Oxygen Uptake Dynamics: From Muscle to Mouth—An Introduction to the Symposium

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ABSTRACT

JONES, A. M., and D. C. POOLE. Oxygen Uptake Dynamics: From Muscle to Mouth—An Introduction to the Symposium. *Med. Sci. Sports Exerc.*, Vol. 37, No. 9, pp. 1542–1550, 2005. The purpose of this paper is to provide an introduction to the study of oxygen uptake ($\dot{V}O_2$) dynamics or kinetics. Following the onset of exercise, both muscle and pulmonary $\dot{V}O_2$ rise in a near-exponential fashion towards the anticipated "steady-state" $\dot{V}O_2$ demand. However, it can take 2–4 min, or even longer at higher work rates, before this steady state is attained. Slow $\dot{V}O_2$ kinetics increase the so-called O_2 deficit and obligate a greater contribution from anaerobic mechanisms of ATP production (involving the breakdown of muscle high energy phosphates and lactate production from glycogen) to meet the ATP requirement of the exercise task. A primary goal in this area of research is therefore to elucidate the physiological mechanisms which control and/or limit the rate at which muscle $\dot{V}O_2$ increases following the onset of exercise. At higher intensities of exercise, a continued increase in both muscle and pulmonary $\dot{V}O_2$ is observed with time despite the external work rate remaining constant. This continued rise in $\dot{V}O_2$, beyond the anticipated steady-state requirement for the work rate, has been termed the $\dot{V}O_2$ "slow component," and establishing the mechanistic basis for this phenomenon is another important goal of research in this field. This paper provides an overview of some of the factors which might contribute to both the fundamental and slow phases of the $\dot{V}O_2$ kinetics and, in so doing, provides general background material for the more specific papers that follow. **Key Words:** KINETICS, EXERCISE SLOW COMPONENT, $\dot{V}O_2$

The articles that follow represent the proceedings from a symposium entitled "Oxygen Uptake Dynamics: From Muscle to Mouth" that was presented at the ACSM Annual Meeting in Indianapolis, Indiana in 2004. Interest in the study of oxygen uptake ($\dot{V}O_2$) dynamics, or kinetics, continues to accelerate, as evidenced by the annual growth in the number of publications in the field. However, the 2004 ACSM symposium was the first to be held on the topic at a major international conference since the 1993 ACSM Annual Meeting.

Before the mid-1990s, most of the investigations in this field relied almost exclusively on the measurement of $\dot{V}O_2$ kinetics at the mouth or the estimation of those occurring across the lungs. Although this technique remains important both in describing the response of the "whole" organism and in gaining insight into muscle $\dot{V}O_2$ kinetics, the advent or application of a number of "new" technologies has meant that O_2 kinetics and its putative control determinants can now be studied from a wider range of perspectives. For example, Brandon Walsh, Michael C. Hogan, and colleagues have used phosphorescence quenching techniques to estimate intracellular oxygen tension (PiO_2) in isolated single amphibian myocytes across the transition from rest to contractions. David C. Poole and colleagues have used similar techniques to examine O_2 dynamics in the microvasculature of rat spinotrapezius muscle following the onset of contractions. Bruno Grassi, with L. Bruce Gladden, Michael C. Hogan, Peter Wagner, and others, has used the isolated *in situ* dog gastrocnemius preparation and the direct Fick technique to examine $\dot{V}O_2$ kinetics across the contracting muscle. Finally, Brian J. Whipp and colleagues have used simultaneous measurement of pulmonary gas exchange and muscle high-energy phosphates (derived from magnetic resonance spectroscopy (MRS)) to explore the characteristics and control of muscle $\dot{V}O_2$ kinetics during exercise in humans.

Collectively, these approaches have been instrumental in furthering our understanding of the regulation of oxidative metabolism in the transition from a lower to a higher metabolic rate. However, whereas these techniques have shed light on

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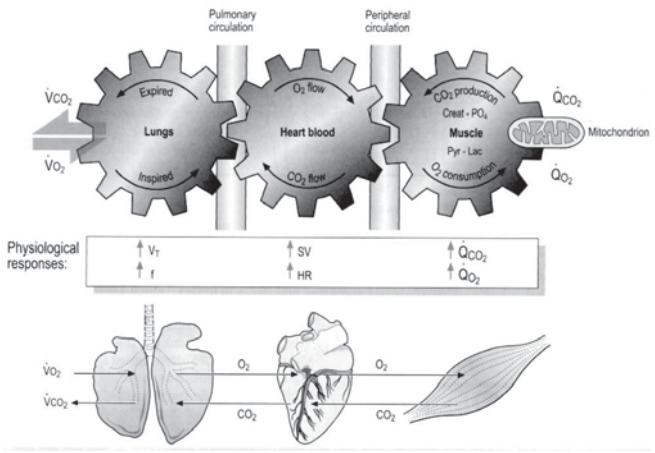

FIGURE 1—Schematic to illustrate the relationship between muscle O_2 consumption and pulmonary O_2 uptake. O_2 is inspired from the atmosphere and delivered by the cardiovascular system to the working muscles, where it is consumed in the mitochondria to produce ATP. The deoxygenated blood is then transported back to the pulmonary circulation enabling muscle $\dot{V}O_2$ to be estimated from pulmonary O_2 exchange, although there will be a temporal misalignment owing to the venous volume and O_2 stores between the muscle and lung. VT, tidal volume; f, breathing frequency; SV, stroke volume; HR, heart rate; $\dot{Q}CO_2$, muscle CO_2 production; $\dot{Q}O_2$, muscle O_2 utilizaion; Creat-PO_4, creatine phosphate; Pyr-Lac, pyruvate-lactate. Adapted from Wasserman et al. (60).

