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Oxygen Uptake Kinetics

David C. Poole^{*1} and Andrew M. Jones²



ABSTRACT

Muscular exercise requires transitions to and from metabolic rates often exceeding an order of magnitude above resting and places prodigious demands on the oxidative machinery and O₂-transport pathway. The science of kinetics seeks to characterize the dynamic profiles of the respiratory, cardiovascular, and muscular systems and their integration to resolve the essential control mechanisms of muscle energetics and oxidative function: a goal not feasible using the steady-state response. Essential features of the O₂ uptake ($\dot{V}O_2$) kinetics response are highly conserved across the animal kingdom. For a given metabolic demand, fast $\dot{V}O_2$ kinetics mandates a smaller O₂ deficit, less substrate-level phosphorylation and high exercise tolerance. By the same token, slow $\dot{V}O_2$ kinetics incurs a high O₂ deficit, presents a greater challenge to homeostasis and presages poor exercise tolerance. Compelling evidence supports that, in healthy individuals walking, running, or cycling upright, $\dot{V}O_2$ kinetics control resides within the exercising muscle(s) and is therefore not dependent upon, or limited by, upstream O₂-transport systems. However, disease, aging, and other imposed constraints may redistribute $\dot{V}O_2$ kinetics control more proximally within the O₂-transport system. Greater understanding of $\dot{V}O_2$ kinetics control and, in particular, its relation to the plasticity of the O₂-transport/utilization system is considered important for improving the human condition, not just in athletic populations, but crucially for patients suffering from pathologically slowed $\dot{V}O_2$ kinetics as well as the burgeoning elderly population.

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Introduction

As a scientific expedient, physiological processes are often studied under “steady-state” conditions which may be approximated at rest and during moderate (below lactate threshold, LT) or even heavy (>LT) intensity exercise. Whilst undoubtedly valuable, it may be argued that this steady-state of exercise is a laboratory contrivance. For, whilst awake, humans and animals transition frequently among different metabolic rates as we, for example, get up from a chair, climb stairs, run to catch a bus or train, or engage in activities such as physical labor and recreational or professional sports and activities (Fig. 1). Because of the very limited nonoxidative muscle energy stores, at the transition from rest to exercise there must be a coordinated pulmonary, cardiovascular, and muscular system response to increase rapidly the flux of O₂ from atmosphere to muscle mitochondria allowing aerobic ATP production (See Section *Integration of Dynamic Responses in the Pathway for O₂*). Thus, the transitory phase(s), prior to achievement of any steady state, provides a window into the fundamental processes of muscle energetics and metabolic control that are otherwise not accessible. Indeed, that $\dot{V}O_2$ does not rise immediately to its steady-state suggests that a finite metabolic capacitance may have evolved as a crucial feature of the energy transfer pathways. Unlike $\dot{V}O_{2\max}$ which may be limited by the capacity of the O₂-transport system in its entirety (review 50, 648, 586, 744) the locus of control of $\dot{V}O_2$ kinetics is believed to be sited principally in the muscle mitochondrion [see Section *Site(s) of Limitation of $\dot{V}O_2$ Kinetics: Oxygen Delivery Versus Cellular Respiration*]. For the major

forms of whole-body exercise such as walking, running, and cycling it is only disease and other system dysfunctions (aging and possibly very low fitness levels) that displace this locus of control upstream into the O₂-transport pathway (Fig. 2). Figure 3 portrays the key systems in the O₂-transport pathway and emphasizes intramuscular energetic control rather than a more proximal limitation in O₂ flux.

Whilst acknowledging the complexity and importance of understanding pulmonary, cardiovascular, and muscle-control mechanisms in facilitating O₂ flux to the mitochondria (see Section *Integration of Dynamic Responses in the Pathway for O₂*) this review focuses on the ultimate end product as it is expressed in the $\dot{V}O_2$ kinetics. In particular, the lively controversy regarding the role of O₂ delivery versus intramuscular metabolic control takes center stage [see Section *Site(s) of Limitation of $\dot{V}O_2$ Kinetics: Oxygen Delivery Versus Cellular Respiration*] (182, 273, 275, 280, 363, 370, 589, 728). Whereas it is acknowledged that impediment at any upstream site (lungs, cardiac, vascular, and microvascular) can, if sufficiently severe, ultimately slow $\dot{V}O_2$ kinetics and impair exercise performance (see Section *Disease States*),

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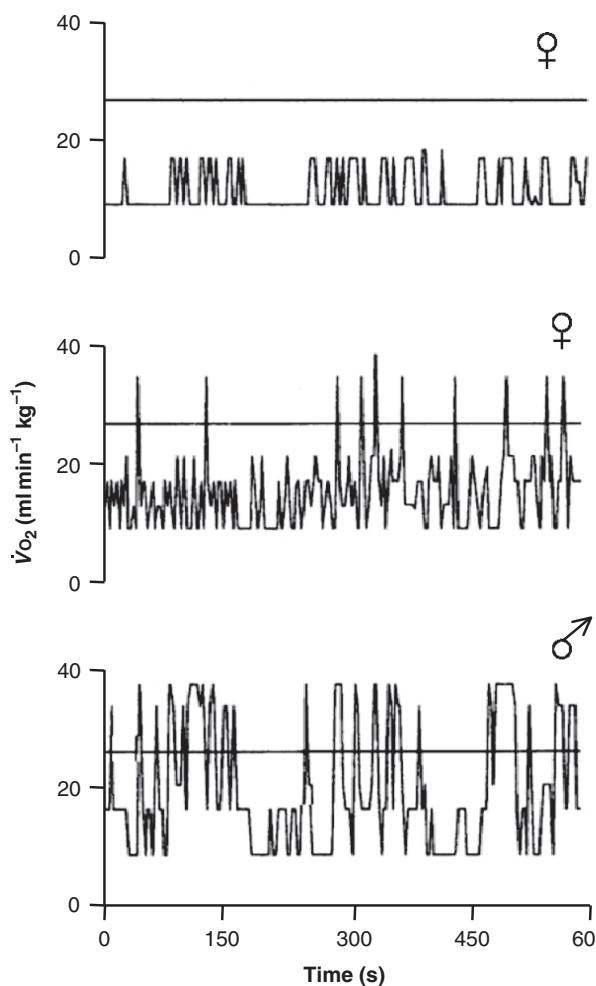


Figure 1 Profiles of children’s (6–10 year olds) $\dot{V}O_2$ during free ranging spontaneous activity. These have been ranked as low, moderate, and heavy activity for (A) (female), (B) (female), and (C) (male), children respectively. Horizontal line denotes the gas exchange threshold, GET. Redrawn, with permission, from Bailey et al. (22).

compelling evidence will be presented that, in healthy young humans cycling or running and horses (424, 425), the speed of the $\dot{V}O_2$ kinetics at exercise onset is limited predominantly by some intramuscular process(es) (most likely oxidative energy system inertia) rather than bulk muscle O₂ delivery *per se* (Fig. 2). However, the balance of control may change with different modes (e.g., leg vs. arm, see Section *Effects of Exercise Modality on $\dot{V}O_2$ Kinetics*) and intensities (i.e., moderate and heavy vs. severe) of exercise, within different fiber-type populations (see Section *Influence of Muscle Fiber Type and Motor Unit Recruitment on $\dot{V}O_2$ Kinetics*), with aging (see Section *Maturation and Aging*), in different experimental perturbations (e.g., hypoxia) and also for diseases that compromise O₂ transport such as heart failure and chronic obstructive pulmonary disease (see Section *Disease States*). Whereas there are many acute and chronic perturbations that slow $\dot{V}O_2$ kinetics, primarily via reduced O₂ transport and the dependence of metabolic control on microvascular and intramyocytic O₂

pressures (74, 372, 511, 512), there is an extraordinary degree of plasticity in both directions. Exercise training causes a speeding of the primary $\dot{V}O_2$ kinetics within very few training bouts and the $\dot{V}O_2$ slow component ($\dot{V}O_{2\text{sc}}$) is reduced by exercise training and often by improved muscle O₂ delivery (See Section *Slow Component of $\dot{V}O_2$ Kinetics: Mechanistic Bases and Exercise Training and Performance*). Because $\dot{V}O_2$ and therefore $\dot{V}O_2$ kinetics is measured most conveniently via pulmonary gas exchange and yet, in most forms of exercises, the predominant response is driven by the muscles performing the work, it is essential to know how closely the temporal profile of pulmonary $\dot{V}O_2$ matches that across the contracting muscles. This crucial perspective is broached in Section *Relationship Between Pulmonary and Exercising Muscle $\dot{V}O_2$ Responses*.

Where possible throughout this review, emphasis is placed on experimental evidence from humans performing voluntary exercise. However, experiments in animals and animal muscles will be featured in so far as they have made important contributions to our understanding of $\dot{V}O_2$ kinetics (see Section *Comparative Physiology of $\dot{V}O_2$ Dynamics*). This is particularly true with respect to determining the dynamic matching of O₂ delivery-to- $\dot{V}O_2$ and the control of microvascular O₂ partial pressures (P_{mVO₂}) within contracting muscle(s) (see Section *Relationship Between Pulmonary and Exercising Muscle $\dot{V}O_2$ Responses*) as well as extending the range of O₂ flux ($\dot{V}O_{2\text{max}}$) achievable from <10 to 240 ml min⁻¹ kg⁻¹. Key points and questions raised in the preceding sections are summarized in section *Conclusions* paying particular attention to points of controversy and pressing directions for future scientific efforts. A modicum of redundancy is retained as an expedient to facilitate ease and convenience of “dipping” into discrete sections.

Brief Historical Perspective

The study of $\dot{V}O_2$ and $\dot{V}O_2$ kinetics has its historical foundations deep within the broader fields of physiology and exercise physiology. Atmospheric O₂ was first created as a byproduct by simple unicellular prokaryocytes that harnessed photosynthesis as an energy source. Over billions of years Earth’s atmosphere increased to 10% to 30% O₂ and powered the mitochondrial energetics of complex multicellular creatures in the Cambrian explosion (542–488 million years ago) (719). In the 17th century, Polish apothecary Michael Sendivogius [1566–1636] produced O₂ by heating saltpeter (potassium nitrate) (717) and Dutch engineer/inventor Cornelis Drebbel [1572–1633] used purified O₂ for life support in his submarine. In 1621, Drebbel demonstrated to King James I and a host of onlookers that this submarine could remain submerged whilst 12 men rowed the 7 miles from Westminster to Greenwich (717). However, it was left to the great 18th-century French chemist Antoine Lavoisier [1743–1794] to name oxygen (*oxygène*) ~1777 for its acid-forming properties and demonstrate quantitatively O₂’s role in

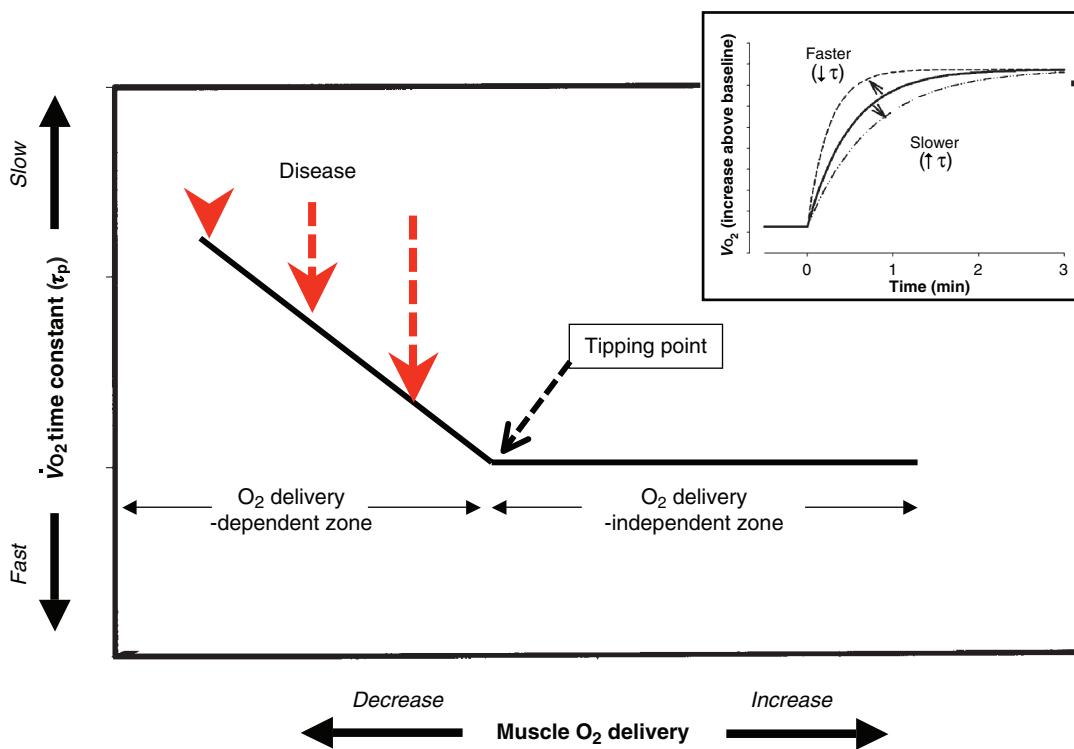


Figure 2 With respect to the speed of $\dot{V}O_2$ kinetics there are O_2 -delivery-dependent and -independent regions. Note that when O_2 delivery falls below the “tipping point” $\dot{V}O_2$ kinetics becomes progressively slowed as evidenced by increasing τ (see inset for graphical portrayal of altered τ). In young healthy individuals conventional locomotor activities such as walking, running, and cycling lie to the right of the tipping point. Many diseases such as chronic heart failure, emphysema [chronic obstructive pulmonary disease (COPD)] and type II diabetes (see Section Disease States) as well as healthy aging (see Section Maturation and Aging) move the individual leftward into the O_2 -delivery-dependent region.

muscular exercise and $(\dot{V}CO_2)$ CO_2 production thereby defining the respiratory quotient (review 16, 87, 191, 394, 577, 763). Working with Pierre-Simon LaPlace [1749–1827] and Armand Seguin [1767–1835], Lavoisier developed what was

likely the world’s first calorimeter and, using it to measure heat production in guinea pigs, recognized that respiration was “...nothing but a slow combustion of carbon and hydrogen similar in all aspects to that of a...lighted candle” (472, 526).

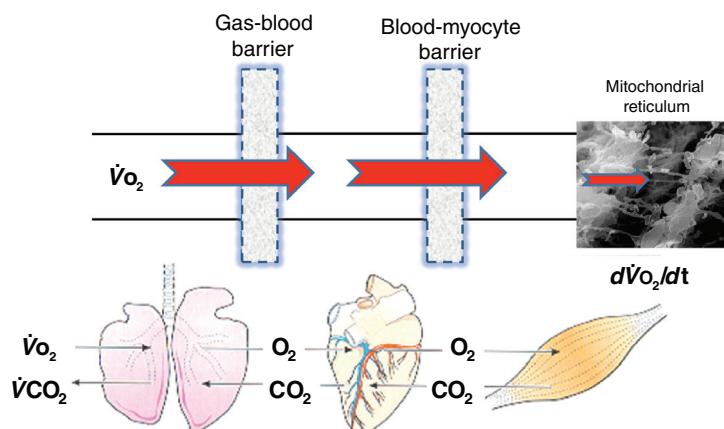


Figure 3 The pathway for O_2 from lung to skeletal muscle mitochondria. For healthy humans performing large muscle mass exercise (e.g., cycling and running) $\dot{V}O_2$ kinetics at exercise onset are controlled by the capacity for mitochondrial O_2 utilization (right-most arrow) rather than upstream perfusive or diffusive flux limitations (larger arrows, left and middle) as is the case for $\dot{V}O_{2\max}$ [see Section Site(s) of Limitation of $\dot{V}O_2$ Kinetics: Oxygen Delivery Versus Cellular Respiration for more details].

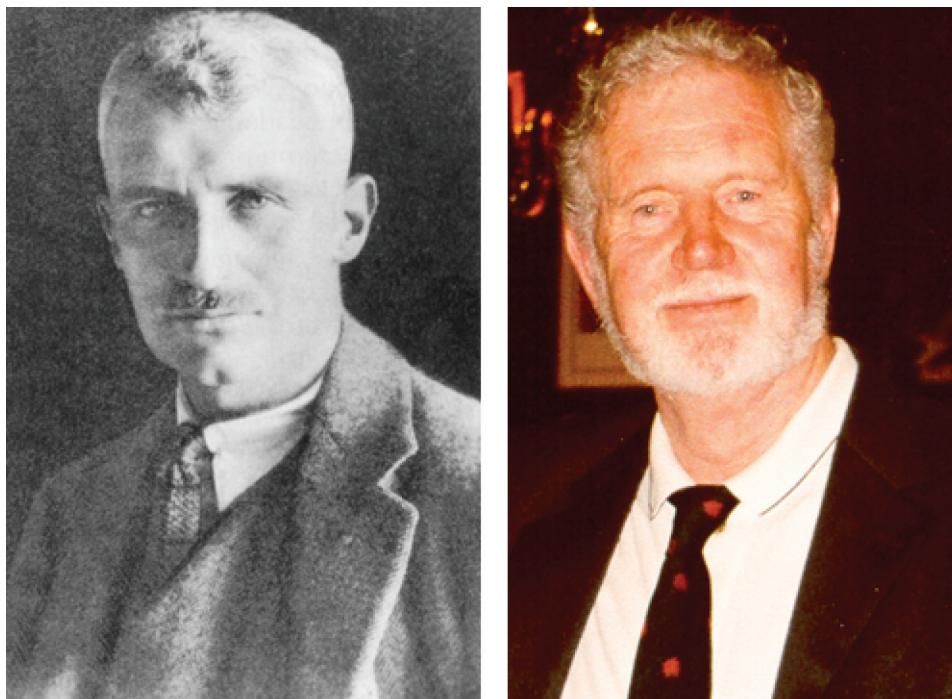


Figure 4 Two of the foremost pioneers in the field of exercise metabolic control and $\dot{V}O_2$ kinetics. Left panel: Nobel laureate Archibald Vivian Hill in 1927. Right panel: Brian J. Whipp in 2002.

Lavoisier mistakenly considered that respiration took place in the lungs and it was up to Lazaro Spallanzani [1729-1799] and later Carl von Voight [1831-1908], Gustav Magnus [1802-1870], and Edward Pfeuger [1829-1910] to correctly site O₂ utilization and $\dot{V}CO_2$ within the muscles and distal organs (191, 763). In the 19th century, German physiologists Nathan Zuntz [1847-1920], Geppert and colleagues (263, 811-815) revolutionized our understanding of pulmonary gas exchange and metabolism based upon their measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ in exercising humans and animals. With technical improvements, by the late 1800s, it was possible for Johansson to follow the rapidity of the heart rate (HR) response of the rabbit to spontaneous movement (i.e., ~ 20 b·min⁻¹ increase within 1.5 s; reference 383 as chronicled by Secher and Ludbrook, 680) and interest was stimulated in other dynamic responses. Subsequently, the Nobel laureates August Krogh [1874-1949] and Archibald Vivian Hill [1886-1977] (Fig. 4, left panel) and their colleagues (345-347, 452, 453) quantified the dynamics of HR (see also Benedict and Cathcart, 78) and $\dot{V}O_2$ at exercise onset and recognized the importance of the metabolic transition in defining the O₂ deficit. With his strong mathematical training, Hill described the exponential nature of the $\dot{V}O_2$ kinetics as a linear and (to a certain degree) symmetrical system (i.e., on- vs. off-transient symmetry). Though Franklin M. Henry [1904-1993] and Janice Demoor (329; see also Henry, 328) and also Rodolfo Margaria [1901-1983], Paolo Cerretelli and Pietro di Prampero (references 496-498) investigated the exponential nature of $\dot{V}O_2$ following the on- and particularly the off-transition their overriding focus was on “lactacid” and

“alactacid” components and analysis of the so-called O₂ debt. Hence the groundwork laid by Krogh and Lindhard (452, 453) and Hill and colleagues (references 345-347) would not be substantially improved upon for several decades until the development of rapidly responding gas analyzers and breath-by-breath determination of pulmonary gas exchange. Hill was an avid runner who studied energetic and thermodynamic processes in isolated animal muscles to gain insights into respiratory control and muscular performance in humans (341-344, 348). In particular, Hill demonstrated the simultaneous contribution of anaerobic and aerobic processes to muscle contractile energetics (review 49). His lectures at Cornell University in 1926 led to the foundation of the Harvard Fatigue laboratory at Harvard University which brought Rodolfo Margaria (University of Milan), H.T. Edwards and David Bruce Dill together to embark on the study of metabolism during exercise. These events signaled the inception of exercise physiology as a legitimate academic discipline (722).

Capitalizing on the early development of breath-by-breath gas exchange technology, in the late 1960s and early 1970s, three different groups helped establish and develop the then-embryonic field of $\dot{V}O_2$ kinetics: Notably, physician scientist Karl Wasserman and the brilliant Welshman, Brian J. Whipp (1937-2011) (Fig. 4, right panel), and their team at Harbor-UCLA Medical Center in Los Angeles, USA, Rodolfo Margaria, Paolo Cerretelli, and Pietro di Prampero in Milan, Italy, and Leon Farhi in Buffalo, USA.

Today the kinetic response of $\dot{V}O_2$ following the onset of exercise is recognized as a sentinel parameter of aerobic

function and its measurement is becoming standard in laboratories around the World. In view of the relationship between physical performance and $\dot{V}O_2$ kinetics (287, 386, review 638) development of therapeutic strategies aimed at speeding $\dot{V}O_2$ kinetics and reducing the size and/or progression of the $\dot{V}O_{2\text{sc}}$ offer hope for improving exercise tolerance and the quality of life for aged and patient populations. This consideration and the scientific prerogative to understand metabolic control during exercise have helped establish and drive the burgeoning scientific interest in the field of $\dot{V}O_2$ kinetics.

Systems Control of Pulmonary $\dot{V}O_2$ Kinetics

Within seconds-to-minutes following the onset of severe-intensity exercise, pulmonary $\dot{V}O_2$ may increase from a resting value of $\sim 0.25 \text{ liters}\cdot\text{min}^{-1}$ (or somewhat higher, $\sim 0.5\text{--}1.0 \text{ liters}\cdot\text{min}^{-1}$ for “unloaded” cycling, Fig. 5) up to its maximum value for the individual (Fig. 5) which, in the extreme, may exceed 5 to 6 $\text{liters}\cdot\text{min}^{-1}$. For skeletal muscle the dynamic range is even greater with $\dot{V}O_2$ rising over 60-fold from $<10 \text{ ml min}^{-1} \text{ kg}^{-1}$ at rest to $\sim 600 \text{ ml min}^{-1} \text{ kg}^{-1}$ during maximal knee-extensor exercise (5, 31, 455, 628).

As early as 1922, Hill and colleagues (345–347, review 771, and see also 328) demonstrated that, following the onset of moderate intensity exercise [i.e., $<$ LT or the gas exchange threshold (GET)], pulmonary $\dot{V}O_2$ as a function of time, t , increases as an exponential process (Fig. 6):

$$\Delta\dot{V}O_2(t) = \Delta\dot{V}O_{2\text{ss}}(1 - e^{-kt}), \quad (1)$$

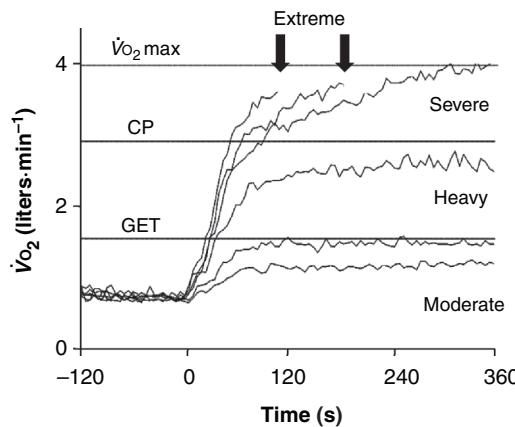


Figure 5 $\dot{V}O_2$ response following the onset of moderate ($<$ gas exchange threshold, GET), heavy ($>$ GET $<$ critical power, CP), severe ($>$ CP leading to $\dot{V}O_2\text{max}$), and extreme ($>$ severe such that fatigue ensues before $\dot{V}O_2\text{max}$ is achieved) exercise. Note that for moderate exercise a steady state is achieved rapidly; for heavy exercise the steady state is delayed; for severe exercise no steady state is evident but $\dot{V}O_2$ projects to $\dot{V}O_2\text{max}$ which is achieved before fatigue ensues (arrows). Both heavy and severe exercise may evince a slow component (i.e., $\dot{V}O_{2\text{sc}}$ see Section Slow Component of $\dot{V}O_2$ Kinetics: Mechanistic Bases). For extreme exercise, fatigue ensues prior to reaching $\dot{V}O_2\text{max}$. Adapted, with permission, from Wilkerson et al. (788).

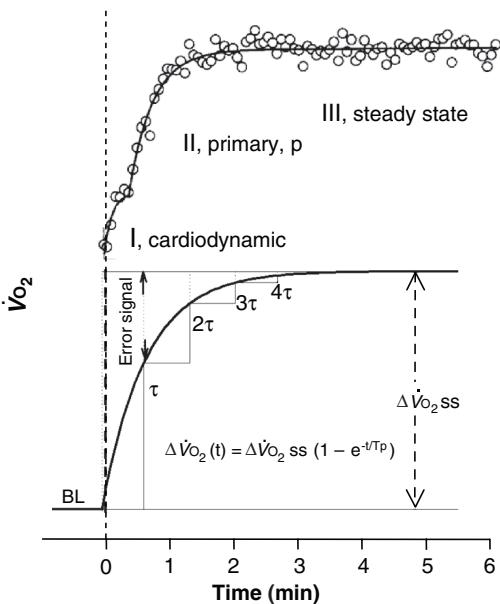


Figure 6 Top: breath-by-breath alveolar $\dot{V}O_2$ response following the onset of moderate intensity cycle ergometer exercise. Phases I (cardiodynamic), II (primary), and III (steady-state) are designated and fit by an appropriate exponential model (see text). Bottom: schematic demonstrating fundamental properties of the single component exponential response. Note that the imposition of a time delay feature (omitted here for clarity) is required to improve the model fit and account for Phase I (see Eq. 5). The rate of $\dot{V}O_2$ increase is quantified by the time constant (τ) of the exponential ($\sim 40 \text{ s}$ for this example) where BL signifies baseline $\dot{V}O_2$ and Δ the increase or amplitude of $\dot{V}O_2$ above baseline (right vertical arrows, $\sim 2 \text{ liters}\cdot\text{min}^{-1}$ for this example). For each multiple of τ $\dot{V}O_2$ increases by 63% of the difference between that value at the previous τ and the required steady state. Thus, after 2τ ($\sim 80 \text{ s}$) $\dot{V}O_2$ has risen to $86\%\Delta$ [$1.0 - 0.63 = 0.37$; $(0.37 \times 0.63) + 0.63 = 0.86$], 3τ 's ($\sim 120 \text{ s}$) = $95\%\Delta$, 4τ 's ($\sim 160 \text{ s}$) = $98\%\Delta$. τ_p designates the time constant of the primary component response. Also shown is the metabolic error signal [difference between $\dot{V}O_2(t)$ and Δ that drives the increase of $\dot{V}O_2$] which decreases with each increment of τ . The O_2 deficit is the area from exercise onset (time = 0) bounded by the actual $\dot{V}O_2$ profile and the asymptotic $\dot{V}O_2$ projected backward to time 0.

where t is the time elapsed from exercise onset and $\Delta\dot{V}O_{2\text{ss}}$ is the steady-state increase of $\dot{V}O_2$ above baseline (typically expressed as $\text{liters}\cdot\text{min}^{-1}$). The rate constant, k , is independent of $\Delta\dot{V}O_{2\text{ss}}$ across a broad range of metabolic demands (771). This relationship is consistent with the existence of an initial error signal (i.e., the difference between the instantaneous and required value and a feedback response that aims to eliminate the error, Fig. 6, bottom) and can also be expressed as:

$$\Delta\dot{V}O_2(t) = \Delta\dot{V}O_{2\text{ss}}(1 - e^{-t/\tau}), \quad (2)$$

where τ is the time constant (i.e., $1/k$ denoting the time to reach 63% $\Delta\dot{V}O_{2\text{ss}}$) which may span a broad range from ~ 10 to $>100 \text{ s}$. Importantly, at these exercise intensities, the off-transient (Eq. 3) is symmetrical to the on-transient (551):

$$\Delta\dot{V}O_2(t) = \Delta\dot{V}O_2(0)e^{-t/\tau}. \quad (3)$$

The faster $\dot{V}O_{2\text{ss}}$ can be achieved (i.e., the more rapid the $\dot{V}O_2$ kinetics) the better, in part, because this incurs a smaller

O_2 deficit (Fig. 6) for any given increase in $\dot{V}\text{O}_2$, and intracellular perturbations (e.g., $\Delta[\text{H}^+]$, $\Delta[\text{lactate}]$, and $\Delta[\text{PCr}]$) will be minimized. The O_2 deficit for moderate exercise is most easily calculated as the area between the actual $\dot{V}\text{O}_2$ and the required $\dot{V}\text{O}_2$ (i.e., baseline + $\Delta\text{steady state}$) which is calculated according to:

$$\text{O}_2 \text{ deficit} = \Delta\dot{V}\text{O}_2 \cdot \tau. \quad (4)$$

Thus, $\tau\dot{V}\text{O}_2$ is a fundamental parameter of aerobic performance (765, 769) and differences in $\tau\dot{V}\text{O}_2$ (i.e., the speed of $\dot{V}\text{O}_2$ kinetics) may help explain the broad range of physical/athletic capabilities and exercise tolerance across populations (110, 386, review 638). Accordingly, trained endurance athletes exhibit extremely fast $\dot{V}\text{O}_2$ kinetics (see Section *Exercise Training and Performance*) whereas detraining, aging (see Section *Maturation and Aging*) and the predations of many chronic disease conditions (see Section *Disease States*) slow $\dot{V}\text{O}_2$ kinetics. Thus, at the transition to exercise, elite cyclists (43, 442, 445) and marathon runners (395) as well as horses (467, 593) and Greyhounds (593) may achieve near-constant exercising $\dot{V}\text{O}_2$'s within 30 to 40 s (i.e., $4 \times \tau$). In contrast, aged individuals or those suffering from chronic heart failure (CHF) or pulmonary disease may require several minutes or more to reach steady state and will consequently, for a given increase in $\dot{V}\text{O}_2$, incur a much larger O_2 deficit which is associated with premature fatigue (see Sections *Maturation and Aging* and *Disease States*).

When exercising work rate is taken as the system input and pulmonary $\Delta\dot{V}\text{O}_2(t)$ as the corresponding output Eqs. 1 to 4 characterize a dynamic linear first-order system that, as such, should be described by a unique transfer function. The relevance here is that, if pulmonary $\dot{V}\text{O}_2$ kinetics reflects closely muscle $\dot{V}\text{O}_2$, the most straightforward (Occam's razor) conclusion is that the ATP-muscle $\dot{V}\text{O}_2$ coupling is rate-limited by a single first-order reaction (review 638, 771) and that $\dot{V}\text{O}_2$ kinetics is not limited by O_2 transport *per se* [see Section *Site(s) of Limitation of $\dot{V}\text{O}_2$ Kinetics: Oxygen Delivery Versus Cellular Respiration*]. Riggs (630) concept of superposition, can be used across different work forcings to test the presumption that muscle $\dot{V}\text{O}_2$ kinetics is governed by such a system (review 638, 771). Thus, considering the pulse/impulse as the input function, which has as its first integral the step and its second integral the ramp, across these different work forcings the parameters of the $\dot{V}\text{O}_2$ (output) (i.e., τ , mean response time, MRT; gain, G , i.e., $\Delta\dot{V}\text{O}_2/\text{Watt}$) should be identical. Tests of superposition have verified that pulmonary $\dot{V}\text{O}_2$ responds generally as a linear first-order system; at least in the moderate domain. Specifically, following a high work rate “impulse” [e.g., 0 → 500 (10 s) → 0 Watts] $\dot{V}\text{O}_2$ rises almost instantaneously to a value that is proportional to the impulse area and then declines exponentially to baseline. For the “step” (e.g., 0 → 50 Watts) in the moderate domain $\dot{V}\text{O}_2$ increases exponentially, after a brief delay, to the steady state. Finally, in the “ramp” the $\dot{V}\text{O}_2$ increase lags by 1τ behind the expected steady-state response for each given work rate.

Across all forcing profiles the parameters are invariant with the exception that the G determination is problematic for the impulse.

Experiments in muscles contracting *in vitro* (frog sartorius, 344, 488-491) and *in situ* (dog gastrocnemius, 580) have supported the characterization of $\dot{V}\text{O}_2$ as a linear first-order system. Because, during large muscle mass exercise, $\dot{V}\text{O}_2$ of the contracting muscles overwhelms that of other tissues (606) pulmonary $\dot{V}\text{O}_2$ reflects changes of muscle(s) $\dot{V}\text{O}_2$ (and high-energy phosphates, e.g., 640, 641) with high fidelity (31, 285, 455). This is true despite the interposition of transit delays and alterations of O_2 stores (primarily in the lungs and venous blood) as detailed in Sections *Site(s) of Limitation of $\dot{V}\text{O}_2$ Kinetics: Oxygen Delivery Versus Cellular Respiration* and *Relationship Between Pulmonary and Exercising Muscle $\dot{V}\text{O}_2$ Responses*. However, whereas with appropriate modeling techniques and parameterization of the response a close facsimile of muscle $\dot{V}\text{O}_2$ kinetics can be extracted from pulmonary data in the moderate exercise intensity domain, system nonlinearities [i.e., manifestation of the $\dot{V}\text{O}_2$ sc (see Section *Slow Component of $\dot{V}\text{O}_2$ Kinetics: Mechanistic Bases*), and asymmetry of $\dot{V}\text{O}_2$ on- versus off-kinetics (455, 551, 645)] occurring at work rates in the heavy and severe-intensity domains dispute the linear first-order characterization of the $\dot{V}\text{O}_2$ response.

Exercise Intensity Domains

In a given individual, the profile of $\dot{V}\text{O}_2$ following the onset of constant-work-rate exercise may be defined with respect to the exercise-intensity domain in which the exercise is performed which, in turn, is determined by the cluster of common metabolic (i.e., $\dot{V}\text{O}_2$ and [lactate]) responses evoked (Figs. 5 and 7, references 174, 258, 350, 749, 751, 788). Specifically, for moderate intensity (<LT or GET, Figs. 5 and 6, top) exercise pulmonary $\dot{V}\text{O}_2$ begins to increase within the first breath (Phase I or cardiodynamic component), there is then a brief surcease prior to the appearance of the exponential increase of $\dot{V}\text{O}_2$ some 15-20 s later [i.e., Phase II, fundamental or primary component, p (latter used herein)] to the steady state (Phase III). This response is best modeled as a time delay (TDP, 10-20 s) followed by an exponential (769, 771):

$$\Delta\dot{V}\text{O}_2(t) = \Delta\dot{V}\text{O}_2(1 - e^{-t-\text{TDP}/\tau_p}). \quad (5)$$

With respect to the Phase I $\dot{V}\text{O}_2$ response, as for $\dot{V}\text{E}$ (see Section *Integration of Dynamic Responses in the Pathway for O_2*), this is believed to be driven by the increase in pulmonary blood flow in the absence of altered arterial or venous O_2 contents (but see 129). The rapidity of the Phase I cardiodynamic response is attributed most convincingly to the almost instantaneous cardiac output increase which is initiated by vagal withdrawal and the mechanical pumping action of the contracting muscles (review 461, 462, 522).

