metabolic and gas exchange responses relative to their individual capacities. However, this discrimination scheme does not differentiate between heavy and severe exercise; consequently, it still leaves a bit to be desired with regard to precise normalization of exercise intensity.

Interestingly, many of the landmark investigations of supra-LT  $\dot{V}O_2$  kinetics analyzed exercise responses at 50% $\Delta$ . In hindsight, this was problematic because this is close to the point along the continuum where CP typically occurs (Jones & Poole 2005; Poole et al. 1988). It has now become common practice to straddle 50% $\Delta$  with a buffer zone (e.g. +/- 20%), depending on the objectives of the research (i.e. 30% $\Delta$  if heavy-intensity efforts are required, 70% $\Delta$  for those that are intended to be severe). While still inexact, this is a far safer way to ensure similar physiological responses.

Supra-LT exercise can be precisely delineated if CP is determined prior to testing because a domain-specific  $\Delta$  for both heavy (difference between LT and CP) and severe (difference between CP and  $\dot{V}O_{2max}$ ) can then be calculated. Heretofore, this would have required the performance of a number (4–5) of exhaustive

constant-work-rate prediction trials on separate days to establish the power/time hyperbola and associated asymptote (i.e. CP); therefore, quantifying intensity in this manner has proved to be quite cumbersome. Consequently, prior research has rarely used this methodology to assign intensities (for examples of studies that did, see Jones et al. 2008a and Endo et al. 2007). However, it has recently been confirmed that a single, 3-minute all-out cycling test can be used to accurately predict CP (Vanhatalo et al. 2008, 2007). This has clear practical advantages and it is, therefore, possible that this test will become a standard fixture of  $O_2$  uptake kinetics research in the future.

## Response System Input-Output Analysis

### *Departures from linearity: implications for identifying mechanisms of $\dot{V}O_2$ control*

One of the key issues that  $O_2$  uptake kinetics researchers have tried to resolve involves identification of the specific controlling determinant(s) of muscle  $O_2$  consumption (Rossiter et al. 2005). For example, while subsequent studies verified the initial exponential rise in  $\dot{V}O_2$  at exercise onset that was forwarded by Henry (1951), the limiting factor he suggested (the provision of oxidizable metabolic substrate within mitochondria) has yet to be confirmed. Adaptation of a response rate in association with an ever-changing error signal (i.e. an exponential response profile indicating first-order kinetics) implies rate modulation by feedback or feed forward control from one specific system reactant. Nonlinear responses of this type of system as a whole can result from nonlinear behavior of this critical rate modulator. Accordingly, assessing response linearity in conjunction with the relationship between stimulation-dictated response demand and regulator-indicated response supply (i.e. system input-output analysis) is a useful way to identify potential locus/loci of control. This has been done for other metabolic response profiles in the past; for example, Fujihara et al. (1973a, 1973b) found that in the majority of cases, Boltzmann's law of superposition was obeyed for work load/ventilation and work load/heart rate relationships when impulse (large, short and small), step (large and small) and ramp (large and small) loads forced oxidative function during cycle ergometer exercise (Fujihara et al. 1973b). Consequently, the authors were able to develop transfer functions that were implicated in establishing these responses (feedback from spatially-distanced chemoreceptors and intramuscular signaling

or cortical irradiation for the ventilatory and chronotropic responses, respectively). Unfortunately, definitive identification of the transfer function that links muscle  $O_2$  consumption with the work rate forcing it is still lacking (Rossiter et al. 2005).

### **$\dot{V}O_2$ control: $O_2$ availability**

One factor that might be responsible for distortions of  $\dot{V}O_2$  linearity for exercise above LT is that the sub-LT rate-limiting step in the oxidative ATP phosphorylation pathway (assumed to be of intracellular origin, i.e. a limitation in the capacity to provide substrate for phosphorylation via electron transfer) is supplanted by an inability to supply sufficient  $O_2$  to support electron transfer. For example, it has been suggested that  $O_2$  availability becomes (increasingly) limiting at higher work rates (Hughson 2005; Hughson et al. 2001) and when different forcing functions elicit the response (e.g. step vs. impulse; see Hughson et al. 1988). However, the discovery of nonlinear behavior below LT (i.e. in a region where  $O_2$  availability should not be limiting; e.g. see Grassi et al. 1998) does not support this suggestion and there is also ample evidence to suggest that *increasing*  $O_2$  availability via “priming” exercise prior to supra-LT transitions does not speed  $\dot{V}O_2$  kinetics in healthy young subjects during upright cycle exercise (DiMenna et al. 2008; Burnley et al. 2005; Endo et al. 2005; Burnley et al. 2001; Koppo & Bouckaert 2001; Scheuermann et al. 2001; Burnley et al. 2000). This suggests that under “normal” conditions,  $O_2$  availability does not modulate  $\dot{V}O_2$  kinetics, either below or above LT. Note: A further discussion of this topic and also of possible limitations to the activation of muscle oxidative enzymes (e.g. pyruvate dehydrogenase) is beyond the scope of this review; however, the interested reader is directed to articles by Poole et al. (2008) and Grassi (2005) where these subjects are considered in depth.

