

POINT-COUNTERPOINT

COUNTERPOINT

Regulation of Oxygen Consumption at Exercise Onset: Is It Really Controversial?

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GRASSI, B. Regulation of oxygen consumption at exercise onset: is it really controversial? *Exerc. Sport Sci. Rev.*, Vol. 29, No. 3, pp 134–138, 2001. *The conflicting hypotheses on the limiting factors for skeletal muscle \dot{V}_{O_2} on-kinetics might be reconciled in a unifying scenario. Under “normal” conditions, during transitions to moderate-intensity exercise, the limiting factor appears to be an inertia of oxidative metabolism. During transitions to exercise of higher metabolic intensity, O_2 delivery could play a relatively minor but significant role as a limiting factor.* **Keywords:** skeletal muscle, oxidative metabolism, metabolic regulation, \dot{V}_{O_2} kinetics

INTRODUCTION

Living organisms are seldom under conditions of metabolic steady state. Skeletal muscle work is associated with increases and decreases in power output, which are apparent in most activities of everyday life, work, or sport. The rate at which skeletal muscle oxidative metabolism adjusts to a new metabolic requirement is one of the factors that determines exercise tolerance; that is, a faster adjustment in oxidative phosphorylation during increases in work rate (“on-transitions”) reduces the need for substrate-level phosphorylation, with less disturbance of cellular and organ homeostasis. This is likely the basis for the long-lasting interest in the limiting factors of the kinetics of adjustment of oxygen uptake (\dot{V}_{O_2}) during on-transitions (\dot{V}_{O_2} on-kinetics). The topic also is of interest from a “basic science” point of view, because the analysis of physiological variables during metabolic transitions can yield valuable insights into the mechanism or mechanisms of regulation of oxidative metabolism during exercise.

CONFLICTING HYPOTHESES?

For many years, there has been significant debate between those in favor of the concept that the finite kinetics of \dot{V}_{O_2} adjustment during on-transitions is attributable to an intrinsic slowness of intracellular oxidative metabolism to adjust to the new metabolic requirement (“metabolic inertia”) (15) and those who suggest that the main limiting factor resides in the finite kinetics of O_2 delivery to muscle fibers (14). However, considering the wide range of work intensity, type of exercise, muscle involvement, and environmental factors (not to mention pathological conditions) possibly associated with metabolic transitions, regulation in all cases by a single factor appears unlikely. In such a complex scenario, it seems more appropriate to hypothesize the involvement, to varying degrees depending on the specific situation, of more than one limiting factor. Thus, the apparently conflicting hypotheses just mentioned might be, at least in part, reconciled in a unified scenario, which is briefly outlined later.

WHICH IS FASTER TO ADJUST: O_2 DELIVERY OR O_2 UTILIZATION?

For some time, the approach to the problem has been to define whether the adjustment of O_2 delivery (usually estimated on the basis of heart rate [HR] or cardiac output [Q]) was indeed faster than that of O_2 utilization (usually inferred by the kinetics of pulmonary O_2 uptake [\dot{V}_{O_2p}]). This type of approach, however, could yield only inconclusive evidence in favor of one of the conflicting hypotheses. Faster HR or Q

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on-kinetics in comparison to $\dot{V}O_{2p}$ on-kinetics (as observed in most studies), for example, does not necessarily demonstrate that the former are not limiting factors of the latter. Moreover, for methodological reasons, the investigated variables (HR, \dot{Q} , $\dot{V}O_{2p}$) were quite “distant” from the relevant ones: muscle blood flow (\dot{Q}_m) and muscle $\dot{V}O_2$ ($\dot{V}O_{2m}$).