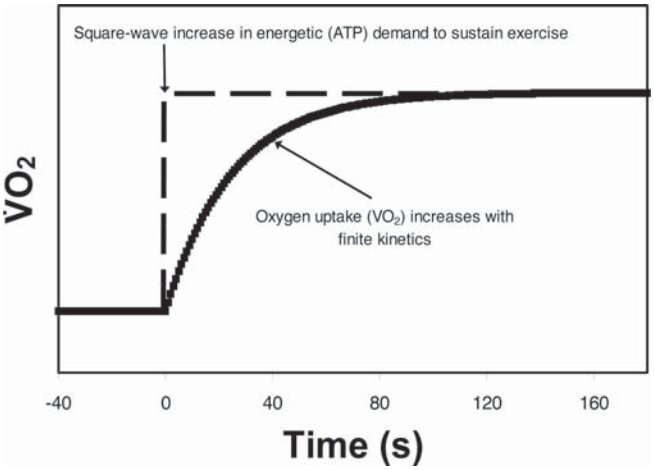

FIGURE 2—Schematic to demonstrate the typical response of muscle O_2 consumption following a "step" transition to constant–work rate exercise of moderate intensity. ATP turnover at the cross bridges increases instantaneously, but muscle $\dot{V}O_2$ increases relatively slowly, not attaining a steady state until approximately 2 min in this example. For clarity and in accordance with recent findings, for example in dog muscle (17), the response is assumed to occur without an appreciable time delay.

some of the key questions in the field of study (see later), they each have their own intrinsic strengths and limitations such that, although the different approaches have generally led to the same conclusions, there are some inconsistencies, and much still to be resolved. The purpose of the symposium was therefore to provide an overview of the present state of knowledge of "$\dot{V}O_2$ kinetics" by drawing together, for the first time, research findings from the new (and older) techniques that are currently being utilized in this field. We took an integrated approach (Fig. 1), starting at the level of the single myocyte (see paper by Walsh et al.), then moving "upstream" to the muscle microcirculation (see paper by Poole et al.), and the whole muscle (see paper by Grassi), and finishing at the level of the whole organism (see paper by Whipp et al.). The symposium was dedicated to the memory of Casey A. Kindig, who was scheduled to contribute to the symposium but who died tragically in a road traffic accident in April 2004. In a short period of time, Casey made an enormous contribution to knowledge in this field from a wide variety of perspectives; he will be greatly missed.

The purpose of this introductory paper is to "set the scene" for the papers that follow, by providing a brief introduction to the field of $\dot{V}O_2$ kinetics. This will involve a description of the muscle (and pulmonary) $\dot{V}O_2$ response to the imposition of a "step" increase in work rate, and a brief commentary on the factors that are currently believed to control, limit, or otherwise influence the kinetic profile of the $\dot{V}O_2$ response to exercise.

MUSCLE AND PULMONARY $\dot{V}O_2$ KINETICS

At the onset of exercise, an immediate increase in adenosine triphosphate (ATP) production in the active muscle cells is required to meet the increased metabolic demand. Measurements of muscle $\dot{V}O_2$, however, reveal that the ATP supplied by oxidative phosphorylation as a proportion of the total ATP requirement rises comparatively slowly, such that a steady-state matching between ATP utilization and ATP supply through oxidative metabolism might not be achieved until at least 2 min following the onset of exercise (Fig. 2). The initial rise in muscle $\dot{V}O_2$ can be well described by an exponential function, consistent with a system under first-order control ((41); see below), and can thus be described with an equation of the form:

$$\dot{V}O_2(t) = \dot{V}O_2 \text{ baseline} + \text{amplitude}(1 - e^{-(t-TD)/\tau}) \quad [1]$$

where $\dot{V}O_2$ (t) is the $\dot{V}O_2$ at any time t, $\dot{V}O_2$ baseline is the $\dot{V}O_2$ before the onset of exercise, amplitude is the "steady state" to which $\dot{V}O_2$ projects, TD is the time delay preceding the increase in muscle $\dot{V}O_2$, and τ is the time constant describing the rate at which $\dot{V}O_2$ rises towards the steady state.

The time constant, τ, is a measure of the time required for $\dot{V}O_2$ to reach 63% of its final amplitude: when two time constants have elapsed, $\dot{V}O_2$ will therefore have attained approximately 86% of its final amplitude (i.e., $0.63 + 0.63 \times (1.0 - 0.63) = 0.86$); when three time constants have elapsed, $\dot{V}O_2$ will have attained approximately 95% of its final amplitude; and when four time constants have elapsed, $\dot{V}O_2$ will have attained more than 98% of its final amplitude and the response will be essentially complete. Low values of τ therefore represent "fast" $\dot{V}O_2$ response kinetics (e.g., a τ of 20 s means that a steady-state $\dot{V}O_2$ is attained in approximately 80 s following the onset of muscle contractions; i.e., 4×20 s), whereas high values of τ represent "slow" $\dot{V}O_2$ kinetics (a τ of 50 s means that a steady-state $\dot{V}O_2$ is attained in approximately 200 s; 4×50 s).