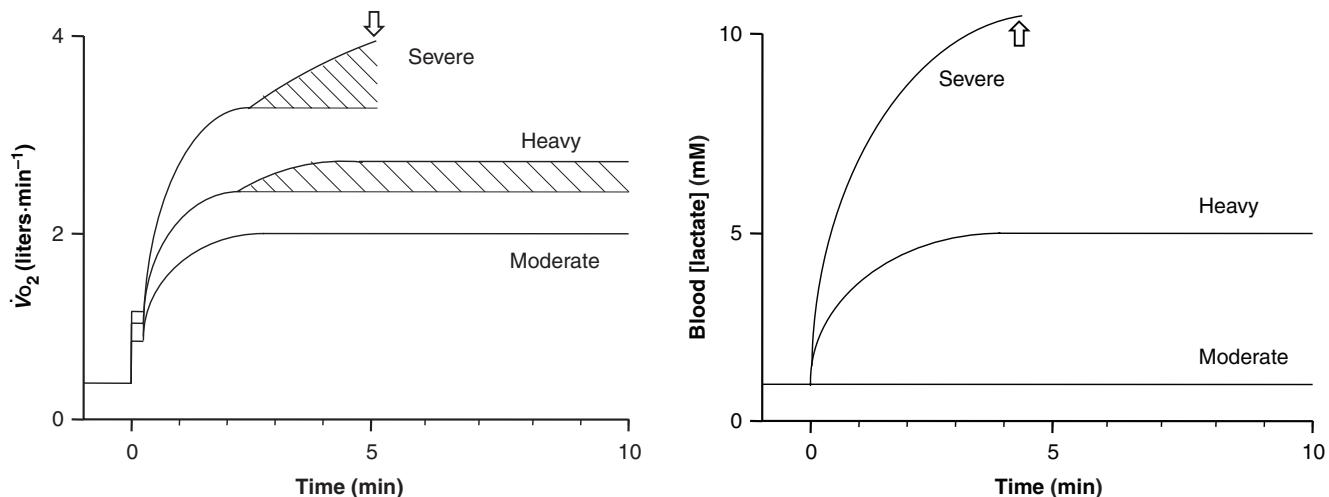


Figure 7 Left panel: schematic representation of the $\dot{V}O_2$ response to constant-work-rate exercise in the moderate, heavy, and severe domains. Note presence of $\dot{V}O_2$ slow component (hatched area) for heavy and severe exercise. Arrow denotes exercise curtailed by fatigue. Right panel: schematic representation of the blood [lactate] response to constant-work-rate exercise in the moderate, heavy, and severe domains. Arrow denotes exercise curtailed by fatigue. Note correspondence between [lactate] and $\dot{V}O_2$ responses within domains.

Figure 6 (bottom) demonstrates some of the pertinent properties of a simple exponential response, in particular, the approach of $\dot{V}O_2$ to its steady state value within about 2 to 3 min in a healthy young individual. For cycle ergometry G or amplitude of the response is 9 to 11 ml O₂ min $^{-1}$ W $^{-1}$ (e.g., 39, 255, 315, 492, 597, 751, 769, 778). In the heavy-intensity domain, which encompasses all metabolic rates between LT/GET and critical power (CP) a secondary $\dot{V}O_2$ elevation (i.e., the $\dot{V}O_{2\text{sc}}$, see Section *Slow Component of $\dot{V}O_2$ Kinetics: Mechanistic Bases*), becomes apparent after \sim 90 to 120 s and is superimposed on the faster primary (p) response (Fig. 7, left panel; 258, 330, 589, 606, 646, 771, 780). CP is the asymptote of the power-duration curve for high-intensity exercise (i.e., notionally the highest work rate or, more properly, $\dot{V}O_2$ that can be sustained for a prolonged period (528, 532; Fig. 5). CP therefore represents the highest submaximal $\dot{V}O_2$ that can be stabilized (i.e., the $\dot{V}O_{2\text{sc}}$ rise can be curtailed, reference 610) which corresponds to the maximal lactate steady state (79, MLSS, depicted in the heavy domain of Fig. 7, right panel, see Section *Slow Component of $\dot{V}O_2$ Kinetics: Mechanistic Bases*); both occurring typically at \sim 50% of the Δ GET- $\dot{V}O_{2\text{max}}$ obtained on the ramp/incremental exercise test (618, 696). CP also constitutes the highest metabolic rate at which intramuscular [creatinine phosphate] and [H $^+$] stabilize (review 400). Given that CP (rather than GET/LT) represents a crucial demarcator of metabolic stability its relevance with respect to understanding exercise tolerance and exhaustion cannot be overemphasized. Fitting the $\dot{V}O_2$ response in the heavy domain requires a more complex model that includes additional delay (TDsc) and exponential (tsc) components related to the $\dot{V}O_{2\text{sc}}$:

$$\Delta\dot{V}O_2(t) = \Delta\dot{V}O_2(1 - e^{-t-TD_p/\tau_p}) + \Delta\dot{V}O_{2\text{sc}}(1 - e^{-t-TD_{\text{sc}}/\tau_{\text{sc}}}). \quad (6)$$

Whereas it is possible to fit a third exponential component to describe Phase I (e.g., 285, 675; Fig. 6, top) this practice yields a double-edged sword: it improves the overall fit mathematically but it may overburden the parameterization which reduces confidence in the individual parameter estimation (772). There is thus a solid argument, in any given instance, for judicious selection of the simplest model that adequately characterizes the response for the parameters of most interest. It is crucial to acknowledge that the $\dot{V}O_{2\text{sc}}$, the exponentiality of which is by no means certain (see Section *Slow Component of $\dot{V}O_2$ Kinetics: Mechanistic Bases*), represents an additional O₂ cost which increases the $\dot{V}O_2 G$ (>11 ml min $^{-1}$ W $^{-1}$) effectively reducing work efficiency and delaying attainment of the $\dot{V}O_2$ steady state for as long as 15 min or more (330, 610, 780). At yet higher work rates in the severe intensity domain (i.e., $>$ CP, Fig. 5) $\dot{V}O_2$ may either rise rapidly and exponentially to $\dot{V}O_{2\text{max}}$ or, alternatively, evince a $\dot{V}O_{2\text{sc}}$ that increases systematically as a function of time, driving $\dot{V}O_2$ to $\dot{V}O_{2\text{max}}$: either profile heralding imminent fatigue once $\dot{V}O_{2\text{max}}$ is attained (350, 610). For severe exercise blood [lactate] rises inexorably to the point of fatigue (Fig. 7, right panel) and there is evidence that the primary component $\dot{V}O_2 G$ may be reduced (389, 616, 673). For heavy and severe exercise where the $\dot{V}O_{2\text{sc}}$ is present, $\dot{V}O_2$ changes as a function of time and not work rate. Thus, in these domains the common practice of describing exercise intensity as % $\dot{V}O_{2\text{max}}$ is indefensible. Finally, there exists a still higher exercise intensity domain, termed “extreme,” where the work rate is so great that fatigue intervenes in approximately <140 s (i.e., <4 τ 's) before $\dot{V}O_{2\text{max}}$ can be achieved (Fig. 5, 350, 394, 397, 589).

The exercise intensity domain schematism described above (i.e., moderate-heavy-severe-extreme, Scheme 1, Figs. 5 and 7) is not the only one proposed. Specifically,

Whipp and Rossiter (638, 772) have proposed a moderate-heavy-very heavy-severe domains classification (Scheme 2). The principal discrimination between the two schemes may be summarized as follows: Scheme 1 is defined by the achieved $\dot{V}O_2$ profile in that all work rates that achieve the independently determined $\dot{V}O_{2\text{max}}$ are considered to reside within the severe domain—irrespective of whether $\dot{V}O_2$ projects to $\dot{V}O_{2\text{max}}$ via the primary or slow component of the response. Scheme 2 discriminates very heavy from severe exercise on the basis of whether or not the primary component is predicted to project below (very heavy) or above (severe) $\dot{V}O_{2\text{max}}$. Notwithstanding the uncertainties of predicting the $\dot{V}O_2$ cost at these high intensities and resolving the mechanistic bases for the $\dot{V}O_{2\text{sc}}$, Scheme 2 makes no provision for work rates that are too high to elicit $\dot{V}O_{2\text{max}}$ (i.e., the extreme domain in Scheme 1). Accordingly, this review will utilize the moderate-heavy-severe-extreme classification (Scheme 1).

$\dot{V}O_2$ Responses Following Exercise

Compared with the on-response the recovery kinetics has received less recent attention and yet they can help facilitate mechanistic interpretation of the on-transient, the effects of priming exercise and possibly exercise intolerance. However, the early O₂ deficit—O₂ debt concept lent itself to mechanistic overinterpretation (256) which forced renaming of the so-called “O₂ debt” to the functionally descriptive “excess postexercise O₂ consumption” or EPOC (21, review 256). As with the on-responses described above, although the off-transient kinetics return $\dot{V}O_2$ toward baseline with a temporal profile resembling closely the primary on-kinetics in some cases, there is a certain domain dependency that dictates the off-kinetics (i.e., presence of a $\dot{V}O_{2\text{sc}}$ or not) and symmetry/asymmetry with the on-kinetics. In the moderate domain, and, in accordance with the linear first-order nature of $\dot{V}O_2$ kinetics discussed above, the on- and off-responses are symmetrical (394, 551, 561). However, for heavy exercise the $\dot{V}O_{2\text{sc}}$ present during the on- is absent from the off-transient. In the severe domain a $\dot{V}O_{2\text{sc}}$ may be apparent for both the on- and off-transient whereas for extreme exercise there is no $\dot{V}O_{2\text{sc}}$ during the on- but one emerges during the off-transient (551, review 638). $\dot{V}O_2$ kinetics in the off-transient will reflect the lumped temporal characteristics of many physiological processes as the homeostasis of the resting condition is restored. These include: dynamics of cardiac output, muscle blood flow, and muscle(s) $\dot{V}O_2$ (locomotory, respiratory, cardiac, and accessory), partial refilling of O₂ stores in venous blood and muscle, and energetic costs associated with hormonal, thermal, and metabolic derangements (review 256, 638). As such, and keeping in mind that the primary and slow components, which may be temporally displaced 1 to 2 min at exercise onset, are conflated at the off-transient, interpretation of off-transient $\dot{V}O_2$ kinetics is challenging. Notwithstanding this consideration, in healthy muscle the off-transient muscle blood flow kinetics are slowed in comparison to that of

$\dot{V}O_2$ (239) permitting elevation of microvascular Po₂'s (70, 510, 511) and presumably aiding oxidative recovery. Impaired vascular control in disease may compromise this process (see Kemps et al. references 413-416 and Section *Disease States*).

The coherence between exercising muscle(s) PCr and pulmonary $\dot{V}O_2$ kinetics (see Section *Site of Limitation of $\dot{V}O_2$ Kinetics*) during the exercise on-transient is found also during recovery (638, 645) and this is consistent with the correlation of PCr recovery kinetics with muscle oxidative capacity (508). Moreover, there is an emergent body of evidence which suggests that recovery of muscle (162) and pulmonary (413) oxidative processes are both more reproducible and a more reliable indicator of dysfunction, for example, in CHF, than the on-transient kinetics. Given the above, the recent demonstration that there may be a dissociation between muscle(s) and pulmonary $\dot{V}O_2$ kinetics following exercise (455) suggests caution is required when interpreting $\dot{V}O_2$ recovery data.

Integration of Dynamic Responses in the Pathway for O₂

The dynamics of the O₂-transport systems upstream of the contracting myocytes—pulmonary, cardiovascular, and muscle microvascular—are such that ventilation ($\dot{V}E$), cardiac output, and skeletal muscle vasomotor control ensure that O₂ is delivered to the exercising muscle as fast, or even faster, than $\dot{V}O_2$ can increase (Figs. 2 and 3, references 31, 64, 285, 455). Whereas the ultimate control mechanisms for each of these systems are discussed in detail elsewhere in this volume, it is pertinent to consider them here as a foundation for understanding why, in health, they may not pose a limitation to $\dot{V}O_2$ kinetics but how specific organ and system dysfunction can often shift the site of $\dot{V}O_2$ limitation upstream (see Fig. 2 and Section *Disease States*).

Pulmonary system

Rather than regulating arterial O₂ levels *per se*, the cardinal function of the exercise hyperpnea (i.e., increased $\dot{V}E$) in humans is to facilitate CO₂ removal at rates which increase from ~0.2 liters·min⁻¹ at rest to, in the extreme, over 6 liters·min⁻¹ during maximal exercise so as to prevent, or at least constrain, the magnitude of any perturbation in arterial blood gas and acid-base status. Mass balance considerations require that $\dot{V}E$ be a determinant of measured gas exchange (review 752). Thus, across the range of work rates achievable, $\dot{V}E$ is coupled closely to CO₂ exchange (133, 209, 750, review 752, 767) and increases according to:

$$\dot{V}E = 863\dot{V}CO_2/[PaCO_2(1 - V_D/V_T)]. \quad (7)$$

Where 863 is the product of barometric pressure, temperature, and water vapor corrections required to express $\dot{V}E$ at body temperature and pressure, saturated (BTPS), $\dot{V}CO_2$ at

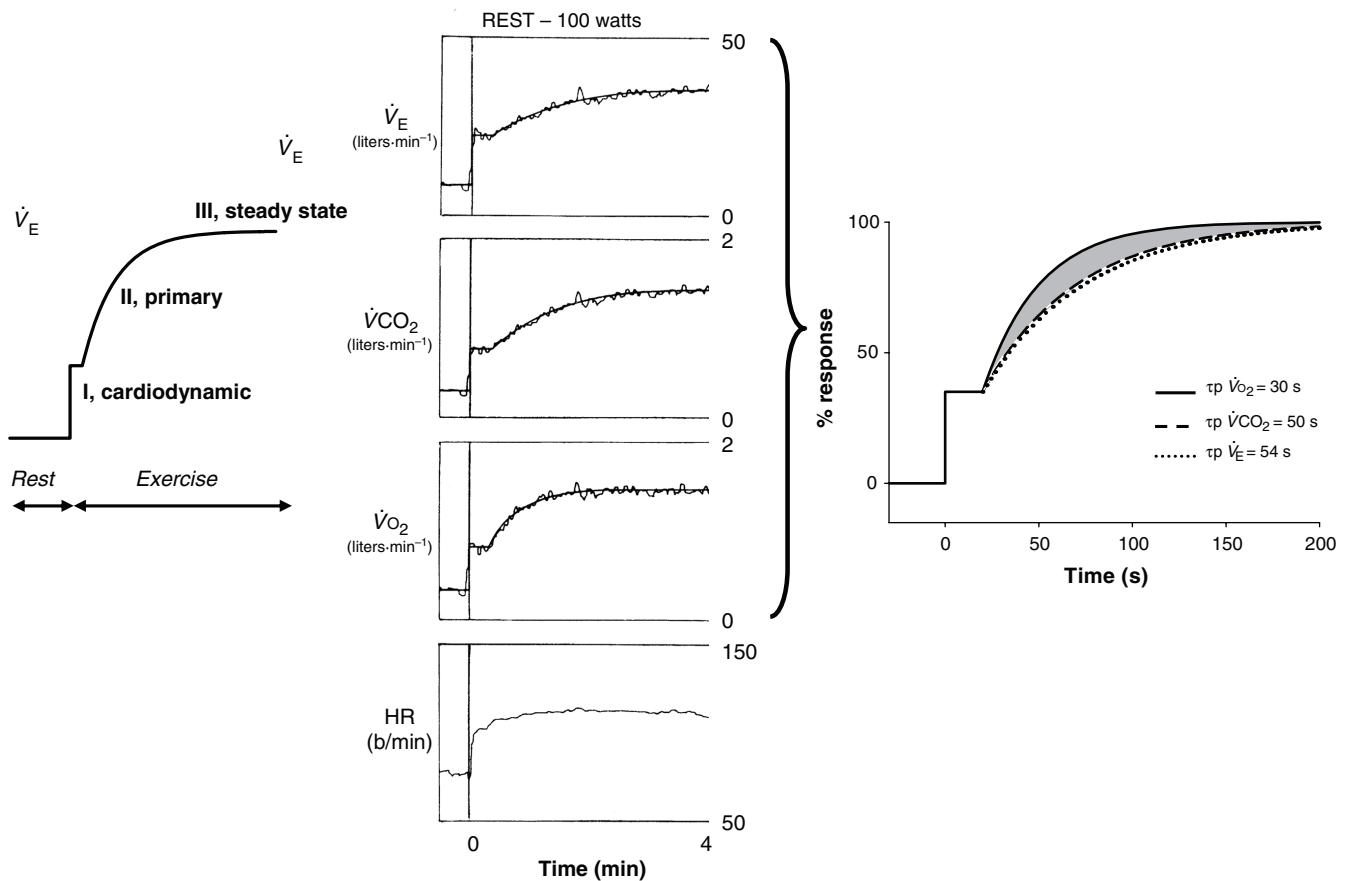


Figure 8 Left panel: schematic of ventilatory (\dot{V}_E) response following the onset of moderate intensity exercise. Phases I, II and III are demarcated. Center panels: breath-by-breath responses of \dot{V}_E , CO_2 output ($\dot{V}CO_2$), O_2 uptake ($\dot{V}O_2$), and heart rate (HR) to a single bout of 100-W (moderate) exercise from rest. The group mean time constants of the responses were 29 ($\dot{V}O_2$), 51 ($\dot{V}CO_2$), and 54 s (\dot{V}_E). Note the almost instantaneous Phase I increases in \dot{V}_E and pulmonary gas exchange as well as very rapid HR kinetics following exercise onset. See text for more details. Vertical line indicates onset of exercise. Adapted, with permission, from Whipp et al. (769). Right panel: schematic overlaying time courses of \dot{V}_E , $\dot{V}CO_2$, and $\dot{V}O_2$. \dot{V}_E tracks $\dot{V}CO_2$ which is far slower than $\dot{V}O_2$ due to higher solubility and tissue storage of CO_2 . One consequence of this behavior is a transient decrease of end-tidal PO_2 and a mild arterial hypoxemia. See text for more details.

standard temperature and pressure, dry (STPD), and arterial CO_2 as a partial pressure ($PaCO_2$). V_D/V_T is the ratio of dead space to tidal volume and this contribution to \dot{V}_E may be removed by considering only the effective, that is, alveolar ventilation (\dot{V}_A):

$$\dot{V}_A = 863\dot{V}CO_2/PaCO_2. \quad (8)$$

Thus, throughout the range of moderate work rates where $PaCO_2$ is regulated close to 40 mmHg \dot{V}_A must increase by ~ 21.6 liters to evolve each liter of CO_2 (767). At higher work rates (i.e., heavy/severe domains) where the peripheral chemoreceptors invoke a hyperventilatory response, in part, to constrain the magnitude of the pH fall, $PaCO_2$ may fall to 30 mmHg or lower (752, 767). In this instance \dot{V}_A must increase by ~ 28.8 liters·liter⁻¹ CO_2 or more and the ability for very fit humans (189, 190, 614), women (320), horses (56, 57, 554, 743), and Greyhound dogs (578, 702) to hyperventilate and drive down $PaCO_2$ may be limited by mechanical constraints on airflow generation and thus \dot{V}_A . This problem is

compounded by the low-limiting red blood cell (RBC) transit times in the pulmonary capillaries as dictated by the presiding pulmonary capillary volume: cardiac output ratio.

Dynamic profile of \dot{V}_E following exercise onset

O_2 flux (i.e., $\dot{V}O_2$) and changes thereof across the alveolar-capillary blood-gas barrier are principally a function of the availability of reduced hemoglobin flowing through the pulmonary capillaries. Across the transient following the onset of moderate exercise the overall profiles of \dot{V}_E , $\dot{V}CO_2$, and $\dot{V}O_2$ evince considerable commonality and hence the \dot{V}_E response at the start of exercise can be partitioned into three discrete phases (Fig. 8; references 171, 177, 382, 452, 563, 747, 752, 767, 769). However, because the dynamics of \dot{V}_E (and \dot{V}_A) track those of $\dot{V}CO_2$ rather than $\dot{V}O_2$, their time courses may be substantially different (i.e., \dot{V}_E kinetics are slower, Fig. 8). As a consequence of this behavior, ~ 20 –90 s after exercise onset there may be a modest transient reduction in arterial PO_2 in Phase II even in healthy subjects performing cycle

exercise (93, 715; see also reference 802 for stair climbing), but arterial O₂ content is not lowered appreciably (however, see 189, 190, 320, 556, 614, 635, 706, 710 for exceptions).

Phase I is initiated simultaneously with the almost instantaneous increase in pulmonary perfusion (13, 17, 266, 452, 563–565, 754, 756, 771, 776, review 752) which occurs within the first breath after exercise onset (Fig. 8) and is associated with a preferential increase of V_T prior to an augmented respiratory rate. At very low work rates, Phase I may constitute the entire \dot{V}_E response and temporarily exceed the inspired ventilation because of a reduced functional residual capacity (382, 476, 752). In accordance with the concept of feed-forward “cardiodynamic hyperpnea” (i.e., precise matching of \dot{V}_A to pulmonary blood flow and thus CO₂ delivery to the lung, 134, 135, 382, 476, 747, 766, 771, 781, but see also 565) for the 10 to 20 s duration of Phase I (17, 452, 476, 754, 756, 771), there is no hypo- or hyperventilation evident and increases in \dot{V}_O_2 and $\dot{V}CO_2$ are proportional to those of \dot{V}_A such that R ($\dot{V}CO_2/\dot{V}O_2$) and the end-tidal Po₂ and PCO₂ remain unaltered (749, 752, 754, 767, 775, 777). This precise matching of \dot{V}_A with pulmonary CO₂ delivery has been used to argue against a purely neural origin of Phase I (review 752, 767).

Phase II is initiated by the arrival at the lung of venous effluent from the exercising muscle(s) (though see reference 129 for contrary data) and \dot{V}_E (and \dot{V}_A) again tracks CO₂ delivery to the lung increasing monoexponentially with a τ of 50 to 70 s to achieve the steady state, Phase III, within 4 to 5 min (Fig. 8). Compared with Phase II $\dot{V}O_2$ kinetics ($\tau \sim 30$ s), those of $\dot{V}CO_2$ ($\tau \sim 50$ s) are more sluggish which is, in part, a consequence of the greater solubility, and hence storage, of CO₂ in the tissues (172, 206, 303, 345, 365, 476, 497, 779, 781, review 205, 752, 767, 771). This disparity in $\dot{V}CO_2$ and $\dot{V}O_2$ kinetics drives R ($\dot{V}CO_2/\dot{V}O_2$) down transiently over ~ 30 s in Phase II prior to increasing to its steady-state value as dictated by the sum total of the different respiratory quotients in the body as expressed across the lungs (476, 566, 622, 767, 781). During Phase II as pulmonary blood flow and mixed venous PCO₂ continue to increase (and mixed venous Po₂ decreases) (13, 452, 756, 767, 771) there is an augmented slope of the alveolar PCO₂ such that end-tidal PCO₂ (P_{ET}CO₂) increases. Furthermore, in Phase II, increases in $\dot{V}CO_2$ precede those of \dot{V}_A by some seconds (476, 752, 769) which may indicate participation of an error signal in the PaCO₂ profile, sensed by the carotid bodies, which controls, or at least contributes to, the exercise hyperpnea. One consequence of the sluggish kinetics of \dot{V}_A relative to those of $\dot{V}O_2$ is that the partial pressure of end-tidal O₂ (P_{ETO}O₂) falls transiently below steady-state values resulting in a mild arterial hypoxemia as discussed above (93, 715, 802). Because, for most subjects, this occurs on the flatter upper end of the O₂ dissociation curve the 10 to 15 mmHg fall in Po₂ seen for cycling exercise does not induce overt arterial hypoxemia (93, 715). However, possibly due to ventilatory constraints not seen in cycling or running, for stair climbing Pao₂ may fall as low as 65 mmHg and significantly lower arterial O₂ content (802).

Whereas there remains considerable debate regarding the relative importance and participation of neural and humoral mechanisms in the rapid Phase I ventilatory (and therefore gas exchange) response following exercise onset (320, 411, 767) one surprising outcome of the astonishingly fast HR and consequent pulmonary blood flow increase in Phase I is that the kinetics of pulmonary $\dot{V}O_2$ may actually be faster than those at the exercising muscle(s) (285; cf. 72, Section *Relationship Between Pulmonary and Exercising Muscle $\dot{V}O_2$ Responses*).

In contrast to the well-defined ventilatory Phase III for moderate exercise where \dot{V}_E (and therefore \dot{V}_A) rises sufficiently to control PaCO₂ close to 40 mmHg and arterial pH ~ 7.4 , at heavy and severe intensities \dot{V}_E continues to increase beyond the initial transient such that there is either no steady state or its attainment is substantially delayed (476, 501, 625, 753, 767, 781). In accordance with the Hey relationship (338) the continued rise in \dot{V}_E is the consequence of increasing breathing frequency in preference to V_T and P_{ET}CO₂ decreases whilst Po₂ increases (749, 752). Similar to the $\dot{V}O_2$ response there is a pronounced difference in the behavior of \dot{V}_E during heavy versus severe exercise and this has lead to the concept of a “ventilatory threshold for long-term exercise” (625). Thus, given sufficient time during heavy exercise, \dot{V}_E approaches quasistable levels whereas for severe exercise \dot{V}_E (and \dot{V}_A) continue to increase and PaCO₂ falls until exhaustion intervenes (258, 625, 752). As for the Phase I \dot{V}_E response the mechanisms responsible for the hyperpnea and hyperventilation that attend heavy and severe exercise have been hotly debated (review 411, 752, 767). Whereas the principal site of the $\dot{V}O_2$ sc is located within exercising skeletal muscle (606) the continued rise in \dot{V}_E in Phase III can only partially be explained by metabolically increased CO₂ production (linked to the $\dot{V}O_2$ sc) within these muscles. Specifically, there may be afferent impulses from exercising muscle and joint receptors and Group III and IV afferent nerves that respond to the increased metabolic requirements and changes in the intra- and extracellular milieu (411, 752, 767). In addition, the increased sense of effort may drive a cortically mediated stimulus to elevate \dot{V}_E and the continuing increase of body and blood temperature as well as blood [H⁺], [catecholamines], [K⁺], and osmolarity all stimulate the carotid body (i.e., peripheral) chemoreceptors and contribute to the progressively increasing \dot{V}_E during severe intensity exercise (411, 752, 767).

Pursuant to the conclusions drawn in Section *Site(s) of Limitation of $\dot{V}O_2$ Kinetics: Oxygen Delivery Versus Cellular Respiration* below, in most healthy young individuals the ventilatory response to exercise is sufficiently well-controlled (albeit CO₂- rather than O₂-linked) that there is no pronounced or sustained reduction of arterial Po₂ or content following the onset of moderate, heavy, and usually severe exercise [elite athletes (189, 190, 614, 635, 710), some female (320, 706), and patient (556) populations excepted] that might compromise O₂ delivery to the exercising muscles and thus $\dot{V}O_2$ kinetics (31, 285, 455).

Cardiovascular system

Heart rate and cardiac output

Across the spectrum of human oxidative potential (i.e., basal or resting $\dot{V}O_2$ up to $\dot{V}O_{2\text{max}}$) cardiac output (\dot{Q}) increases with a slope (S) between 5 and 6 liter/liter $\dot{V}O_2$ (with an intercept (I) of 5 to 6 liters·min $^{-1}$ (review 586, 648) according to:

$$\dot{Q} = S \cdot \dot{V}O_2 + I. \quad (9)$$

And thus,

$$\dot{Q}(\text{L}/\text{min}) = 5.5 \cdot \dot{V}O_2 + 5.5. \quad (10)$$

The point is made earlier that the rapid Phase I pulmonary $\dot{V}O_2$ kinetics is driven by increased pulmonary blood flow secondary to an almost immediate HR (lag time ≤ 600 ms, references 97, 324, 359, 383, 452, 565, 575, 783; review 136, 648), stroke volume and \dot{Q} response (τ as low as ~ 10 s). This is facilitated during moderate intensity exercise by the acceleration of HR and \dot{Q} principally by essentially instantaneous vagal withdrawal (139, 225, 227, 378, 404, 461, 476, 648, 769, 799, review 136). At greater work rates, in the heavy or severe domains, the higher HR requires sympathetic stimulation, and both HR and \dot{Q} kinetics become much slower and biphasic (324, 378, 404, 648). However, over at least the majority of the range of moderate, heavy, and severe work rates the initial increase in HR [and also \dot{Q} (141, 172, 405) and feed artery blood flow (e.g., 432; Fig. 9) are far faster than that of $\dot{V}O_2$ (as assessed via the τ , MRT or half-time (e.g., 324) of the response] (review 136, 182). This is a crucial

observation because, as considered next (see Section *Muscle Microvascular System*), if the increased central cardiovascular O_2 transport can be redistributed away from other vascular beds [i.e., splanchnic organs (647, 648), kidneys (291), skin, and resting skeletal muscle (94, 647, 648, 807)] and delivered to the contracting muscles, the time course is adequate to support muscle $\dot{V}O_2$ kinetics when they are changing most rapidly (i.e., in the first few seconds of exercise).

Muscle blood flow

The realization that mechanisms responsible for initiating muscle exercise hyperemia are likely to be very different from those that sustain it beyond the transient (152, 239, review 163) has made development of techniques for following rapid changes in blood flow a high priority. Over the past two decades or so, several techniques have provided the temporal fidelity necessary for resolution of arterial or muscle blood flow kinetics and also muscle $\dot{V}O_2$ kinetics. These include: thermodilution (31, 285, 455), ultrasound (215, 368, 432, 482-485, 668, 727, 729, 730), and near-infrared spectroscopy (NIRS) which, in combination with pulmonary $\dot{V}O_2$ measurements, have been used to resolve microvascular flow dynamics in human muscle (241, 321). In animal muscles during contractions, it has also been possible to resolve blood flow and $\dot{V}O_2$ kinetics in the dog gastrocnemius-plantaris complex (277-281, 334, 335) and the temporal profile of RBC flux within the capillary bed in rats (64, 161, 428, 629). Thus, although there are exceptions (e.g., 229, 368) the overall kinetic profile of HR (and \dot{Q} as well as muscle blood flow, half-time 2 to 10 s in humans, 660) is usually faster than $\dot{V}O_2$ (Fig. 9; 324, 432, 800 review 182, 275, 589) such that there is no overshoot of muscle O_2 extraction at least in health (31, 285, 405, 455) and blood flow can be manipulated independently of $\dot{V}O_2$ kinetics (799). These observations, and the logic that it is difficult to conceive of a faster process (cardiovascular and muscle blood flow dynamics) limiting the speed of a slower one ($\dot{V}O_2$ kinetics) provide strong support that bulk O_2 transport *per se* does not limit the kinetics of muscle (and therefore pulmonary) $\dot{V}O_2$. This conclusion has subsequently been verified for moderate (285) as well as heavy and severe (31, 455) intensity exercise where blood flow kinetics are so fast that effluent venous O_2 content may even become elevated above resting values for 10 to 15 s as fractional O_2 extraction is reduced. In contrast, in the heart with its prodigious oxidative capacity (mitochondrial volume density approaching 30%, in humans, references 47, 671), $\dot{V}O_2$ kinetics are so fast relative to those of blood flow that such a transient overshoot is found in coronary sinus O_2 desaturation (i.e., very low venous O_2 content) immediately following the onset of supramaximal exercise (406).

Powerful additional evidence for a surfeit of O_2 delivery to the exercising muscles under normal healthy exercising conditions has emerged from experiments designed to either reduce blood flow and/or speed $\dot{V}O_2$ kinetics. Specifically, blockade of nitric oxide (NO) synthase [horse (424, 425), human (402,

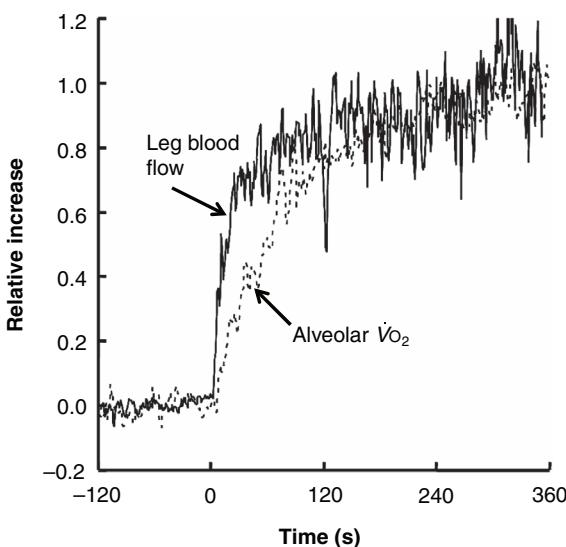


Figure 9 Relative increase in femoral artery blood flow (solid line) compared with alveolar $\dot{V}O_2$ (dotted line) across the transient from unloaded to heavy intensity knee extension exercise. Note far faster blood flow (mean response time, MRT, 46 s) than $\dot{V}O_2$ (MRT, 69 s) response. Redrawn from Koga et al. (432), with permission.

403) which decreases \dot{Q} (420), and skeletal muscle blood flow (353) speeds pulmonary $\dot{V}O_2$ kinetics presumably by relieving the NO impediment to mitochondrial function (103, 104). Similarly, any reduction of muscle blood flow induced either by means of applying lower limb positive pressure (792) or simultaneous blockade of cyclooxygenase and NO synthase (546) which reduced exercising muscle blood flow and O_2 delivery by 25% to 50% (546) does not slow pulmonary (792) or muscle (546) $\dot{V}O_2$ kinetics.

Muscle blood flow is highly stratified within and among contracting skeletal muscles as demonstrated using radiolabelled microsphere infusions in running rats (9, 10, 213, 535, 607, review 470). Thus, highly recruited very oxidative muscles and muscle fibers can receive a prodigious blood flow surpassing 5 liters $kg^{-1} \text{ min}^{-1}$ whereas that to their low oxidative highly glycolytic counterparts is constrained to a small fraction of this. Combining phosphorescence quenching technology with microspheres and intravital microscopy measurements it has been determined that microvascular blood flow relative to $\dot{V}O_2$ increases with the same slope (i.e., $S \sim 5\text{-}6 \text{ liters}\cdot\text{min}^{-1}$) as seen for \dot{Q} and whole muscle(s) and this is relatively invariant among fiber types (238). However, the intercept (I for the relationship expressed in Eq. 10, and resting blood flow) is far lower for fast twitch (type IIA, IIB, and IIX/D) muscle fibers and even at low $\dot{V}O_2$'s these fibers are forced to rely on a greater fractional O_2 extraction such that $Pmvo_2$ is lower and falls faster and to a greater extent than seen for slow twitch (type I) fibers (74, 238, 512, 589). Thus, it should be recognized that exercise of a sufficient intensity to recruit fast twitch fibers will encroach closer toward (or perhaps beyond, i.e., leftward of) the tipping point seen in Figure 2 where $\dot{V}O_2$ kinetics are O_2 -delivery dependent and may potentially be more susceptible to slowing consequent to impaired blood-muscle O_2 flux and also lowered intracellular Po_2 (see Section *Influence of Muscle Fiber Type and Motor Unit Recruitment on $\dot{V}O_2$ Kinetics*).

Muscle microvascular system

Were \dot{Q} to rise substantially, as it does almost immediately upon initiation of rhythmic exercise, and (muscle) vascular conductance not increase, mean arterial blood pressure (MAP) would spike upward. That this does not happen—indeed MAP may fall briefly (e.g., 484)—implies that effective muscle vascular conductance must increase almost simultaneously with \dot{Q} and this phenomenon has been recognized at least since the 1930s (6). Despite this rationale and the demonstrated speed of the muscle (6, 164, 540, 729, 730, review 182), arteriolar (735), and capillary blood flow (428) responses to muscle contractions its mechanistic bases have not been unequivocally resolved. Specifically, there is debate over the relative importance of the muscle pump versus active feed artery and arteriolar vasodilation and whether or how arterioles might dilate so rapidly (149, 150, 152, 308, 310, 471, 683-685, 720, 728, 729, 731).

Proponents of the muscle pump argue that, as it is a mechanical event driven by muscle relaxation, it should certainly be fast enough to explain the observed hyperemic responses on a contraction-by-contraction basis. However, the muscle pump *in separatum* cannot explain the prolonged elevation of blood flow that follows a single contraction (e.g., 729) nor the finding that blood flow matches metabolic demands rather than mechanical force *per se* (309). In contrast, earlier investigations did not support that contraction-induced vasodilation was fast enough (~20 s latency, 272) though others found far faster responses (~2 s, reference 500); or that single arterioles from the rat soleus or gastrocnemius muscles could dilate to putative mediators of the exercise hyperemia [potassium chloride (KCl), adenosine (AD), acetylcholine (ACh), and sodium nitroprusside (SNP)] with sufficiently fast dynamics (i.e., within 1-2 s) to account for the responses observed (797). However, more recent studies have found significantly faster vasodilation in arterioles from these very muscles in response to physiological stimuli including KCl, AD, ACh, and SNP (Fig. 10, rat, first order, 66; rat, first and third order, 637), and muscle contractions (hamster, retractor, feed artery, first and third order and terminal arterioles, 735; see also 524, 533) establishing active arteriolar vasodilation as a potential mechanism for driving the rapid contraction-induced hyperemia.