### **$\dot{V}O_2$ control: the influence of muscle fiber type and motor unit recruitment**

Another possible reason for intensity-dependent departures from linear  $\dot{V}O_2$  behavior is that these deviations are related to the metabolic properties of the muscle fibers recruited to meet the increased force requirements at higher work rates (DiMenna et al. 2008; Wilkerson & Jones 2007, 2006; Brittain et al. 2001). Human skeletal muscle comprises fibers with distinctly different bioenergetic properties that are recruited in a hierarchical manner depending primarily on the intensity level of contractile activity that is required (Henneman et al. 1965). Consequently, responses to

exercise transitions comprising discrete ranges of force development relative to maximal capacity (e.g. at ~15% of the maximal voluntary contraction for moderate exercise compared to ~30–40% for supra-LT work) would be expected to reflect these differences. For example, higher intensity transitions would involve a contribution from higher-order (i.e. type II fast-twitch) fibers that have been shown to possess a blunted microvascular pressure head for  $O_2$  (McDonough et al. 2005; Behnke et al. 2003), slower  $\dot{V}O_2$  kinetics (Crow & Kushmerick 1982) and less energetic efficiency (i.e. less ATP yielded per volume  $O_2$  consumed and/or more ATP required per contractile tension developed) (Reggiani et al. 1997; Crow & Kushmerick 1982; Wendt & Gibbs 1973) in rat/mouse muscle. If high-order fibers also have a poor capacity to receive and utilize  $O_2$  and less oxidative efficiency in human muscle *in vivo* (e.g. as indicated by Pringle et al. 2003a; Barstow et al. 1996; Coyle et al. 1992), it could explain departures from  $\dot{V}O_2$  linearity (e.g. slower primary phase kinetics, an additional slow component and increased overall G) at exercise intensities that mandate their involvement (Jones et al. 2005).

It has long been suggested that the slow component is associated in some way with the recruitment of higher-order fibers (Endo et al. 2007; Krstrup et al. 2004a, 2004b; Pringle et al. 2003a, 2003b; Burnley et al. 2002; Barstow et al. 1996). For example, a progressive recruitment of higher-order fibers as high-intensity exercise proceeds and/or a loss of contractile efficiency within these fatigue-sensitive fibers if they are recruited at or near exercise onset have each been advanced as potential causative factors. It is also possible that a high-intensity exercise transition requires the initial recruitment of a heterogeneous pool of fibers with such a wide range of individual  $\tau$  values that the profiles of the slowest responders might project past the established phase II exponential (Wilkerson & Jones 2007). This could serve to create a “separate” response phase (i.e. a  $\dot{V}O_2$  slow component) and might also explain at least part of the reduced  $G_p$  above CP. However, the observation by Barstow and Molé (1991) that the slow component is better described by a function with an independent time delay (i.e. its emergence is not aligned with the initiation point of the primary exponential) does not support this notion.

Fiber-type heterogeneity might also explain the moderate domain nonlinearity discovered by Brittain et al. (2001) that is depicted in Figures 5 and 6. For example, by its very nature, the pulmonary  $\dot{V}O_2$  signal will homogenize any oxidative response diversity within

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an activated pool during a transition that requires input from a heterogeneous population of recruited muscle fibers. However, if a similar transition is divided into a lower and upper step, response characteristics that would more closely represent those displayed by fibers at opposite ends of the pool would be unveiled. Consequently, subtle departures from linear behavior within the moderate domain (e.g. a lengthened  $\tau$  and increased  $G$ ) might only be identifiable when the domain is split into an upper and lower region (Brittain et al. 2001). A progressive slowing of  $\dot{V}O_2$  kinetics and increase of  $G_p$  for work-to-work compared to full transitions of greater magnitude (e.g. to heavy- and severe-intensity exercise) has also been reported, which is what would be predicted according to this proposal (DiMenna et al. 2008; Wilkerson & Jones 2007, 2006).