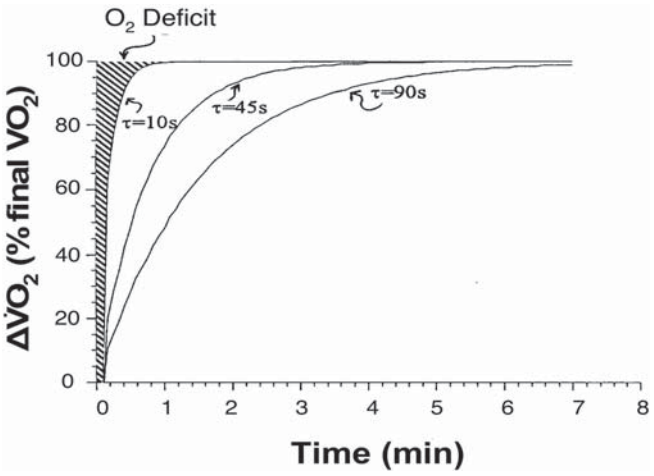

FIGURE 3—Examples of the O_2 deficit that would be incurred by individuals with different values for the fundamental component $\dot{V}O_2$ time constant (τ) following the onset of exercise. For the same increase in metabolic rate, represented by the $\dot{V}O_2$ attained in the steady state, an individual with fast $\dot{V}O_2$ kinetics would incur a much smaller O_2 deficit than would individuals with slower $\dot{V}O_2$ kinetics (see text for details).

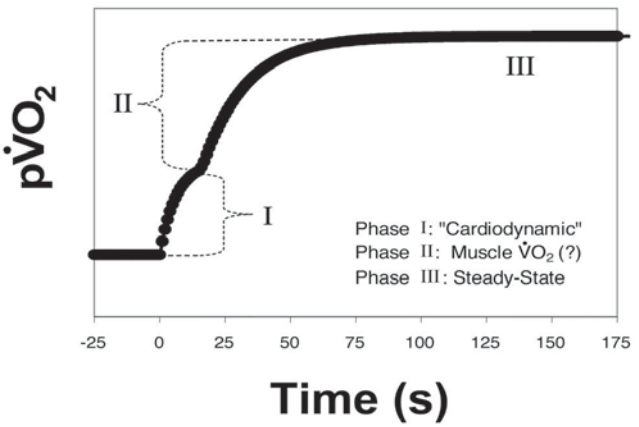

FIGURE 4—Schematic to demonstrate the typical response of pulmonary O_2 uptake following the sudden onset of "step" or constant–work rate exercise of moderate intensity. Note the similarity to the muscle $\dot{V}O_2$ response schematized in Figure 2. The time constant describing the predominant, near-exponential, rise in pulmonary $\dot{V}O_2$ in phase II has been shown to provide a close representation of the time constant for the increase in muscle $\dot{V}O_2$.

The τ of the $\dot{V}O_2$ response following an increase in metabolic rate is an important determinant of the so-called "O_2 deficit," which is calculated as follows:

$$O_2 \text{ deficit} = \text{amplitude}^*\tau \quad [2]$$

It should be noted here that this calculation relies on the assumption that the ATP turnover rate (and thus the amplitude term in equation 2) is constant from the onset of exercise; however, there are recent challenges to this notion (36). Nevertheless, applying equation 2 to a work rate requiring a steady-state increase in $\dot{V}O_2$ of 1 $L \cdot min^{-1}$ above baseline, an extremely fit subject with very fast muscle $\dot{V}O_2$ kinetics (τ of 10 s) would incur an O_2 deficit of 0.17 L (i.e., $1 \times 10/60$), whereas a cardiac or pulmonary disease patient with very slow muscle $\dot{V}O_2$ kinetics (τ of 90 s) would incur a substantially larger O_2 deficit of 1.5 L ($1 \times 90/60$), (Fig. 3). The magnitude of the O_2 deficit principally reflects the contribution of nonoxidative mechanisms of ATP resynthesis to the ATP turnover rate, although there will also be a small contribution from the O_2 bound to myoglobin at higher work rates. Therefore, a larger O_2 deficit is associated with a greater depletion of muscle phosphocreatine (PCr) and, particularly at higher work rates, a greater production of lactic acid through anaerobic glycolysis to meet the energy requirement. A depletion of muscle high-energy phosphates and a reduction in muscle pH have both been implicated in the fatigue process (14), such that faster muscle $\dot{V}O_2$ kinetics should be associated with enhanced exercise tolerance.