The latter problem has been at least in part overcome in recent years. For example, Grassi et al. (8) determined the kinetics of adjustment of leg blood flow (\dot{Q}_{leg}) and leg $\dot{V}O_2$ in exercising humans during transitions from unloaded pedaling to constant-load cycling exercise below the “ventilatory threshold” (VT). These authors showed that \dot{Q}_{leg} was significantly faster, during the first 10 to 15 s of the transition, than the kinetics of $C(A-v)O_2$ determined across the exercising limb. These data provide indirect evidence in favor of the metabolic inertia hypothesis. In that study, $\dot{V}O_2$ was not determined across an exercising muscle but rather across an exercising limb. Thus, there was a “dead space” volume of venous blood, the washout of which needed to be accounted for in the interpretation of the observed venous O_2 concentration kinetics. Prudent estimates of such dead space volume, however, suggest that its washout was responsible for only a part of the observed $C(A-v)O_2$ delay (8). An excess of O_2 delivery in relation to O_2 needs at the skeletal muscle level was also more recently described by Bangsbo et al. (1) in exercising humans during transitions to intense leg-kick exercise.

Recent preliminary studies performed by different groups approached the same problem but were able to obtain information from inside the muscle, or even from inside a single muscle fiber. The obtained results appear to be in striking agreement with those of the study by Grassi et al. (8). Behnke et al. (2) determined muscle microvascular PO_2 kinetics by a phosphorescence-quenching technique across exercise transitions in the spinotrapezius muscle of the rat. Hogan (9) determined, by a similar technique, the kinetics of intracellular PO_2 in isolated single skeletal muscle fibers obtained from frogs. In both studies, PO_2 did not change significantly during the first few seconds of a rest-to-contraction transition. The absence of an immediate fall in microvascular/intracellular PO_2 at contraction onset suggests that O_2 availability is not limiting oxidative metabolism in these conditions.

As mentioned, however, these types of evidence are only indirectly in favor of the metabolic inertia hypothesis. To demonstrate whether O_2 delivery is (or is not) the limiting factor, experiments showing that faster-than-normal O_2 delivery kinetics is (or is not) associated with a faster-than-normal $\dot{V}O_2$ kinetics are needed.

DOES ENHANCED O_2 DELIVERY SPEED $\dot{V}O_2$ ON-KINETICS?

This approach was recently followed in several studies that used the isolated *in situ* canine gastrocnemius preparation. This preparation offers several advantages compared with human models: it allows direct measurement of the kinetics of O_2 delivery to muscle and the kinetics of $\dot{V}O_2$ across the muscle ($\dot{V}O_{2m}$) and allows manipulations of the relevant

independent variable (i.e., O_2 delivery to muscle fibers). It was first tested whether *convective O_2 delivery* to muscle was a limiting factor for $\dot{V}O_{2m}$ on-kinetics: all delays in the adjustment of O_2 delivery were eliminated by keeping \dot{Q}_m constantly elevated during transitions from rest to 4 min of electrically induced isometric tetanic contractions corresponding to $\approx 60\%$ (5) and $\approx 100\%$ (7) of the muscle peak $\dot{V}O_2$. A vasodilatory drug (adenosine) was infused intra-arterially in association with the constantly elevated \dot{Q}_m to prevent vasoconstriction. Elimination of all delays in convective O_2 delivery during the transition did not affect the $\dot{V}O_{2m}$ on-kinetics at the lower contraction intensity (5), whereas the kinetics was slightly but significantly faster (versus the control condition) at the higher intensity, leading to an $\approx 25\%$ reduction in the calculated O_2 deficit (7) (Figure 1). These results suggest that for transitions from rest to submaximal $\dot{V}O_{2m}$, $\dot{V}O_{2m}$ on-kinetics is not limited by convective O_2 delivery to muscle, whereas for transitions to peak $\dot{V}O_2$, convective O_2 delivery plays a relatively minor, although significant, role as a limiting factor for the $\dot{V}O_{2m}$ on-kinetics.