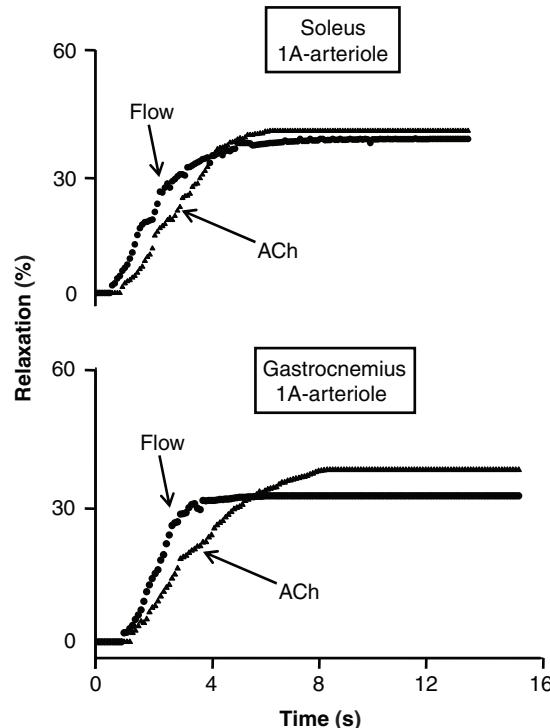


Figure 10 Vasodilator dynamics of isolated arterioles from the soleus and red gastrocnemius muscles of young rats to intraluminal flow (~13 nl/s) and acetylcholine (ACh, $1 \times 10^{-6} \text{ M}$). Exposure to each condition was initiated at time 0. Adapted, with permission, from the data of Behnke and Delp (66).

Notwithstanding that muscle blood flow can increase very rapidly following the onset of contractions, the tacit presumption has been that the kinetics of bulk muscle blood flow (i.e., that is present in the feed artery) reflects that present in the microcirculation at the site of blood-myocyte O₂ flux. In contrast to this opinion, Ferreira and colleagues (241, 321) found that muscle microvascular blood flow kinetics appeared somewhat slower than those measured upstream at the arterial level (Doppler ultrasound) such that they approximated the $\dot{V}\text{O}_2$ kinetics. Using phosphorescence-quenching technology to measure the mixed fiber-type spinotrapezius microvascular Pmvo₂, which resolves the temporal matching of O₂ delivery-to- $\dot{V}\text{O}_2$ within the microcirculation with high temporal fidelity), Behnke and colleagues (72) found that, across the first few seconds of contractions, there was a delay in the fall of Pmvo₂ for 10 to 20 s. This indicated that O₂ delivery kinetics were either tightly coupled with those of $\dot{V}\text{O}_2$ (~70%) or somewhat faster (~30%). In healthy muscles there was no indication that O₂ delivery was constraining $\dot{V}\text{O}_2$ kinetics (see Fig. 2 and Sections *Site(s) of Limitation of $\dot{V}\text{O}_2$ Kinetics: Oxygen Delivery Versus Cellular Respiration and Relationship Between Pulmonary and Exercising Muscle $\dot{V}\text{O}_2$ Responses*).

Putative mechanisms for rapid arteriolar vasodilation

As considered by Clifford and Tschakovsky (152) candidate mechanisms would have to be capable of: (i) initiating dilation within 1 s (428, 540, 729). (ii) Evoking a vasodilation that is proportional to contraction intensity (309, 730) for effective matching of O₂ delivery to $\dot{V}\text{O}_2$ (64, 72). (iii) Functioning effectively from rest or lower exercise levels (634, 667) and being resistant to desensitization during sequential transitions (634). (iv) Reversing in concert with decreasing metabolic requirements and \dot{Q} (239, 634).

Neither feedforward neural (757, see also 720) or feedback metabolic (review 152) control processes have provided a wholly satisfactory solution to this problem and contemporary interest has focused on intrinsic mechanosensitive properties of arterioles (308, 527, 730). Endothelial cells may act through NO, endothelium-derived hyperpolarizing factor(s) and prostaglandins to initiate dilation in response to intraluminal shear stress and smooth muscle cells regulate myogenic tone when transmural pressure changes; probably via mechanosensitive ion channels (211) and integrins (502). Intramuscular pressures can increase profoundly (i.e., >270 mmHg) during muscle contractions in moderate intensity running (29) and during maximal isometric contractions (i.e., >570 mmHg, review 681) and these changes can affect vasodilation via endothelium-dependent and independent pathways (151).

Irrespective of the precise cluster of mechanisms that facilitates the close-to-immediate hyperemia in concert with muscle contractions, the responses can be emplaced within one of two groups: Those that: (A) increase blood flow and O₂

delivery to all muscle fibers irrespective of metabolic demands and (B) spatially fine-tune the matching of O₂-delivery-to- $\dot{V}\text{O}_2$. The observation that, in health Pmvo₂ (reflecting O₂ delivery-to- $\dot{V}\text{O}_2$ ratio) in young healthy muscle(s) does not decrease immediately at the onset of isotonic contractions (31, 64, 72, 285, 455 see also NIRS-derived deoxy(Hb+Mb) responses in human muscle, 178, 241, 284, review 275) is a testament to the efficacy of “A” whereas the subsequent proportionality of increased blood flow relative to $\dot{V}\text{O}_2$ that achieves fractional O₂ extractions >0.85 implies a superb spatial distribution of blood flow and O₂ delivery—which is all the more remarkable considering that individual capillary units (clusters of ~10 capillaries emanating from one terminal arteriole) do not relate topographically to the muscle fibers of a discrete motor unit in what has been termed “discordant spatial domains” (review 245). Resolution of the precise mechanisms responsible for O₂ delivery-to- $\dot{V}\text{O}_2$ matching in health are expected to provide powerful insights into how these processes are deranged in diseases such as CHF (69, 199, 426, 511, 629) and type II diabetes (55, 552, 553) and in aged muscles (66, 67, 161, 213, 535, 694) leading to slowed $\dot{V}\text{O}_2$ kinetics (54, 589, 604, 605, 623, review 594, 601; see Sections *Maturation and Aging and Disease States*).

Events in the capillary

In resting muscle, the arteriolar bed is responsible for a significant portion of the blood-myocyte (and blood-venular) O₂ flux (review 583, 584). However, as first recognized by August Krogh in 1919, during exercise the capillaries are believed to become overwhelmingly important in this regard and hence capillary hemodynamics are of sentinel interest in understanding the dynamics of blood-myocyte O₂ flux and $\dot{V}\text{O}_2$ kinetics. Krogh, in a remarkable series of papers that was to secure him the Nobel prize, developed the concept of capillary recruitment (i.e., initiation of RBC flux in previously nonflowing capillaries) as a means of reducing intramyocyte mitochondrial O₂ diffusion distances from rest to contractions (449-452). Despite the mainstream acceptance of this notion in academia (i.e., in research publications, reviews, and textbooks), there is compelling evidence that most capillaries can, and do, support RBC flux at rest; negating their *de novo* “recruitment” during contractions (review 590, 591). Moreover, the concept of the importance of intramyocyte O₂ diffusion distances, fundamental to the capillary recruitment theory, has been eroded by the finding of very low intramyocyte Po₂’s during contractions without discernible gradients (review 361, 626). This means that the predominant increase in blood-myocyte O₂ flux from rest to exercise (convective and diffusive O₂ transport, 235, 292) occurs via increased RBC flux and hematocrit within already flowing capillaries (61, 404, review 590, 591, 595, 604). Thus, additional RBC-capillary endothelial surface “contact” during contractions may be provided by increasing the length of capillary over which O₂ flux occurs and increasing the RBC number along each capillary (i.e., increased capillary hematocrit). These

processes facilitate an exponential muscle $\dot{V}O_2$ kinetics profile (64, 72) that resembles closely the primary component pulmonary and muscle $\dot{V}O_2$ response in humans (e.g., 31, 285, 455).

Relationship Between Pulmonary and Exercising Muscle $\dot{V}O_2$ Responses

The $\dot{V}O_2$ kinetics response is measured most conveniently breath-by-breath using rapidly responding gas analyzers and applying algorithms that estimate changes of alveolar O_2 uptake. Despite the presence of intervening transit time delays, an almost instantaneous increase in \dot{Q} and hence pulmonary blood flow following exercise onset as well as changes in lung and venous blood gas stores, the tacit presumption has been that pulmonary $\dot{V}O_2$ kinetics faithfully reflects muscle $\dot{V}O_2$ kinetics. Additional strengths of this “whole-body” approach include measuring the sum total of gas exchange within all body compartments and the ecological validity of studying more physiological exercise paradigms without restraints such as anesthesia or invasive surgical interventions. However, its scientific utility depends, in large part, upon rigorous demonstration that measurements made at the mouth relate meaningfully to events occurring within the exercising muscles (review 65).

Modeling approaches

In conflict with di Prampero's (205) calculations showing faster muscle than pulmonary $\dot{V}O_2$ kinetics, experiments in conscious and anesthetized dogs had suggested a broad correspondence in the temporal profile of pulmonary and muscle $\dot{V}O_2$ kinetics (132, 495, 580). This latter notion was reinforced by the elegant theoretical studies of Barstow and colleagues (41, 42) who modeled the contracting leg muscles, venous circulation, and pulmonary gas exchange. Such an approach permitted examination of the effects of independent changes in the venous volume separating the sites of O_2 utilization from the lungs, the kinetics of vascular responses and muscle $\dot{V}O_2$ kinetics on pulmonary $\dot{V}O_2$ kinetics. Their results, which have far-reaching implications for the interpretation of pulmonary $\dot{V}O_2$ kinetics in healthy and patient (see Section *Disease States*) populations, indicated that: (i) venous volume size affects the duration of Phase I but not the fidelity with which the primary pulmonary $\dot{V}O_2$ kinetics reflects muscle $\dot{V}O_2$ kinetics. (ii) Experimental or pathological blunting of the \dot{Q} response following exercise onset exerts a complex effect on pulmonary $\dot{V}O_2$ kinetics. Specifically, the pulmonary Phase I becomes extended and the primary pulmonary component may be appreciably faster than that present at the muscle. This latter response may have led to the erroneous opinion that muscle energetics in, for example, heart failure patients, are normal (see Section *Disease States*).

Experimental investigations

Returning to the conflict between di Prampero's (205) calculations and empirical findings, the interposition of venous and pulmonary O_2 stores between muscle and lungs (please see Rossiter 638 for a comprehensive consideration of the effects of body O_2 stores on $\dot{V}O_2$ kinetics) would not be expected to dissociate muscle and lung $\dot{V}O_2$ kinetics if changes in these stores occurred only in Phase I (i.e., cardiodynamic phase) (41, 42). This notion has received experimental confirmation with respect at least to pulmonary O_2 stores (798). Notwithstanding those earlier studies mentioned above, in the mid-1990s the stage was set for simultaneous measurement of pulmonary and muscle $\dot{V}O_2$ kinetics in humans. Grassi and colleagues (285) adapted the constant-infusion thermodilution technique described by Andersen and Saltin (5) to follow the temporal responses of muscle (leg) blood flow, O_2 extraction and $\dot{V}O_2$ across the rest-moderate intensity cycle ergometer exercise transition and compare them with simultaneous measurements of alveolar $\dot{V}O_2$ kinetics (61, 285) in young healthy subjects. Their results are shown in Figure 11 and, as predicted by Barstow and colleagues earlier (41, 42), evidenced no significant difference in the primary $\dot{V}O_2$ kinetics across the exercising muscles and alveolar measurement sites (see also Fig. 12). However, one surprising observation in Phase I was that pulmonary $\dot{V}O_2$ increased either in the absence of altered muscle $\dot{V}O_2$ or at a very slow rate of rise of muscle $\dot{V}O_2$ such that elevations of pulmonary $\dot{V}O_2$ actually preceded those across the muscle. Given the almost instantaneous increase of muscle perfusion this mandated a decreased fractional O_2 extraction (i.e., reduced arterial-venous difference) and elevated femoral venous O_2 content (see Fig. 11, inset). Subsequently, Bangsbo and colleagues (31, 455) broadly validated these results within the technically challenging severe-intensity domain (31) and also for various intensities of knee-extension exercise (Fig. 12, references 455, 546; see also 432). Some of these latter studies (i.e., 31, 455) employed an indocyanine green infusion paradigm to adjust their measurements for intramuscular vascular transit delays which effectively reduced, but did not abolish, the time delay prior to the increase of muscle(s) $\dot{V}O_2$ seen in Figure 11. NIRS investigations in human muscle have confirmed noninvasively that muscle fractional O_2 extraction does not increase immediately following the onset of contractions (178, 241, 275, 284). Rather, there is most often an initial decrease of the deoxy(Hb+Mb) signal over the first few seconds of exercise prior to its rapid subsequent increase.

Muscle $\dot{V}O_2$

Following the onset of contractions, the presence of a delay or gentle increase prior to the subsequent rapid increase of muscle $\dot{V}O_2$ (Fig. 11, references 31, 285, 455) is inconsistent with current models of metabolic control. Mitochondrial $\dot{V}O_2$ and ATP production are thought to be regulated by: (i) thermodynamic control via the phosphorylation potential ($[ATP]/[ADP + Pi]$). (ii) Alterations in $[ADP]_{free}$ and/or

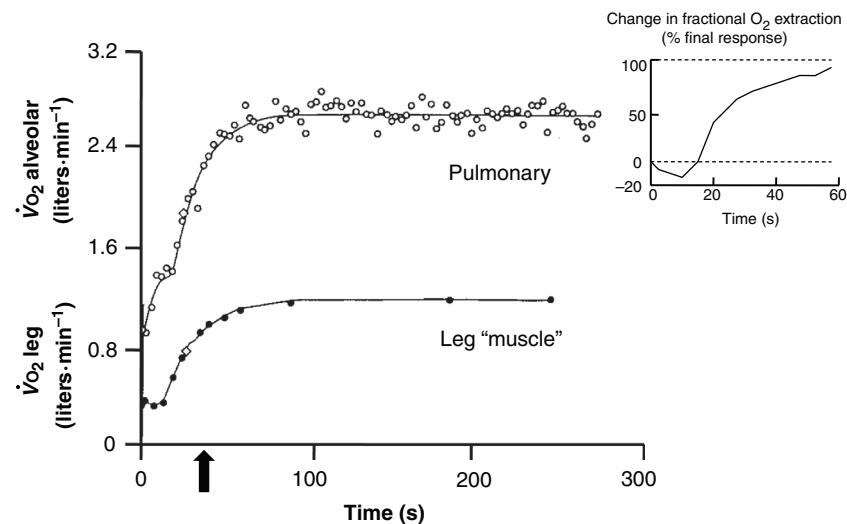


Figure 11 Pulmonary (alveolar) and leg muscle $\dot{V}O_2$ response to moderate intensity cycling for one subject. Note that, in the original investigation four of six subjects demonstrated a brief period following the onset of work where leg “muscle” $\dot{V}O_2$ did not increase. See Grassi (273 and 285) for all individual and mean responses. Arrow (and open diamonds) denotes time taken to reach 50% of final response. Inset: the consequence of blood flow increasing faster than $\dot{V}O_2$ is a transient reduction in fractional O_2 extraction. Redrawn, with permission, from Grassi et al. (285).

[inorganic phosphate] ($[Pi]$) as dictated by Michaelis-Menten enzyme kinetics. (iii) Changes of Gibbs free energy of cytosolic ATP hydrolysis (522). Thus, as intramuscular [PCr] falls and therefore estimated $[ADP]_{free}$ increases immediately at the onset of contractions (e.g., Fig. 13, references 37, 322, 400, 638-645) the presence of any delay, particularly of several seconds, in the $\dot{V}O_2$ response contradicts directly our understanding of metabolic regulation.

There are two options here: either our understanding of metabolic regulation, and the nuclear magnetic resonance spectroscopy (MRS) measurement, is fundamentally flawed or there are technical limitations to the measurement of muscle $\dot{V}O_2$. MRS of intramuscular phosphagens has the singular advantage that measurements can be made within

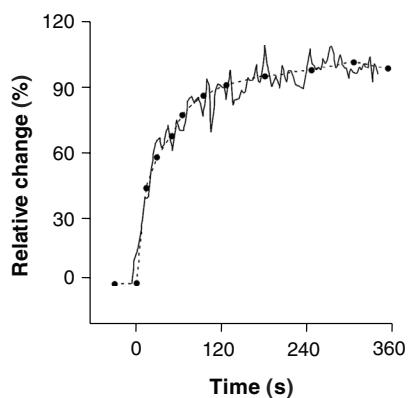


Figure 12 Relative increase in time-aligned alveolar (solid line) and leg muscle (dashed line) $\dot{V}O_2$ across the transient from unloaded to heavy-intensity knee-extension exercise. Note strong similarity in time courses. Redrawn, with permission, from Koga et al. (432).

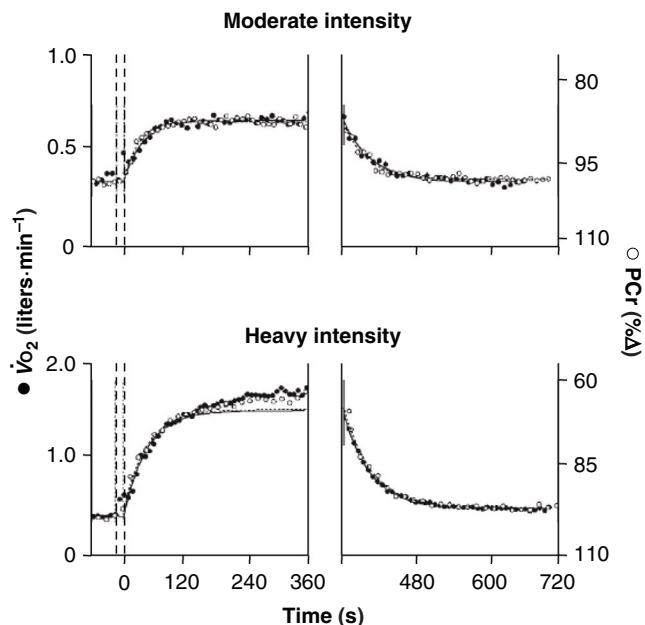


Figure 13 Pulmonary $\dot{V}O_2$ (solid circles) and intramuscular [PCr] (expressed as a relative change from baseline of 100% and “flipped” to facilitate more direct comparison with the $\dot{V}O_2$ responses; hollow circles) kinetic responses during and following moderate- and heavy-intensity square-wave exercise transitions. The on-responses are phase-aligned (dashed vertical lines) to account for the muscle-to-lung transit time. All responses are fit with a monoexponential curve (dashed curves) with the exception of the $\dot{V}O_2$ slow component behavior evident only for the high intensity on transition (i.e., lower left). Note exceptionally close correspondence between $\dot{V}O_2$ and [PCr] responses in all instances. Redrawn, with permission, from Rossiter et al. (645).

rhythmically contracting human muscle. However, MRS is subject to spatial and temporal limitations. On the other hand, the measurement of leg and muscle $\dot{V}O_2$ relies on the Fick principle where $\dot{V}O_2$ is the product of blood flow and the arterial-venous O₂ content difference each of which are measured at extramuscular sites. Whereas the Fick principle is grounded in strict conservation of mass principles, as O₂ flux cannot be measured at the actual site within the microcirculation some transit delays and heterogeneities thereof must be present. The question is whether such behavior is responsible for introducing an artificial lag in the $\dot{V}O_2$ kinetics.

This issue was addressed by combination of intravital microscopy and phosphorescence quenching techniques to resolve capillary-myocyte O₂ flux in spinotrapezius muscle of the rat contracting at 1 Hz (64, 428). This muscle is an excellent analog of human quadriceps being comprised of each major fiber type and possessing an oxidative enzyme capacity within the range of that described for humans (183, 473). As reported for conduit artery/vein blood flow following the onset of rhythmic contractions in human muscle (152, 182, 215, 248, 369, 634, 729, 730) spinotrapezius capillary blood flow (measured as RBC flux) increased rapidly and within the first contraction-relaxation cycle (Fig. 14, upper panel, reference 428). Had muscle $\dot{V}O_2$ not increased in concert with this response $PmvO_2$ would have had to increase precipitously. However, $PmvO_2$ remained constant for the first 15 or so seconds (Fig. 14, middle panel) which indicated that capillary-myocyte O₂ flux i.e., muscle $\dot{V}O_2$ began increasing immediately with contractions (Fig. 14, bottom panel and also 240, 608). These findings agree with recent time-course evidence for $\dot{V}O_2$ kinetics in single muscle fibers of the frog (Fig. 15, reference 423) and the canine gastrocnemius-plantaris complex (279). Collectively, therefore, there is strong support for the conclusion that, muscle $\dot{V}O_2$ evidences no delay or delay-like component (i.e., Phase I): this profile is in accord with current models of metabolic control (522, 595).

In conclusion, beyond the first few seconds of contractions (i.e., Phase I) the primary pulmonary $\dot{V}O_2$ kinetics provides a close analog of muscle $\dot{V}O_2$ kinetics. Time alignment of the spatially displaced responses to account for active muscle-to-mouth transit delays (Fig. 12) thus unveils the muscle energetic profile and supports the contention that muscle, and the primary component of the pulmonary, $\dot{V}O_2$ kinetics is regulated by some phosphagen-linked controller of mitochondrial function [see Section *Site(s) of Limitation of $\dot{V}O_2$ Kinetics: Oxygen Delivery Versus Cellular Respiration*].

Heterogeneity of $\dot{V}O_2$ responses within muscle

Because the pulmonary (and muscle) $\dot{V}O_2$ response(s) to moderate exercise are well fit by a single exponential it is tempting to ascribe this behavior to one compartment with uniform metabolic characteristics (i.e., blood flow, O₂ delivery, and $\dot{V}O_2$). However, this notion can be challenged from theoretical and empirical perspectives.

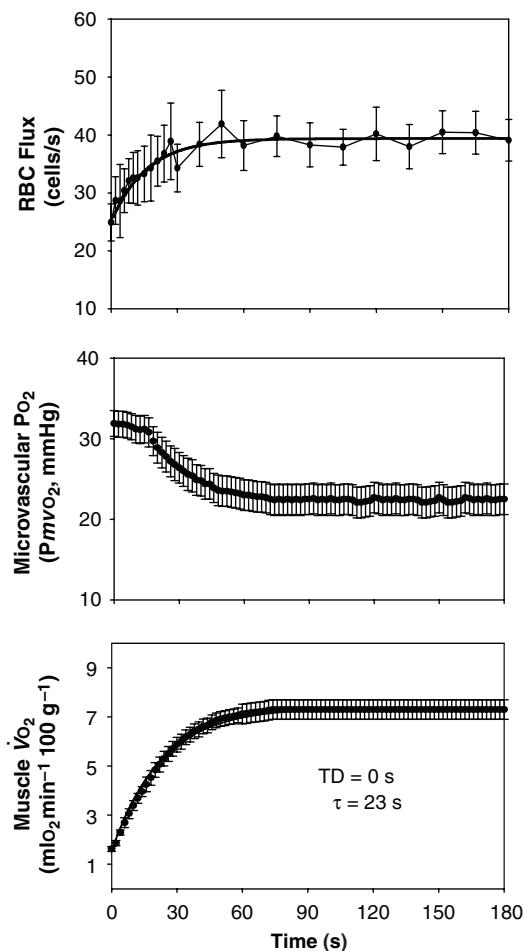


Figure 14 Mean data for increase in rat spinotrapezius red blood cell (RBC) flux (upper) and microvascular PO₂ (middle) are conflated to estimate $\dot{V}O_2$ (lower) in response to 1 Hz contractions. Model fits are shown. Both RBC flux and $\dot{V}O_2$ (but not $PmvO_2$) were fit by a single exponential with no delay. TD, time delay. τ , time constant. Redrawn, with permission, from Behnke et al. (64).

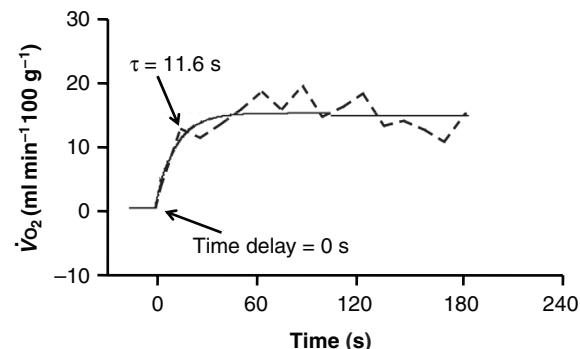


Figure 15 $\dot{V}O_2$ (jagged curve) time delay and monoexponential fit (smooth curve) as determined in a single isolated myocyte from *Xenopus laevis* lumbrical muscle in response to 3 min of isometric tetanic contractions (1 Hz). Kinetics analysis evidenced no time delay prior to the increase of $\dot{V}O_2$ and far more rapid muscle than pulmonary $\dot{V}O_2$ kinetics in amphibians. Figure redrawn, with permission, from Kindig and colleagues (423).

Theoretical considerations

As pointed out by Whipp and colleagues (770, 772, 773), whereas two exponential compartments with widely disparate τ 's may not provide a good fit to a single exponential when averaged, multiple compartments with a range of τ 's (and/or amplitudes, 94) from 20 to 65 s, for example, may sum to yield a well-fit monoexponential response. The consequences of this behavior include: (i) an underestimation of the O_2 deficit, that is, the sum of the individual deficits will exceed slightly that calculated from the single best-fit τ and the steady-state amplitude. (ii) Insensitivity to major metabolic differences among individuals. Just as in the lung alveolar ventilation-to-perfusion ($\dot{V}A/Q$) mismatch will always portend arterial hypoxemia, amongst individuals with similar overall $\dot{V}O_2$ τ 's those with a large distribution of regional τ 's will likely experience greater metabolic stress in those compartments with a longer τ (770). Particularly at higher work rates this behavior would have important consequences for myocyte energetics, $\dot{V}O_{2sc}$ generation and exercise tolerance.

Empirical observations

Human and animal skeletal muscles are comprised of different fiber types, classified according to contraction time and/or metabolic potential or myosin isozyme content (14, 183, 659). These different fiber types may be stratified among or within muscles or alternatively arranged as a mosaic and are believed to be systematically recruited during voluntary exercise according to the motor neuron size principle (i.e., ST/I \rightarrow FT/IIa \rightarrow FT/IIb/x, review 91, 325-327). Within a given human population muscles such as the quadriceps may evidence a wide variation in fiber-type composition (39, 616, 659) and, as discussed in Sections *Priming Exercise and $\dot{V}O_2$ Kinetics* and *Influence of muscle fiber type and motor unit recruitment on $\dot{V}O_2$ kinetics*, this has been related to discrete features of the $\dot{V}O_2$ kinetics response.

Whereas measurement of regional variations in muscle $\dot{V}O_2$ presently has severe spatial and temporal limitations several lines of evidence argue for appreciable intramuscular heterogeneity with respect to O_2 delivery, QO_2 , $\dot{V}O_2$, and $QO_2/\dot{V}O_2$ matching during muscle contractions. Specifically, using radioactive microspheres enormous fiber-type specific blood flow differences have been resolved, particularly in rats running on the motor-driven treadmill (10, 11, 469, 470, 607). Moreover, Piiper (579) and Piiper and colleagues (582) have reported a temporal heterogeneity of blood flow within the contracting: canine gastrocnemius. Regionally (i.e., within clusters of up to thousands of muscle fibers) magnetic resonance T2 activation maps support a substantial activation heterogeneity within active human muscles (562). In electrically stimulated rat muscles there is evidence that slow versus fast-twitch muscles regulate their blood flow in a fundamentally different fashion such that the $QO_2/\dot{V}O_2$ ratio (which determines $Pmvo_2$ and influences intracellular Po_2 and metabolism) falls faster and to lower values in fast versus

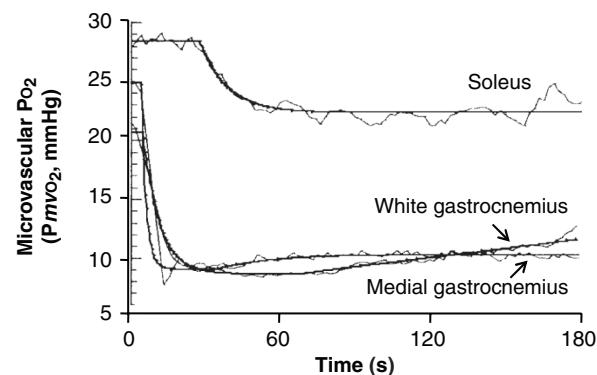


Figure 16 Microvascular O_2 partial pressure ($Pmvo_2$) responses for soleus (slow twitch) and the mixed and white gastrocnemii (both fast twitch) during high-intensity electrical stimulation at 1 Hz beginning at time = 0 s. Thin line is actual data, thick line denotes model fit. Note the "undershoot" in both of the fast-twitch muscle responses and also the much lower contracting $Pmvo_2$. Redrawn, with permission, from McDonough et al. (512).

slow-twitch muscles (Fig. 16, references 74, 238, 621). Thus, recruitment of these fast-twitch muscle(s) and possibly such fibers in muscles of a heterogeneous fiber type might be more likely to infringe on the O_2 -delivery-limited region of the $\dot{V}O_2$ kinetics seen in Figure 2.

Recently, using NIRS, Koga and colleagues (431, 657; see also 459) have quantified spatial heterogeneity of muscle deoxygenation kinetics (notionally akin to $Pmvo_2$), among ten sites in the human quadriceps during moderate and heavy exercise. With respect to the initial time delay and primary exponential component of muscle deoxygenation there was a substantial intersite coefficient of variation within subjects (~5%-50%). Extreme examples are shown in Figure 17. Whereas fiber type was not determined, these profiles suggest interregional differences in the regulation of QO_2 -to- $\dot{V}O_2$ relationships (and hence $Pmvo_2$) that may be driven by heterogeneities of either QO_2 and/or $\dot{V}O_2$. This overall heterogeneity within and among subjects did not correlate with the simultaneously measured pulmonary $\dot{V}O_2$ kinetics (431). However, as considered theoretically above for different $\tau\dot{V}O_2$ compartments, in those individuals with a greater variability in the response there is the opportunity for very low regional $Pmvo_2$'s, greater metabolic stress and possibly O_2 -delivery constraint of $\dot{V}O_2$ kinetics. Interestingly, the degree of interregional heterogeneity in the deoxygenation profile is reduced by priming exercise which also decreases the $\dot{V}O_{2sc}$ without discernibly speeding the primary component of the $\dot{V}O_2$ kinetics (657).

Site(s) of Limitation of $\dot{V}O_2$ Kinetics: Oxygen Delivery Versus Cellular Respiration

There is no question that muscle O_2 availability has the potential to influence metabolic control (e.g., 219 but see also

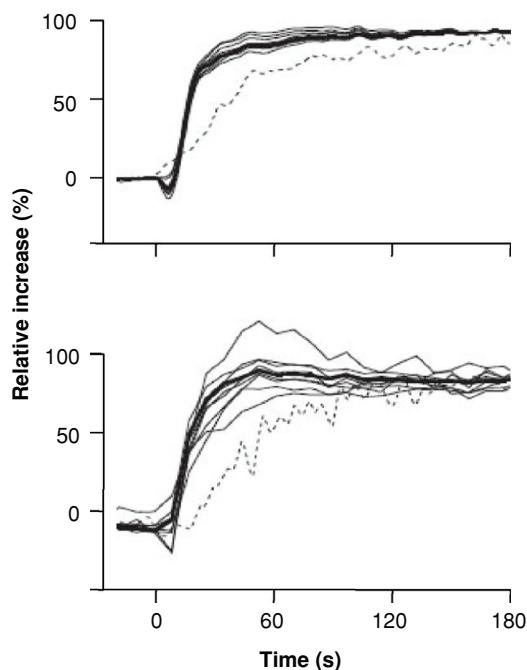
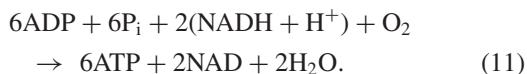


Figure 17 Relative increases in quadriceps muscle deoxygenation [deoxy(Hb+Mb)] (solid lines) for ten sites (measured by near infrared spectroscopy) and pulmonary $\dot{V}O_2$ (dashed line, note comparatively slower response) during heavy exercise. Values are normalized to end-exercise increase over baseline. Subjects shown had the least (top) and most (bottom) intersite heterogeneity of group. Thick line denotes response at the single site most often studied. Adapted, with permission, from Koga et al. (431). See text for details.

494): as can be seen from Eq. 11, if mitochondrial O₂ supply is truly insufficient, the rate of oxidative metabolism will be restricted and this will be manifest as slower $\dot{V}O_2$ kinetics across a metabolic transient.



Indeed, there are a number of situations in which muscle O₂ availability might be considered to be amongst the factors responsible for relatively slow $\dot{V}O_2$ kinetics: for example, during exercise where the muscle perfusion pressure is reduced (supine and prone leg exercise; arm exercise performed above the level of the heart; 368, 371), muscle O₂ supply is deliberately restricted (ischemia, hypoxia, β -blockade; 217, 362), and in older age and a variety of disease conditions (CHF, peripheral vascular disease, diabetes; review 601). These situations would lie in the “O₂-delivery-dependent zone” shown in Figure 2. However, the contention in this review is that muscle O₂ delivery does not limit $\dot{V}O_2$ kinetics during most forms of exercise (i.e., those in which the heart is positioned above the bulk of the working muscle mass such as in running, cycling, and rowing) in most subjects (i.e., apparently healthy, physically active people below the age of approximately 50 years), and even when the exercise intensity is high (i.e., severe).

The first line of evidence against O₂ as a limitation to $\dot{V}O_2$ kinetics under the conditions described above is that bulk muscle blood flow kinetics (and thus the kinetics of muscle O₂ delivery) is almost always faster than muscle $\dot{V}O_2$ kinetics during both low- and high-intensity exercise (31, 285, 484). As reviewed earlier, it is difficult to envisage a situation in which the kinetics of a relatively slow physiological process can be limited by a faster one unless, of course, there are substantial O₂-distribution heterogeneities across the recruited muscle(s). Also, although experimental interventions which might be expected to reduce muscle O₂ supply during upright exercise in healthy subjects have the potential to slow $\dot{V}O_2$ kinetics, this is not consistently the case: following blood withdrawal (112), hemodilution (80), and with the application of lower-body positive pressure (792), $\dot{V}O_2$ kinetics are not significantly altered. The fact that compensatory adjustments can apparently be made to maintain adequate muscle O₂ supply in these circumstances indicates that the exercise must be located some distance to the right of the “tipping point” in Figure 2. In any case, “proof” that muscle O₂ delivery is limiting in these conditions requires that $\dot{V}O_2$ kinetics is speeded when O₂ supply is increased—evidence which is. Classic studies by Grassi and colleagues in the isolated *in situ* canine gastrocnemius preparation have shown that setting muscle blood flow at the required “steady-state” level across a metabolic transient does not alter muscle $\dot{V}O_2$ kinetics for moderate/heavy exercise (described therein as 60% $\dot{V}O_{2\text{max}}$) (277) and only barely (but statistically significantly) does so at $\dot{V}O_{2\text{max}}$ (280). Moreover, enhancing the potential for muscle O₂ diffusion through a combination of pump-perfusion, hyperoxia, adenosine, and administration of a drug to right-shift the HbO₂ dissociation curve had no further effect on $\dot{V}O_2$ kinetics (278). Similarly, in humans, improving the potential for increased muscle O₂ availability through administration of recombinant human erythropoietin (790) or having subjects inspire a hyperoxic gas mixture (482, 784) does not speed the primary component pulmonary $\dot{V}O_2$ kinetics even during high-intensity exercise.

