POINT

Regulation of Oxygen Consumption at the Onset of Exercise

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HUGHSON, R.L., M.E. TSCHAKOVSKY, and M.E. HOUSTON. Regulation of oxygen consumption at the onset of exercise. *Exerc. Sport Sci. Rev.*, Vol. 29, No. 3, pp 129–133, 2001. *Increased aerobic production of ATP at the onset of exercise could be limited by availability of metabolic substrates independent of O_2, or interaction between O_2 and metabolic substrates. We point out the importance of feedback control to match O_2 supply to demand and discuss metabolic control at the onset of exercise.*
Keywords: oxygen uptake, $\dot{V}O_2$, oxidative phosphorylation, feedback control, blood flow, metabolism, oxygen deficit

INTRODUCTION

At the onset of exercise, O_2 uptake ($\dot{V}O_2$) measured at the lungs increases following an approximately exponential time course after a brief transport delay from the muscles (4). An idealized description of the potential sources of ATP in the transition of rest to exercise is shown in Figure 1. At rest and in steady-state exercise (selected here to be $\approx$ 50% $\dot{V}O_2$peak), oxidative phosphorylation meets 100% of the energy demands. In the transition phase, phosphocreatine (PCr) hydrolysis contributes markedly in the early seconds of exercise, but this contribution decreases progressively with time (Figure 1). Anaerobic glycolysis with a net accumulation of lactate will certainly contribute at least a small amount in the rest-to-exercise transition. The total contribution of anaerobic glycolysis will depend on the relative activation of glycolytic enzymes as well as on changes in the concentrations of glycolytic substrates (i.e., glucose 6-phosphate, inorganic phosphate [Pi], and ADP) and the rapidity of the adaptation of oxidative phosphorylation (i.e., $\dot{V}$kinetics). The rate of increase in oxidative phosphorylation can be appreciated from the time constant (τ) for $\dot{V}O_2$ kinetics, which is the time required to achieve 63% of the difference between the baseline and steady state. There are two primary hypotheses that describe the limiting factors that determine the rate at which $\dot{V}O_2$ increases in the rest-to-exercise transition.

O_2 Utilization Hypothesis

The rate at which oxidative phosphorylation increases so that ATP supply meets ATP demand could be limited by the adaptation of metabolic pathways and availability of metabolic substrates without any impact of O_2 on these mechanisms.

O_2 Delivery and Metabolic Control Hypothesis

For this alternative hypothesis, the substrates for oxidative metabolism, including O_2, progressively adapt to the required level at the onset of exercise to sustain ATP production via oxidative phosphorylation. A key concept within this hypothesis is that a given ATP production can be attained across a range of intracellular P_{O_2} by altering the concentrations of other substrates.

It is possible that either of these scenarios could be correct under different experimental conditions. Whether O_2 utilization or O_2 delivery limits the rate at which $\dot{V}O_2$ increases at the onset of exercise has been debated for many years (4). Today, some researchers hypothesize that metabolic factors independent of O_2 establish $\dot{V}O_2$ in the rest-to-exercise transition (2), whereas others suggest that the interaction of O_2 supply with metabolic factors (15) limits the increase in $\dot{V}O_2$.

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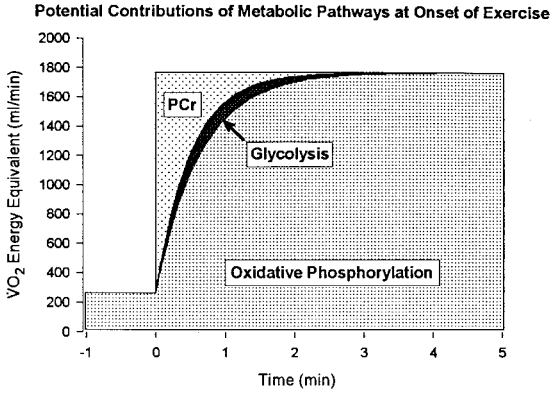

Figure 1. Schematic illustrating the potential sources of ATP, expressed in $\dot{V}O_2$ energy equivalents, at the onset of moderate intensity exercise (steady-state $\dot{V}O_2$ = 1750 mL/min or 50% $\dot{V}O_2$peak for individual with $\dot{V}O_2$peak = 3500 mL/min). The major source of energy in the first seconds of exercise is PCr hydrolysis. The net contribution from anaerobic glycolysis to ATP supply will be expected to vary as a function of the rate of increase in oxidative phosphorylation during this transition in metabolic demand.

We believe that this debate can be reduced to one primary question.

Can O_2 Supply During the Entire Adaptation Phase Precisely Anticipate or Exceed O_2 Demand?

Because there is an approximately linear relationship in the steady state between metabolic rate ($\dot{V}O_2$) and each of heart rate (HR), cardiac output, and muscle blood flow (7,12), the O_2 utilization hypothesis requires that O_2 demand must somehow be "anticipated" so that O_2 supply can be precisely matched to or exceed the demand by *feed forward* control. With the exception of very light exercise, there does not appear to be an overshoot in the O_2 delivery response, further highlighting the need for exquisite precision of this mechanism.

"Feed Forward" Control of O_2 Delivery

Figure 2 indicates potential mechanisms for feed forward control (thin lines) that might be involved in matching O_2 delivery to metabolic demand during exercise. On the initiation of muscle contraction, signals from the motor cortex cause, through "central command," an immediate increase in HR by parasympathetic nervous system (PNS) withdrawal as well as resetting of the arterial baroreflex (12). Skeletal muscle contraction will activate the muscle pump to achieve an increase in muscle blood flow and venous return. The increase in flow will be to inactive as well as active fibers, such that total blood flow in this phase is an overestimation of flow directed to sites of metabolic demand. In addition, the muscle pump activation is not by itself sufficient to increase flow to the required level for moderate to heavy exercise (10,14).