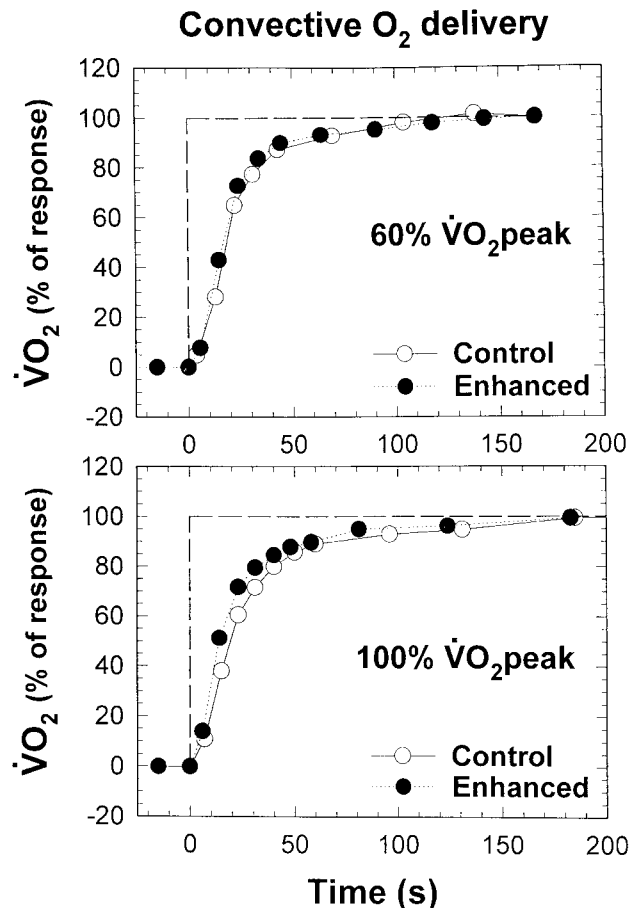


Figure 1. Skeletal muscle $\dot{V}O_2$ on-kinetics during transitions from rest to electrically stimulated contractions corresponding to 60% (top) and 100% (bottom) of peak $\dot{V}O_2$ (isolated canine gastrocnemius *in situ*). Two conditions were compared: control (\circ) and enhanced convective O_2 delivery (\bullet). The area delimited by the broken lines and the lines connecting experimental points indicates the “ O_2 deficit.” $\dot{V}O_2$ data are expressed as a percentage of the total $\dot{V}O_2$ response (i.e., of the difference between steady-state values at the end of contractions and resting values).

Further experiments were conducted to determine the role of *peripheral O₂ diffusion* as a potential limiting factor for the \dot{V}_{O_2m} on-kinetics. Again, two types of transitions were investigated: from rest to 4 min of electrically induced isometric tetanic contractions corresponding to $\approx 60\%$ (6) and $\approx 100\%$ (Grassi et al., unpublished observations) of the muscle peak \dot{V}_{O_2} . Peripheral O_2 diffusion was enhanced by increasing capillary P_{O_2} and therefore the O_2 partial pressure gradient from the capillary to the inside of the cell. The increase in capillary P_{O_2} was obtained by having the dogs breathe a hyperoxic gas mixture ($F_{iO_2} = 1.00$) and by the administration of a drug (RSR13; Allos Therapeutics), which, as an allosteric inhibitor of O_2 binding to hemoglobin, causes a rightward shift of the hemoglobin- O_2 dissociation curve. In both the control and the “treatment” condition, Q_m was kept constantly elevated through the transition, and the vasodilatory drug adenosine was infused. The resulting enhancement of peripheral O_2 diffusion did not significantly affect the \dot{V}_{O_2m} on-kinetics during transitions to either submaximal (6) (Figure 2) or peak \dot{V}_{O_2} .

Considered together, these studies provide compelling evidence in favor of the hypothesis that metabolic inertia within the muscle is the limiting factor for the \dot{V}_{O_2} on-kinetics during transitions to contractions of relatively low metabolic intensity. On the other hand, during transitions to contractions of relatively high metabolic intensity, convective O_2 delivery would play a relatively minor but significant role as a limiting factor.