One intervention which has received considerable attention with regard to its effects on $\dot{V}O_2$ kinetics is that of prior (priming) exercise. In situations where muscle O₂ supply might be expected to be limiting in the “control” condition (e.g., during arm exercise or leg exercise performed in the supine position, and in senescent or very sedentary subjects), there is some evidence that the performance of prior exercise, which will increase muscle vasodilatation and rightshift the HbO₂ dissociation curve, is associated with a speeding of the primary component $\dot{V}O_2$ kinetics (385, 440, 674, 676, cf. 248). During upright cycle exercise in young healthy subjects, however, the overwhelming majority of studies have reported that the performance of prior exercise does not speed the primary component $\dot{V}O_2$ kinetics during subsequent heavy exercise (review 109). Rather, the principal effect of prior exercise appears to be to attenuate the size of the $\dot{V}O_{2\text{sc}}$ which is characteristic of exercise performed above the LT, and thus to bring the overall $\dot{V}O_2$ response back toward a

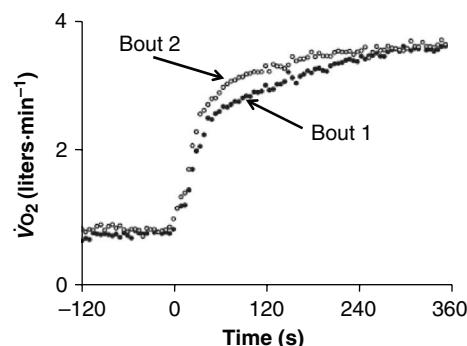


Figure 18 Pulmonary $\dot{V}O_2$ responses to an initial (solid circles) and subsequent (i.e., primed, hollow circles) heavy exercise bouts separated by 12 min. Data are averaged and superimposed. Redrawn, with permission, from data of Burnley et al. (106). Note increased amplitude of $\dot{V}O_2$ primary component and reduced $\dot{V}O_2$ slow component.

monoexponential profile (106, 108, 109; Fig. 18). While these data do not rule out a possible role for (regional) muscle O₂ insufficiency in the development of the $\dot{V}O_{2sc}$, they do suggest that the primary response of $\dot{V}O_2$ across a metabolic transient is principally regulated by factors more proximal to the contracting myocytes.

Specifically, mitochondrial respiration is intimately linked to the rate of muscle ATP hydrolysis, and one or more of the reactants of this process (e.g., [ADP] and [P_i], phosphorylation potential, and/or [PCr] and [Cr]) is/are thought to activate oxidative phosphorylation through feedback control (136, 207, 498, 771). Several groups (36, 37, 507, 640, 641, 643–645) have provided evidence consistent with this theory by demonstrating close agreement between muscle [PCr] kinetics (as estimated using ³¹P-MRS techniques) and pulmonary $\dot{V}O_2$ kinetics during both moderate- and heavy-intensity exercise (Fig. 13). Moreover, Kindig et al. (422) reported that acute inhibition of creatine kinase (CK) in isolated *Xenopus* myocytes led to significantly faster intracellular P_O kinetics (equivalent to faster $\dot{V}O_2$ kinetics in this model) (see also reference 288 for canine muscle). These data indicate that the CK reaction buffers changes in [ADP] across a metabolic transient thus attenuating one of the principal signals responsible for an acceleration of oxidative phosphorylation. Glancy et al. (267) studied O₂-consumption kinetics in isolated rat skeletal muscle mitochondria and reported that τ increased linearly with total creatine and varied linearly and inversely with the mitochondrial protein added. Jones et al. (401) reported that dietary creatine supplementation, which increased the resting muscle [PCr]-to-[ATP] ratio consistent with a significant increase in total creatine content, resulted in a slowing of [PCr] dynamics in exercise and subsequent recovery. *In toto*, these results conform to the predictions of the “electrical analog” model of Meyer (521, 522) in which $\tau\dot{V}O_2$ is the product of the mitochondrial resistance to energy transfer and the metabolic capacitance determined primarily by the cellular total creatine pool. It is pertinent that Meyer’s model (521, 522) does not predict the emergence of the $\dot{V}O_{2sc} > \text{GET/LT}$.

The kinetics of $\dot{V}O_2$ therefore appears to be principally under feedback control through the CK reaction (it is worth noting here that this will also be true even when other “limitations” to the $\dot{V}O_2$ response, such as O₂ availability, are “superimposed”). However, it is possible that other factors also contribute to the inertia of muscle oxidative metabolism that is evident in the transition from a lower to a higher work rate. Indeed, theoretically any one of the enzymes in the oxidative metabolic pathway might be rate-limiting. Pharmacological activation of pyruvate dehydrogenase with dichloroacetate (DCA) reduces substrate-level phosphorylation during subsequent exercise, suggesting an enhancement of the contribution of oxidative phosphorylation to energy turnover (289). Whilst, to date, this intervention has not been shown to speed muscle or pulmonary $\dot{V}O_2$ kinetics, there are suggestions that muscle efficiency might be improved with DCA, thus reducing the amplitudes of the primary and/or slow components of $\dot{V}O_2$ and reducing the magnitude of the O₂ deficit (279, 392, 643). Another possible limitation to $\dot{V}O_2$ dynamics is the influence of NO on mitochondrial function. In addition to its well-known role in the regulation of muscle vasodilatation, NO has the potential to inhibit several mitochondrial enzymes and to compete with O₂ for the binding site at cytochrome c oxidase (103, 104). Studies in the horse (e.g., 424, 425) and the human (e.g. 402, 403, 785) have shown that inhibition of NO synthesis with L-NAME results in a significant speeding of the primary component $\dot{V}O_2$ kinetics. The impact, at least in humans, appears to be greatest at higher work rates, suggesting that the effect might be especially pronounced in type II muscle fibers (785); if so, this might also explain why a speeding of $\dot{V}O_2$ kinetics was not observed following L-NAME administration in isolated canine muscle (281). As mentioned earlier, NO also plays an important role in muscle vasodilatation and thus the inhibition of NO synthesis might impair muscle blood flow. The speeding of the primary component of $\dot{V}O_2$ kinetics with L-NAME therefore potentially provides simultaneous evidence for an NO-linked muscle metabolic limitation to $\dot{V}O_2$ kinetics and against an important role for O₂ supply, at least under the conditions of these studies. Intriguingly, recent studies have reported that augmenting NO bioavailability through dietary nitrate supplementation reduces the O₂ cost of submaximal exercise (27, 468, 732). While the mechanistic basis for this effect remains obscure, it has been shown that the reduction in steady-state $\dot{V}O_2$ for the same external work rate is associated with a sparing of muscle [PCr] depletion of similar magnitude (23). This implicates an improvement in muscle contractile efficiency, rather than changes in mitochondrial P-O ratio, as being primarily responsible for the lower O₂ cost of exercise (23).

There is often a tendency for the primary component $\dot{V}O_2$ kinetics to become slower at higher work rates, especially above the LT (599). While this has been attributed to an (increasing) muscle O₂-delivery limitation by some authors, another explanation is that the slower overall $\dot{V}O_2$ kinetics reflects the increasing contribution to force production

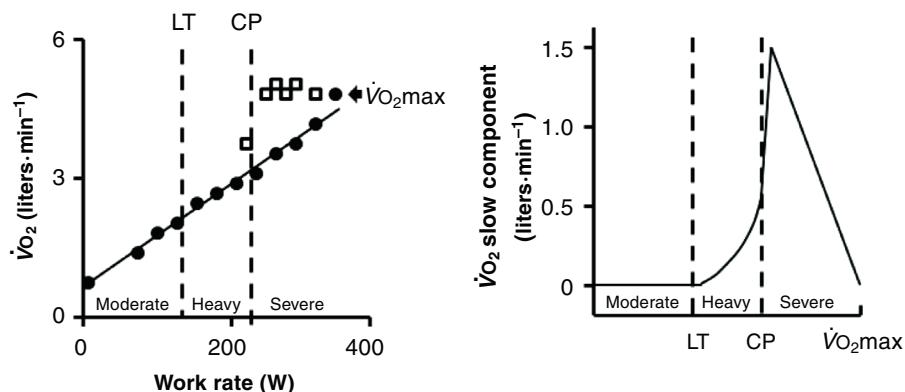


Figure 19 Left: $\dot{V}O_2$ —work-rate relation for incremental exercise (25 Watts min^{-1} to fatigue, solid symbols and line) and $\dot{V}O_2$ achieved during constant-work-rate exercise (hollow symbols) for a representative healthy subject. The leftmost hollow symbol denotes $\dot{V}O_2$ at 24 min of heavy exercise (at critical power, CP); all others are at fatigue in the severe domain ($>\text{CP}$) where $\dot{V}O_2$ achieves its maximum value. Right: schematic demonstrating the magnitude of the $\dot{V}O_2$ slow component as calculated from the vertical displacement of constant-work-rate $\dot{V}O_2$'s (hollow symbols) from their respective iso-work-rate counterparts measured during incremental exercise (solid symbols) in left panel. Note that, for this subject, the $\dot{V}O_2$ slow component peaks ~ 1.5 liter $O_2 \text{ min}^{-1}$. Constructed, with permission, from the data of Poole et al. (610).

of muscle fibers that are higher in the recruitment hierarchy (i.e., type II fibers). There is evidence to suggest that these “higher-order” fibers might have slower $\dot{V}O_2$ kinetics (and also lower efficiency) relative to early-recruited fibers (396, 616, 617). Alterations in motor unit recruitment might underpin the reduced $\dot{V}O_{2\text{sc}}$ (and faster overall $\dot{V}O_2$ kinetics) observed for the same work rate with interventions such as endurance training, hyperoxia, and priming exercise (390, 396; Fig. 18). When exercise is initiated from a higher compared to a lower baseline metabolic rate, markedly slower primary component $\dot{V}O_2$ kinetics and a higher $\dot{V}O_2$ response (G_p) are typically reported (102, 204, 366, 786, 787). Again, these observations are consistent with the metabolic responses that would be expected when a population of higher-order fibers is recruited to meet the augmented muscle force production requirements, and are not necessarily indicative of any impairment in muscle O_2 delivery (200, 203, 204). It should be acknowledged, however, that these two effects might not be mutually exclusive (73, 74, 396, 512).

Slow Component of $\dot{V}O_2$ Kinetics: Mechanistic Bases

The existence of the $\dot{V}O_{2\text{sc}}$ that elevates $\dot{V}O_2$ above that predicted from the sub-GET $\dot{V}O_2$ —work rate relation, challenges sentinel physiological concepts, and, like the proverbial ugly stepchild, has been frequently ignored. Thus, the notion that $\dot{V}O_2$ increases linearly with work rate to $\dot{V}O_2\text{max}$ (true only for rapidly incremented/ramp exercise tests) has become dogma in research publications and standard texts (14, 195, 244, 506, 544, 613, 794). This position is difficult to defend when the $\dot{V}O_{2\text{sc}}$ is invariably present for sustained constant-work-rates in the heavy and severe domains, irre-

spective of the absolute work rate (330, 646, Figs. 5 and 7), and may, in the extreme, account for as much as 1.5 liter $O_2 \text{ min}^{-1}$ (Fig. 19, references 258, 330, 646). Moreover, the $\dot{V}O_{2\text{sc}}$ may result in, or at least accelerate, the upward curvature of the $\dot{V}O_2$ -work-rate relation during incremental cycle ergometry (315, 809). Crucially, in the severe domain the $\dot{V}O_{2\text{sc}}$ drives $\dot{V}O_2$ to $\dot{V}O_2\text{max}$ and is inextricably entwined with the fatigue process(es). Throughout the heavy and severe domains the developing $\dot{V}O_{2\text{sc}}$: (i) undermines the fundamental concept of the steady state. (ii) Reduces estimates of muscle and exercise efficiency (Fig. 20). (iii) Confounds calculation of the O_2 deficit (58, 59, 772, 773). (iv) Renders description of exercise intensity as a percentage of $\dot{V}O_2\text{max}$ inappropriate.

Definition and historical precedence

Possibly the first evidence of the $\dot{V}O_{2\text{sc}}$ is found in the data of Krogh and Lindhard in 1913; though these pioneers reported problems setting the absolute work rate on the ergometer (452). In 1923, Hill and Lupton found a substantial $\dot{V}O_{2\text{sc}}$ -like increase in $\dot{V}O_2$ for one subject running at constant speed on the treadmill but ascribed this phenomenon to a “painful blister” (347). Åstrand and Saltin (15) presented $\dot{V}O_2$ responses for one subject over a range of constant-work-rates that can subsequently be characterized as severe or heavy. Despite the presence of substantial prolonged (beyond 2–3 min) increases of $\dot{V}O_2$, some of which drove $\dot{V}O_2$ to $\dot{V}O_2\text{max}$ and, in so doing, clearly disrupted the linearity of the $\dot{V}O_2$ —work-rate relation, their subsequent depiction of a linear increase of $\dot{V}O_2$ as a function of work rate became the accepted standard for ensuing decades.

The $\dot{V}O_{2\text{sc}}$, as distinct from the relatively modest “ O_2 drift” (<200 ml O_2) that may attend moderate exercise of a prolonged duration (i.e., ≥ 60 min, references 165, 311, 407),

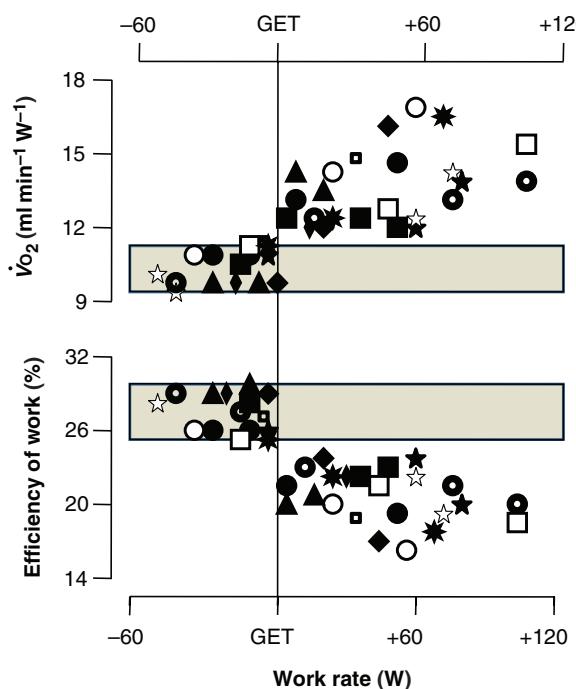


Figure 20 $\dot{V}O_2$ slow component increases O_2 cost of constant-work-rate exercise and reduces efficiency of work for all supra-gas exchange threshold (GET) work rates. Redrawn, with permission, from the data of Henson et al. (330).

occurs only above LT (or GET) (Figs. 5 and 7). Prior to the common advent of breath-by-breath gas exchange measurement capabilities the $\dot{V}O_2$ sc was generally defined as the continued rise in $\dot{V}O_2$ beyond 3 min of constant-work-rate exercise (304, 646, review 258). As such, the $\dot{V}O_2$ sc has most commonly been identified during cycle ergometry where the external work rate can be most accurately set and maintained (35, 38, 42, 43, 48, 115, 118, 127, 131, 160, 192, 303, 316, 330, 476, 561, 606, 609, 610, 646, 686, 795). However, this behavior is also evident for running (e.g., 121, 125, 347, 539, 707), rowing (377, 632), and isometric exercise (e.g., 664, 739).

Modeling the $\dot{V}O_2$ slow component

Unlike the primary $\dot{V}O_2$ response which has been characterized by a delay followed by an exponential rise (see Section *Introduction*; though see 712 for a dissenting opinion) the $\dot{V}O_2$ sc has so far eluded rigorous characterization (43, 123, 561, 780). In fact, there is no consensus regarding whether it is a linear or exponential process (258, 774) which, on occasion, has lead to model fits expressing unphysiologically long τ 's (e.g., 217, 476). In part, this situation is not surprising given the uncertainty regarding the $\dot{V}O_2$ sc's, as yet, undefined mechanistic bases (see below) and contrasting projections in the heavy (i.e., asymptotic) versus severe (i.e., truncated at $\dot{V}O_{2\max}$ /exhaustion) exercise intensity domains. It is pertinent that the all-too-common practice of truncating exercise bouts at 6 min duration rather than prolonging them either

until $\dot{V}O_2$ stabilizes or exhaustion ensues has compounded this problem. Whereas it is evident that the $\dot{V}O_2$ sc represents an additional or “excess” energetic cost (Figs. 7, 19 and 20) that is superimposed upon the primary response, the notion that it is of delayed onset (43, 561) has been challenged (772, 787). What is defensible, at least statistically, is that the $\dot{V}O_2$ sc emerges discernibly from the confidence interval of the primary kinetics after some delay (772).

This uncertainty regarding modeling the $\dot{V}O_2$ sc is by no means trivial, in part, because it erodes confidence in calculation of the O_2 deficit for heavy and severe exercise (58, 59, 772) and also, by selection of a given fitting procedure, may imply underlying mechanisms that are physiologically indefensible. In the heavy and severe domains the primary component remains exponential with approximately unchanged kinetic features [τ and G (but see 389, 616, 673)]. However, the exponential fitting procedure for the $\dot{V}O_2$ sc must often estimate both the amplitude and τ from a very limited data set. Moreover, it should be recognized that a well-fit monoexponential $\dot{V}O_2$ sc does not necessarily indicate that a solitary “new” metabolic compartment (with a unitary amplitude and τ) has been recruited at some time after exercise onset. Rather, Whipp and Rossiter (772) have considered that this response may reflect a compartment or compartments with a progressively increasing G (and a single τ). In this instance the τ of the metabolic units generating the $\dot{V}O_2$ sc may be appreciably faster than that of the τ estimated from the data fit (i.e., 45 vs. 250 s in Fig. 3.11 in reference 772). It has been recognized that, for heavy exercise, the asymptotic or end-exercise $\dot{V}O_2$ does not provide a justifiable frame of reference and, if used for this purpose, will lead to a gross overestimation of the O_2 deficit (59, 772). The theoretical considerations of Whipp and Rossiter (772) further suggest that, depending on the precise kinetic features of the metabolic control response, use of the measured amplitude and overall estimated τ of the $\dot{V}O_2$ sc may also artifactually increase the estimated O_2 deficit. Thus, whereas multiparameter model fitting (see Section *Introduction*) can usefully isolate the $\dot{V}O_2$ primary component and define the amplitude of the $\dot{V}O_2$ sc, physiologically justifiable parameterization of the $\dot{V}O_2$ sc remains elusive.

Mechanistic bases—indirect experimental approaches

In the 1970s and 1980s, multiple putative mediators of the $\dot{V}O_2$ sc had been considered including: (i) Calorigenic processes such as elevated core or body temperature (Q_{10} effect), endocrine effects (primarily catecholamines), metabolically active metabolites (e.g., lactate, potassium, hydrogen ions, and inorganic phosphate) that may be manifested within the exercising muscle(s) (258, 585, 588, 589, 609, 610), and the rest of the body (e.g., liver, resting muscles, etc.). (ii) Increasing ventilatory, cardiac and auxiliary (for example, body stabilization) muscle work (606, 609, 610). (iii) Intramuscular processes such as the recruitment of lower efficiency motor units, reduced mechanical coupling efficiency, and less

efficient mitochondrial P-O coupling (622, 780). During heavy or severe exercise the body is, by definition, not in a steady state and consequently many of these factors may be changing simultaneously (606, 609, 610). To link cause and effect with respect to the $\dot{V}O_{2sc}$ the most popular experimental approaches entailed either deriving an O₂ cost for a given process (e.g., O₂ cost of respiratory muscle work or elevated temperature), measuring that process during exercise and estimating how much of the $\dot{V}O_{2sc}$ might be accounted for by that process (304). One alternative approach was to correlate the temporal profile of change, for each mediator considered, with that of the $\dot{V}O_{2sc}$ during heavy or severe exercise (131, 646). Such approaches were mired in assumptions as evident from the conclusions of Hagberg and colleagues (304), who, based on published values for the O₂ cost of ventilation and increased core temperature, concluded that these processes could account for well over 100% of the $\dot{V}O_{2sc}$. As evident from the work of McKerrow and Otis (516) and subsequently Aaron and colleagues (1) the O₂ cost of ventilatory work, whilst not trivial, shows substantial interindividual variation and must be measured during the same ventilatory pattern as present during exercise (1, 258). By the same token, an erroneous frame of reference likely biased Hagberg et al.'s conclusions regarding the role of increased body temperature in the $\dot{V}O_{2sc}$. Specifically, any Q₁₀ effect manifested will be in proportion to the metabolic rate of the tissue and it is thus temperature changes within the exercising muscle(s) not rectum that are relevant. Importantly, exercising muscle temperature may increase far more than body core temperature (658). However, to increase $\dot{V}O_2$ it may be necessary to elevate muscle temperature above 43°C (review 256) which is unlikely during exercise (at least in humans).

With respect to the correlative approach, the close temporal relationship between blood [lactate] and the $\dot{V}O_{2sc}$, which is typically far better than ventilation, catecholamines, or temperature, provided some support for a causal role of this metabolite (e.g., 131, 610, 646, 780 but see also 672 and 707). Sodium L-(+)-lactate infusion does increase $\dot{V}O_2$ at rest (650) possibly due, in part, to stimulation of gluco/glyconeogenesis within the exercising muscles where the requisite enzymes are present (718, review 258). Alternatively, Ryan et al.'s findings (650) may merely have been an artifact related to the alkalinizing effects of the particular infusion protocol utilized (408, 588, 598).

Mechanistic bases—direct experimental approaches

Poole and colleagues (606) have argued that discrimination amongst several of the putative $\dot{V}O_{2sc}$ mediators could be achieved by determination of the site(s) of its generation. Using constant-infusion thermodilution to measure leg blood flow and paired arterial and femoral venous blood sampling to approximate muscle(s) $\dot{V}O_2$ simultaneously with pulmonary $\dot{V}O_2$ during severe-intensity cycle ergometry it was resolved that skeletal muscle was responsible for over 80% of the

$\dot{V}O_{2sc}$. This finding relegated processes outside the exercising muscle(s) including increasing ventilatory, cardiac and auxiliary muscle work and metabolic stimulation by catecholamines, metabolites and temperature to a secondary role, at least in healthy individuals. Subsequently, attention focused more clearly on candidate mechanisms within the exercising muscle(s) and powerful incisive experimental manipulations evaluated specific potential mediators. Specifically, iso-pH L-(+)-lactate infusions raised arterial blood [lactate] to ~10 mM but failed to induce a $\dot{V}O_{2sc}$ in the contracting dog gastrocnemius (598). Similarly, infusing sufficient epinephrine so as to increase venous concentrations to levels found in supramaximal exercise did not increase $\dot{V}O_2$ in heavily exercising subjects (260). This latter protocol also substantially elevated blood [lactate] thereby reaffirming the conclusion that lactate, in and of itself, is not causal to the $\dot{V}O_{2sc}$. Finally, Koga and colleagues (433) used hot water pants to elevate exercising muscle(s) temperature by as much as 2°C to 3°C but could not discern any associated $\dot{V}O_2$ increase. These studies forced consideration of events within and among skeletal muscle motor units themselves as progenitors of the $\dot{V}O_{2sc}$.

Muscle fiber energetics

Glycogen depletion studies indicate that type II fibers are recruited in addition to type I fibers at heavy and severe work rates (e.g., 63, 270, 380, 737, 738) and much interest has therefore focused on the energetic differences between type I and II fiber populations. Increased muscle $\dot{V}O_2$ during constant-work-rate exercise may potentially result from either an increased ATP turnover (unchanged P-O ratio) or, alternatively, an increased O₂ cost of ATP turnover (decreased P-O ratio). The elegant ³¹P Magnetic Resonance Spectroscopy (MRS) studies of Rossiter and colleagues (641-643) demonstrating a progressive fall in [PCr] that occurs simultaneously with the $\dot{V}O_{2sc}$ (Fig. 13) supports the former proposition as does the finding that the P-O ratio is unchanged by high-intensity exercise (724, see also 31). Given this, what is the evidence for some facet of fiber type recruitment patterns and/or energetic processes occurring within discrete fiber-type populations playing an important role in the $\dot{V}O_{2sc}$?

The energetic cost of isometric or isotonic contractions is far greater (and therefore contractile efficiency lower) in fast (type II) versus slow (type I)-twitch muscles (rat 265, 624, 761; mouse 168; and human 313, 314, 711). This effect may result from different chemical-to-mechanical coupling efficiencies, faster actomyosin turnover as well as the several-fold faster calcium pump activity (716) in fast- versus slow-twitch muscles or muscle fibers. In addition, the α-glycerol phosphate shuttle activity, which is flavin adenine dinucleotide (FAD) rather than nicotin adenine dinucleotide (NAD)-linked, is higher in fast-twitch muscles which reduces the P-O ratio ~18% (793). There is therefore some evidence that type II muscle fibers have both a higher ATP cost of force production and O₂ cost of ATP turnover. Regarding these extraordinary fiber-type differences, a cautionary note emerges

from He and colleagues (323) who demonstrated that, despite a 4-fold greater ATP hydrolysis rate and maximal power in human vastus lateralis single fibers (type II vs. I) contracting isotonically, peak thermodynamic efficiencies were not significantly different (type II 0.27, type I 0.21). It is also pertinent that, because type II fibers achieve their peak efficiency at higher shortening velocities and relative loads than type I fibers (663), depending on the pedal frequency and thus shortening velocity the O₂ cost of force production may not be as disparate in humans *in vivo* as suggested by animal studies.

In humans, efficiency correlates with the proportion of type I fibers in the vastus lateralis when cycling at 80 rpm (166) where shortening rates may approximate those yielding peak efficiency for type I fibers (for type II fibers this is ~100 rpm, reference 663). Is it possible therefore that the progressive appearance of the $\dot{V}O_{2\text{sc}}$ above LT or GET reflects the orderly recruitment of more fast-twitch fibers? As mentioned above, there is evidence that a substantial fast-twitch fiber population is recruited whilst cycling at submaximal $\dot{V}O_2$'s (380, 737; though see 675 for a dissenting opinion) and that the $\dot{V}O_{2\text{sc}}$ is greater in those subjects with a higher proportion of type II fibers in the vastus lateralis (Fig. 21, references 39, 616). In addition, faster pedal rates (100–135 rpm) that recruit proportionally more fast-twitch fibers (62, 323) engender a greater $\dot{V}O_{2\text{sc}}$ than seen at 35 to 75 rpm (255, 617). This increased $\dot{V}O_{2\text{sc}}$ occurs concomitant with a reduced G of the primary kinetics such that end-exercise $\dot{V}O_2$ may be unaffected (617).

Despite the strong correlation between % type II fiber composition of the quadriceps and the magnitude of the $\dot{V}O_{2\text{sc}}$ evident in Figure 21, attempts to investigate a mechanistic role for specific fiber type involvement in the $\dot{V}O_{2\text{sc}}$ have been hampered by the poor temporal and spatial resolution of techniques available (i.e., integrated electromyogram (EMG), iEMG; mean power frequency analysis, MPF; magnetic res-

onance imaging, MRI). There is also ambiguity as to whether increased MPF reflects type II fiber recruitment or, alternatively, increased firing frequency of type I motor units or even increased temperature (95, 796). Consequently, it is not surprising that these approaches have yielded conflicting results. For instance, in 1992 Shinohara and Moritani (686) reported a weak correlation between increases of iEMG and the $\dot{V}O_{2\text{sc}}$ amplitude. Subsequently, the start of the MPF increase and $\dot{V}O_{2\text{sc}}$ was found to correspond in the vastus lateralis and gastrocnemius lateralis (95). Also, priming exercise that increased the primary $\dot{V}O_2$ response and decreased the $\dot{V}O_{2\text{sc}}$ increased the gluteus maximus, vastus lateralis, and vastus medialis iEMG close to 20% (106, 108). This latter finding was interpreted as evidence for priming exercise leading to the early recruitment of more fibers (type I and II) in the subsequent bout and thus reducing the metabolic perturbation within each fiber which in turn attenuated the $\dot{V}O_{2\text{sc}}$. In contrast to the above, Scheuermann and colleagues (675) dissociated the $\dot{V}O_{2\text{sc}}$ reduction consequent to priming exercise from iEMG and MPF profiles which remained unchanged (see also 571, 725). Thus, some EMG studies provide supportive evidence for a progressive recruitment of more (possibly type II) muscle fibers contributing to the $\dot{V}O_{2\text{sc}}$ (11, 85, 95, 106, 108, 251, 352, 381, 550, 570, 654, 686) whereas others support an increased metabolic requirement within already recruited fibers (115, 116, 261, 480, 571, 675, 725; see also 331 and 810 for increased $\dot{V}O_2/\text{tension}$ ratio during constant electrical stimulation of canine gastrocnemius-plantaris complex and *Xenopus* single-fibers, respectively). Perhaps the clearest evidence for the $\dot{V}O_{2\text{sc}}$ arising from within already-recruited fibers in humans is Vanhatalo and colleagues' demonstration that the $\dot{V}O_2:\text{Watt}$ ratio rises sharply during 3 min all-out cycle ergometer exercise as quadriceps integrated EMG falls (734).

MRI interrogation of the vastus lateralis, rectus femoris and whole leg found progressive increases in muscle recruitment by T2 analysis simultaneous with the rising $\dot{V}O_{2\text{sc}}$, which cohered with iEMG and MPF signals (vastus lateralis only, 666). In addition, after an exercise training program reduced the $\dot{V}O_{2\text{sc}}$, there were associated decreases in T2-assessed muscle activation (665) and Endo and colleagues (216) analyzed the T2 profile within ten thigh muscles and reported progressive increases in muscle activation associated with the $\dot{V}O_{2\text{sc}}$. All these studies are consistent with a fiber recruitment basis for the $\dot{V}O_{2\text{sc}}$.

Direct evidence linking altered fiber-type recruitment patterns and the $\dot{V}O_{2\text{sc}}$ was determined from selective manipulation of fiber-type recruitment patterns (456–458). Krstrup and colleagues demonstrated that preferential glycogen depletion of the type I fibers, which forced recruitment of type II fibers, actually raised the $\dot{V}O_2$ during what had previously been considered moderate intensity (<LT) exercise (458). Moreover, selective blockade of type I fiber recruitment using cisatracurium (a nondepolarising neuromuscular blocking agent) increased thigh $\dot{V}O_2 \sim 20\%$ (Fig. 22, reference 456).

Interestingly, the magnitude of the $\dot{V}O_{2\text{sc}}$ is sensitive to perturbations that alter blood flow and O₂ delivery and

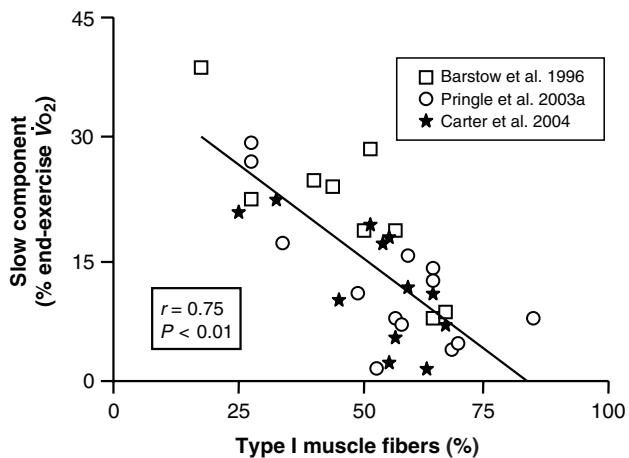


Figure 21 Relative contribution of the $\dot{V}O_2$ slow component to end-exercise $\dot{V}O_2$ during 6 min of heavy-intensity cycle exercise plotted as a function of vastus lateralis % type I muscle fibers. Data extracted, with permission, from Barstow et al. (39), Pringle et al. (616), and Carter et al. (124).

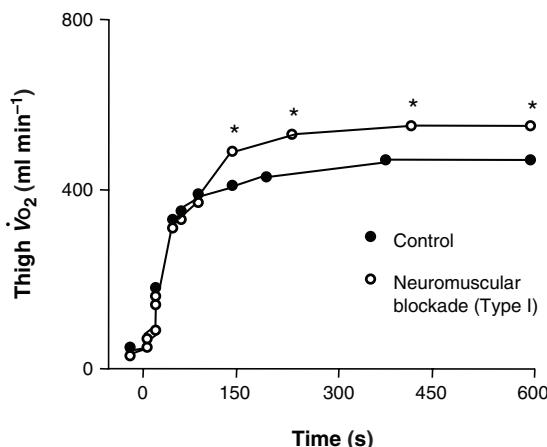


Figure 22 Thigh $\dot{V}O_2$ response to knee-extension exercise under control (solid symbols) and with preferential CUR of type I fibers (cisatracurium, hollow symbols). Values are means (SE omitted for clarity, $n = 8$). Redrawn, with permission, from Krustrup et al. (456). *CUR $P < 0.05$ versus control.

increased (but not decreased, 217) arterial O₂ content. For example, priming (106–108, 111, 264, 656) and hyperoxic (482, 784) conditions both decrease whereas supine exercise increases (435) the $\dot{V}O_{2sc}$. Also, given the modest contribution of ventilatory muscle(s) to the $\dot{V}O_{2sc}$ it is intriguing that breathing a heliox (21% O₂, 79% He) mixture reduced the $\dot{V}O_{2sc}$ ~45% during high-intensity exercise (167). It is known that unloading the respiratory muscles can increase blood flow to locomotory muscles (319, 764) and it is likely that this effect, rather than the decrease in respiratory muscle $\dot{V}O_2$ *per se*, caused the decreased $\dot{V}O_{2sc}$. This interpretation would be consistent with the finding that specific training of the inspiratory muscles reduces the $\dot{V}O_{2sc}$ (24). Finally, reduced muscle blood flow induced by partial vascular occlusion impacts muscle fiber recruitment profiles (459) and, as detailed above, profoundly impacts the $\dot{V}O_2$ response. Collectively, these findings suggest that either blood flow or at least O₂-delivery conditions within the muscle can fundamentally impact the mechanisms responsible for the $\dot{V}O_{2sc}$.

Accepting that the $\dot{V}O_{2sc}$ constitutes a high phosphate cost of force production (639, 641) and the mitochondrial P-O ratio remains unchanged during high intensity exercise (724), is it possible that the $\dot{V}O_2$ cost of force production can increase within a given fiber population? Calcium handling by the sarcoplasmic reticulum is estimated to constitute up to half of the total ATP requirement of contractions (84). During heavy/severe exercise when type II fibers are recruited metabolites and ions accumulate (i.e., H⁺, H₂PO₄⁻ and K⁺, Mg²⁺) and may impact sarcoplasmic reticulum Ca²⁺ dynamics, troponin Ca²⁺ sensitivity and force production at the cross bridges (review 3 see also 529). This phenomenon may account for the close relationship between increasing intramuscular H⁺ (and H₂PO₄⁻) and the $\dot{V}O_2$ and [PCr] slow components (200, 641, 643).

Conclusions

(i) The $\dot{V}O_{2sc}$ is generated principally within the exercising muscle(s) at supra-LT or GET metabolic rates (330, 606) where: (a) metabolite/ion accumulation within select fibers increases ATP requirements to sustain the required power output (consistent with 571, 675, 725) and (b) fibers experiencing fatigue reduce their power contribution (but not necessarily their $\dot{V}O_2$) which necessitates either increased power generation from already recruited motor units or recruitment of additional motor units (most likely type II but possibly also type I) (consistent with 95, 106, 352, 457, 458, 665, 666, 734, 810). (ii) Blood flow and O₂-delivery conditions can modulate the metabolic status within fibers and also fiber recruitment patterns thereby affecting the expression of the $\dot{V}O_{2sc}$. (iii) Calculation of the O₂ deficit for a bout of heavy or severe exercise should not presume that the asymptotic or end-exercise $\dot{V}O_2$ is the appropriate reference O₂ cost of exercise from its onset (59, 60, 772). At present, however, physiological uncertainties regarding the expression, mechanistic bases and day-to-day variability (58) of the $\dot{V}O_{2sc}$ have hampered its modeling and extraction of physiologically relevant parameters (772). Figure 23 summarizes the current knowledge regarding the etiology of the $\dot{V}O_{2sc}$.

Effects of Exercise Modality on $\dot{V}O_2$ Kinetics

The fundamental features of the $\dot{V}O_2$ kinetics response to moderate, heavy, and severe exercise are qualitatively similar among different modes of exercise, suggesting that $\dot{V}O_2$ kinetics is modulated by the same fundamental physiological mechanisms. However, some variability is apparent when different ergometers are utilized (88, 121, 393, 431, 434, 441, 443, 632) and analysis of such variability may offer insights into the underlying control mechanisms. This section will summarize evidence that the modality dependence of $\dot{V}O_2$ kinetics suggests that, in addition to metabolic factors *per se*, perhaps O₂ delivery to the working muscle (589, 726) and also the muscle contraction regimen and the ensuing muscle fiber recruitment profile influence the $\dot{V}O_2$ kinetics response.