### ***$\dot{V}O_2$ control: [PCr] kinetics***

In addition to the aforementioned research, input-output analysis has been used to test Boltzmann's principle of superposition for intramuscular metabolite responses to metabolic transitions, and departures from linearity that mirror those present in  $\dot{V}O_2$  have been observed for phosphocreatine concentration ([PCr]) kinetics. Specifically,  $^{31}\text{P}$  magnetic resonance spectroscopy ( $^{31}\text{P}$ -MRS) has revealed a [PCr] slow component during supra-LT exercise (Jones et al. 2008a, 2008b; Rossiter et al. 2002a, 2002b), a longer [PCr]  $\tau_p$  for heavy compared to moderate exercise (Jones et al. 2008b), a longer [PCr]  $\tau_p$  and greater [PCr]  $G_p$  during work-to-work compared to full transitions (Jones et al. 2008b) and marked differences in [PCr] responses for heavy (10% below CP) and severe (10% above CP) exercise (Jones et al. 2008a). Furthermore, on-off asymmetry (a [PCr] slow component and a monoexponential [PCr] response profile for the on- and off-response, respectively) has been reported for [PCr] within the heavy domain by Rossiter et al. (2002b).

Collectively, the similar departures from linear behavior observed for [PCr] and  $\dot{V}O_2$  kinetics in exercising humans suggest a functional coupling between these two variables. Interestingly, this has resonance with previous observations by Meyer (1988), who used similar technology to study [PCr] degradation in response to different stimulation/recovery cycles during electrically-induced contractions in anesthetized rats. Meyer (1988) found a [PCr]  $\tau$  that was invariant across a range of stimulation rates and also at the onset and offset of stimulation (i.e. a [PCr] response that obeyed the law of superposition and displayed on-off symmetry). This prompted him to advance a model of respiratory

control based on a simple electrical analog for a first-order linear system transformed to accommodate chemical components. In his model, Meyer suggested that the capacitance associated with the circuit is due to the creatine kinase reaction and, therefore, [PCr] is analogous to the stored charge on a capacitor. Although subsequent discoveries of nonlinear behavior in both the  $\dot{V}O_2$  and [PCr] responses suggest greater complexity than this first-order model indicates, the role of the [PCr] response as perhaps a proxy for ADP (Grassi 2005; Rossiter et al. 2005) that acts as either a direct (Meyer 1988; Mahler 1985) or indirect (e.g. in "parallel activation"; see Menuet & Arsac 2008; Korzeniewski 2007) modulator of cellular respiration during metabolic transitions has generally been supported.

### **Conclusion**

During the 200-plus years since the discovery of  $O_2$  and its role in cellular respiration, many scientists have contributed to our understanding of  $\dot{V}O_2$  response dynamics and there is now a large body of evidence to suggest the existence of departures from linear behavior during the  $\dot{V}O_2$  response to exercise. The existence of a  $\dot{V}O_2$  slow component and slower primary phase  $\dot{V}O_2$  kinetics for exercise above LT, a reduced primary phase  $G$  for exercise above CP and slower  $\dot{V}O_2$  kinetics for work-to-work transitions all suggest that departures from linearity are intensity related. Intensity is the stimulus that drives motor unit recruitment; therefore, an attractive explanation is that these deviations reflect different metabolic response characteristics of diverse segments of the fiber recruitment pool. Responses that mirror  $\dot{V}O_2$  departures from linearity have been identified for intramuscular [PCr], which provides support for the notion that [PCr] acts directly or indirectly as an important respiratory control mechanism during metabolic transitions. It is well-established that high-order fibers have greater total creatine content; therefore, it is possible that departures from linear  $\dot{V}O_2$  behavior observed via the homogenized pulmonary signal reflect differences in [PCr] modulation within the range of recruited fibers. However, at present, this can only be speculated and more research is clearly needed to elucidate the precise influence of [PCr] kinetics and fiber-type heterogeneity in determining nonlinear aspects of the  $\dot{V}O_2$  response.

Despite uncertainty regarding the mechanisms that underpin departures from  $\dot{V}O_2$  response linearity, the fact that this system does not consistently display

first-order, linear kinetics throughout the range of metabolic capacity in exercising humans cannot be questioned. It is, therefore, vital that these departures be universally recognized by the exercise physiology community. Unfortunately, this is presently not the case. Furthermore, traditional constructs that have been based on a linear model of  $\dot{V}O_2$  control must be reshaped to accommodate what we now know. In a science-based discipline, failure to do so is inexcusable. After all, many brilliant researchers have given us the “proof” that has allowed us to achieve our current level of understanding of  $\dot{V}O_2$  kinetics. However, as Dennett (1998) so appropriately reminds us, even “advanced thinkers” can fall victim to a perceived “sophisticated appreciation of the futility of proof” that, in reality, is not so sophisticated after all.

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