In substantial agreement with this concept are data obtained by, among others, MacDonald et al. (10) in exercising humans. These authors demonstrated a slightly faster \dot{V}_{O_2p} on-kinetics during constant-load exercise above VT, when the exercise was preceded by a high-intensity “warm-up” exercise that presumably enhanced O_2 delivery during the

subsequent bout and/or when the subjects were inspiring a hyperoxic mixture. On the other hand, the same maneuvers (high-intensity warm-up and/or hyperoxic breathing) did not affect \dot{V}_{O_2p} on-kinetics during constant-load exercise below VT. Thus, in humans, VT could discriminate between work intensities at which O_2 delivery is not (i.e., those below VT) or is (those above VT) one of the limiting factors for the \dot{V}_{O_2p} on-kinetics. The scenario could be more complex due to the presence of the slow component of \dot{V}_{O_2p} on-kinetics during exercise above VT. For example, recent data (3) suggest that the speeding of the overall (no distinction between the “primary” and the “slow” component) \dot{V}_{O_2p} on-kinetics during exercises above VT, obtained by the preceding high-intensity warm-up, is mainly attributable to a reduction in amplitude of the slow component. On the other hand, the “primary” \dot{V}_{O_2p} component of the kinetics would be substantially unaffected. However, these data would fit in the previously described scenario if the slow component itself is considered an expression of inadequate O_2 delivery to muscle: in the heavy- and severe-intensity exercise domains, muscle would then be recruiting fast-twitch fibers, less efficient in terms of the ratio between consumed O_2 and performed work. After the warm-up exercise, an improved O_2 delivery would reduce the need for recruiting fast-twitch fibers, thereby reducing the amplitude of the slow component and determining a faster overall \dot{V}_{O_2p} on-kinetics.

INTRAMUSCULAR \dot{Q}/\dot{V}_{O_2} MALDISTRIBUTION, MYOGLOBIN O_2 STORES

A limitation of the studies performed in the isolated *in situ* canine gastrocnemius preparation, as mentioned, lies in the rather unphysiological contraction pattern. Muscle contraction was obtained by electrical stimulation that determined synchronous tetanic contractions of all fibers within the muscle. This is obviously different from the asynchronous and heterogeneous fiber activation pattern in physiologically contracting muscle. It is well known that there are both spatial and temporal heterogeneities of Q_m within active muscle. At the present, it is not known whether this corresponds to \dot{V}_{O_2} heterogeneity. \dot{Q}/\dot{V}_{O_2} maldistribution within the muscle could in theory influence the \dot{V}_{O_2} kinetics by producing areas of tissue anaerobiosis. Some degree of intramuscular \dot{Q}/\dot{V}_{O_2} maldistribution appears likely, considering the different patterns of distribution and/or activation of motor units and “microvascular units” within the muscle. It is not known whether a \dot{Q}/\dot{V}_{O_2} maldistribution is a limiting factor for \dot{V}_{O_2} kinetics in physiologically contracting skeletal muscle. Clarification of this issue awaits the development of methods that allow the precise determination of \dot{Q}/\dot{V}_{O_2} distribution in tissues.

Another aspect to be clarified through the use of innovative experimental approaches is related to the contribution of myoglobin O_2 stores to the \dot{V}_{O_2} on-kinetics. O_2 derived from myoglobin cannot be determined with measurements carried out across the muscle. The contribution of myoglobin O_2 stores to \dot{V}_{O_2} , although presumably rather small in quantitative terms, might be relatively more relevant during the early phase of the transition, critical for the \dot{V}_{O_2} on-kinetics.