Whereas Hill and Lupton (347) investigated the $\dot{V}O_2$ responses to various constant running speeds and established the O₂ deficit and debt concept in human subjects, the majority of the subsequent work in this field has been conducted using cycle ergometry (e.g., 328, 476, 779). This latter mode of exercise possesses clear advantages over treadmill running with respect to the accuracy and stability of work-rate imposition and data acquisition (246, 464, 498). Notwithstanding the scientific prerogative for conventional cycle ergometry, $\dot{V}O_2$ kinetics data have been acquired during swimming (187), rowing (376, 632), arm cranking (128, 434, 441), supine cycling (364, 385), recumbent cycling (792), knee extension exercise (455, 484, 687), prone kicking exercise (638–645),

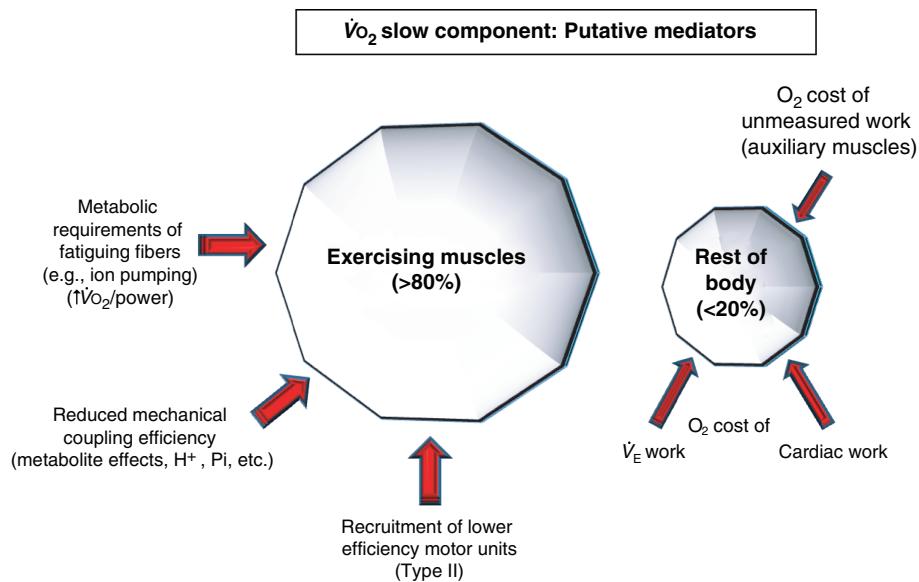


Figure 23 Current array of putative mediators of $\dot{V}O_2$ slow component which has been severely truncated since 1980. See text for further details.

single-legged cycling (430), and handgrip exercise (368), as well as running (88, 120-122, 393).

Across a wealth of treadmill running $\dot{V}O_2$ kinetics studies (88, 90, 121, 122, 125, 349, 393, 615) it appears that, as running speed is increased from moderate to heavy/severe: (i) τ_p is similar or tends to lengthen slightly and (ii) G_p is similar or tends to fall (120-122, 125, 791). Moreover, a $\dot{V}O_2\text{sc}$ becomes manifested as running speed exceeds LT/GET. Consequently, the $\dot{V}O_2$ response to running evinces similar characteristics to cycling, and can be well described with the same modeling procedures (120). Using these procedures to make direct comparisons in the same subjects, subtle differences are revealed in the $\dot{V}O_2$ response to different modes of exercise. Running and cycling $\dot{V}O_2$ kinetics were first compared utilizing mathematical modeling techniques that characterized the individual components of the $\dot{V}O_2$ response by Carter et al. (122, but see also 90, 393). These investigations revealed that the $\dot{V}O_2\text{sc}$ was greater in amplitude during cycling compared to running and that the $\dot{V}O_2\text{sc}$ accounted for a significantly greater percentage (i.e., 7%-17% vs. 3%-10%) of the total $\dot{V}O_2$ response during cycling exercise. This was true despite the absolute metabolic rate (at an equivalent relative exercise intensity) being consistently lower during cycling than running. The τ_p was, however, similar between cycling and running at all the relative exercise intensities studied (122). Somewhat differently, Hill et al. (349) found τ_p to be significantly shorter in running compared to cycling (~14 vs. ~25 s) for high-intensity exercise such that $\dot{V}O_2$ peak was reached appreciably faster during running. Across all investigations to date, τ_p appears to be somewhat faster in running (15-25 s; 121, 122, 125, 349) compared to cycling (20-30 s; 39, 121, 122, 349) in young healthy subjects. In addition to differences in muscle contraction regimen (see later), for most subjects,

the muscles used in day-to-day activities (such as walking) are likely to be relatively better trained than those used in other exercise modes and this may help explain the cycling versus running differences.

Fundamental differences in muscle contraction regimes between running and cycling likely underlie the qualitatively similar but quantitatively dissimilar $\dot{V}O_2$ responses (i.e., greater component of eccentric muscle action during running). Perrey et al. (570) investigated this specific issue using an electrically-braked cycle ergometer that allowed subjects to perform bouts of moderate and heavy exercise either concentrically (conventional) or eccentrically (pedals driven backward). For the eccentric exercise $\dot{V}O_2$ was markedly lower than during concentric exercise such that the $\dot{V}O_2$ response amplitude to the heavy eccentric work rate (317 Watts) was not different from concentric exercise performed at ~60 W. Moreover, no $\dot{V}O_2\text{sc}$ was observed for eccentric exercise, suggesting that metabolic demand rather than external work rate, is a crucial determinant of the presence or otherwise of the $\dot{V}O_2\text{sc}$ (330). It is pertinent that the normalized integrated electromyogram only increased for the heavy concentric exercise bout in which a $\dot{V}O_2\text{sc}$ was present. A logical explanation for this behavior is that the lower metabolic demand during eccentric exercise (18, 651) limited fatigue development and thus the requirement for additional motor unit recruitment as exercise proceeded. Consistent with Perrey et al. (570), Pringle and Jones (618) found that when subjects ran at the same relative exercise intensity with the treadmill set at 10% versus 0% grade, which would increase the proportion of concentric to eccentric muscle action (from ~1:1 to ~9:1; reference 525), there was a 40% greater amplitude of the $\dot{V}O_2\text{sc}$ despite there being no difference in the amplitude of the primary $\dot{V}O_2$ response. These studies indicate that

differences in the muscle contraction regimen can impact $\dot{V}O_2$ kinetics.

Altering body position for a given exercise task can change $\dot{V}O_2$ kinetics. Specifically, supine (158, 364, 385, 484) and prone (200, 639, 641) exercise generally results in a longer τ_p (i.e., slower kinetics) compared to upright exercise at the same work rate. However, Koga et al. (435) reported that supine exercise resulted in a significantly longer MRT for $\dot{V}O_2$ compared to the upright control condition during moderate and heavy exercise, with no difference in the τ_p between conditions. For heavy exercise, the supine position caused a significant reduction of the primary component amplitude and a significant increase in the $\dot{V}O_{2\text{sc}}$ amplitude (but see 385 for an exception). These data may indicate that the amplitudes of the primary and slow components are themselves sensitive to alterations in muscle blood flow which would be expected to be reduced consequent to the decreased “gravitational assist” (i.e., decreased vertical height of the exercising muscle below the heart) in the nonupright position. However, other factors such as muscle pumping activity and fiber recruitment profiles may also be impacted and cause or contribute to the altered $\dot{V}O_2$ kinetics.

Early studies documented that, for the same absolute work rate, arm crank exercise engenders a higher $\dot{V}O_2$ (173, 736) and a slower $\dot{V}O_2$ kinetics response following the onset of work (140, 569) compared to leg exercise (Fig. 24, reference 441). Subsequently, Casaburi et al. (128) found slowed $\dot{V}O_2$ kinetics for arm versus leg exercise even at work rates that did not elicit an elevated blood [lactate]. More recent studies have helped to clearly partition the $\dot{V}O_2$ response at the onset of arm exercise into its discrete components and compared these to the response at the onset of leg exercise of the same relative intensity (434, 441, 677). For instance, Koppo et al. (441) compared the $\dot{V}O_2$ kinetics during arm cranking (with the arms below the level of the heart) and leg cycle exercise at 90% $\dot{V}O_2$ peak. For arm versus leg exercise, τ_p was significantly longer (~48 vs. ~21 s), and G_p significantly greater (~12.1 vs. ~9.2 ml min⁻¹ W⁻¹), although the $\dot{V}O_{2\text{sc}}$ contribution to the end-exercise $\dot{V}O_2$ was similar (~20%) be-

tween exercise modes. Although the $\dot{V}O_{2\text{sc}}$ has been reported to attain ~240 ml min⁻¹ during high-intensity front crawl swimming (187), it is possible that this reflects a larger-than-normal contribution of respiratory muscle work due to the increased work of breathing against external resistance.

The mechanistic bases for the slower $\dot{V}O_2$ kinetics in arm versus leg exercise are unclear. On the one hand, there is evidence from impedance cardiography that stroke volume is limited and that \dot{Q} kinetics might be slower for arm exercise (434) such that the rate at which $\dot{V}O_2$ rises following the onset of exercise may be constrained by muscle perfusion. On the other hand, muscle blood flow is higher per unit muscle mass for the same metabolic rate in arm versus leg exercise (147) and there appears to be no appreciable difference in muscle blood flow kinetics (569) between arm and leg exercise. Theoretically, if the arms are working below the level of the heart, one might expect enhanced perfusion in this small muscle group. In this case, the slower $\dot{V}O_2$ kinetics in arm exercise must be explained by factors other than inadequate O₂ delivery. Possible explanations include inherently slower kinetics as the result of the relatively high % type II fibers that comprise the muscles of the arms (269, 384) and/or earlier or possibly greater recruitment of type II fibers resulting from higher intramuscular tension development and impeded blood flow during arm exercise (669).

Comparative Physiology of $\dot{V}O_2$ Dynamics

Under the auspices of understanding $\dot{V}O_2$ kinetics in humans and recognizing the association between $\dot{V}O_2$ kinetics and aerobic capacity ($\dot{V}O_{2\text{max}}$) this section adopts a cross-species approach. Whereas elsewhere in this review recourse is made to experimental animal data only when such data in humans is absent, the present section follows the comparative physiologists’ edict that “*for every physiological question, there is an animal model designed specifically to answer it.*” Using this strategy $\dot{V}O_2$ kinetics can be examined across a far broader range of aerobic capacities than found in healthy humans (i.e., $\dot{V}O_{2\text{max}}$ 20–95 ml min⁻¹ kg⁻¹; review 587, 593). Specifically, judicious selection of, for example, the lungless salamander ($\dot{V}O_{2\text{max}} < 10$ ml min⁻¹ kg⁻¹; 234, 252, 581) at the lower extremity up to the Thoroughbred horse ($\dot{V}O_{2\text{max}}$ 160–220 ml min⁻¹ kg⁻¹; 427, 801; review 587, 592, 593) extends the range of aerobic potential up to 20-fold. That range reflects partly environmental pressures (Darwinian evolution) and, in other species such as the horse and dog, several millennia of selective breeding for athletic potential. Of particular interest, disparate species have found different anatomical and physiological solutions to their O₂ transport and utilization needs. Notwithstanding the often extraordinary methodological challenges involved, analysis of these solutions provides an invaluable perspective within which to consider the determinants of $\dot{V}O_2$ kinetics in our own species.

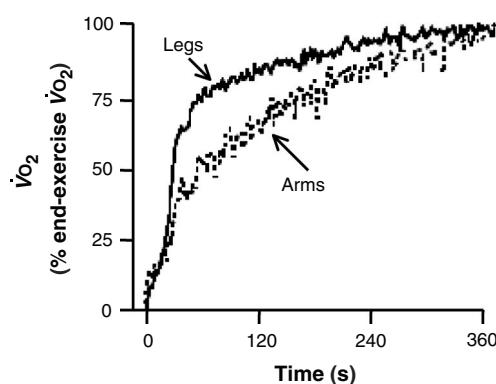


Figure 24 Pulmonary $\dot{V}O_2$ response to arm cranking versus leg cycle ergometer exercise scaled to end exercise $\dot{V}O_2$. Redrawn, with permission, from Koppo et al. (441).

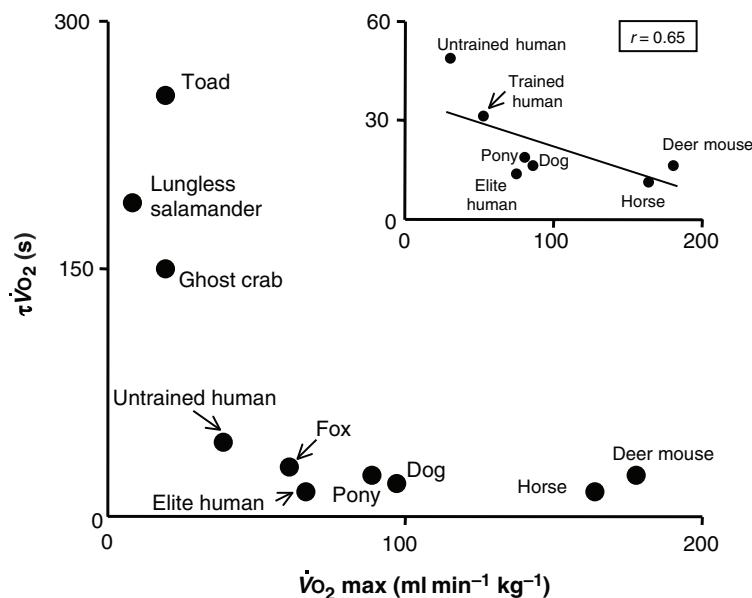


Figure 25 $\dot{V}O_2$ kinetics across species portrayed as the time taken to reach 63% of the final $\dot{V}O_2$ (i.e., τ here is synonymous with mean response time, MRT) and the mass-specific $\dot{V}O_2$ max. Note that, in most species, distinction between Phase I and the primary component was not possible. Inset features the mammalian species separately. Redrawn, with permission, from Poole et al. (602).

Association between $\dot{V}O_2$ kinetics and $\dot{V}O_2$ max

As true within the human population, those species with a greater $\dot{V}O_2$ max have faster $\dot{V}O_2$ kinetics (Fig. 25). Accepting that interspecies locomotory mechanics may impose certain constraints and that the breath-by-breath measurement fidelity available in humans and horses may not be possible, Figure 25 presents some of the best available data across diverse species. As the inset exemplifies, within mammals there is a weak linear correlation with $\dot{V}O_2$ kinetics becoming appreciably faster at higher $\dot{V}O_2$ max's. It is also evident that nonmammalian species (e.g., lungless salamander, *Plethodon jordani*; Ghost crab, *Ocypode guadichaudii*; and Fowler's toad, *Bufo woodhousei fowleri*) that typically have an extremely low $\dot{V}O_2$ max have extraordinarily slow $\dot{V}O_2$ kinetics.

Despite this relationship between $\dot{V}O_2$ max and $\dot{V}O_2$ kinetics any inference of a mechanistic connection between these two parameters of aerobic function must be made with caution. Whereas Wagner (740, 744) has championed the notion that $\dot{V}O_2$ max can be limited or constrained by a reduced lung, cardiovascular or muscle O₂ conductance it is evident that the strongest determinant of $\dot{V}O_2$ max in healthy individuals is the cardiovascular capacity for O₂ delivery. The O₂-delivery limitation to $\dot{V}O_2$ max is particularly evident in the racehorse where selective breeding has increased average heart mass to ~1% body mass (0.5% in humans) resulting in a Q to lung capacity discordance and overt exercise-induced arterial hypoxemia with arterial O₂ pressures falling routinely below 70 mmHg such that hemoglobin O₂ saturation is compromised (56, 220, 351, 427, 568, 721, 742; review 587, 592, 593, 602). In contrast to the cardiovascular O₂ delivery limiting $\dot{V}O_2$ max,

this review presents the compelling case for $\dot{V}O_2$ kinetics control residing within the exercising muscle(s), most likely at the mitochondrial level, at least in healthy humans performing upright locomotory exercise. Given the variations in O₂ transport pathway designs evident across species, it might be expected that the site of $\dot{V}O_2$ kinetics control would move upstream in species where the capacity of the gas exchanger and/or the cardiovascular system(s) have not kept pace with that of skeletal muscle. This consideration is explored below across the available breadth of the animal kingdom.

Invertebrates

Insects and crustaceans (i.e., arthropods) constitute the largest and most diverse animal group on earth. However, most of them have eluded systematic study of locomotory energetics and metabolism: one notable exception being the ghost crab (Fig. 25). This animal relies on gill chambers for O₂ diffusion which must occur through a chitin layer of its gills that possesses a far lower diffusive O₂ conductance than the very thin (0.3 μ m) human blood gas barrier. It has been proposed that this chitin layer poses the major rate limitation for O₂ diffusion into the blood (517). Moreover, the ghost crab has a single-chambered heart which responds very sluggishly following the start of locomotion (i.e., running sideways, 336). Despite these considerations, the temporal profile of $\dot{V}O_2$ kinetics, whilst ponderously slow, is qualitatively similar to that of humans in that it appears close to monoexponential with $\tau\dot{V}O_2 \sim 144$ s at 0.28 km/h. It is pertinent that this particular

crab is less pedestrian than other crab species who exhibit even slower $\dot{V}O_2$ kinetics (253, 254, 336).

Amphibians

The lungless salamander lies toward the lower end of measured vertebrate aerobic function. In the salamander, absence of lungs places reliance on the skin for O₂ diffusion and CO₂ elimination (234, 581) and this animal has been considered as a useful model of O₂ diffusion limitation with relevance for understanding impaired gas exchange in severe lung disease patients. Lungless salamanders exhibit $\dot{V}O_{2\max}$ values of 7 to 8 ml min⁻¹ kg⁻¹ and locomote using a quick sprint type of running that must be powered principally by substrate-level phosphorylation given that $\tau\dot{V}O_2$ is ~180 s (252). Another amphibian, Fowler's toad (an anuran order amphibian, i.e., lacking a tail), has been studied during locomotion which consists of salutatory movements (hopping) at 0.09 km/h. Whereas toads and frogs may utilize transcutaneous O₂ diffusion, they also have lungs which are necessary to achieve their $\dot{V}O_{2\max}$ of ~20 ml min⁻¹ kg⁻¹ (745). The data presented by Walton and Anderson (745) indicates that these animals have a $\tau\dot{V}O_2$ ~254 s at this very low speed (Fig. 26). Interestingly, when hopping five times faster (0.45 km/h) $\dot{V}O_2$ kinetics appeared to be even slower ($\tau\dot{V}O_2$ ~403 s); possibly resulting from the imposition of a $\dot{V}O_{2\text{sc}}$ that resembles qualitatively that present in humans performing heavy or severe intensity exercise (cf. Figs. 5 and 7, left panel).

Whereas the design of the amphibian cardiorespiratory system does not appear to support either rapid $\dot{V}O_2$ kinetics or a high $\dot{V}O_{2\max}$ the same cannot be said for skeletal muscle. Over 80 years ago Fenn (236) reported that, following 5–10 s of tetanic contraction, the rise in $\dot{V}O_2$ of the isolated Sartorius muscle of the English frog (*Rana pipiens*) was “immediate.” This observation must be qualified in that the sealed chamber used in those experiments resulted in a system response time too slow to follow any rapid kinetic response. However, subsequent investigations into contraction energetics in this muscle by Hill (344) and Mahler (488) demonstrated

the temporal coherence between $\dot{V}O_2$ and heat production and also the pH dependence of $\dot{V}O_2$ kinetics. Moreover, by demonstrating that $\tau\dot{V}O_2$ during recovery from contractions of different duration was invariant with metabolic demand Mahler (488) concluded that muscle $\dot{V}O_2$ was a linear, first-order process (see Section *Introduction*). The profile of $\dot{V}O_2$ increase in Mahler's study indicates kinetics far faster than that seen for the intact amphibian (Fowler's toad, Fig. 26, reference 745). However, within the isolated muscle preparation the abolition of vascular O₂ supply compromised O₂ delivery which had to be facilitated by creating a hyperoxic environment over the muscle. Despite this exigency it is likely that hypoxia and even anoxia developed within deeper muscle regions. Notwithstanding these methodological concerns a series of technically brilliant studies using single frog lumbrial myocytes from the African clawed frog (*Xenopus laevis*) determined that $\tau\dot{V}O_2$ was as short as ~12 s in the highly oxidative fibers (Fig. 15) and somewhat slower in the lower oxidative fibers (355, 421, 423; see also 538). Interestingly, in this preparation where O₂ pressures and $\dot{V}O_2$ were measured by phosphorescence quenching, a technique which possesses high temporal and spatial fidelity and accuracy (355, 421, 423), progressively increasing extracellular Po₂ from 20 to 60 mmHg did not speed $\dot{V}O_2$ kinetics (421). This observation suggests that an extracellular Po₂ of 20 mmHg is sufficient to facilitate unimpeded $\dot{V}O_2$ kinetics.

Notice that the $\dot{V}O_2$ profile for the lumbrial myocyte shown in Figure 15 demonstrates no time delay prior to $\dot{V}O_2$ increase. Hogan (356) did, however, find that, like intact muscles (72–74) some myocytes evidenced ~13 s delay prior to intramyocyte Po₂ falling and further that this could be reduced to ~5 s by priming the muscle with prior contractions. In this preparation, the priming response could obviously not be dependent on either altered muscle fiber recruitment profiles or elevated muscle blood flow and O₂ delivery as has been considered for vascularly intact contracting whole muscle (see Section *Priming Exercise and $\dot{V}O_2$ Kinetics*). Further evidence that at least some of the $\dot{V}O_2$ inertia has an intracellular enzymatic locus emerges from studies using pharmacological blockade of the CK reaction with iodoacetamide and 2,4-dinitrofluorobenzene. Specifically, Kindig et al. (422) found that, independent of extracellular Po₂, $\dot{V}O_2$ kinetics was speeded by CK blockade.

In conclusion, the evidence supports that, in the amphibians considered above, the very slow $\dot{V}O_2$ kinetics expressed during locomotion is likely the result of low-limiting O₂ conductances at sites proximal to the contracting muscles which in-and-of themselves have the potential for rapid $\dot{V}O_2$ kinetics. Thus, these animals are positioned within the O₂-delivery-dependent zone of Figure 2. For these species evolutionary pressures seem not to have favored cardiorespiratory adaptations as a means to avoid predators. Rather, their survival and species success may have depended more on either short explosive bursts of movement within a habitat conducive to concealment (frogs) or development of poison strategies (frogs and toads) to evade predators.

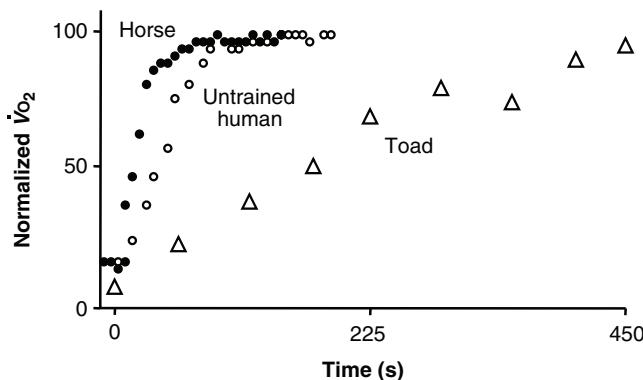


Figure 26 Comparison of $\dot{V}O_2$ response among the Thoroughbred horse, untrained human, and toad following a stepwise increase in metabolic demand.

Mammals

Horses

Equus caballus, the modern horse, has been selectively bred for athletic potential for over six millennia (review 593). Given the dependence of running speed on effective O₂ transport in this species and its amenability for scientific investigation it can provide powerful mechanistic insights into the extremes of structural and functional adaptability along the O₂-transport pathway and control of $\dot{V}\text{O}_2$ kinetics. Today, the elite Thoroughbred racehorse has a mass-specific $\dot{V}\text{O}_{2\text{max}}$ in the upper echelon of mammals ($>200 \text{ ml min}^{-1} \text{ kg}^{-1}$, i.e., 2-3-fold that present in elite human athletes) and can transport and utilize well over 80 liters O₂ min⁻¹ and possibly up to 120 liters O₂ min⁻¹ during high-speed running (592, 593, 801).

Earlier investigations had assessed the speed of the $\dot{V}\text{O}_2$ response in ponies (243, see also 409 and 611) as well as Standardbred, Thoroughbred and Quarter horses (e.g., 354, 636). However, prior to Langsetmo and colleagues (467) measurements had lacked the temporal fidelity to characterize $\dot{V}\text{O}_2$ kinetics formally. Using a flow-by or “bias flow” system Langsetmo et al. (467) measured pulmonary $\dot{V}\text{O}_2$ kinetics with a second-by-second resolution in Thoroughbred and Quarter horses transitioning to running on a treadmill within the moderate and heavy-exercise domains. For moderate intensity cantering/trotting (~15 mph for these horses) $\dot{V}\text{O}_2$ kinetics was well fit by a two-component exponential model with cardiodynamic and subsequent primary phases. The $\tau_p \dot{V}\text{O}_2$ was only 10 s, on average (Figs. 25 and 26). For heavy intensity galloping $\tau_p \dot{V}\text{O}_2$ was slowed to ~21 s and a subsequent $\dot{V}\text{O}_{2\text{sc}}$ emerged some 135 s after exercise onset. Geor and colleagues (262) later determined that $\tau_p \dot{V}\text{O}_2$ following the onset of supramaximal running (i.e., speeds 15% higher than that attained at $\dot{V}\text{O}_{2\text{max}}$ on a fatiguing incremental test) was ~23 s in Standardbred horses with $\dot{V}\text{O}_2$ max ~60 liters·min⁻¹, 150 ml min⁻¹ kg⁻¹). Interestingly, preceding this test with a warm-up or so-called priming exercise reduced $\tau \dot{V}\text{O}_2$ by 30%.

Why is $\dot{V}\text{O}_2$ kinetics so fast in the horse? Selective breeding has endowed the elite Thoroughbred racehorse with an anatomy and physiology superbly adapted for O₂ transport. This is exemplified by the following.

Pulmonary system Total lung capacity may exceed 80 liters and, during maximal exercise minute ventilations in excess of 1,700 liters (estimated alveolar ventilation $>1,400 \text{ liters} \cdot \text{min}^{-1}$) achieved at a respiratory frequency ~120 b/s have been determined (113, 554, 593).

Cardiovascular system The Thoroughbred has an enormous heart [up to 20-22 lbs (9-10 kg) in the extreme, review 592, 593] which facilitates stroke volumes in the region of 2 liters. As maximal HR in these animals can be as high as 240 b min⁻¹ \dot{Q} may exceed 450 liters·min⁻¹. Despite a profound exercise-induced arterial hypoxemia arterial O₂ content

increases from rest to exercise as the large muscular spleen disgorges ~14 liters of RBCs into the circulation elevating systemic hematocrit up to 70% (573, 592, 593).

Muscular system Fifty percent or more of the Thoroughbred's mass is skeletal muscle, the vast majority of which is believed to be recruited during running as judged from determination of regional blood flows (e.g., 8) and disappearingly small mixed venous O₂ contents (review 593). Equine skeletal muscle has relatively high capillary and mitochondrial volume densities (8; review 593). Whilst neither is extraordinary in itself the sheer mass of skeletal muscle recruited (~250 kg for a 500 kg horse) confers some remarkable functional properties: (i) the prodigious total muscle blood flow is distributed such that no muscles receive more than 1 to 2 liters·min⁻¹·kg⁻¹ (8, 593) which is considerably lower than the 4 liters·min⁻¹·kg⁻¹ found in the human quadriceps during leg extension exercise (628). (ii) Total muscle mitochondrial volume may exceed 25 liters (593). This estimation is consistent with the conclusion of Weibel, Taylor, Hoppeler and colleagues (755) that each milliliter of mitochondria can consume 4 to 5 ml O₂ min⁻¹ which would be necessary to achieve a $\dot{V}\text{O}_{2\text{max}} \sim 100 \text{ liters} \cdot \text{min}^{-1}$.

Of these three elements in the O₂-transport pathway, the pulmonary system appears clearly to represent the “weak link” at least with respect to $\dot{V}\text{O}_{2\text{max}}$ and RBC transit time becomes inadequate to fully oxygenate the arterial blood (56, 220, 351, 427, 568, 721, 742; review 587, 592, 593). This situation is exacerbated by the presence of a thicker blood-gas barrier (1.0 vs 0.3 μm) than found in humans (92) which nonetheless is subject to rupture causing exercise-induced pulmonary hemorrhage (EIPH; review 226, 593) and further increasing the diffusion distance for gas exchange.

Pursuant to the focus on $\dot{V}\text{O}_2$ kinetics herein, the question arises whether the relative shortcomings of the pulmonary system at maximal exercise are sufficient to shift the site of control of $\dot{V}\text{O}_2$ kinetics upstream from the exercising muscles in this species? To address this issue Kindig and colleagues (420, 424, 425) used the NO synthase inhibitor N^ω-nitro-L-arginine methyl ester (L-NAME) to relieve any NO inhibition on mitochondrial function following the onset of moderate- and heavy-intensity running in the horse. Despite L-NAME decreasing \dot{Q} and presumably muscle blood flow and O₂-delivery (353) $\dot{V}\text{O}_2$ kinetics was speeded by up to 30% (424, 425). This places the horse well to the right of the O₂-delivery-dependence region of Figure 2.

Dogs

Like the horse, the domestic dog (*Canidae*) has been adapted to human needs for millennia and those breeds such as the Greyhound and Foxhound as well as Alaskan husky and other sled dogs that have fulfilled racing, hunting and highly physical working roles have superbly developed O₂-transport systems. In the extreme, a $\dot{V}\text{O}_{2\text{max}}$ of ~240 ml min⁻¹ kg⁻¹ was achieved by one extraordinary Greyhound (702; review 593).

In addition, whereas pulmonary gas exchange measurements on dogs are particularly challenging, in part, because of their reliance on ventilation for thermoregulation, they are possible and so, physiologically, the dog has helped bridge the gap between isolated single-fiber (often amphibian) and intact organism preparations. Hence, the dog is responsible for considerable insights into the control of $\dot{V}O_2$ kinetics.

Physiological commonalities between the elite (Greyhound) dog and horse include: (i) large heart ~1.7% of body mass (157, 295, 479, 555, 678, 708) and high stroke volume (702). (ii) High maximal HR ($>300\text{ b min}^{-1}$, reference 224, 662, 702, 746) and \dot{Q} ($1,200\text{ ml min}^{-1}\text{ kg}^{-1}$, reference 702). (iii) Splenic discharge that can elevate systemic hematocrit above 60% (218, 373, 543, 697, 702, 723). (iv) Large muscle mass (up to 58% body mass, 293; review 593). (v) Skeletal muscle blood flows that range from 1 to 3 $\text{liters}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ (in Foxhounds, possibly higher in Greyhounds) at maximal running speeds. (vi) High capillary and mitochondrial volume densities of skeletal muscle (294, 557). Whereas there is evidence of exercise-induced arterial hypoxemia and EIPH in the racing Greyhound the severity does not appear to approach that found in the horse and less athletic species may achieve $\dot{V}O_2$'s well above $100\text{ ml min}^{-1}\text{ kg}^{-1}$ without overt arterial hypoxemia or EIPH (536, 549).

In 1968, Piiper and colleagues (580) found that $\tau\dot{V}O_2$ for the surgically isolated electrically stimulated dog gastrocnemius-plantaris complex was 15 to 17 s. Subsequently, using a respiratory mask and mass spectrometer Marconi and colleagues (495) reported a $\tau\dot{V}O_2$ ~20 s for mongrel dogs following transitions to between 4 and 12 km/h at a 10% incline. Moreover, Casaburi et al. (132) demonstrated that, during electrically stimulated muscle contractions in anesthetized dogs, muscle and pulmonary $\dot{V}O_2$ kinetics were not different (i.e., $\tau\dot{V}O_2$ for muscle and pulmonary measurements was ~17 s). That such close agreement existed between measurements made across the exercising muscles and at the mouth (as more fully developed in Section *Relationship Between Pulmonary and Exercising Muscle $\dot{V}O_2$ Responses*) helped reinforce that measurements of pulmonary gas exchange could provide an accessible and valuable window into the dynamics of muscle energetics during metabolic transitions. This concept grounded the elegant modeling studies of Barstow and Molé (42) in humans which were then validated by Grassi and colleagues (285) by making simultaneous $\tau\dot{V}O_2$ measurements across the exercising leg and whole body.

In addition to the far superior $\dot{V}O_{2\max}$ of dogs compared with humans there are other important considerations to bear in mind when using this model as an analog of human energetics. Paramount amongst these are: (i) in the mongrel dogs studied by Marconi et al. (495) there was no evidence of a $\dot{V}O_{2\text{sc}}$ response even at the highest running speed evaluated ($\dot{V}O_2 \sim 75\text{ ml min}^{-1}\text{ kg}^{-1}$). (ii) The dog has extremely oxidative muscles and the gastrocnemius-plantaris complex lacks fast-glycolytic fibers (557)—which may underlie the very low lactate efflux from these muscles during even intense electrical stimulation (357, 358). Despite these differ-

ences between species the dog gastrocnemius-plantaris preparation first described by Stainsby and Welch in 1966 (703) has been invaluable for investigating the control of $\dot{V}O_2$ kinetics. For example, in a series of investigations Bruno Grassi and colleagues (277, 278, 280; review 273, 274) have provided substantial evidence that, across the range of metabolic rates achievable in this model $\dot{V}O_2$ kinetics is either not, or is only minimally, impacted by increased O_2 delivery. Specifically, neither increased peripheral O_2 diffusing capacity using RSR-13 (2-[4-[(3,5-dimethylanilino)carbonyl]methyl]phenoxy]-2-methylpropionic acid, reference 278) nor elevated O_2 delivery using pump-perfused hyperemic and hyperoxic conditions even in the presence of adenosine-mediated vasodilation (277), resulted in faster $\dot{V}O_2$ kinetics for moderate/heavy contraction intensities. At higher metabolic rates there was some evidence that $\tau\dot{V}O_2$ was reduced by elevating O_2 delivery. However, this effect was modest and inconsistent across animals. In contrast, most recently, Grassi and colleagues (288) demonstrated that acute CK inhibition substantially speeded $\dot{V}O_2$ kinetics in this dog gastrocnemius model adding further support to an intramyocyte locus of $\dot{V}O_2$ kinetics control.

Rodents

Despite the reliance placed on *rodentia* in scientific discovery their relatively small size and technical challenges have limited the range of kinetics studies on these species. Nonetheless, Chappell (142) reported $\tau\dot{V}O_2$'s of 20 to 25 s in the deer mouse (*Peromyscus maniculatus*) which also has a $\dot{V}O_{2\max}$ in the upper range of that measured in mammals ($\sim 175\text{ ml min}^{-1}\text{ kg}^{-1}$). Rats have a somewhat lower $\dot{V}O_{2\max}$ which is generally reported in the range of 70 to $80\text{ ml min}^{-1}\text{ kg}^{-1}$ (268, 534) but, to date, the rat remains the only species in which $\dot{V}O_2$ kinetics has been measured within the microcirculation, that is, at the site of blood-myocyte O_2 flux (64). Using paired measurements of capillary hemodynamics (intravital microscopy) and $Pmvo_2$ (phosphorescence quenching) in the spinotrapezius muscle during contractions, Behnke and colleagues (64) reported that $\dot{V}O_2$ began increasing without discernible delay and with mono-exponential kinetics ($\tau\dot{V}O_2 \sim 20\text{ s}$, Fig. 14). As this particular muscle exhibits only a modest oxidative capacity (citrate synthase activity $\sim 14\text{ }\mu\text{m min}^{-1}\text{ g}^{-1}$, reference 183) it is quite likely that other muscles, such as the red gastrocnemius which has an almost threefold greater oxidative potential, has more rapid $\dot{V}O_2$ kinetics. Rodent models occupy a pivotal position in understanding human diseases such as CHF and diabetes. The mechanistic link between the impact of such diseases on $\dot{V}O_2$ kinetics and impaired muscle performance provides a pressing mandate to use these models and techniques only available in rodent animal models to assess the efficacy of therapeutic strategies.

In conclusion, within the animal kingdom distinct features of the $\dot{V}O_2$ kinetics response are conserved. These include: (i) association between $\dot{V}O_{2\max}$ and the speed of $\dot{V}O_2$ kinetics

across most species examined. (ii) Temporal characteristics of the pulmonary $\dot{V}O_2$ kinetics response (human and horse). Specifically, for pulmonary $\dot{V}O_2$ at moderate exercise intensities the response is well fit by a delay (which incorporates a cardiodynamic Phase I of almost immediate onset) followed by the Phase II monoexponential increase (primary component) to the steady state. The retained monoexponentiality of the primary component in the horse is remarkable given that it is manifested simultaneously with the spleen dumping up to 14 liters of RBCs into the circulation (593). For heavy or severe intensities a $\dot{V}O_{2sc}$ is superimposed on the more rapid primary response which may, in the severe domain, increase $\dot{V}O_2$ to $\dot{V}O_{2max}$. (iii) $\dot{V}O_2$ kinetics does not appear to be O_2 -delivery limited in mammals (humans, horses, rats, and dogs). (iv) Whereas muscle-to-pulmonary transit times mandate more complex whole body $\dot{V}O_2$ kinetics (i.e., imposition of a Phase I or delay-like component) the muscle $\dot{V}O_2$ response is initiated without discernible delay (frog, rat, and dog). In contrast, there are also noteworthy variations among animal species which include: (A) in more primitive animals such as amphibians, which have lower capacity respiratory and cardiovascular systems, the discordance between slow whole body and fast single fiber $\dot{V}O_2$ kinetics suggests that muscle O_2 delivery might limit $\dot{V}O_2$ kinetics. (B) In dogs, the $\dot{V}O_{2sc}$ is very modest (muscle, 277) or absent (495) which might, actually, be an artifact of the falling force output in this model (810) such that the $\dot{V}O_2/\text{force}$ ratio does rise indicative of a $\dot{V}O_{2sc}$ -like effect. (C) In the horse, priming exercise appears to speed the primary $\dot{V}O_2$ kinetics at severe exercise intensities (262) whereas this is generally not the case in humans (see Section *Priming Exercise and $\dot{V}O_2$ Kinetics*).