The measurement of muscle $\dot{V}O_2$ kinetics is invasive and technically challenging, and not suitable for routine laboratory use. Fortunately, the available evidence indicates that measurement of $\dot{V}O_2$ kinetics at the lung provides an accurate and convenient method of estimating the kinetics of O_2 consumption at the level of the working muscles, although there are naturally a number of factors which complicate this relationship (see paper by Whipp et al.). One obvious difference between the dynamic profiles of muscle and pulmonary $\dot{V}O_2$ kinetics following the onset of exercise is the existence of an additional component in the pulmonary $\dot{V}O_2$ response in the first 15–20 s of exercise (Fig. 4). This "phase I" response represents an increase in $\dot{V}O_2$, resulting from a rapid increase in blood flow through the lung consequent to the immediate increase in cardiac output at the onset of exercise and, importantly, does not reflect an increased muscle O_2 consumption. The arrival of deoxygenated blood at the lung, resulting from an increased muscle O_2 consumption following the onset of exercise, is marked by a fall in the end-tidal pressure of O_2 ($PETO_2$), and it is this that signifies the end of phase I and the beginning of phase II, where phase II represents the predominant, or fundamental, exponential rise in $\dot{V}O_2$ towards the expected steady state.

The absolute $\dot{V}O_2$ measured at the lung will always be higher than the absolute $\dot{V}O_2$ measured across the working muscles (this will vary according to the exercise mode and intensity, but the difference is typically approximately 10–15% during cycle exercise) due to the O_2 cost associated with cardiac and ventilatory work, the maintenance of posture, etc. However, although the responses are "offset" by some 10–15 s, there is evidence that the τ describing the rate with which pulmonary $\dot{V}O_2$ rises in phase II faithfully reflects the τ for O_2 consumption in the exercising muscles, to within $\pm 10\%$ (19,55).

To this point, this paper has summarized the muscle and pulmonary $\dot{V}O_2$ responses to "moderate" work rates at which a steady state in $\dot{V}O_2$ is attained rather rapidly, and that provides a close match to the muscle ATP turnover rate. At higher work rates that elicit a lactic acidosis (i.e., above the lactate threshold, LT), however, additional complexities in the muscle (and pulmonary) $\dot{V}O_2$ kinetic response to exercise begin to emerge (11,42,57,64). Most striking, perhaps, is the continued increase in $\dot{V}O_2$ observed beyond 2–3 min of exercise that leads, eventually, to $\dot{V}O_2$ attaining

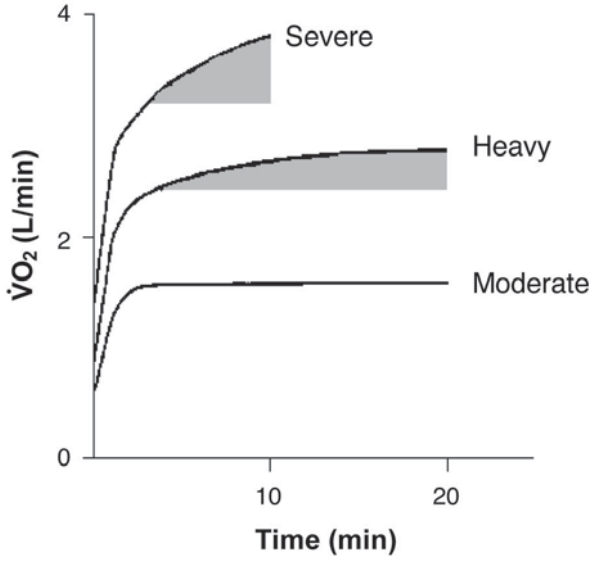

FIGURE 5—Schematic representation of the pulmonary $\dot{V}O_2$ response to constant–work rate exercise in the moderate (below LT), heavy (above LT), and severe (above the critical power) exercise domains. For clarity, the phase I $\dot{V}O_2$ response occurring at exercise onset has been omitted. Note that for moderate-intensity exercise, $\dot{V}O_2$ increases monoexponentially to the steady state, which in healthy subjects is achieved within 3 min. In contrast, for heavy- and severe-intensity exercise, the steady state is either delayed (heavy) or not achieved (severe) because of the slow component (*shaded area*), which occurs only above the LT.

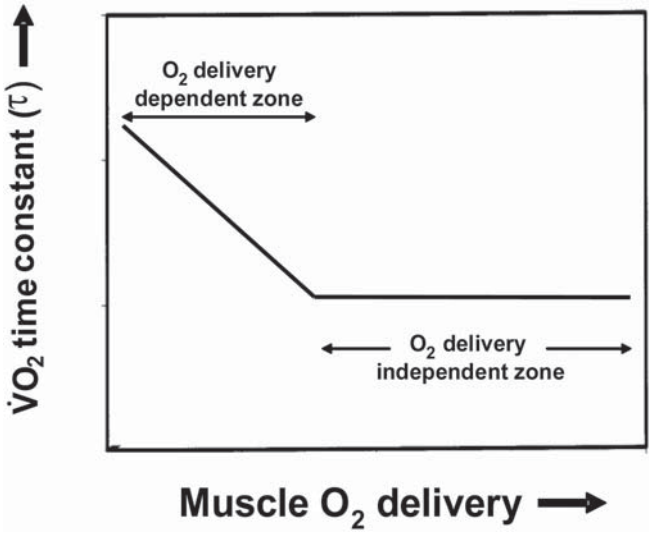

FIGURE 6—Schematic representation of the limitation of $\dot{V}O_2$ kinetics by muscle O_2 delivery in some, but not all, circumstances. See Table 1 for specific conditions lying in the O_2 delivery–dependent and independent zones. This concept was developed, in part, through discussions with Drs. S. Koga and T. J. Barstow.