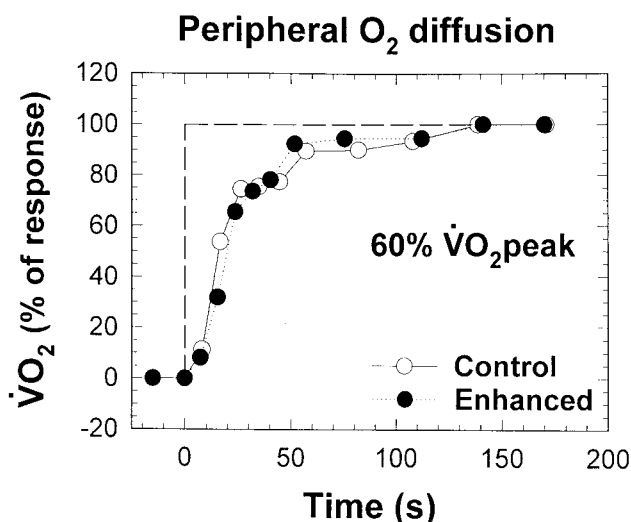


Figure 2. Skeletal muscle \dot{V}_{O_2} on-kinetics during transitions from rest to electrically stimulated contractions corresponding to 60% of peak \dot{V}_{O_2} (isolated canine gastrocnemius *in situ*). Two conditions were compared: control (○) and enhanced peripheral O_2 diffusion (●). The area delimited by the broken lines and the lines connecting experimental points indicates the “ O_2 deficit.” \dot{V}_{O_2} data are expressed as a percentage of the total \dot{V}_{O_2} response (i.e., of the difference between steady-state values at the end of contractions and resting values).

DOES RESTRICTION OF O₂ DELIVERY SLOW DOWN V_{O₂} ON-KINETICS?

It is generally accepted that a restriction of O₂ delivery to muscle, obtained, for example, by acute hypoxia, by the administration of β -blockers, or by the performance of arm exercise with the arms above (versus below) the heart level, results in a slower-than-normal V_{O₂} on-kinetics (14). These types of observation do not demonstrate *per se* that O₂ delivery is a limiting factor for V_{O₂} on-kinetics in normal conditions. Nevertheless, these data suggest some conditions under which O₂ delivery is undoubtedly a limiting factor for the V_{O₂} on-kinetics.

V_{O₂}*p* on-kinetics is known to be slower than normal in patients with congestive heart failure, chronic obstructive pulmonary diseases, peripheral vascular disease, or type II diabetes, as well as in heart and heart-lung transplant recipients (4). In these patients, some limitations in the rate of adjustment of O₂ delivery to muscle during exercise transitions are likely present. However, evidence for the presence of intrinsic defects of skeletal muscle oxidative metabolism in these patients has also been obtained. Therefore, the slower-than-normal V_{O₂}*p* kinetics observed in these patients could be ascribed to several factors, related to both O₂ delivery and O₂ utilization.

METABOLIC CONTROL OF MUSCLE RESPIRATION

Within the metabolic inertia hypothesis, the rate of adjustment of oxidative phosphorylation during the on-transition would be mainly determined by the levels of cellular metabolic controllers and/or enzyme activation. There are several possible rate-limiting reactions within the complex oxidative pathways. Recent research has pointed to acetyl group availability within mitochondria, determined by the activity of the pyruvate dehydrogenase complex, as a possible limiting step. It has been indeed demonstrated that activation of pyruvate dehydrogenase complex by pharmacological interventions determines, in both canine and human muscle, a “sparing” of phosphocreatine (PCr) during exercise transition, suggesting a lower O₂ deficit and therefore a faster adjustment of V_{O₂}*m* on-kinetics (13).

The role of PCr appears critical, whether the molecule is considered mainly as an energy buffer or as a “driving force” for muscle respiration (11,15). The monoexponential increase in V_{O₂}*m* during the “primary component” of the V_{O₂} on-kinetics, as described in canine muscle after convective and diffusive O₂ constraints were eliminated or reduced, appears in agreement with metabolic models of muscle respiratory control during contractions, according to which a single reaction with first-order kinetics controls V_{O₂}*m* during the transition. Such a reaction can be identified with ATP resynthesis, the rate of which is directly proportional to creatine concentration (i.e., to one of the products of PCr splitting). This hypothesis, forwarded several years ago (15), has also recently received support by the observation of substantially identical time-constants of [PCr] decrease (as determined by ³¹P nuclear magnetic resonance spectroscopy) and of the simultaneously determined V_{O₂}*p* on-kinetics dur-