Priming exercise and $\dot{V}O_2$ kinetics

Historically prior exercise has been recognized as an acute intervention that affects profoundly the metabolic, acid-base, and cardiovascular responses to subsequent exercise. Early studies documented the effects of prior exercise on the $\dot{V}O_2$ response during subsequent exercise, although many of these studies lacked the temporal resolution required to elucidate the specific time course of $\dot{V}O_2$. For instance (105, 301, 760), prior high-intensity exercise that raised blood [lactate], followed by 20 to 25 min of recovery pedaling, resulted in an increase in the $\dot{V}O_2$ response (first 2 min) during the subsequent exercise bout which was accompanied by a blunting of the $\dot{V}CO_2$, blood [lactate] and pH responses. These results clearly demonstrated that prior exercise could serve to “prime” the physiological response to exercise, resulting in an apparent increase in the oxidative contribution to subsequent exercise.

Gerbino et al. (264) generated renewed interest in this topic when they demonstrated that prior heavy (but not moderate) exercise could speed the overall $\dot{V}O_2$ kinetics during a second bout of heavy exercise performed 6 min after the first and reduce concomitant lactate accumulation. The implications of these findings were profound: no other study of the $\dot{V}O_2$ response in exercising humans during upright exercise

had shown that the kinetics could be speeded by an acute, non-pharmacological intervention. The resultant increased aerobic contribution to energy turnover in the second heavy exercise bout was associated with, and considered potentially consequent to, an improved O_2 delivery to muscle. That both prior heavy exercise and hyperoxia speeded the overall $\dot{V}O_2$ kinetics during heavy (i.e., $>LT/GT$), but not moderate, intensity exercise supported the concept that an O_2 -transport limitation may be impacting on heavy exercise $\dot{V}O_2$ kinetics (482).

In the study of Germino et al. (264), the data were fit using a simple monoexponential function applied from 25 s to the end of exercise. While this approach is appropriate when multiple exercise transitions have not been completed to reduce breath-to-breath noise, a major shortcoming is that the resultant “effective” τ may be reduced either as a consequence of a speeding of the primary kinetics, or due to a reduction of the $\dot{V}O_{2sc}$ amplitude. This problem also impacted MacDonald et al.’s (482) conclusions: although they characterized their data with a three-component exponential function, they chose to use the “MRT” when interpreting the data; this parameter also reflects the rate at which the end exercise $\dot{V}O_2$ is attained and cannot be used to discriminate between changes in the primary and slow component responses. Subsequently, other groups used more complex modeling procedures to provide insights regarding the physiological mechanisms responsible for the overall speeding of the $\dot{V}O_2$ kinetics (111, 438). Collectively, the results confirmed that there was a significant speeding of the overall $\dot{V}O_2$ kinetics but demonstrated, crucially, that this overall speeding was not a consequence of a speeding of the primary kinetics, but rather was the consequence of a reduction in the amplitude of the $\dot{V}O_{2sc}$ (111, 438). These findings have subsequently received much additional support (e.g., 24, 60, 106-108, 247, 443, 572, 657, 675).

In addition to the intransigence for the τ_p of the $\dot{V}O_2$ response, it was originally reported that the primary $\dot{V}O_2$ amplitude was unaltered by prior heavy exercise (111, 438): a conclusion possibly resulting from an increased baseline $\dot{V}O_2$ prior at the onset of the subsequent heavy exercise bout. To eliminate this elevated baseline $\dot{V}O_2$ effect, Burnley et al. (107) extended the recovery duration from 6 to 12 min to allow baseline $\dot{V}O_2$ to be restored. The results confirmed that τ_p was unaltered and the amplitude of the $\dot{V}O_{2sc}$ was reduced. Additionally, however, these data also showed that the primary component amplitude was increased by prior heavy exercise (as confirmed by 60, 106, 247, 443, 558, 572). Collectively, the above studies can be used to describe the characteristic effect of prior heavy exercise on the heavy exercise $\dot{V}O_2$ response during upright cycle exercise. Figure 18 illustrates the essence of the effect. In short, it appears that prior heavy exercise that normally results in a residual blood lactacidosis speeds the overall $\dot{V}O_2$ response (249), as a result of an increased primary component amplitude and a reduced $\dot{V}O_{2sc}$ amplitude, with no change in the τ_p (107, 111, 437, 438).

Despite prior heavy exercise not altering the primary $\dot{V}O_2$ kinetics in most instances ($>90\%$ of studies), some studies (228, 229, 639, 725) have presented evidence that, in

special circumstances, τ_p may be reduced in the second heavy exercise bout. Rossiter et al. (639) observed that prior heavy exercise speeded the primary $\dot{V}O_2$ kinetics in a second bout of heavy exercise when subjects exercised in the prone position (necessary for measurement of muscle [PCr] responses by nuclear-MRS). These investigators found that prior heavy exercise reduced the $\dot{V}O_{2\text{sc}}$ amplitude and attenuated the decrement in muscle [PCr] at the onset of exercise, consistent with the speeded pulmonary $\dot{V}O_2$ kinetics. Exercise in the prone position provides the cardiovascular system with very similar control challenges to that faced in the supine position, because the exercising muscle is at a relative perfusion disadvantage compared to the upright condition, which may contribute to the slowed primary component kinetics (364). This being the case, the prior heavy exercise may have improved muscle perfusion, thus speeding the kinetics toward values that would be encountered during upright exercise.

In apparently healthy older individuals (~ 65 years) Scheuermann et al. (674) found that prior heavy exercise speeded $\dot{V}O_2$ kinetics during moderate intensity upright exercise (from ~ 50 to ~ 27 s); an effect the investigators attributed to an improved muscle perfusion. Thus, specific conditions exist whereby prior heavy exercise can speed the primary $\dot{V}O_2$ kinetics, possibly as a consequence of an improved muscle perfusion, in exactly the manner first proposed by Gerbino et al. (264). Indeed, several studies from the research group headed by John Kowalchuk and Donald Paterson at the University of Western Ontario have reported that prior heavy exercise can speed $\dot{V}O_2$ kinetics even during subsequent moderate intensity exercise. DeLorey et al. (179) found that prior heavy exercise speeded moderate intensity $\dot{V}O_2$ kinetics in older (from ~ 38 -30 s) but not younger (from ~ 26 -25 s) subjects. In contrast, Gurd et al. (300) reported that prior heavy exercise resulted in faster $\dot{V}O_2$ kinetics in moderate exercise in young subjects, although the effect was much more pronounced when the subjects had relatively slow kinetics (>30 s) in the control condition.

Mechanisms

Multiple mechanisms might contribute to the changes in $\dot{V}O_2$ kinetics observed following prior exercise, the importance of each being dependent upon the experimental models employed. For instance, experiments placing the exercising muscle at or above heart level are likely to result in different $\dot{V}O_2$ response profiles and hence different mechanistic inferences (639; cf. 111, 385, 440).

Muscle temperature

One of the features of prior exercise interventions is that, depending on the intensity and duration of the prior bout, muscle temperature will be elevated during the performance of the subsequent bout. Koga et al. (433) reported a small but statistically significant reduction in the $\dot{V}O_{2\text{sc}}$ after raising leg muscle temperature by $\sim 3^\circ\text{C}$ by passive heating using

hot-water-perfused pants. The authors suggested that the mechanical efficiency was improved due to a reduction in muscle viscous resistance. This hypothesis might explain why prior exercise, irrespective of whether or not it induces a metabolic acidosis, reduces the $\dot{V}O_{2\text{sc}}$ during the subsequent exercise bout.

To investigate whether elevated muscle temperature, *per se*, was responsible for the $\dot{V}O_{2\text{sc}}$ reduction following prior exercise, Koppo et al. (444) measured vastus lateralis intramuscular temperature and pulmonary $\dot{V}O_2$ simultaneously during two consecutive 6 min bouts of heavy exercise. On a subsequent day, passive leg heating was used, in the absence of prior exercise, to raise muscle temperature to the level achieved during heavy exercise. This procedure did not reduce the $\dot{V}O_{2\text{sc}}$ in contrast to what was seen following prior exercise. Identical results were presented in another paper that demonstrated that prior sprint exercise elicited the characteristic effects of prior heavy exercise (increased primary amplitude, reduced $\dot{V}O_{2\text{sc}}$), whereas prior heating in a hot bath had no significant impact on the $\dot{V}O_2$ responses (108, see also 237 and 433). It appears that prior “warming up” alone, in the strictest sense of increased muscle or core temperature, cannot account for the effect of prior heavy exercise on the $\dot{V}O_2$ response.

Improved muscle perfusion

It was originally proposed that the effect of prior heavy exercise on heavy exercise $\dot{V}O_2$ kinetics may be attributed largely to an acidosis-mediated increase in O_2 delivery (264, 714). This remains a plausible explanation for speeded overall $\dot{V}O_2$ kinetics (639, 725). It is well established that metabolites produced during muscle contraction are vasoactive (302, 337), though this effect in nonrecruited muscle must be limited, and it is clear that the performance of prior (high-intensity) exercise is associated with increased HR (60, 106, 725), estimated \dot{Q} (725), muscle oxygenation (106, 247, 748) and muscle blood flow (32, 454). Thus, there is consistent evidence that O_2 delivery is increased at the onset of the second of two bouts of heavy exercise.

Even in the presence of increased O_2 delivery at the onset of a second bout of heavy exercise, most studies have not observed a speeding of the primary $\dot{V}O_2$ kinetics, indicating that factors probably intrinsic to the exercising muscle are the dominant mediators of the primary component time course even for exercise of heavy intensity (773). Consistent with this suggestion, recent evidence from both amphibian (355, 356) and mammalian (73) muscle preparations has shown that the kinetics of the fall in microvascular or intracellular Po_2 ($Pmvo_2$, which reflects the dynamic relationship between O_2 delivery and O_2 utilization) are speeded in a second contraction period. That the speeded Po_2 kinetics was the result of a reduced time delay before the fall in Po_2 in both studies suggests that the foreshortened time delay had an intracellular origin. In addition, Behnke et al. (73) demonstrated no residual lactacidosis or improved muscle blood

flow in the second bout of muscle contractions. These results demonstrate that an improved blood flow is not a prerequisite for a “priming” effect to be observed in contracting muscle. Human studies have reached similar conclusions (215, 248). Although increased O_2 availability in this instance does not appear to alter $\tau_p \dot{V}\text{O}_2$, it is possible that the primary and slow component amplitudes are sensitive to muscle O_2 delivery.

Interestingly, Jones et al. (385) reported differential effects of prior heavy exercise according to body position which in itself may impact the muscle blood flow and O_2 -delivery conditions. During upright cycle exercise, prior heavy exercise did not alter τ_p (from ~29 to 28 s) but reduced the $\dot{V}\text{O}_{2\text{sc}}$ amplitude. However, during supine exercise where the kinetics are relatively slow in the control condition, prior heavy exercise reduced τ_p (from ~38 to 24 s) but without altering the $\dot{V}\text{O}_{2\text{sc}}$ amplitude. Koppo and Bouckaert (440) reported similar effects during arm cranking according to whether the arms were positioned below or above the level of the heart. These results highlight the importance of the initial conditions with regard to the adequacy of O_2 availability on the effects of prior exercise.

Increased activity of mitochondrial enzymes and/or availability of metabolic substrate

It has been proposed that the pyruvate dehydrogenase complex (PDC) constitutes a functional stenosis to substrate flux and is, therefore, a key component of the metabolic inertia that determines the $\dot{V}\text{O}_2$ kinetics in the transient phase of exercise (289, 290). Campbell-O’Sullivan et al. (114) reported that a 10-min cycling exercise at 55% $\dot{V}\text{O}_{2\text{max}}$ resulted in a stockpiling of acetyl groups prior to the onset of a second exercise bout. Since these authors observed a “speeding” of the $\dot{V}\text{O}_2$ response during that second exercise bout, they proposed that a lag in the activation of the PDC at the onset of exercise might prevent adequate acetyl group flux into the tricarboxylic acid cycle, and that the performance of prior exercise might overcome this limitation by enhancing metabolic substrate availability. However, studies that have measured both muscle metabolites and muscle $\dot{V}\text{O}_2$ kinetics in isolated dog gastrocnemius preparations (279) and in humans (30) found that DCA administration increased PDC activation but did not impact $\tau_p \dot{V}\text{O}_2$. This indicates either that the effects of PDC activation on muscle $\dot{V}\text{O}_2$ might be too small to be measurable, or that acetyl group availability is not a significant limitation to the acceleration of oxidative metabolism in the transition to a higher metabolic rate. Rossiter et al. (643) observed that DCA did not alter either the $\tau_p \dot{V}\text{O}_2$ or [PCr] during heavy exercise, but, rather, reduced the amplitude of the primary $\dot{V}\text{O}_2$ (and [PCr]) response. These responses are quite unlike those observed following prior heavy exercise, and it is therefore unlikely that increased mitochondrial substrate provision is responsible for the effect of prior heavy exercise.

Motor unit recruitment

Surface EMG evaluation of muscle activation (185, 186) paired with pulmonary $\dot{V}\text{O}_2$ measurements have proved insightful for addressing the mechanistic bases for the $\dot{V}\text{O}_{2\text{sc}}$ and the concept that the recruitment of additional motor units is responsible for the emergence of the $\dot{V}\text{O}_{2\text{sc}}$ during heavy exercise is well-established (106, 570, 588, 666, 686, 768; see Section *Slow Component of $\dot{V}\text{O}_2$ Kinetics: Mechanistic Bases*). Accordingly, the fact that the $\dot{V}\text{O}_{2\text{sc}}$ is reduced by prior heavy exercise may suggest that there have been alterations either in the motor unit recruitment pattern or alternatively in the metabolic characteristics of the recruited fiber population. In compliance with this notion, both the primary $\dot{V}\text{O}_2$ amplitude and the leg muscle iEMG are increased in the second of two exercise bouts, and these increases appear proportional to one another (106). Whereas other studies may not have detected significant changes in leg muscle EMG after priming exercise (675, 725), their data indicate a trend for higher iEMG values in the second heavy-exercise bout. Conclusions from these studies must therefore be tempered in light of the limited sensitivity of surface EMG to motor unit recruitment changes during cycle ergometry.

That prior exercise alters $\dot{V}\text{O}_2$ kinetics through a combination of the above-named effects is entirely plausible (391). Such an argument has been posited by Gurd et al. (296) who suggest that the faster $\dot{V}\text{O}_2$ kinetics they observe following prior exercise is a consequence of both increased muscle O_2 delivery and increased O_2 utilization due to the elevated activity of key rate-limiting enzymes. DiMenna et al. (201, 202) examined the interaction of prior exercise and pedal rate on $\dot{V}\text{O}_2$ kinetics. Intriguingly, when priming was performed at a low pedal rate (35 rpm) the primary $\dot{V}\text{O}_2$ kinetics was not altered, whereas when priming was performed at a high pedal rate (115 rpm) $\tau_p \dot{V}\text{O}_2$ was speeded irrespective of the pedal rate used in the criterion bout. NIRS indices of muscle oxygenation were higher following priming in all conditions but faster $\dot{V}\text{O}_2$ kinetics was only evident when estimated muscle fractional O_2 extraction was enhanced. The authors concluded that use of a high pedal rate can speed $\dot{V}\text{O}_2$ kinetics during subsequent high-intensity exercise through specific priming effects on type II fibers.

The implications of the effects of priming exercise on sport or exercise performance, though seemingly obvious, have been little explored. Koppo and Bouckaert (439) showed no change in the time to exhaustion at 90% $\dot{V}\text{O}_2$ peak following moderate or heavy exercise, whereas Jones et al. (399) showed significant increases in cycling time at 100%, 110%, and 120% $\dot{V}\text{O}_2$ peak following 6 min of heavy exercise and 10-min recovery. In a comprehensive recent study, Bailey et al. (25) manipulated both the intensity of the priming exercise bout and the subsequent recovery duration. The results showed that prior high-intensity exercise could appreciably enhance exercise tolerance (15%-30% increase in time-to-exhaustion) if coupled with appropriate recovery duration. This is an important practical application of $\dot{V}\text{O}_2$ kinetics

that is significantly impacting on the way athletes prepare for competition.

Influence of muscle fiber type and motor unit recruitment on $\dot{V}O_2$ kinetics

Human skeletal muscle comprises muscle cells (fibers) with distinct metabolic properties which are thought to be recruited in an orderly hierarchy with smaller low-threshold fibers being recruited before larger high-threshold fibers as force requirement increases (325–327). Moreover, during sustained exercise at the same constant work rate, there may be alterations in fiber recruitment as “fresh” fibers replace “fatigued” fibers (737, 738). It is also evident that higher-order fibers (i.e., type II) contribute more importantly to force production at higher contraction frequencies (e.g., 62).

Appreciating the well-known distinctions in energy metabolism and efficiency in the different muscle fiber types, it has been suggested that alterations in muscle fiber recruitment might, at least in part, be responsible for the development of the $\dot{V}O_{2\text{sc}}$ at work rates above the LT, (588, 768; see Section *Slow Component of $\dot{V}O_2$ Kinetics: Mechanistic Bases* for a detailed analysis of the role of fiber recruitment in the $\dot{V}O_{2\text{sc}}$). Differences in efficiency (in terms of differences in the ATP cost of force production and/or the O₂ cost of ATP resynthesis) or in $\tau\dot{V}O_2$ following the onset of contractions in fibers of different “types,” might also impact upon the muscle (and pulmonary) $\dot{V}O_2$ response (787). In reality, however, linking directly differences and/or changes in fiber recruitment profiles at higher work rates with the altered $\dot{V}O_2$ kinetics observed at these higher work rates, has proven challenging.

An array of empirical approaches has been exploited to explore whether a relationship does exist between muscle fiber type and/or fiber recruitment and the parameters of the pulmonary $\dot{V}O_2$ response to ramp and square-wave exercise. Amongst these are assessments of:

- the temporal relationship between $\dot{V}O_{2\text{sc}}$ development and alterations of neuromuscular activation as assessed using electromyography (EMG) or magnetic resonance imaging (95, 106, 261, 480, 570, 618, 666, 675, 676; see Section *Slow Component of $\dot{V}O_2$ Kinetics: Mechanistic Bases*);
- differences in $\dot{V}O_2$ kinetics amongst individuals displaying contrasting muscle fiber type distributions (Fig. 27, references 39, 40, 387, 492, 567, 616);
- the effects of manipulating substrate availability to alter recruitment patterns (by means of exercise/dietary regimes designed specifically to deplete target muscle fiber pools of their glycogen content) on $\dot{V}O_2$ kinetics (98, 124, 458, 550, 571);
- the effects of manipulations of movement frequency/ muscle contraction velocity (to modify fiber recruitment pat-

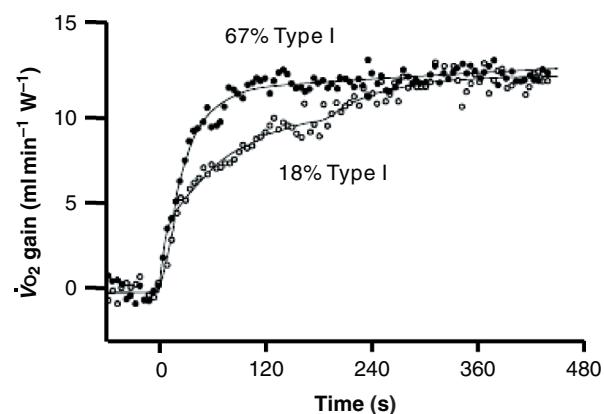


Figure 27 $\dot{V}O_2$ kinetics following onset of heavy-intensity cycle exercise in subjects with a high proportion of type I (solid circles) and type II (hollow circles) in their quadriceps muscles. Reproduced, with permission, from Barstow et al. (39).

terns) on $\dot{V}O_2$ kinetics (Fig. 28, references 39, 201, 202, 352, 387, 617).

These essentially indirect approaches each have their own inherent weaknesses. Paramount among these are: (i) establishment of relationships between muscle fiber-type distribution, *per se*, and $\dot{V}O_2$ kinetics presumes that a small needle biopsy can provide a representative sample of the muscle fiber-type proportions across the entire muscle mass engaged during exercise. (ii) The muscle fibers are recruited in these same proportions during exercise. While the former assumption may be reasonable, the latter is almost certainly not. Noise, inherent in the quantification of both pulmonary $\dot{V}O_2$ and EMG, makes it difficult to resolve any relationship

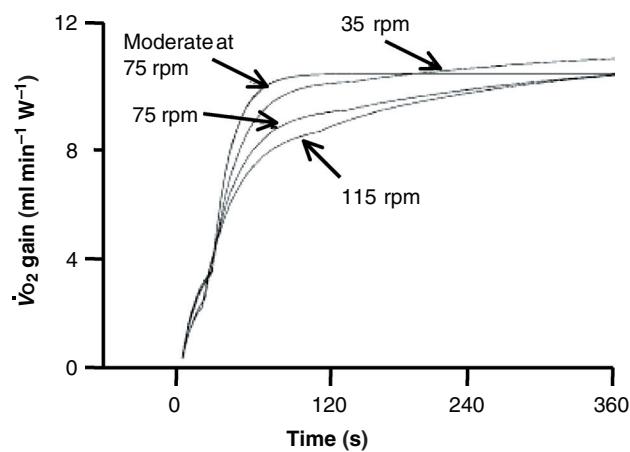


Figure 28 Schematic illustration of $\dot{V}O_2$ kinetics (expressed as $\dot{V}O_2$ per Watt, i.e., gain, G) following onset of heavy-intensity exercise at pedal rates of 35, 75, and 115 rpm. Note the progressive fall in primary component gain (G_p) and increased $\dot{V}O_2$ slow component with faster speeds expected to recruit more type II fibers (compare with Fig. 27). Moderate exercise at 75 rpm is shown for comparison. Reproduced, with permission, from Pringle et al. (617).

which may exist between these two variables. This situation is exacerbated because muscle fiber recruitment varies across work rates, time, and different muscles, as well as with fatigue, and in different exercise modes. Whereas interventions such as muscle contraction frequency manipulation (e.g., by altering pedal rate) and selective fiber glycogen depletion regimens should, in theory, produce predictably altered muscle fiber recruitment patterns, this is challenging to confirm experimentally. It is also pertinent that quantitative changes in muscle $\dot{V}O_2$ cannot be estimated precisely from pulmonary $\dot{V}O_2$, in part, because the $\dot{V}O_2$ associated with baseline metabolic processes is undoubtedly altered upon the transition to exercise (412, 704). Accordingly, statements relating fiber recruitment to altered $\dot{V}O_2$ kinetics between low and higher work must be made with caution.

Recruitment of type II muscle fibers might impact not only efficiency (see Section *Slow Component of $\dot{V}O_2$ Kinetics: Mechanistic Bases*), but also muscle $\tau\dot{V}O_2$ following exercise onset. For instance, mouse soleus $\tau\dot{V}O_2$ (predominantly type I and IIA fibers; ~ 36 s) is appreciably faster than that of the extensor digitorum longus muscle (type IIA and IIX fibers; ~ 138 s) (168). This likely reflects the greater oxidative enzyme activity in type I muscle fibers and/or the lower PCr concentration and faster PCr kinetics in type I compared to type II muscle fibers (698). If the mouse represents a suitable analog of human muscle and type II fibers comprise a substantial proportion of total fibers recruited upon initiation of heavy exercise, this would be expected to slow the primary $\dot{V}O_2$ response in comparison to moderate exercise that recruited solely type I fibers (787). An alternative scenario might be that type II fibers are “progressively” recruited as heavy exercise proceeds; the slower kinetics in these fibers would then be superimposed on the primary response and account for the “slow” continued rise in $\dot{V}O_2$ with time (see also Section *Integration of Dynamic Responses in the Pathway for O_2*). This scenario has been schematized by Wilkerson and Jones (787, Fig. 29).

Muscle fiber type and $\dot{V}O_2$ kinetics

In the first study of its kind, Barstow et al. (39) investigated the relationship between muscle fiber type and $\dot{V}O_2$ kinetics in subjects of heterogeneous fitness. During 8 min of heavy/severe exercise (50% Δ GET- $\dot{V}O_2$ max, i.e., 50% Δ) the % type I muscle fiber composition of the quadriceps correlated with the relative contribution of the $\dot{V}O_{2sc}$ to end-exercise $\dot{V}O_2$ (Fig. 21). No difference in G of the $\dot{V}O_2$ response at end exercise was apparent. However, the greater $\dot{V}O_{2sc}$ amplitude in subjects having low % type I muscle fibers was striking (Fig. 27) and implied that end exercise $\dot{V}O_2$ might have been higher in these subjects if the exercise duration had been extended. Interestingly, in that study the % type I muscle fibers correlated significantly with the G of the primary component $\dot{V}O_2$ response (G_p ; $r = 0.78$ at 60 rev min^{-1} ; $P < 0.01$). Unfortunately, given the positive relationship between aerobic

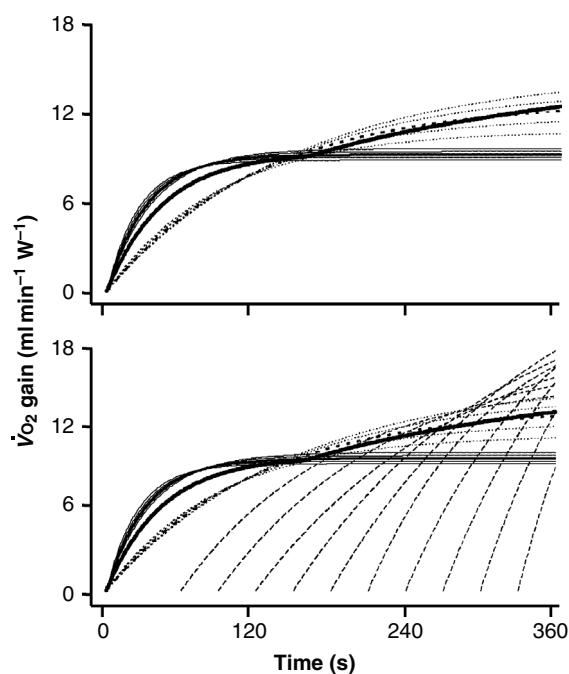


Figure 29 Conceptual model exploring recruitment of muscle fiber populations with varying metabolic characteristics on the $\dot{V}O_2$ response to heavy ($>$ gas exchange threshold, GET, but $<$ critical power, CP, top) and severe (i.e., $>$ CP, bottom) exercise. Solid lines denote responses of muscle fibers having relatively fast kinetics and high “efficiency” (low gain, G), and dashed lines those fibers with comparatively slow kinetics and high G . These two disparate fiber populations are notionally equivalent to type I and type II fibers, respectively. The overall $\dot{V}O_2$ response is given by the bolded solid line. Note the slow component that eventually stabilizes for heavy exercise (top) but not for severe exercise where $\dot{V}O_2$ projects toward $\dot{V}O_{2\max}$ (bottom). Hypothetically, these disparate behaviors might be explained by severe exercise mandating a progressive recruitment of additional higher-order fibers (which is not seen for heavy exercise): Though, as discussed in the text, this is not a requirement. Redrawn, with permission, from Wilkerson and Jones (787).

fitness (as $\dot{V}O_{2\max}$) and % type I muscle fibers, the possibility that differences in fitness, *per se*, also influenced the results cannot be excluded.

Subsequently, Pringle et al. (616) demonstrated that quadriceps % type I fibers was correlated with the relative amplitude of the $\dot{V}O_{2sc}$ (and G_p) during both heavy and severe cycle exercise. Pringle et al. (616) additionally reported that % type I fibers correlated negatively with the $\tau_p \dot{V}O_2$ during heavy exercise. This is consistent with the observation that the $\dot{V}O_2$ kinetics in predominantly type II mouse muscle is appreciably slower than that for predominantly type I muscle (168). Similar to Barstow et al. (39), the data of Pringle et al. (616) demonstrate clearly that a subjects’ muscle fiber type has the potential to influence $\dot{V}O_2$ kinetics. However, given the inherent measurement error in both the dependent and independent variables, large subject sample sizes are necessary to investigate the influence of muscle fiber type on $\dot{V}O_2$ kinetics. Figure 21, combines the data from three studies (references 39, 124, 616 making a total of 35 subjects) to better

elucidate the relationship between muscle fiber type and the amplitude of the $\dot{V}O_2sc$ relative to the end-exercise $\dot{V}O_2$.

Interventions designed to modify fiber recruitment

Pedal rate

The proportional contribution of type II fibers to force production is enhanced at high compared to low pedal rates (62, 63, 499). Consequently, at the same relative exercise intensity, manipulation of pedal rate has been used to explore the relationship between alterations of type II fiber recruitment and $\dot{V}O_2$ kinetics. The results of such studies have proven insightful despite potential complications arising from the varying proportional recruitment of different muscles at higher pedal rates and of changes in efficiency of the principal fiber types at higher forces and contraction velocities.

For heavy intensity constant work rate exercise at four different pedal rates (45, 60, 75, and 90 rev min^{-1}) there is no significant difference in the relative contribution of the $\dot{V}O_2sc$ to the total increase in $\dot{V}O_2$ above baseline across the pedal rates (16%–22%) (39). Pringle et al. (617) extended the range of pedal rates (35, 75, and 115 rev min^{-1}) to amplify differences in the effect of fiber recruitment on $\dot{V}O_2$ kinetics. At higher pedal rates G_p was reduced whereas the absolute and relative amplitude of $\dot{V}O_2sc$ increased, normalizing the total end-exercise G across pedal rates. Reduced peak power output (6-s maximal cycle ergometer sprint) 10 s after the criterion test supported that type II fiber recruitment was indeed enhanced at the highest pedal rate (115 rev min^{-1}) compared to 35 rev min^{-1} and therefore that greater fatigue of this fiber population was associated with a greater $\dot{V}O_2sc$ amplitude.

Glycogen depletion/prior exercise

Prior exercise and/or dietary regimes constitute additional ways in which muscle fiber recruitment during exercise might be modified. For example, depleting type I muscle fibers of their glycogen content (i.e., glycogen would be the principal substrate used during heavy exercise) would be hypothesized to result in greater fatigue of type I fibers and thus increase recruitment of type II muscle fibers, and *vice versa*.

An exercise protocol designed to deplete type I fibers preferentially, elevated baseline and high-intensity exercise $\dot{V}O_2$ by ~100 to 200 ml min^{-1} , but there were no significant differences in the primary or slow component amplitudes or τ_p (98, 571). Moreover, iEMG or MPF were unchanged (571). The data of Perrey et al. (571) and Bouckaert et al. (98) might be interpreted to indicate that alterations in muscle fiber recruitment caused by prior fatiguing exercise do not influence $\dot{V}O_2$ kinetics. However, to the extent that EMG data can be used to infer changes in motor unit recruitment, the data of Perrey et al. (571) suggest that no changes in fiber recruitment occurred. Moreover, Bouckaert et al. (98) argued that glycogen depletion of low-order muscle fibers might not be expected to

alter fiber recruitment because these fibers could simply increase their use of free fatty acids as a metabolic substrate. In this respect, selective glycogen depletion of the type II muscle fiber population may be more likely to result in a change in fiber recruitment because type II fibers are not well suited to using fat as a metabolic substrate. Accordingly, Carter et al. (124) used repeated bouts of moderate and heavy exercise preceded by no prior exercise (control), 3 h of cycling at 30% $\dot{V}O_{2max}$ (to deplete type I muscle fibers), and 10 × 1 min bouts of high-intensity exercise at 120% $\dot{V}O_{2max}$ separated by 5-min recovery (to deplete type II fibers). Neither of the glycogen depletion regimens had any effect on $\dot{V}O_2$ kinetics during moderate exercise and, consistent with Bouckaert et al. (98), glycogen depletion of the type I fibers did not affect $\dot{V}O_2$ kinetics during heavy exercise. However, type II fiber depletion increased G_p and reduced the $\dot{V}O_2sc$. The increase in G_p and the reduced $\dot{V}O_2sc$ in a condition where the recruitment of type II muscle fibers was presumably reduced is consistent with the responses observed in subjects with a high proportion of type I muscle fibers (39, 616) and with the alteration in $\dot{V}O_2$ kinetics when muscle fiber recruitment is biased with extreme pedal rates (617). In perhaps the most convincing study involving glycogen depletion to date, Krstrup et al. (458) reported that glycogen depletion of type I fibers increased type II fiber recruitment (measured by biopsy) and generated a $\dot{V}O_2sc$ during ostensibly moderate-intensity exercise. These results strongly suggest that type II fiber recruitment elevates the O_2 cost of exercise and has an important role in the development of the $\dot{V}O_2sc$ (see Section *Slow Component of $\dot{V}O_2$ Kinetics: Mechanistic Bases*).

In line with the glycogen depletion studies above, when type I fiber activation is blocked pharmacologically, the greater activation of type II fibers increases muscle ATP turnover and reduces mechanical efficiency (456). Moreover, muscle $\tau_p \dot{V}O_2$ becomes slowed indicating that the recruitment of type II fibers can impact both the primary and slow component $\dot{V}O_2$ responses to exercise. When high-intensity exercise is initiated from a baseline of moderate-intensity exercise, the $\dot{V}O_2$ kinetics is also slowed and the overall response G is increased (787), and this is reflected in the intramuscular [PCr] profile (400). This response is consistent with what would be expected if the moderate-to-heavy exercise transition required the recruitment of a discrete pool of fibers positioned higher in the recruitment hierarchy. Such slower primary $\dot{V}O_2$ kinetics is not affected by prior exercise (204) supporting a role for fiber recruitment profile rather than O_2 delivery (200, 203).

Conclusions

There is substantial evidence from cross-sectional (i.e., % fiber-type distribution) and manipulative (i.e., pedal rate, glycogen depletion, neural blockade, and baseline modulation) investigations that the intrinsic fiber-type composition of exercising muscle(s) and modulation of fiber-type recruitment patterns can substantially impact $\dot{V}O_2$ kinetics. Thus,

individuals with greater quadriceps type I muscle fiber composition evince a greater G_p and decreased τ_p of the $\dot{V}O_2$ response. Experimental manipulations (i.e., faster pedal rates) designed to recruit more type II fibers reduce the primary component gain whilst increasing the $\dot{V}O_{2sc}$. In contrast, preferential glycogen depletion of type II fibers (biasing recruitment of type I fibers) increases the amplitude of the $\dot{V}O_2$ primary component and delays emergence of a diminished $\dot{V}O_{2sc}$: a response akin to that seen in subjects with greater quadriceps type I fiber composition. Preferentially reducing type I fiber contribution (glycogen depletion or neural blockade) can elevate $\dot{V}O_2$ during moderate intensity exercise creating a $\dot{V}O_{2sc}$ -like effect. Finally, initiating heavy exercise from a moderate exercise baseline unveils effectively the slowed $\dot{V}O_2$ kinetics and increased overall G expected from recruitment of higher-order (type II) fibers.

Maturation and Aging

The human lifespan encompasses several sequential stages consisting of rapid growth, adolescence and maturation, and adult life leading into senescence and, finally, death. Along this pathway the sentinel organ systems of the O_2 -transport pathway—cardiopulmonary, vascular, and muscular—each increase their capacity, peak and then undergo a progressive reduction in functional integrity. These processes may occur at varying rates within the different systems and, thus, the control of oxidative function may change across the lifespan. Much is known about the effects of maturation and advancing age on $\dot{V}O_{2max}$ (155, 208, 242, 463, 513, 514, 659). However, one common theme throughout this review is that humans rarely exercise at $\dot{V}O_{2max}$ and this is even truer for children and adults of advanced age. Unless constrained by disease or circumstance individuals in these age groups undergo myriad metabolic transitions daily to submaximal $\dot{V}O_2$'s (Fig. 1) and the ability to preserve the intramyocyte milieu and exercise capacity will be dependent, in part, on the integrity of O_2 transport and $\dot{V}O_2$ kinetics. Indeed, with the average life expectancy in developed countries ~ 80 years it is worth exploring the hypothesis that maintaining our quality of life into old age may be contingent on retaining some minimal speed of $\dot{V}O_2$ kinetics.