higher values than would have been predicted for the external work rate (61) (Fig. 5). This feature of the response has been termed the $\dot{V}O_2$ "slow component." Functionally, the $\dot{V}O_2$ slow component is important in that it represents an (increasing) inefficiency, reflected in an increased muscle energy turnover (2) and continued reduction in muscle [PCr] (55). Moreover, at work rates above the so-called "critical power," the $\dot{V}O_2$ slow component can cause $\dot{V}O_2$ to attain its maximum, with exhaustion occurring soon afterwards (48). The $\dot{V}O_2$ slow component therefore appears to be linked in some way to the fatigue process, such that understanding its mechanistic bases could lead to interventions or treatments that enhance exercise tolerance both in health and disease.

KEY RESEARCH QUESTIONS

Perhaps the fundamental question in research into $\dot{V}O_2$ kinetics concerns the factor or factors which control and/or limit the rate at which $\dot{V}O_2$ increases following the onset of exercise; this is a key focus in the papers that follow. A secondary (but no less important or interesting) question concerns the physiological basis to the $\dot{V}O_2$ slow component that is observed at higher relative work rates.

Fundamental component time constant. Traditionally, the possible sites of control or limitation have been considered to reside within the muscle cells themselves (so-called "oxidative metabolic inertia"), or to be related to an inadequate delivery of O_2 to muscle (cardiovascular or muscle perfusion limitation), although this arbitrary division might well be overly simplistic (23) (Fig. 6 and Table 1). The answer to this question is not just of academic interest; understanding the cause(s) of the obligatory O_2 deficit that is incurred following the onset of exercise might facilitate the development of treatments to improve exercise tolerance and the quality of life in older age and in a variety of disease states.

There is compelling evidence that the rate at which muscle $\dot{V}O_2$ increases following the onset of exercise is principally under "feedback" control through one or more of the products of high-energy phosphate hydrolysis (41,55). For example, Rossiter et al. (55) have reported the existence of a close temporal relationship between the kinetics of muscle [PCr] depletion (measured by ^{31}P-MRS) and the simultaneously measured pulmonary $\dot{V}O_2$ kinetics (see Fig. 4 in the paper by Whipp et al. in this series). Kindig et al. (29) have recently shown that acute inhibition of creatine kinase (CK) in single isolated myocytes resulted in a significant speeding of PiO_2 kinetics (equivalent to faster $\dot{V}O_2$ kinetics in this model). These data suggest that CK activity acts as an energy buffer in the transition to a higher metabolic rate, reducing the stimulation of mitochondrial respiration by, for example, [ADP] or the phosphorylation potential.

The site(s) of any further inertia to the increase in $\dot{V}O_2$ might reside in the activation of any of the enzymes involved in oxidative metabolism. Of these, significant research attention has been paid to the pyruvate dehydrogenase complex (PDC), which irreversibly commits acetyl groups to the tricarboxylic acid cycle for oxidation. It has been demonstrated that preexercise activation of the PDC with dichloroacetate (DCA) can reduce substrate-level phosphorylation (SLP) (i.e., PCr hydrolysis and anaerobic glycolysis) early in exercise, and this has led to suggestions that oxidative metabolism must be greater in this condition (20). However, although there is evidence for a speeding of PiO_2 kinetics with DCA in the frog single-fiber model (22), no studies to date have been able to discern any effect of

TABLE 1. Examples of exercise models and conditions residing in the O_2 delivery–dependent and independent zones (see Figure 6).

O_2 Delivery–Dependent	Ambiguous	O_2 Delivery–Independent
Dog gastroc–plantaris complex at 100% $\dot{V}O_{2max}$	Upright cycling in heavy/severe domains?	Upright cycling and running in moderate domain
Supine cycling exercise		Horse exercising in moderate and heavy domains
Arm exercised above heart		Rat muscles stimulated in moderate domain
β-blockade		Dog gastroc–plantaris complex at 60% $\dot{V}O_{2max}$
Exercise with blood flow impeded		
Hypoxia		
Various disease states (e.g., diabetes, chronic heart failure, systemic hypotension)		

DCA on whole muscle or pulmonary $\dot{V}O_2$ kinetics (1,17,24,35,53). This might relate to altered muscle efficiency with DCA (e.g., reduced ATP turnover and/or greater P/O (17,53)) or to the fact that any (disputed) "acetyl group deficit" is so short-lived (52) that any effect on $\dot{V}O_2$ would be too small to be measurable. In any event, it appears that substrate availability does not represent a principal limitation to $\dot{V}O_2$ kinetics in healthy humans.