ing the “phase II” (or “primary component”) (12) (i.e., during the phase that should directly reflect skeletal muscle oxidative metabolism [15]). Substantially identical time constants of [PCr] decrease and V_{O₂}*p* on-kinetics during phase II have so far been demonstrated during transitions from rest to low-intensity exercise (i.e., during a transition in which no slow component of V_{O₂}*p* occurs and the V_{O₂}*p* on-kinetics behaves according to a linear system). This is consistent with a linear [PCr]-related control of muscle respiration during moderate-intensity exercise. Further studies on [PCr] and V_{O₂} kinetics during higher-intensity exercise are clearly needed. Although it is known that in the heavy- and severe-intensity exercise domains V_{O₂}*p* on-kinetics becomes more complex, displaying time- and amplitude-based nonlinearities, at the present it is not clear whether this is associated with nonlinearities of [PCr] kinetics as well. Future studies should also attempt to manipulate the putative controller (i.e., PCr splitting) to determine the effects on V_{O₂} kinetics.

RESPONSE TO POINT

In their introduction, Hughson and associates state that “there does not appear to be an overshoot in the O₂ delivery response at the onset of exercise... .” I do not agree. An “overshoot” in O₂ delivery (relative to O₂ utilization) at the onset of exercise is exactly what was described, among others, by Grassi et al. (8) and more recently by Bangsbo et al. (1) in exercising humans, during transitions to both moderate-intensity cycling (8) and intense leg-kick exercise (1). Further indirect evidence of the presence of an “excess” of O₂ delivery or O₂ availability (at the microvascular and at the muscle fiber level) at exercise onset derives from data by Behnke et al. (2) as well as from the study by Hogan (9). Moreover, there is a substantial agreement on the concept that skeletal muscle blood flow increases more rapidly than V_{O₂} at exercise onset. Such a rapid increase might be attributable, as pointed out by Hughson and associates, to an almost immediate acceleration of heart rate (parasympathetic withdrawal) as well as to the “muscle pump” effect. Although this initial increase in blood flow may not be selectively directed to the contracting muscle fibers, it can nonetheless determine an excess of O₂ availability in relation to needs. Thus, there might be no need to hypothesize an exquisitely precise feed forward control of O₂ delivery at the transition, as proposed by Hughson and associates. Within this scenario, a metabolic “feedback control” would ensue after the initial phase of the transition, to precisely match O₂ delivery in relation to O₂ needs. For transitions to metabolic levels that impose a significant burden on the various systems and mechanisms responsible for the delivery of O₂ to muscle fibers, such delivery might not be able to rapidly and/or completely match O₂ needs, thereby representing a relatively minor (although significant) limiting factor for the V_{O₂} on-kinetics. As pointed out in my article, this concept would be in agreement both with human (10) and animal (5–7) studies that attempted to enhance O₂ delivery to muscle fibers during metabolic transitions and to evaluate the effects on V_{O₂} on-kinetics.

CONCLUSIONS

The limiting factors for skeletal muscle $\dot{V}O_2$ on-kinetics are presumably more than one, and the relative role of the various proposed mechanisms may differ in relation to factors such as the type of metabolic transition, environmental or exogenous factors, and the presence of pathological conditions. In normal subjects during transitions to relatively low-intensity exercise, the limiting factor for the $\dot{V}O_2$ on-kinetics seems to reside in an inertia of oxidative metabolism. During transitions to exercise of higher metabolic intensity (above VT?), O_2 delivery to muscle seems to play a relatively minor but significant role as a limiting factor. The presence of more than one limiting factor for exercises above VT would be compatible with the time- and amplitude-based nonlinearities described for $\dot{V}O_{2p}$ on-kinetics in this exercise domain.

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