Children

In children, the lower work capacity, and therefore range of metabolic rates achievable, coupled with their generally more erratic breathing pattern reduces the signal-to-noise ratio of their pulmonary gas exchange kinetics. Whereas confidence in the parameters of the $\dot{V}O_2$ kinetics in children can be improved by multiple exercise transitions (465) these issues and lack of rigorous adherence to specific work rate domains is problematic when interpreting the extant literature. The available data for prepubertal children indicates a higher G (decreased work efficiency) and a faster τ_p for moderate and heavy/severe in-

tensity domain exercise than seen in their adult counterparts (review 232).

Moderate intensity exercise

Phase I (cardiodynamic component) Compared with adults, the \dot{Q} , and therefore pulmonary blood flow, increases less as a function of exercising $\dot{V}O_2$ in children consequent to a smaller stroke volume and forces greater reliance on fractional O_2 extraction (160). Because Phase I (cardiodynamic component) is driven by the almost immediate increase of pulmonary blood flow it might be expected that this would be proportionally smaller in children. However, the available data do not support this contention. Specifically, Cooper et al. (160) found no difference in the magnitude of Phase I in 7- to 10- versus 15- to 18-year-old whereas Springer et al. (701) noted that mass-specific Phase I $\dot{V}O_2$ represented a greater percentage of the steady-state $\dot{V}O_2$ response in 18- to 33-year-old adults than 6- to 10-year-old children. Moreover, there is evidence that, unlike the situation in adults, in children the Phase I duration is not reduced at higher metabolic rates.

Primary component (Phase II) There is no apparent consensus regarding whether a systematic difference in the primary $\dot{V}O_2$ kinetics exists between children and adults. For instance, there are reports of no differences between children and adults (cycling, 160, 324, 701, 805; treadmill running, 791) and faster, (7, 233, 487) primary $\dot{V}O_2$ kinetics in children. In a superbly designed investigation, Fawkner and colleagues (233) demonstrated unequivocally that primary component kinetics were faster in girls than women (21 vs. 26 s) and boys than men (19 vs. 28 s). Despite the boys having a higher $\dot{V}O_{2max}$ than the girls, there was no discernible sexual $\dot{V}O_2$ kinetics dimorphism. Moreover, in-and-of itself there does not appear to be any menstrual cycle variation in $\dot{V}O_2$ kinetics (Gurd et al. 299).

O_2 cost of exercise (gain, G) During cycling children may exhibit a 30% to 50% higher G than adults (Fig. 30, left panel, references 7, 701 but see also 324). Despite the concern regarding normalization procedures (see 758) Williams et al. (791) reported that, during walking or running, children had a substantially higher O_2 cost ($239 \pm 8 \text{ ml kg}^{-1}\text{km}^{-1}$) than adults ($168 \pm 3 \text{ ml kg}^{-1}\text{km}^{-1}$).

Heavy/severe intensity exercise Whereas CP for children lies in a similar average range as for adults (i.e., 73%-79% $\dot{V}O_{2max}$, references 231, 233, 610) investigations measuring $\dot{V}O_2$ kinetics in children have not generally distinguished between heavy and severe intensity exercise. This is a crucial point as the conclusions regarding children-adult differences may contrast markedly. Thus, the subsection below titled “*Severe exercise*” is reserved for studies where the work rate was situated unambiguously in this domain. As for moderate cycle ergometry exercise children espouse far faster primary $\dot{V}O_2$ kinetics than adults in the heavy intensity

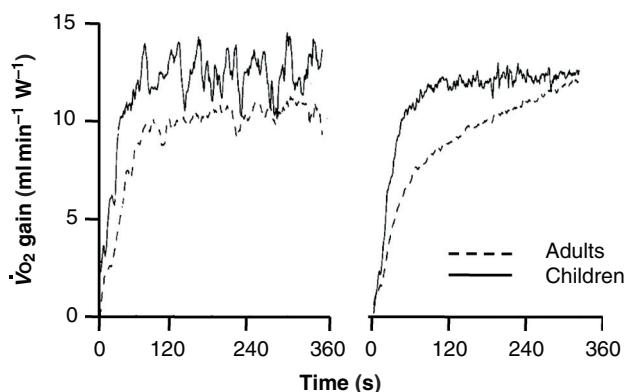


Figure 30 Group mean $\dot{V}O_2$ cost (expressed as $\text{ml O}_2 \text{ min}^{-1} \text{W}^{-1}$) for moderate- (left panel) and heavy/severe- (right panel) intensity exercise in children and adults. Note that for moderate-intensity exercise and in the first several minutes of heavy/severe-intensity exercise the O_2 cost or gain (G) is far greater in children. Also, for heavy/severe exercise there is a pronounced $\dot{V}O_2$ slow component in adults that appears largely absent in the children who exhibit a far greater primary component G . Adapted from Armon et al. (7), with permission.

domain (Fig. 30, right panel; reference 7). In children G_p is high and very similar to that seen during moderate intensity exercise (cycling, 7, 324; treadmill running, 791) and the $\dot{V}O_{2\text{sc}}$, where present ($\sim 25\%$ of instances), drastically reduced (7); such that the end-exercise $\dot{V}O_2 G$ may be no different for children and adults (Fig. 30, right panel ~ 360 s). However, for adults the end-exercise $\dot{V}O_2$ reflects a substantial $\dot{V}O_{2\text{sc}}$ that elevates G 20% or more above that seen in the moderate domain (compare right and left panels in Fig. 30). These responses described above were also found during treadmill exercise (791). Although the notion that blood lactate might be causative for the $\dot{V}O_{2\text{sc}}$ has been largely dismissed (357; review 258; see Section *Slow Component of $\dot{V}O_2$ Kinetics: Mechanistic Bases*) the greater $\dot{V}O_{2\text{sc}}$ in adults was accompanied by a several-fold higher [blood lactate]. Mechanistically, the reduced [blood lactate] in children may result from the lower glycolytic enzyme capacity (221, 317) or possibly reflect that the faster $\dot{V}O_2$ kinetics relieve the requirement for substrate-level phosphorylation (e.g., 805).

Severe exercise Resolving $\dot{V}O_2$ kinetics parameters in the severe intensity domain becomes problematic when the achievable $\dot{V}O_2$ (i.e., $\dot{V}O_{2\text{max}}$) is less than that estimated for the work rate. In such instances, the process of estimating the $\dot{V}O_2$ requirement is contentious and the primary component parameters obtained differ substantially depending on the model (e.g., exponential vs. logarithmic) selected (review 367). Given this situation, and often methodological concerns (e.g., infrequency of data collection; every 15 s, reference 655, 30 s, references 487, 633) it is not surprising that the literature is ambiguous regarding whether $\dot{V}O_2$ kinetics for severe intensity exercise is faster (487, 633, 655) or not (324, 805) for children than adults. With respect to the $\dot{V}O_{2\text{sc}}$, which is absent or reduced in children in the heavy domain, the relative size of the $\dot{V}O_{2\text{sc}}$ was not different in children ver-

sus adults for severe-intensity exercise (considered to require 90% $\dot{V}O_{2\text{max}}$, reference 548). At least in adults, the bulk of the $\dot{V}O_{2\text{sc}}$ originates within the exercising limbs and muscles (606) and muscle metabolic status and fiber type recruitment profile are believed to be important (258, 456–459, 548, 589; see Section *Slow Component of $\dot{V}O_2$ Kinetics: Mechanistic Bases*). It is plausible that, in children, a relatively higher metabolic stress is necessary to recruit the appropriate fiber population or generate the required metabolic status before the $\dot{V}O_{2\text{sc}}$ becomes manifested.

In toto the mechanistic bases for the substantially different $\dot{V}O_2$ kinetics in children compared with their adult counterparts (i.e., faster $\dot{V}O_2$ kinetics, increased G_p , reduced $\dot{V}O_{2\text{sc}}$ for heavy intensity exercise) may originate in the fiber type composition of the exercising muscles. Specifically, within the adult population there is a range of $\dot{V}O_2$ kinetics responses: individuals possessing a proportionally greater type I fiber profile versus those with more type II fibers have a $\dot{V}O_2$ kinetics profile that tends toward that displayed by children (cf. Figs. 27 and 30, right panel, references 39, 616). However, as children are not thought to undergo substantial fiber type changes during puberty (review 28) the critical changes may be metabolic in nature. Accordingly, the lower peak blood [lactate] and “anaerobic” power in children (222–224, 230, 374, 486, 560, 652; though see 574 for a dissenting opinion) may be the consequence of enhanced oxidative enzyme activities (317) and/or reduced glycolytic enzyme activities (222). Whereas there is an understandable paucity of these data in humans it is pertinent that, from birth to puberty (2 months), rats undergo a ~ 17 -fold increase in phosphofructokinase (PFK) activity accompanied by an upregulation of the muscle-type PFK subunit and downregulation of the cardiac type subunit (212, review 44, 804). Moreover, MRS investigations have found that, compared with adults, children have a reduced gastrocnemius Pi/PCr increase and less pH perturbation during fatiguing calf exercise (804). Whereas the veracity of these results has been questioned (see 574), in part, because the modest mass of the gastrocnemius may have biased sampling toward the underlying soleus muscle in the children versus adults (804), Petersen and colleagues’ (574) data showed a strong tendency for higher Pi/PCr ratios in calf muscles of post- versus prepubertal female swimmers amidst substantial variability. In conclusion, the available evidence supports a greater bias toward oxidative versus glycolytic metabolism in children compared to adults which helps explain the faster $\dot{V}O_2$ kinetics and reduced $\dot{V}O_{2\text{sc}}$ in children despite their potential for lower muscle O_2 delivery (resulting from lower \dot{Q}) at a given work rate and $\dot{V}O_2$.

Aged adults

As was the case for children, measurement of $\dot{V}O_2$ kinetics in the aged and senescent adult population presents substantial challenges which include: (i) selection of individuals free from chronic cardiorespiratory disease and/or medications that may impact the pulmonary gas exchange response

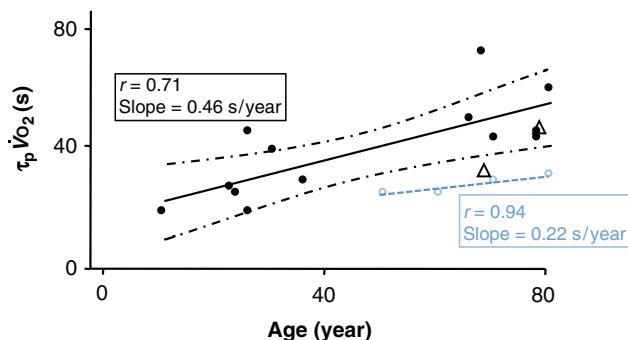


Figure 31 Effects of maturation and aging on primary component $\dot{V}O_2$ kinetics (τ_p) in healthy males and females. Solid symbols, black regression curve with 95% confidence interval (dashed lines) denote mean data from references 76, 145, 233, 542, 674, and 769 for untrained subjects. Open circles and blue dashed regression curve are adapted, with permission, from Berger et al. (80) for endurance-trained track athletes. Notice that, unlike for $\dot{V}O_{2\text{max}}$ (14, 513), the age-related decline in $\dot{V}O_2$ kinetics (i.e., slower τ_p) appears to be almost completely curtailed by endurance training, at least in some individuals. Open triangles are from a rare longitudinal study where six males and one female were tested 9 years apart (76). For these individuals, despite the absence of overt disease, τ_p slows at a rate (i.e., 1.8 s/year) that was several-fold greater than that calculated from the other investigations.

to exercise. (ii) Reduced size of the metabolic transients resulting from compression of the exercise intensity domains. (iii) Wide variation in exercise and activity levels. (iv) Increased breath-to-breath variability. (v) Reduced motivation particularly for intense exercise. (vi) Increasingly conservative institutional human subjects review boards. Despite these challenges, there is excellent evidence that $\dot{V}O_2$ kinetics becomes increasingly slowed as adults age (Fig. 31, references 19, 20, 76, 143–146, 169, 179–181, 297, 298, 559, 674). This effect is likely the product of age-related structural and functional alterations in the O₂-transport pathway that alter the balance between exercising muscle(s) O₂ delivery and O₂ utilization: some of which may be secondary to reduced activity and aerobic fitness.

Aged or senescent individuals generally (208, 242, 463) but not always (513, 514) demonstrate an impaired ability to increase \dot{Q} during exercise. Thus, muscle blood flow can be reduced by decreased bulk flow and/or a preferential redistribution of that flow away from the more oxidative toward low oxidative, highly glycolytic muscle fiber types (379, 535). Muscle capillary density and capillary-to-fiber ratio as well as mitochondrial volume density and oxidative function may decline with age (human, 153, 154, 156). However, depending on the presence and extent of muscle fiber atrophy capillary density and the matching of capillary surface to oxidative potential may actually increase (rat, 333, 503). Notwithstanding the above, the lineal density of capillaries supporting RBC flux is decreased in aged muscles and the ability to increase that flux during muscle contractions is compromised (rat, 161, 312, 649). Paramount among the mechanisms responsible for this compromised O₂ delivery is the reduced vasodilatory ability of arterioles within aged muscle(s) (66, 694). Reduc-

tion of the O₂-delivery-to- $\dot{V}O_2$ ratio across the rest-exercise transition (human, 179–181, 297, 298) causes $Pmvo_2$ in aged muscle, following the onset of contractions, to plummet temporarily far below than seen in healthy individuals (rat, 67). These microvascular alterations, combined with the blood flow redistribution described by Musch and colleagues (535), likely contribute to a reduced ability for aged individuals to elevate fractional whole-body arterial-venous O₂ extraction to the extent seen in their younger counterparts (513) and the ability for exercise training to reverse this effect (514).

Moderate intensity exercise Slow $\dot{V}O_2$ kinetics is almost ubiquitous in aged individuals performing moderate intensity large muscle mass exercise such as cycling, walking, or running (20, 76, 145, 146, 169, 179–181, 297, 523, 559, 674). Specifically, Phase I is prolonged by ~50% from the third to the seventh decade in men (523) and $\tau_p \dot{V}O_2$ averaged 50 to 70 s in untrained but otherwise healthy 59- to 78-year olds compared with ~30 s in young healthy populations (20, 674). Other forms of exercise that require a smaller muscle mass, for example calf muscle, may not evince this magnitude of age-related disparity, in part, because of the effects of daily activities sustained by the elderly. Thus, Chilibeck et al. (146) determined that, in aged individuals performing plantar flexion, $\dot{V}O_2$ kinetics was markedly faster than for conventional cycling. Moreover, MRS determination of PCr kinetics, which may be considered a close approximation of $\dot{V}O_2$ kinetics (640, 774), resolved no age-related slowing of PCr (and $\dot{V}O_2$) kinetics for small muscle groups that were engaged in daily activities such as walking (144, 417). These findings support that age-related reduced activity levels are an important component of the aging response for $\dot{V}O_2$ (and PCr) kinetics (508, 509) and that exercise training speeds $\dot{V}O_2$ kinetics in concert with improved cardiovascular and muscle function in older individuals (longitudinal studies, 76; cross-sectional studies, 82, 145, 196) sometimes to a greater extent than seen in their younger or less “kinetically compromised” compatriots (20, 82, 250). In agreement with this notion, Berger and colleagues (82) demonstrated that competitive endurance athletes maintained impressively fast $\dot{V}O_2$ kinetics (mean $\tau_p \dot{V}O_2$ 25–29 s) into their mid-80s. Thus, unlike sprint athletes whose $\dot{V}O_2$ kinetics was generally slower and slowed progressively more with advancing age, there was no discernible decline for the endurance athletes from their fifth to ninth decade (82).

Other than the evidence presented above for an aging-impaired muscle O₂ delivery there is support for and against the notion that advanced age moves the individual onto the O₂ supply-dependent arm of the relationship depicted in Figure 2. Thus, whereas in aged individuals: (i) a bout of prior heavy exercise speeds moderate domain $\dot{V}O_2$ kinetics (674) and (ii) exercise training speeds $\dot{V}O_2$ and HR kinetics in concert (19), it is also true that: (i) the faster $\dot{V}O_2$ kinetics resulting from a one-legged training program can be related to increased muscle oxidative enzyme activity rather than improved femoral

arterial blood flow (77) and (ii) inspired hyperoxia does not uniformly speed $\dot{V}O_2$ kinetics in aged individuals (76).

Heavy/severe intensity exercise As detailed elsewhere [see Section *Site(s) of Limitation of $\dot{V}O_2$ Kinetics: Oxygen Delivery Versus Cellular Respiration*], except possibly for horses (see Section *Comparative Physiology of $\dot{V}O_2$ Dynamics*) the compelling weight of evidence suggests that, for young individuals, the primary component $\dot{V}O_2$ kinetics is not slowed for heavy compared with moderate-intensity exercise. However, whether the already very slow primary component kinetics becomes even more sluggish in the higher exercise intensity domains in aged individuals, remains to be resolved unequivocally. What is evident is that, given the reduced $\dot{V}O_{2\max}$ of the aged, the “excess” O_2 cost obligated by the $\dot{V}O_{2\text{sc}}$ may be of even greater importance for limiting exercise tolerance in this population. The potential for this greater limitation arises from the $\dot{V}O_{2\text{sc}}$ being manifested at lower absolute metabolic rates and thus, for the aged, may be incurred during tasks performed within the moderate domain (i.e., no $\dot{V}O_{2\text{sc}}$) in their younger days. Given the putative role of less-efficient type II muscle fibers in the $\dot{V}O_{2\text{sc}}$ and the preferential loss of these fibers and motor units with advancing age it might be expected that older individuals would exhibit a reduced $\dot{V}O_{2\text{sc}}$ (75). Whereas Bell et al. (75) and also Sabapathy et al. (653) found that heavy/severe exercise did indeed elicit a $\dot{V}O_{2\text{sc}}$ that decreased in magnitude as a function of age, when expressed as $\Delta\dot{V}O_2/\Delta\text{work rate}$ or relative to absolute $\dot{V}O_2$ it was no different from that in young adults. This observation supports the view that compression of the work rate domains with aging such that GET and CP may be 70% and 88% $\dot{V}O_{2\max}$, respectively, in old versus 50% and 79% $\dot{V}O_{2\max}$ in young individuals (75, 541) reduces the available scope for $\dot{V}O_{2\text{sc}}$ development with advanced age.

In conclusion, based on cross-sectional and a modicum of longitudinal data, the speed of the primary component $\dot{V}O_2$ kinetics slows progressively from childhood to senescence. There is emerging evidence that, unlike $\dot{V}O_{2\max}$, this decline in adulthood can be curtailed or possibly even prevented by rigorous endurance (but not sprint) training (81). For post-menopausal females the age-related slowing of $\dot{V}O_2$ kinetics does not appear to be impacted by hormone-replacement therapy (705). There is little evidence for a pronounced $\dot{V}O_{2\text{sc}}$ response in prepubertal children and the absolute size of the $\dot{V}O_{2\text{sc}}$ peaks in young adults and decreases as a function of reduced work capacity with further advancing age (75). Thus, in adulthood, as distinct from childhood and advanced age, there is the potential to increase exercise tolerance by both improvement of the speed of $\dot{V}O_2$ kinetics and reduction or elimination of the $\dot{V}O_{2\text{sc}}$.

Disease States

Because the $\dot{V}O_2$ kinetics profile assesses the integrated capacity of the O_2 transport pathway its measurement has a

Table 1 Chronic Diseases or Conditions Assessed using $\dot{V}O_2$ Kinetics Measurement

Disease/condition	Exemplar reference(s)
Atrial fibrillation	(478)
Chronic fatigue syndrome	(375)
Chronic/congestive heart failure/postmyocardial infarction, CHF	(436) (332, 670, 688)
Chronic obstructive pulmonary disease, COPD, and emphysema	(556, 620, 699)
Congenital heart disease	(518)
Coronary artery disease	(2)
Cyanotic heart disease	(689)
Cystic fibrosis	(460)
Diabetes (noninsulin dependent, type II)	(101, 623, 789)
Dilated cardiomyopathy	(176)
Heart transplant recipients	(96, 137, 282, 466)
Heart and lung transplant recipients	(276)
HIV	(713)
Mitral stenosis	(475, 519)
McArdle's disease	(286)
Metabolic myopathies	(286)
Obesity	(661)
Pulmonary arterial hypertension	(34)
Peripheral vascular disease	(51-54)
Primary pulmonary hypertension	(631)
Prolonged immobility	(159)
Renal disease	(446, 447)
Spinal cord injury	(45, 46, 249)

broad utility for investigating the predilections of many different disease conditions (Table 1). Importantly, determination of $\dot{V}O_2$ kinetics, unlike $\dot{V}O_{2\max}$, does not require that the subject perform intense exercise which may well be contraindicated for their condition. Moreover, as the absolute $\dot{V}O_2$ at a given work rate may be unchanged in disease, steady-state measurements may be of little utility whereas measurement of $\dot{V}O_2$ kinetics may have great prognostic value (superior to $\dot{V}O_2$ max), for example in CHF patients (670, 749). It is also pertinent that, notwithstanding the complexity of chronic diseases in particular, investigation of the effects of specific classes of pathology can help unveil the mechanistic bases for $\dot{V}O_2$ kinetics control and test predictions based upon theoretical models (e.g., 41). Within the context of the O_2 transport pathway, four broad classes of conditions will be considered here: those that impair primarily the ventilatory, cardiovascular, and muscle blood flow responses to exercise, and muscle metabolic myopathies. In addition, the prevalence of obesity within the developed world argues for its inclusion herein. It is also recognized that such conditions will, either secondary to the primary dysfunction or via reduced activity levels, down-regulate muscle vascular control as well as muscle structure and oxidative enzyme capacity [e.g., chronic obstructive pulmonary disease (COPD), emphysema, 126, 130, 493, 504; CHF, 194, 197-199, 210]. If sufficiently severe, the net effect of a reduction in muscle O_2 availability will be to shift the $\dot{V}O_2$ response leftward in Figure 2 into the O_2 -delivery-dependent

region of $\dot{V}O_2$ kinetics control where increased O₂ delivery speeds and decreased O₂ delivery further slows the response.

Before considering these different categories of dysfunction there are several major considerations that potentially confound interpretation of the available literature. These include: (a) *Lack of standardization of exercise intensity domains*. In severely affected patient populations where exercise remains feasible, the maximum work rate achievable may be reduced by as much as 80% to 90% of age-matched healthy individuals. Thus, although possessing a certain ecological validity (the $\dot{V}O_2$ cost of daily activities does not change in most disease conditions) any absolute work rate will constitute a far greater percentage of their maximum and may mean that the patient is performing heavy or severe compared with moderate exercise for the healthy counterpart. This effect will serve to slow the overall $\dot{V}O_2$ kinetics (i.e., primary + slow components) independent of the disease *per se* and is beautifully portrayed in the MRT analyses of Sietsema and colleagues (690) for subjects ranging in $\dot{V}O_{2\max}$ from ~30 to 70 ml min⁻¹ kg⁻¹ exercising across a broad range of absolute work rates. Whereas it is true that appropriate modeling procedures may remove the $\dot{V}O_2$ sc effect there may be alterations in Phase I and/or the primary component that confound rigorous characterization of the $\dot{V}O_2$ kinetics. (b) *Differences in absolute work rate*. Pursuant to point 1 above, the investigator may select different absolute work rates for the patients and healthy subjects such that each falls within a discrete exercise intensity domain. Often it is advisable to select a higher work rate within that domain to maximize the signal-to-noise ratio and therefore improve confidence in the model parameters extracted (465). Unfortunately, this practice confounds data interpretation by altering the proportional contribution of Phase I, the primary component and, for heavy and severe exercise, $\dot{V}O_2$ sc. For instance, at very light work rates, Phase I (cardiodynamic component) may constitute the entire $\dot{V}O_2$ response, or, in the extreme, even overshoot the subsequent steady-state $\dot{V}O_2$ (690). This will yield an overall very fast pulmonary $\dot{V}O_2$ kinetics that is not indicative of the muscle V_{O_2} response. Moreover, removal of Phase I as is routine in many studies may not be possible because there is little or no primary component to analyze. (c) *Interdependence of Phase I and primary component*. As discussed below and predicted by Barstow and colleagues (41), conditions such as CHF (520) and aging (523) that prolong Phase I, in so doing, accelerate pulmonary primary component $\dot{V}O_2$ kinetics. (d) *Emphysema may lead to a progressive increase in end expiratory lung volume*, which will act to increase alveolar O₂ stores and thus dissociate pulmonary from alveolar $\dot{V}O_2$ (542, 619).

Pulmonary diseases

Pulmonary diseases impact O₂ transport via arterial hypoxemia (803) and/or reduced pulmonary blood flow and therefore \dot{Q} . Thus, COPD, emphysema, chronic bronchitis, bronchial asthma, fibrotic lung disease, cystic fibrosis, alkapton spondylitis, pulmonary edema, alveolar proteinosis

as well as respiratory muscle and nerve disorders each may induce arterial hypoxemia (review 601, 749) which acts to slow $\dot{V}O_2$ kinetics (e.g., 217). Despite the fact that, at a given $\dot{V}O_2$, minute ventilation ($\dot{V}E$) and thus $\dot{V}E/\dot{V}O_2$ may be elevated, there may be profound ventilation-perfusion mismatch and increased dead space ventilation (V_D/V_T) resulting in inadequate alveolar ventilation ($\dot{V}A$) for effective CO₂ clearance such that alveolar and arterial CO₂ rise (130, 542, 741, 749). This effect reduces alveolar and arterial Po₂ and further impairs hemoglobin oxygenation by right-shifting the O₂ dissociation curve. In COPD patients, bronchodilator therapy speeds \dot{Q} and $\dot{V}O_2$ kinetics in the presence of improved contracting muscle oxygenation as judged by NIRS measurement of deoxy(Hb+Mb) and exercise performance (86). In addition, conditions such as pulmonary edema and alveolar proteinosis thicken the blood-gas barrier and decrease pulmonary O₂-diffusing capacity. Other diseases, for example, pulmonary emboli and idiopathic pulmonary hypertension act to decrease \dot{Q} and thus cardiovascular O₂ transport. Moreover, in ~20% of the adult population the foramen ovale is potentially patent (749) and therefore a sufficient increase of right atrial pressures consequent to pulmonary disease may produce right-to-left shunting resulting in reduced \dot{Q} and arterial hypoxemia. In recent years, it has become increasingly evident that, in addition to reduced muscle O₂ delivery consequent to arterial hypoxemia and sometimes impaired \dot{Q} , there may be a reduction in locomotory muscle oxidative capacity, for example, in emphysema/COPD (126, 493, 504). Decreased activity levels undoubtedly contribute to this downregulation of mitochondrial oxidative function in humans. However, experiments in emphysematous hamsters indicate that these changes are present even in the absence of altered locomotory activity (504) and that emphysema-induced elevations of reactive O₂ species may promote mitochondrial dysfunction (505). It is also pertinent that oxidative function in the diaphragm (600, 603) and possibly other respiratory muscles may improve simultaneously with declining function in the locomotor muscles (119). The degree to which this phenomenon might impact pulmonary $\dot{V}O_2$ kinetics is unknown.

For nonhypoxic pulmonary arterial hypertension (PAH) patients there is emerging evidence that the matching of muscle O₂ delivery-to- $\dot{V}O_2$ is impaired and this has been linked mechanistically to slowed pulmonary $\dot{V}O_2$ kinetics in these patients (34). Thus, in PAH it appears that vascular function is impaired to a greater degree than that of muscle oxidative processes. Akin to phosphorescence quenching in animal muscles, NIRS technology is becoming a standard for mechanistic assessment of skeletal muscle O₂ delivery-to- $\dot{V}O_2$ matching in health and disease (33).

Where pulmonary disease does not impair the cardiodynamic response to exercise and thus arterial hypoxemia is the principal impediment in the O₂ transport pathway Phase I $\dot{V}O_2$ kinetics would be expected to be relatively intact as for the patient in Figure 32 and as seen for healthy subjects breathing hypoxic gas mixtures (F_iO₂, 0.15, and 0.12, reference 217). However, for the overall population [forced expiratory

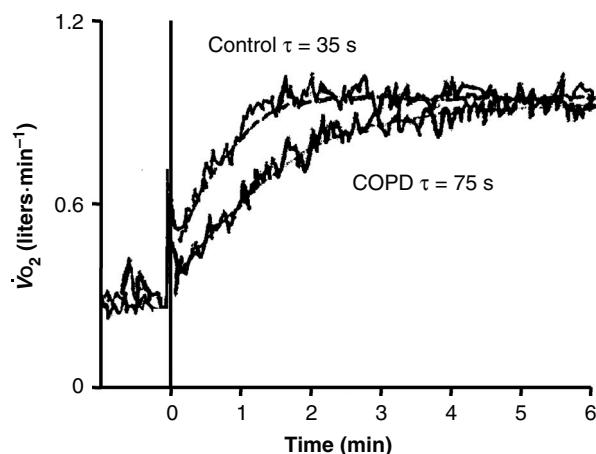


Figure 32 Marked slowing of $\dot{V}O_2$ kinetics in chronic obstructive pulmonary disease (COPD) following the onset of moderate intensity cycle exercise compared with age-matched control subjects. Drawn, with permission, from data of Nery et al. (542).

volume (FEV_1) <40% predicted, mean $Pao_2 \sim 70$ mmHg] studied by Nery and colleagues Phase I was significantly reduced (542). Regarding the primary component, and not surprisingly given the profound impact of pulmonary diseases on arterial oxygenation, primary component $\dot{V}O_2$ kinetics is markedly slowed (Fig. 32, references 542, 699). Depending, presumably, on the degree of underlying cardiovascular disease and possibly vascular effects of high PO_2 's in the lung and/or skeletal muscle, improvement in arterial oxygenation by raising the F_1O_2 to 0.3 to 0.5 may (556) or may not (695, 699) speed primary component $\dot{V}O_2$ kinetics towards, but not to, control values.

Cardiac dysfunction

As discussed in Section *Integration of Dynamic Responses in the Pathway for O₂*, in healthy individuals following exercise onset, \dot{Q} increases nearly instantaneously consequent to elevated venous return, cardiac inotropy, and accelerated HR. Within the four principal classes of cardiac dysfunction (i.e., cardiomyopathic, coronary artery occlusive, valvular insufficiency, and congenital), their potential to impair $\dot{V}O_2$ kinetics is dependent largely upon their impact on \dot{Q} . Thus, cardiac myopathies such as cyanotic congenital heart disease, for example, decrease or abolish the almost immediate increase in \dot{Q} with exercise and, in so doing, attenuate or abolish the Phase I $\dot{V}O_2$ response (Fig. 33, reference 689). Many cardiac defects reduce stroke volume leading to a higher HR response at submaximal $\dot{V}O_2$'s whereas the chronotropic response to exercise is constrained in sinoatrial node pathologies and patients treated with β -adrenergic blockers (749). Ultimately, however, as seen in Figure 33 in the patient suffering from cardiac dysfunction the primary component $\dot{V}O_2$ kinetics might be extraordinarily slow as dictated by the inability to rapidly elevate peripheral O₂ delivery and utilization.

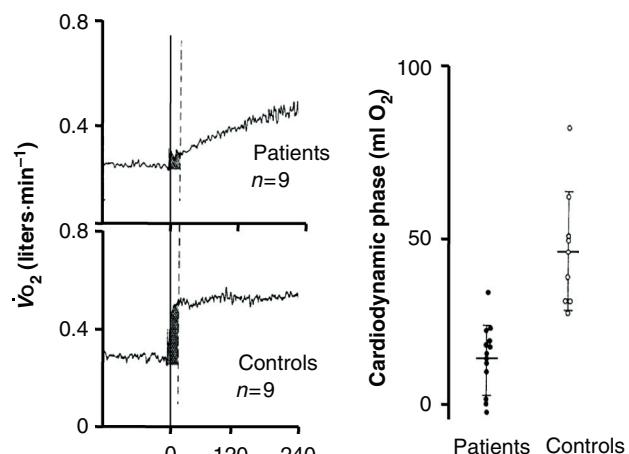


Figure 33 Left panel: mean $\dot{V}O_2$ response following the onset of unloaded (0 Watt) cycling in patients with cyanotic congenital heart disease compared with age-matched healthy control subjects. Shaded area denotes Phase I. Right panel: magnitude of the Phase I $\dot{V}O_2$ (cardiodynamic component) in ml O₂. Redrawn, with permission, from Sietsema et al. (689).

As with pulmonary disease, sequelae to the primary cardiac dysfunction exert a dramatic effect on exercising muscle that exacerbates the central O₂-transport dysfunction. Specifically, in CHF skeletal muscle vasodilation is impaired by elevated sympathetic activity and levels of circulating vasoconstrictors such as norepinephrine and angiotensin II which, together with venous congestion, conspire to retard microvascular hemodynamics following the onset of contractions (426, 629, 806). In addition, NO bioavailability is reduced and the muscle pump action less effective. These mechanisms are believed to be responsible for the severe blunting of the normally rapid increase in capillary RBC flux seen following the onset of contractions in skeletal muscle (Fig. 34, reference 629). In the face of reduced capillary blood flow the O₂-delivery/ $\dot{V}O_2$ ratio falls and microvascular O₂ pressures

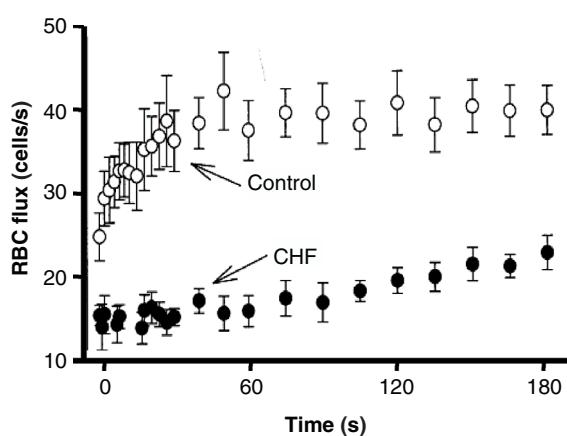


Figure 34 Red blood cell (RBC) flux following the onset of 1 Hz contractions of the rat spinotrapezius muscle in control and chronic heart failure (CHF) animals. Data taken from Kindig et al. (428) and Richardson et al. (629), with permission.

are decreased far below those found in healthy muscle (68, 69, 72, 199) and recover far more slowly after contractions cease (162). Moreover, although capillary hematocrit and its response to contractions appears to be preserved to some degree in CHF muscle the proportion of capillaries supporting RBC flux is decreased in relation to the severity of heart failure which reduces the number of RBCs in the capillary bed and consequently the diffusing capacity for O₂ (426). Thus, in CHF skeletal muscle suffers from both impaired conductive and diffusive O₂ transport and the net effect is that muscle venous effluent O₂ content is extremely low even at low-to-moderate work rates (410). Lowered microvascular O₂ pressures elevate the degree of intramyocyte metabolic perturbation, accelerate glycolysis, and promote muscle and systemic lactic acidosis at very low work rates (749). This scenario is the product of CHF acting to lower intramyocyte Po₂ which stimulates glycolysis directly (12, 627) and also the reduced blood-myocyte O₂ flux will slow $\dot{V}O_2$ kinetics and mandate a greater O₂ deficit that relies more heavily on substrate-level phosphorylation for energy production.

As mentioned above, the finding of a “normal” primary component following a Phase I of reduced amplitude and prolonged duration has led some to conclude that muscle function is preserved in CHF (520). In contrast, the modeling studies of Barstow and colleagues (41) demonstrate that any prolongation of Phase I will necessarily act to speed pulmonary primary component $\dot{V}O_2$ kinetics (see also reference 523 in aged individuals). Thus, even in those patients in whom, on the basis of pulmonary gas exchange, the primary component appears normal no conclusions regarding preservation of muscle oxidative function should be made. Indeed, it is apparent that CHF acts to downregulate oxidative enzymes, impair vascular and microvascular function, lower microvascular Po₂, and constrain blood-myocyte O₂ flux (69, 184, 194, 197-199, 210, 426, 629). Even in the absence of slowed Q kinetics, these local muscle effects would be expected to slow primary component $\dot{V}O_2$ kinetics.