It is well known that nitric oxide (NO) has important effects in a wide array of physiological processes, although its role in the regulation of vasodilatation has been particularly well studied (28). Recently, it has been suggested that NO can both interfere with muscle contraction (43,51) and regulate mitochondrial respiration by inhibiting a number of key muscle metabolic enzymes and by competing with O_2 for the binding site at cytochrome c oxidase, the terminal electron acceptor in the electron transport chain (7). Several studies have examined the possibility that NO represents one component of the inertia to oxidative metabolism following the onset of exercise (26,27,30,31,62). Kindig et al. (30,31) studied the influence of NO synthase inhibition with the drug nitro l-arginine methyl ester (L-NAME) on $\dot{V}O_2$ kinetics during treadmill running in the thoroughbred horse and reported an approximately 31% reduction in the phase II τ for both moderate and heavy exercise. More recently, in a series of separate experiments, Jones and colleagues studied the influence of L-NAME on $\dot{V}O_2$ kinetics during moderate (26), heavy/severe (27), and extreme (62) exercise in humans (Fig. 7). The reduction in the phase II τ was 19, 13, and 44%, respectively, in these studies. Although these results remain to be confirmed across the working muscles, in combination, these studies strongly suggest that NO exerts an important inhibitory influence on mitochondrial respiration following the onset of exercise, and that relieving this can result in faster phase II $\dot{V}O_2$ kinetics. That NO has the potential to (simultaneously) influence muscle blood flow, muscle contraction, and mitochondrial function suggests that it might play a key role in the integration of muscle O_2 delivery and utilization.

In situations in which O_2 delivery to muscle might be reduced, for example during supine (relative to upright) exercise (33), inspiration of hypoxic gas (13), and also in a variety of cardiovascular disease conditions (46), the phase II τ is lengthened (Fig. 6 and Table 1). These data suggest a delicate balance between O_2 supply and demand that, if perturbed, can result in slower $\dot{V}O_2$ kinetics. However, "proof" that O_2 supply limits the $\dot{V}O_2$ kinetics requires the demonstration of a reduction in the phase II τ when muscle O_2 supply is elevated above that observed in the normal "control" condition. Evidence for this is mixed. For example, in young healthy subjects performing upright cycle exercise, the performance of a "priming" bout of high-intensity exercise that increases muscle blood flow before and during subsequent exercise (37) has not significantly altered the phase II τ in the vast majority of studies (for review, see (9)). Furthermore, the inspiration of hyperoxic gas has not been found to alter SLP during the early phase of exercise (56), the phase II τ (40), or the τ of muscle [PCr] kinetics (21). Grassi et al. (16) fixed muscle blood flow at the steady-state requirement across the transition from rest to muscle contractions requiring 60% $\dot{V}O_{2max}$ in the isolated canine gastrocnemius model and found no change in the τ for muscle $\dot{V}O_2$ compared with the spontaneous blood flow condition. These data have collectively been interpreted to suggest that muscle O_2 availability does not normally represent a significant limitation to $\dot{V}O_2$ kinetics during moderate and heavy exercise.

On the other hand, in situations in which muscle blood flow might have been compromised in the "control" condition, such as in exercise modalities where the body position reduces perfusion pressure, or where elderly subjects have been studied, priming exercise has resulted in faster $\dot{V}O_2$ kinetics (9,54,58). Also, Perrey et al. (44) have reported that an increase in forearm blood flow brought about by a

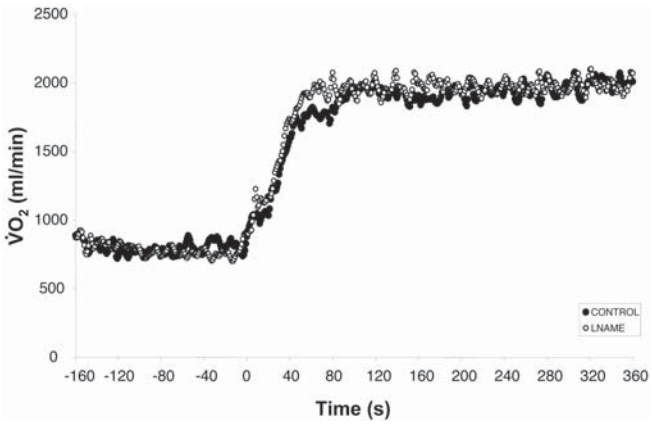

FIGURE 7—Influence of nitric oxide synthase (NOS) inhibition with L-NAME on pulmonary $\dot{V}O_2$ kinetics in the transition from unloaded cycling to a moderate intensity (<LT) work rate. The control condition is represented by the *filled symbols*, and the L-NAME condition is represented by the *open symbols*. Note the faster $\dot{V}O_2$ kinetics following NOS inhibition, leading to the more rapid attainment of a steady state. Redrawn from Jones et al. (26).