Three primary therapeutic strategies for treating cardiac disease are heart transplantation (end-stage option), exercise training and pharmacologic intervention. Whereas, given the prevalence of CHF, information regarding the effect of each treatment strategy on $\dot{V}O_2$ kinetics is surprisingly scarce, there is some evidence that: (i) despite peak $\dot{V}O_2$ increasing in heart transplant recipients over 2 years postsurgery, $\dot{V}O_2$ kinetics (primary component) was speeded only in a subgroup of those patients having the slowest $\dot{V}O_2$ kinetics (96). (ii) There is intriguing evidence that recovery $\dot{V}O_2$ kinetics may be improved in heart failure patients by means of inspiratory muscle training (170) but not two months of “high-intensity residential exercise training” (537). (iii) Advanced treatments with angiotensin-converting enzyme (ACE) inhibitors and third generation beta-blockers failed to return either pulmonary $\dot{V}O_2$ or muscle deoxy(Hb+Mb) kinetics to that of healthy age-matched controls (700).

Whilst much interest has focused on the predations of CHF on $\dot{V}O_2$ kinetics during the rest-exercise transition analysis

of the exercise-rest recovery responses may prove extremely valuable in unraveling the mechanistic bases for dysfunction. Recovery $\dot{V}O_2$ kinetics can be determined with greater fidelity (414) and more reproducibly (413) than onset kinetics in this population. Importantly, the CHF off-transient may discriminate CHF patients from their healthy counterparts in the presence of similar on-transient responses (688) and relate closely to the degree of functional impairment (176). With CHF patients lying in the O₂-delivery-dependent region of Figure 2 (415, 416) slowed muscle and therefore pulmonary $\dot{V}O_2$ kinetics are likely to be the result of compromised muscle O₂ delivery (74, 372, 511, 512). Indeed, that muscle microvascular Po₂ kinetics is slowed drastically in recovery and that this slowing correlates closely with the degree of myocardial dysfunction (as assessed by elevated left-ventricular pressures) (162) suggests that the dysregulation of microvascular Po₂ constitutes a key step in the transduction of heart failure into slowed $\dot{V}O_2$ kinetics.

Diseases that reduce blood flow to exercising muscle(s)

Two prevalent conditions that act to impair $\dot{V}O_2$ kinetics via their impact on the periphery (in addition to central cardiovascular effects) are diabetes (type I and II) and peripheral arterial disease (PAD). As would be expected when cardiac function is intact, both diabetes and PAD may substantially slow $\dot{V}O_2$ kinetics primarily by increasing τ_p (54, 101, 623). However, cardiac dysfunction does develop in many diabetic patients and, when this becomes sufficiently severe to limit the speed of Q increase following exercise onset, would be expected to reduce the magnitude of Phase I whilst prolonging its duration. Notwithstanding the above, a recent investigation by Wilkerson and colleagues (789) found that, in older (seventh decade) type II diabetic patients with longstanding disease histories (average 9 years), τ_p may not be different from that in healthy age-matched individuals despite a profoundly reduced $\dot{V}O_{2\max}$. It was hypothesized that either with advancing age, some limiting value for τ_p was achieved or, alternatively, structural or functional adaptations in the exercising muscles over time may have offset the diabetes-induced dysfunction.

Interestingly, PAD increases muscle oxidative enzyme capacity (214, 481) which is opposite to the effects of diabetes (99, 679, 692, 693). In the presence of inadequate O₂ delivery and other oxidative dysfunction that might be present in PAD (51-54) these alterations *in separatum* would be expected to cause divergent changes in $\dot{V}O_2$ kinetics. However, in both conditions compromised O₂ delivery either via reduced bulk blood flow as well as the microvascular alterations present in muscle of diabetic animals (i.e., type I, decreased capillary luminal diameter; type I and II, reduced % capillaries supporting RBC flux, impaired capillary hemodynamics, 429, 552, 682) acts to slow τ_p . In type II diabetes there is evidence in animals [553; and also type I diabetes (71)] and humans (55) that, following the onset of contractions, this disease decreases the

$\dot{V}\text{O}_2$ -delivery/ $\dot{V}\text{O}_2$ ratio increasing microvascular deoxygenation and thereby reducing the O_2 pressure head that drives blood-myocyte O_2 flux and ultimately $\dot{V}\text{O}_2$ kinetics.

Muscle metabolic myopathies

Muscle metabolic myopathies form a disparate cluster of diseases in which substrate metabolism (glycogen or lipid) derangements or mitochondrial mutations obstruct myocyte energetics pathways. Two prominent examples of these diseases that are attended by profound oxidative dysfunction are McArdle's disease (myophosphorylase deficiency) and mitochondrial myopathies (review 286). As with the three classes of diseases discussed above $\dot{V}\text{O}_{2\text{max}}$ is reduced (283, 306, 307, 474). However, in contrast to the primary site of $\dot{V}\text{O}_2$ control moving from its intramuscular mitochondrial locus upstream into the O_2 -transport pathway, in McArdle's disease and mitochondrial myopathies arterial O_2 content and muscle blood flow may be well preserved or even substantially exaggerated (306). Thus, in the face of adequate or surplus exercising muscle O_2 supply [i.e., increased \dot{Q} -to- $\dot{V}\text{O}_2$ ratio (\dot{I}/\dot{V}) of as much as 20 to 30 versus 5 to 6 in healthy individuals, references 305, 306, 586], impaired oxidative function increases the O_2 -delivery/ $\dot{V}\text{O}_2$ ratio and decreases fractional O_2 extraction, as assessed either by arterial-venous O_2 difference or NIRS determination of deoxy(Hb+Mb), which either fails to reach levels found in healthy muscle or may not increase at all (283, 286). Figure 35 demonstrates that, in these patients, primary component $\dot{V}\text{O}_2$ kinetics is slowed in relation to the inability to increase Hb+Mb deoxygenation (i.e., fractional O_2 extraction) (286). Moreover, these patients may exhibit an increased G of the $\dot{V}\text{O}_2$ response (286); however, this latter finding remains to be explored rigorously.

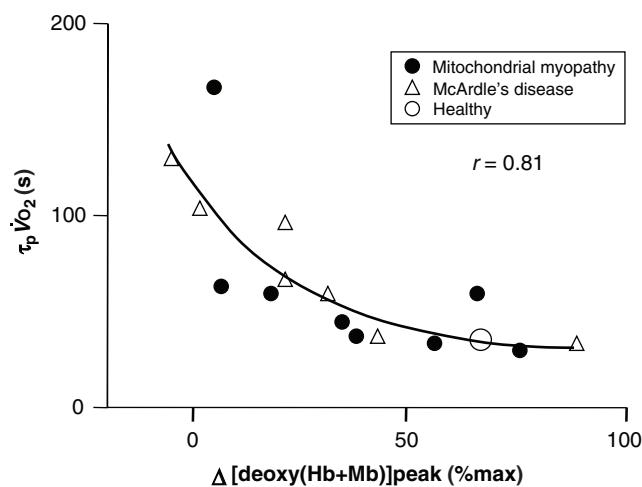


Figure 35 Time constants (τ_p) of pulmonary $\dot{V}\text{O}_2$ kinetics in mitochondrial myopathy and McArdle's disease patients are negatively related ($r = 0.81$, $P < 0.05$) to the near infrared spectroscopy-derived muscle deoxygenation index ($\Delta[\text{deoxy}(\text{Hb} + \text{Mb})\text{peak}]$) (estimate of muscle fractional O_2 extraction) during cycle ergometry. Healthy control subject data also shown for comparison. Reconstructed, with permission, from the data of Grassi et al. (286).

The high prevalence of obesity in the developed world argues for its consideration herein whether or not it is accompanied by overt disease symptoms. Obesity may or may not be accompanied by extreme inactivity; nonetheless the locomotory muscles often lack so-called aerobic conditioning and yet are simultaneously subjected to strength training (review 661). Moreover obese individuals might have an elevated proportion of type IIb muscle fibers (448) and a lower muscle mitochondrial content and oxidative capacity (691) than their more svelte counterparts. Salvadego and colleagues (661) demonstrated that adolescent obese males exhibited slowed primary component $\dot{V}\text{O}_2$ kinetics. Moreover, the majority evinced a $\dot{V}\text{O}_{2\text{sc}}$ that increased linearly as a function of time with a slope that related inversely to exercise tolerance.

In conclusion, diseases that compromise the O_2 -transport pathway slow $\dot{V}\text{O}_2$ kinetics as a function of the inability to deliver adequate O_2 to the muscle mitochondria. Where the effects of pulmonary dysfunction are mediated by arterial hypoxemia and \dot{Q} remains unaffected primary component $\dot{V}\text{O}_2$ kinetics is slowed whereas Phase I may be normal. However, this is often not the case and Nery et al. (542) found a significant decrease of Phase I in their cohort of COPD patients consistent with the accompanying presence of cardiovascular abnormalities. In COPD patients, elevating the inspired O_2 content may or may not speed $\dot{V}\text{O}_2$ kinetics but does not return them to control values (556). Somewhat differently, cardiac diseases that decrease the rate and/or extent of \dot{Q} increase impact Phase I directly by reducing its magnitude and extending its duration. Because of the increased muscle(s)-to-lung transit time the primary component becomes distorted such that it is unlikely to be a close facsimile of muscle $\dot{V}\text{O}_2$ kinetics (41, 42). Whereas the $\dot{V}\text{O}_{2\text{sc}}$ has evaded systematic characterization in each of these conditions, as with aging, disease-driven reductions in $\dot{V}\text{O}_{2\text{max}}$ will serve to compress the work rate domains such that the $\dot{V}\text{O}_{2\text{sc}}$ is expected to emerge at far lower absolute metabolic rates. Thus, across the spectrum of diseases considered here exercise tolerance will be challenged by slowed $\dot{V}\text{O}_2$ kinetics that mandate an increased O_2 deficit. Moreover, the “early” onset of the $\dot{V}\text{O}_{2\text{sc}}$ at low metabolic rates will drive $\dot{V}\text{O}_2$ to $\dot{V}\text{O}_{2\text{max}}$ thereby exacerbating the fatigue process and heralding imminent, and premature, exhaustion. An exemplar of the emerging value of $\dot{V}\text{O}_2$ kinetics determination in patient populations is that their prognostic value, for example, in heart failure patients, may be better than that of $\dot{V}\text{O}_{2\text{max}}$ (670).

Exercise Training and Performance

Slow $\dot{V}\text{O}_2$ on-kinetics is associated with a greater depletion of intramuscular high-energy phosphates and accumulation of lactate and hydrogen ions. Across diverse populations (endurance trained, healthy young, healthy old, and COPD patients) CP, which defines the upper limit for prolonged exercise, decreases as an approximately linear function of the

speed of $\dot{V}\text{O}_2$ kinetics ($\tau_p \dot{V}\text{O}_2$, reference 638). The development of the $\dot{V}\text{O}_{2\text{sc}}$ during exercise performed above the LT, which causes $\dot{V}\text{O}_2$ to rise above the predicted steady-state requirement, is also closely associated with the fatigue process (110). It has also been shown that the τ_p is correlated with indices of aerobic fitness while the amplitude of the $\dot{V}\text{O}_{2\text{sc}}$ is correlated with indices of “anaerobic” fitness (81). Consequently, interventions that either speed the $\dot{V}\text{O}_2$ response towards the expected steady state (and decrease the O₂ deficit, 188) or reduce the magnitude of the $\dot{V}\text{O}_{2\text{sc}}$ should improve exercise tolerance. The most potent intervention, in this regard, is endurance exercise training.

Cross-sectional studies

One of the first such studies demonstrated that, for the same sub-GET work rate, $\dot{V}\text{O}_2$ kinetics was appreciably faster in eight men with a high $\dot{V}\text{O}_{2\text{max}}$ ($4.85 \pm 0.38 \text{ liters} \cdot \text{min}^{-1}$) versus their counterparts with a lower $\dot{V}\text{O}_{2\text{max}}$ ($3.92 \pm 0.36 \text{ liters} \cdot \text{min}^{-1}$) (759). Similarly, Cerretelli et al. (138) reported a faster $\dot{V}\text{O}_2$ half-time for trained kayakers during supine arm cranking compared to sedentary subjects. Powers et al. (612) also reported that $\dot{V}\text{O}_2$ kinetics (at 50% $\dot{V}\text{O}_{2\text{max}}$) correlated with $\dot{V}\text{O}_{2\text{max}}$ in highly trained athletes with similar training routines but disparate $\dot{V}\text{O}_{2\text{max}}$'s. In addition, over a range of work rates chosen to be 25%, 50%, 75%, and 100% of the subject's maximum work capacity, whereas $\dot{V}\text{O}_2$ kinetics became progressively slower with increasing work rates, for each intensity, the $\dot{V}\text{O}_2$ kinetics was faster in the fitter subjects (808).

In a comprehensive study, Koppo et al. (442) investigated the interaction between training status and exercise intensity. As expected, τ_p was significantly shorter in trained cyclists versus their untrained counterparts; however, τ_p became progressively greater at higher work rates in all subjects. The slowing of τ_p within the moderate intensity domain, where O₂ availability is presumed not to be limiting, raised the possibility that the recruitment of higher threshold motor units may impact τ_p at these work rates. Consistent with the results of Barstow et al. (39, 40), Koppo et al. (442) also observed a significantly greater G_p in the trained subjects. An intriguing observation in highly trained subjects is the presence of a transient “overshoot” in $\dot{V}\text{O}_2$ above the eventual steady-state during moderate-intensity exercise (445). The mechanistic basis for this phenomenon is unclear but the overshoot is observed more frequently when the athletes perform their habitual activity, that is, runners running and cyclists cycling (418), perhaps suggesting that patterns of motor unit recruitment are, at least in part, responsible.

From the above, fast $\dot{V}\text{O}_2$ kinetic responses are expected for highly trained subjects ($\dot{V}\text{O}_2 \text{ max} > 65 \text{ ml min}^{-1} \text{ kg}^{-1}$) performing constant work rate exercise. Accordingly, the τ_p of 12 to 17 s in regional-level competitive runners (95, 419), 14 s in elite rowers (376), and 21 s for well-trained cyclists (148) are considerably shorter than that observed in healthy, young, nonspecifically trained subjects (~25–30 s). Corre-

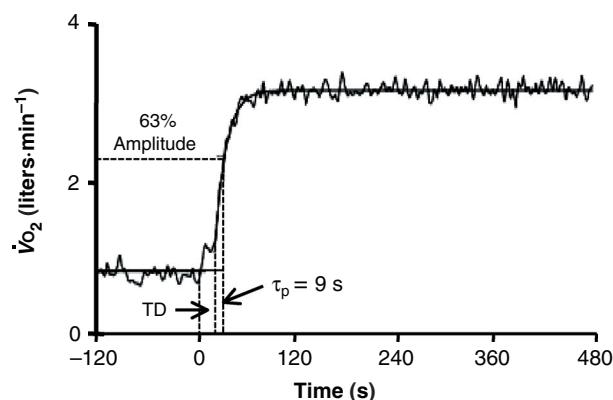


Figure 36 $\dot{V}\text{O}_2$ kinetics following the onset of moderate-intensity cycle exercise (230 Watts) in a Belgian junior cycle champion. The time constant (τ_p) of the primary component response is a remarkable 9 s, close to that found in Paula Radcliffe, the World record holder in the women's marathon as well as in Thoroughbred horses.

sponding values for the World record holder for the women's marathon (8–10 s, reference 395) and highly trained cyclists (9 s, Fig. 36, references 43, 442) possibly approach the upper limits for humans. Intriguing as these data may be, they cannot discriminate between genetic endowment and physiological plasticity to training as can longitudinal experimental designs.

Longitudinal studies

Endurance-type exercise training is known to result in significant improvements in the LT/GET (175, 192, 193, 257, 259, 596), CP (609, 733), and $\dot{V}\text{O}_{2\text{max}}$ (340), (see 388 for review). These parameters of aerobic fitness demarcate the boundaries between the various exercise intensity domains within which the metabolic and pulmonary gas exchange responses to exercise are predictable. It is therefore crucial to appreciate that the effects of training on $\dot{V}\text{O}_2$ kinetics will depend, in part, on whether the frame of reference is the same absolute or relative work rate. For example, an absolute work rate that was originally “heavy” (i.e., above the LT) might become “moderate” (i.e., below the LT) following a period of endurance training if the work rate at the LT increases appreciably. Similarly, a work rate that was originally “severe” (i.e., above the CP) might become heavy (i.e., below the CP) if, with training, the CP exceeds the original work rate. In these situations, if $\dot{V}\text{O}_2$ kinetics was measured at the same absolute work rate pre-versus posttraining, a reduced end-exercise $\dot{V}\text{O}_2$, an attenuated $\dot{V}\text{O}_{2\text{sc}}$, and faster $\dot{V}\text{O}_2$ kinetics (at least when expressed as the MRT over the entire response) would be anticipated. If, however, the $\dot{V}\text{O}_2$ kinetics was measured at the same relative work rate (e.g., 90% LT, or some percentage of the difference between LT and $\dot{V}\text{O}_{2\text{max}}$) as calculated from the pre- and posttraining values, then relatively little change in the $\dot{V}\text{O}_2$ kinetics would be expected because these would essentially be “normalized” in relation to the changed boundaries of the exercise intensity domains.

The parameters of aerobic function: efficiency, LT/GET, $\dot{V}O_{2\text{max}}$, and $\dot{V}O_2$ kinetics (782), along with CP (609), are sensitive to features of the training program that is undertaken. Specifically: the initial training status of the subject; the total duration of the training program; and the volume of the training per unit time (comprising the frequency, duration, and intensity of all training sessions completed in a certain time frame which is typically 1 week; 762). It is easier to detect physiological changes evoked by any training program in subjects who are initially untrained; however, it is more difficult both to recruit and to retain such subjects. Accordingly, the longitudinal studies investigating the effects of training on $\dot{V}O_2$ kinetics typically have involved relatively short “generic” endurance training programs in young relatively fit student subjects (although there is a growing literature base on the effects of training on $\dot{V}O_2$ kinetics and functional capacity in clinical populations).

One of the earliest studies in this regard was conducted by Hickson et al. (339) in which seven men performed 10 weeks of training (6×40 min sessions of exhaustive running and cycling per week). $\dot{V}O_2$ kinetics was assessed at 40%, 50%, 60%, and 70% of the pretraining $\dot{V}O_{2\text{max}}$ (i.e., same absolute and relative work rates pre- and posttraining). $\dot{V}O_2$ kinetics was faster at the same absolute and generally the same relative work rate posttraining (Fig. 37, upper panel, see also 303). Subsequently, Cerretelli et al. (138) using running and swimming training determined that the speeding of the $\dot{V}O_2$ kinetics was highly specific to the muscle group(s) trained. In addition, Convertino et al. (159) found that 7 days of continuous head-down bed rest resulted in a significant increase in the O₂ deficit (consistent with slowed $\dot{V}O_2$ kinetics) during up-

right, but not supine, cycle exercise. These early studies provided important general descriptions of the impact of physical training and deconditioning on the $\dot{V}O_2$ response to exercise.

$\dot{V}O_2$ kinetics adapts extremely rapidly in response to exercise training in previously untrained individuals (Fig. 37, lower left panel, reference 576, see also 515, 530, 531) with $\tau_{\dot{V}O_2}$ (on and off) decreasing significantly after as little as only 2 to 4 days of cycle training (2 h per day at 60% $\dot{V}O_{2\text{max}}$) and continuing to decrease up to 30 days (515, 576). The faster initial (4 days) $\dot{V}O_2$ kinetics was associated with a reduced fall of muscle [PCr] and a blunting of the increase in blood [lactate] and occurred before there was a measurable increase in either muscle citrate synthase activity or $\dot{V}O_{2\text{max}}$. The authors proposed that this initial speeding might be related to faster muscle blood flow kinetics or increased capillary-to-fiber ratio. However, it was not possible to exclude that changes in the activity of other oxidative enzymes, not measured in that study, may have influenced $\dot{V}O_2$ kinetics.

Exercise training may also speed $\dot{V}O_2$ kinetics in previously trained (but clearly not highly trained) cyclists ($\dot{V}O_{2\text{max}} \sim 57 \text{ ml min}^{-1} \text{ kg}^{-1}$) (545). Increases in the exercise training volume for these individuals decreased τ_p from 29 s to 24 and 22 s at 4 and 8 weeks, respectively, as well as improving $\dot{V}O_{2\text{max}}$ (at 4, but not further at 8 weeks), GET and 40 km time trial performance. Supplementing the training of runners ($\dot{V}O_{2\text{max}} \sim 61 \text{ ml min}^{-1} \text{ kg}^{-1}$) with severe-intensity bouts for 8 weeks reduced τ_p (pre: 26 ± 1 vs. post: 14 ± 1 s) and O₂ deficit, which correlated with the increased time-to-exhaustion at high running speeds, but not the $\dot{V}O_{2\text{sc}}$ amplitude (187). Billat and colleagues (89) have demonstrated a similar effect after 4 weeks of supplemented training. In contrast, Carter et al. (122) reported that, in a subject population of recreationally active students with heterogeneous fitness levels, training may speed τ_p in the least fit cohort (initial $\dot{V}O_{2\text{max}} \sim 40 \text{ ml min}^{-1} \text{ kg}^{-1}$) but not in their more highly fit peers in whom τ_p was already very fast (~ 19 s). This finding highlights the important interactive influences of initial training status and training program on changes in $\dot{V}O_2$ kinetics.

As seen for τ_p the $\dot{V}O_{2\text{sc}}$ is highly plastic and is decreased substantially with endurance exercise training in previously untrained individuals (Fig. 37, right panel, references 131, 795). Moreover, these adaptations are extremely rapid: At 60% Δ as calculated from the pretraining LT and $\dot{V}O_{2\text{max}}$ values the $\dot{V}O_{2\text{sc}}$ decreased significantly after 7 days and reached the nadir of its response after 14 days of the 6 wk training period (795). Interestingly, in the first two weeks of training the reduction in the $\dot{V}O_{2\text{sc}}$ was dissociated from that of blood [lactate], minute ventilation, and plasma [norepinephrine]. Furthermore, and reinforcing the conclusions from Section *Slow Component of $\dot{V}O_2$ Kinetics: Mechanistic Bases*, infusion of epinephrine during exercise posttraining did not influence the magnitude of the $\dot{V}O_{2\text{sc}}$ despite causing significant increases in plasma [epinephrine], minute ventilation and blood [lactate]. Accordingly, Womack et al. (795) suggested that changes in motor unit recruitment patterns (i.e.,

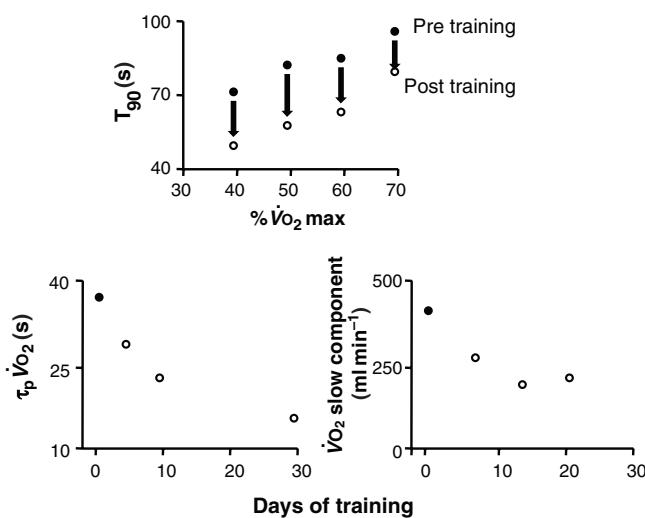


Figure 37 The training-induced speeding of $\dot{V}O_2$ kinetics evidenced from the time-to-90% of steady-state response [top panel, redrawn, with permission, from Hickson et al. (339)] results from a speeding of the primary $\dot{V}O_2$ response time constant [τ_p] $\dot{V}O_2$, see lower left panel redrawn, with permission, from data of Phillips et al. (576)] and, a reduction in the size of the $\dot{V}O_2$ slow component [i.e., above the gas exchange threshold, GET, right panel redrawn, with permission, from Womack et al. (795)].

a reduced recruitment of “less efficient” type II fibres) with training might help to explain both the reduction in the $\dot{V}O_{2sc}$ with training and the relationship between the $\dot{V}O_{2sc}$ and blood [lactate]. Carter et al. (122) speculated that enhanced muscle mitochondrial density and/or capillarization (4, 360) with training might result in the recruitment of fewer type II fibers posttraining. The available data therefore indicate that the amplitude of the $\dot{V}O_{2sc}$ may be reduced after only 1 to 2 weeks of training (795), and that reductions are also possible in subjects who are reasonably fit at the start of training and in whom ‘traditional’ markers of aerobic fitness such as $\dot{V}O_{2max}$ and LT do not therefore increase substantially (122).

$\dot{V}O_2$ kinetics and muscle activation were assessed (by contrast shifts in MR images) during both moderate and heavy exercise pre- and post-4 weeks endurance training to test the hypothesis that the resultant reduced $\dot{V}O_{2sc}$ was the result of changes in motor unit recruitment (665, 666). Training had no effect on the $\dot{V}O_2$ or muscle transverse reaction times (T_2) during moderate intensity exercise, but there were significant reductions in end-exercise $\dot{V}O_2$ and T_2 of the vastus lateralis during heavy intensity exercise. The authors argued that these data provided evidence that the $\dot{V}O_{2sc}$ is linked to changes in muscle activation (665) and that the reduction in the $\dot{V}O_{2sc}$ with training resulted from a reduced muscle activation. This is potentially consistent with evidence that the muscle [PCr] slow component is also attenuated following a period of endurance training (398).

Both cross-sectional and longitudinal studies indicate that enhanced “fitness” is associated with faster $\dot{V}O_2$ kinetics and, for absolute work rates initially $>$ LT, with a reduced $\dot{V}O_{2sc}$ amplitude. A plethora of central and peripheral physiological adaptations to endurance training (388, 586) collectively drive improvements in the capacity to deliver O_2 to skeletal muscle and for muscle to utilize that O_2 . The factor or factors decisive in speeding $\dot{V}O_2$ kinetics after training will depend ultimately upon whether O_2 availability is limiting or controlling in the pretraining situation. In turn, this will be dependent upon the training status, health, and age of the subjects studied, the exercise modality in which the training is conducted and the exercise intensity domains that are investigated. It must be borne in mind that the exercise $\dot{V}O_2$ comprises an integration of structural and functional attributes deterministic for both O_2 delivery and utilization. Notwithstanding this consideration, the available evidence indicates that the speeding of the primary $\dot{V}O_2$ response is limited essentially to exercise engaging the trained musculature (138) and is generally (but not always demonstrably) associated with an elevated oxidative enzyme activity within those muscles (77). τ_p is reduced quickly following training onset and, in most instances, appears to have a time course of adaptation similar to that of muscle fiber oxidative enzyme activity (271 but see also 576). These data therefore suggest that, in most instances, improvements in metabolic potential may play a pivotal role in the reduction of τ_p with training. However, an intriguing recent series of investigations, which again demonstrated that training speeded $\dot{V}O_2$ kinetics in young and older

individuals (male and female), has revealed that there may be an improved matching of O_2 delivery-to- $\dot{V}O_2$. Thus, with training the initial overshoot in the $\Delta\text{deoxy(Hb+Mb)}/\Delta\dot{V}O_2$ ratio evident initially was abolished in young and older men and young women (530, 531). Any conclusions regarding whether the proportionally greater deoxygenation pretraining may have limited $\dot{V}O_2$ kinetics in these individuals are premature. However, these findings do suggest that the vascular adaptations resulting in improved O_2 delivery occur to a proportionally greater extent than speeding of the $\dot{V}O_2$ kinetics. In this regard, it is known that a single bout of running can improve endothelium-mediated vasodilation in rat abdominal aorta (318) and $\dot{V}O_2$ kinetics can be speeded with just two days of training without decrement in O_2 delivery-to- $\dot{V}O_2$ matching (515).

The mechanism responsible for the reduction in the amplitude of the $\dot{V}O_{2sc}$ at the same absolute work rate following training also remains to be determined but could relate to improvements in muscle O_2 delivery or the homogeneity of its distribution as well as muscle fiber oxidative capacity that are linked to alterations in muscle fiber recruitment patterns. The training program that “optimizes” improvements in $\dot{V}O_2$ kinetics remains to be determined. However, there is recent evidence that high-intensity interval training might be at least as effective as traditional endurance training paradigms for altering both τ_p and the $\dot{V}O_{2sc}$, at least in previously untrained populations (26, 83, 515). Specifically, just \sim 20 min repeated all-out sprinting performed in six sessions of 30 s bouts over 2 weeks induced \sim 25% speeding of τ_p for moderate and severe exercise. This response was accompanied by faster deoxy(Hb+Mb) kinetics of greater amplitude, a reduced $\dot{V}O_{2sc}$ and substantial improvements in exercise tolerance (26). Collectively, these responses suggest that training-induced muscle mitochondrial function adaptations exceeded those of vascular function and O_2 delivery in contrast to the Murias et al. (530, 531) endurance training protocol. Thus, with respect to $\dot{V}O_2$ kinetics, through this specific very high intensity training protocol subjects may have expended more of their O_2 delivery buffer and come closer to an O_2 -delivery limitation. It is anticipated that future investigations which exploit these differential rates of adaptation of elements in the O_2 transport-utilization pathway will prove to be invaluable mechanistic tools for $\dot{V}O_2$ kinetics research.

Environmental factors

Acute responses. (i) Inspired hypoxia (12% O_2 but not 15% O_2) slows the pulmonary primary $\dot{V}O_2$ on- and off-kinetics \sim 60% for moderate intensity cycle ergometry in the absence of altered HR kinetics (217, see 74, 372, 477, 511, 512 for discussion of O_2 dependence of metabolic control). (ii) Hyperthermia ($+1^\circ\text{C}$ and $+6^\circ\text{C}$ elevation in esophageal and mean skin temperature) and hyperthermia with dehydration (\sim 4% reduction in blood volume and body mass) reduced the $\dot{V}O_2$ MRT \sim 20% in the presence of an impaired $\dot{V}O_{2max}$ during severe-intensity cycle ergometry and impaired exercise

tolerance (547). Interestingly, however, this occurred concomitant with a reduced $\dot{V}O_2\text{max}$ (and thus $\dot{V}O_2$ at exhaustion) such that when the MRT was defined with respect to the same absolute $\dot{V}O_2$ (i.e., time-to-reach 63% of the euhydrated euthermic $\dot{V}O_2\text{max}$) the response kinetics was unchanged.

Chronic adaptations. The two principal environments of interest here are altitude and microgravity/bed rest. In both instances the likelihood that altered activity patterns (i.e., de-training and training) might confound the results must be considered. $\dot{V}O_2$ kinetics adaptations to hypobaric hypoxia (as differentiated from the consequences of pulmonary disease, see Section *Disease States*) have eluded formal characterization. However, there is evidence that 6 weeks at or above 5,200 m slows the overall $\dot{V}O_2$ kinetics response (as assessed by O_2 deficit and half-time) at the onset of cycle exercise but not in recovery (100). As a model of microgravity head-down tilted bed rest for 7 days slowed the $\dot{V}O_2$ kinetics response to pseudorandom binary sequences (709) and constant-work-rate cycle ergometry in the heavy intensity domain (159) performed on the upright cycle ergometer. In contrast, Capelli and colleagues (117) found no detectable change in response to moderate-intensity exercise after 14 days. It is possible that this disparity among studies resulted from differences in the preexposure fitness or activity patterns of the subjects.

cising muscles. This $\dot{V}O_2\text{sc}$, which can be discriminated from the primary $\dot{V}O_2$ response after a delay of some 90 to 120 s and represents an emergent inefficiency of oxidative metabolism, is thought to be the consequence of fiber-type recruitment patterns and metabolic events within already-recruited fibers. Whereas the primary $\dot{V}O_2$ kinetics for pulmonary gas exchange can be a close facsimile of muscle $\dot{V}O_2$ (and PCr) kinetics even “well-behaved” 1 or 2 component exponential responses likely conceal a substantial heterogeneity of $\dot{V}O_2$ and $QO_2/\dot{V}O_2$ matching within the exercising musculature.

Within an individual, there is considerable plasticity with respect to the speed of $\dot{V}O_2$ kinetics. From adolescence onwards $\dot{V}O_2$ kinetics slows progressively with advancing age and the predations of disease (Table 1). In contrast, priming exercise, exercise training, and enhancing mitochondrial function with NO synthase blockade speed $\dot{V}O_2$ kinetics as may elevating systemic O_2 transport—but only when the locus of control lies within the O_2 -transport system as distinct from the exercising musculature. Given the relationship between $\dot{V}O_2$ kinetics and exercise tolerance there is a clear mandate to develop effective strategies for improving $\dot{V}O_2$ kinetics particularly in those populations in which pathological or longevity-induced slowing has compromised mobility, quality of life, and conceivably life expectancy.

Conclusions

Each day humans transition among myriad different metabolic rates: their $\dot{V}O_2$ response to each transition being dependent upon the speed of their $\dot{V}O_2$ kinetics. Faster $\dot{V}O_2$ kinetics is beneficial because this limits reliance on finite-capacity substrate phosphorylation and minimizes the challenge to homeostasis within exercising muscle and systemically. This relationship likely underlies, in part, the greater exercise tolerance of individuals with fast $\dot{V}O_2$ kinetics. For healthy young individuals walking, running or cycling upright, for example, the compelling weight of evidence supports an intramuscular locus of control most likely within the mitochondrial oxidative machinery. As such, the speed of the $\dot{V}O_2$ kinetics is not thought to be limited by upstream O_2 transport processes. However, reductions in O_2 transport resulting from pathology, aging and/or environmental/experimental conditions can move the locus of control upstream. There is also recent evidence that $\dot{V}O_2$ kinetics control in fast-twitch muscle fibers lies closer to an O_2 limitation than their slow-twitch counterparts and individuals with proportionally more fast twitch fibers generally have slower $\dot{V}O_2$ kinetics.

The $\dot{V}O_2$ kinetics profile itself is highly conserved across exercise modalities in humans and across the animal kingdom and is crucially dependent upon the exercise-intensity domain in which the exercise is performed (i.e., moderate, heavy, severe, and extreme). The first-order linearity of the primary response evinced following exercise onset in the moderate domain is disrupted in the heavy and severe domains by imposition of a $\dot{V}O_2\text{sc}$ that originates principally within the exer-

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The logical sequence for this review and synthesis of information pre-2005 is based, in part, upon the text “*Oxygen uptake kinetics in sport, exercise and medicine*” edited by Andrew M. Jones and David C. Poole which constitutes the first book devoted entirely to $\dot{V}O_2$ kinetics. We wish to acknowledge our colleagues who contributed significantly to that work: Shunsaku Koga, Tomoyuki Shiojiri, Narihiko Kondo, Brian J. Whipp, Harry B. Rossiter, Mark Burnley, Casey A. Kindig, Brad J. Behnke, Thomas J. Barstow, Franklyn A. Howe, Susan A. Ward, Richard L. Hughson, Bruno Grassi, Katrien Koppo, Jamie S. Pringle, Helen Carter, and Barry W. Scheuermann. In addition, the seminal works by Nathaniel Zuntz, J. Geppert, Francis G. Benedict, August Krogh, J. Lindhard, A. V. Hill, Erling Asmussen, Brian J. Whipp, Michael Mahler, Karl Wasserman, Pietro di Prampero, Bengt Saltin, Richard Casaburi, Paolo Cerretelli, Bruno Grassi, Michael C. Hogan, L. Bruce Gladden, Dag Linnarsson, Donald H. Paterson, John Kowalchuk, David A. Cunningham, Paul Molé, Harry B. Rossiter, Jerzy A. Zoladz, Glenn A. Gaesser, and Michael D. Delp have been drawn upon extensively. The anonymous reviewers significantly improved the manuscript with their numerous insightful suggestions. We are also appreciative of Steven W. Copp, Daniel M. Hirai, Scott K. Ferguson, and Clark T. Holdsworth who proof read the final draft. Funding from the National Institutes of Health, Heart Lung and Blood Institute and the American Heart Association has supported, in part, a portion of the work presented herein.

Dedication

We dedicate this work to Professor Brian J. Whipp (1937-2011) who passed away in his beloved Wales as we were in press. Our mentor and dear friend's legacy was to found and shape the contemporary field of $\dot{V}O_2$ kinetics. The influence of his genius endures through those who have stood on the shoulders of this Welsh giant. Nos da, Doctor Mirabilis.

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