combination of leg occlusion and ischemic calf exercise was associated with a more rapid increase in estimated muscle $\dot{V}O_2$ towards the steady state during dynamic handgrip exercise. Furthermore, although relatively few studies have examined the influence of O_2 availability on $\dot{V}O_2$ kinetics during near maximal–intensity exercise, the available evidence suggests that O_2 might impact upon either the τ (18) or the amplitude (57,62,63,64) of the $\dot{V}O_2$ response in this situation. For example, in contrast to their earlier study at a lower intensity of exercise (16), Grassi et al. (18) reported a significant speeding of $\dot{V}O_2$ kinetics when the requisite "steady-state" blood flow was held constant across the transition from rest to muscle contractions requiring 100% $\dot{V}O_{2max}$ in the isolated canine gastrocnemius model. These data illustrate the importance of factors such as exercise modality (44,54), subject population (58), and exercise intensity (18) when considering the influence of O_2 supply on $\dot{V}O_2$ kinetics (59). It should also be appreciated that, even if the measured $\dot{V}O_2$ is unchanged, an alteration in the phosphorylation potential with relatively greater breakdown of PCr will be required to maintain the same rate of oxidative ATP production in conditions where there is a low muscle PO_2 (66). The increase in muscle and pulmonary $\dot{V}O_2$ following the onset of exercise should therefore be considered to be dependent upon a complex integration of cardiovascular and metabolic factors that regulate the supply and consumption of O_2. The role of O_2 supply in regulating and limiting $\dot{V}O_2$ kinetics across the continuum of exercise activities is schematized in Figure 6.

$\dot{V}O_2$ slow component. A second important question in $\dot{V}O_2$ kinetics research concerns the mechanistic bases to the $\dot{V}O_2$ slow component. It has been shown that the vast majority of the $\dot{V}O_2$ slow component (>85%) derives from within the exercising muscles (47,55), ruling out a major contribution to the $\dot{V}O_2$ slow component from extramuscular sources such as an increased O_2 cost of additional ventilatory or cardiac work. The close temporal relationship between the profiles of pulmonary $\dot{V}O_2$ and blood [lactate] for exercise greater than LT led some researchers to suggest that the O_2 cost of glucogenesis from lactate might be an important determinant of the $\dot{V}O_2$ slow component. However, infusion of epinephrine, which resulted in a significant increase in blood [lactate], was found not to significantly influence the magnitude of the $\dot{V}O_2$ slow component (15), suggesting only a coincidental link between the two variables. One possible intramuscular mechanism for the $\dot{V}O_2$ slow component is a temperature-induced uncoupling of the mitochondria (65). However, passive elevation of muscle temperature to values similar to those reached during exercise has not resulted in an augmented $\dot{V}O_2$ slow component (32). By a process of elimination, therefore, differences in the energetic properties in muscle fibers, their recruitment profiles, and the metabolic effects of heavy/severe exercise within those muscle fibers, must be considered to represent plausible mechanisms for the $\dot{V}O_2$ slow component. Exercise at higher work rates is associated with the recruitment of fibers that are larger, faster to contract, and more readily fatigued, with a greater type IIA and IIX myosin heavy

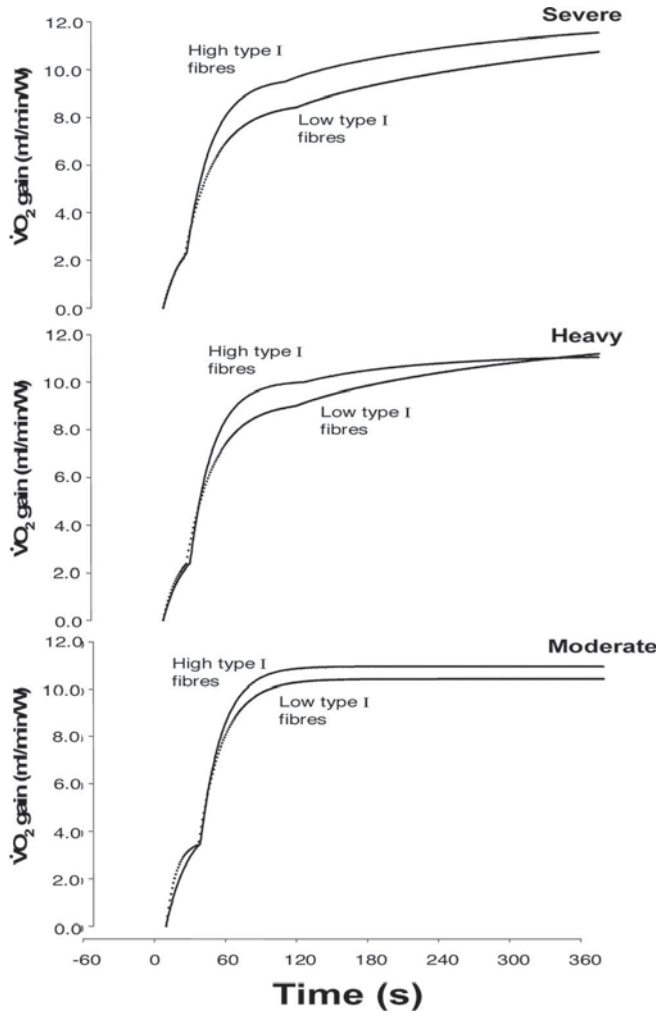

FIGURE 8—Influence of muscle fiber type distribution in the m. vastus lateralis on pulmonary $\dot{V}O_2$ kinetics at three different exercise intensities. Note that subjects with a high percentage of type I muscle fibers demonstrate a greater gain of the fundamental component of $\dot{V}O_2$ and a smaller gain of the $\dot{V}O_2$ slow component. Redrawn from Pringle et al. (49).

chain complement, faster cross-bridge cycling rate, greater glycolytic capacity, but reduced oxidative capacity and capillarity (5). It is widely believed that these fibers are "less efficient" (i.e., have a greater phosphate cost of force generation and/or a greater O_2 cost of high-energy phosphate resynthesis) than the fibers recruited early in the recruitment hierarchy, although both contraction intensity and velocity are known to influence efficiency in human fibers (5,25).

Several approaches have been taken to investigate the relationship between fiber type activation and $\dot{V}O_2$ kinetics. Barstow et al. (3) and Pringle et al. (49) both reported that the percentage of type I muscle fibers in the vastus lateralis was negatively correlated with the relative amplitude of the $\dot{V}O_2$ slow component (Fig. 8). Other studies have examined the relationship between electromyographic (EMG) markers of fiber recruitment and the $\dot{V}O_2$ slow component. In one such study, Burnley et al. (8) reported a close association between the temporal profiles of pulmonary $\dot{V}O_2$ and iEMG during both an initial and a subsequent bout of high-intensity exercise. But perhaps not surprisingly, given the num-

ber of potentially confounding factors, a relationship between measurements of muscle activation and the $\dot{V}O_2$ slow component has not been consistently found (25). It has recently been reported that glycogen depletion of the type I muscle fiber pool increased type II fiber recruitment and resulted in what appeared to be a $\dot{V}O_2$ slow component response during what was ostensibly "moderate" exercise (39). In another study, glycogen depletion of the type II fiber pool resulted in a reduced $\dot{V}O_2$ slow component compared with the control condition (10). Using another type of intervention to alter muscle fiber recruitment, Pringle et al. (50) reported that the $\dot{V}O_2$ slow component was greater when heavy cycle exercise was performed at a high pedal rate (where a greater proportional contribution of type II fibers to force generation was expected) compared with a low pedal rate. The first direct evidence of a role for fiber recruitment in the etiology of the $\dot{V}O_2$ slow component has recently been provided by Krustrup et al. (38). These authors demonstrated that the increase in pulmonary $\dot{V}O_2$ with time after 2–3 min of heavy exercise was associated with the recruitment of both type I and II fibers from the onset of exercise, with a subsequent continued increase in the recruitment of both fiber types with time.

These studies collectively indicate that the recruitment of type II fibers at the onset of and/or during exercise is intrinsically linked to the $\dot{V}O_2$ slow component. Intriguingly, however, many of the conditions or interventions that are related to or can influence the $\dot{V}O_2$ slow component have a corresponding, but directionally opposite, influence on the "gain" (i.e., increase in $\dot{V}O_2$ per unit increase in work rate) of the fundamental $\dot{V}O_2$ response (3,6,25,33,40,49,50). This potentially provides important clues concerning the regulation of oxidative metabolism during both the fundamental and slow phases of the $\dot{V}O_2$ response to exercise that remain to be resolved. The precise nature of the relationship between muscle fiber recruitment profiles and the $\dot{V}O_2$ slow component is also presently unclear. It was originally hypothesized that the $\dot{V}O_2$ slow component represented a reduced efficiency due to the recruitment of higher order fibers with time. However, it is also possible that the $\dot{V}O_2$ slow component might reflect, at least to some extent, the cost of recovery and other metabolic processes in the initially recruited fibers (of either principal "type") that have become fatigued (25,50).

Interestingly, the recruitment of higher order fibers with low oxidative capacity at higher work rates might also be expected to impact upon the "net" $\dot{V}O_2$ kinetic response measured across the muscle or at the lung during the fundamental phase of the response (6,25,34,49,50). The τ for the increase in $\dot{V}O_2$ has been reported to be considerably longer in type II compared with type I muscle fibers in some animal models (5,12), although whether this is also true in human muscle is not clear. The recruitment of higher order fibers with innately slower $\dot{V}O_2$ kinetics at higher work rates might explain why the majority of studies suggest a lengthening of the fundamental component τ at work rates above, compared to below, the LT (45). An additional consideration, however, is that the relatively slow blood flow dynamics in fast compared with slow muscle (4) reduces the PO_2 gradient between the capillary and the myocyte and potentially slows the $\dot{V}O_2$ kinetics in type II fibers.

SUMMARY

This paper has described the muscle and pulmonary $\dot{V}O_2$ response to a sudden increase in work (and therefore metabolic) rate, and highlighted some of the contentious issues and ongoing questions in this buoyant subdiscipline of exercise physiology. The following papers focus specifically on the factors that regulate or modulate the increase in $\dot{V}O_2$ following the onset of muscle contractions or exercise. Each paper summarizes recent research findings derived from a variety of experimental models including the measurement of O_2 or $\dot{V}O_2$ kinetics in the isolated single myoctye (Walsh et al.), the microvasculature (Poole et al.), the whole muscle (Grassi) and, finally, the human (Whipp et al.). It should be appreciated in reading these papers that, whereas simpler animal muscle models have the advantage of allowing a more direct investigation of the factors which regulate and/or limit $\dot{V}O_2$ kinetics, the extent to which the results from these experiments reflect the control of, and constraints to, $\dot{V}O_2$ kinetics in humans (where factors such as alterations in motor unit recruitment and regional heterogeneities in regional perfusion and metabolic rate may exist) is presently unclear.

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