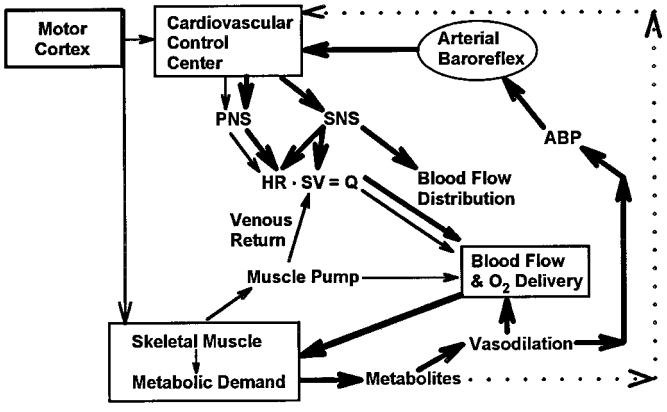

Figure 2. A simplified block diagram indicating potential feed forward (thin lines) and feedback (heavy lines) control of O_2 supply to meet O_2 demand during exercise. Dotted line represents the potential feedback control from muscle chemoreflex. Not illustrated in the feedback loop is the effect of P_{CO_2} and pH on the release of O_2 with rightward shift of the O_2-Hb dissociation curve. ABP indicates arterial blood pressure; SV, stroke volume; Q, cardiac output.

"Feedback Control" of O_2 Delivery

The achievement of the ultimate matching of steady-state O_2 delivery to metabolic demand requires *feedback* control mechanisms during the adaptation to exercise. The biphasic nature of blood flow adaptation in humans (10,14) is consistent with a delayed onset of feedback control of muscle blood flow. Figure 2 illustrates two distinct pathways that act synergistically to achieve appropriate matching of O_2 supply and demand. Metabolic feedback can consist of factors released related to muscle activation (e.g., K^+), related to the rate of ATP consumption (e.g., adenosine), and similarly related to the rate of oxidative metabolism relative to the rate of consumption of ATP (e.g., Pi, NADH, lactate, H^+), with the latter accumulation acting as the signal for mismatch between O_2 supply and demand (7,14). However, vasodilation by itself would cause a decrease in arterial blood pressure unless the baroreflex effected cardiovascular control through further PNS withdrawal and sympathetic nervous system (SNS) activation (12). Thus, increases in HR and stroke volume as well as appropriate vasoconstriction to vascular beds of nonworking regions (splanchnia or resting skeletal muscle) are an integral part of determining the delivery of O_2 to the exercising muscles. Although it is not tonically active, the muscle chemoreflex might be activated by the accumulation of metabolites under conditions of low blood flow and high-intensity exercise (12).

An additional factor that determines whether O_2 supply is adequate in addition to bulk O_2 transport is the affinity of the hemoglobin (Hb) molecule for O_2. In the rest-to-exercise transition, progressive increases in P_{CO_2} and H^+ facilitate O_2 release to the muscle.

In summary, precise cardiovascular control can be achieved only by superimposing feedback regulation on top of the feed forward actions associated with muscle activation. That skeletal muscle blood flow has a time course for its adaptive response that is similar to that of $\dot{V}O_2$ is strong evidence for this proposal (6,15).

O_2 TRANSPORT AND $\dot{V}O_2$ KINETICS

The very rapid increase in HR at the onset of exercise by withdrawal of PNS activity can increase HR to ≈ 100 to 110 beats/min, beyond which slower-acting SNS contributes with

a lag of ≈ 20 s (5,12). The effect of this slower SNS-mediated HR response on $\dot{V}O_2$ is evidenced by a slower $\dot{V}O_2$ and HR adjustment from 40% to 80% ventilatory threshold (VT) cycling versus rest to 40% and rest to 80% (5). Slower $\dot{V}O_2$ kinetics have been observed in some experiments with rest-to–heavy exercise transitions. These results suggest a link between O_2 transport, indicated by HR, and $\dot{V}O_2$ kinetics.

The rate of increase in $\dot{V}O_2$ at the onset of exercise is also slowed under hypoxia or conditions where the HR response is inhibited by β-adrenergic receptor blockade (4,15). That is, conditions that impair O_2 transport at the onset of exercise are associated with slower adaptation of oxidative phosphorylation even with exercise below VT.

Several authors have stated that the absence of faster kinetics for $\dot{V}O_2$ under conditions where O_2 transport has been increased is proof that a metabolic mechanism, independent of O_2, limits oxidative phosphorylation at the onset of exercise in normoxia (2). A faster increase in $\dot{V}O_2$ has been observed during the breathing of a hyperoxic gas mixture during higher-intensity exercise (8) and when blood flow is increased by exercising with the muscle below heart level (6). It has been established that PCr is not decreased to the same extent in hyperoxic as in normoxic testing (3), and this must be accompanied by faster $\dot{V}O_2$ kinetics (15). However, a problem addressed in the next section is the sensitivity of the methods to detect a significant change in $\dot{V}O_2$ kinetics at the onset of submaximal exercise.

INSIGHT FROM CONTROL THEORY AND MODELING

The results of Hughson and Morrissey (5) show that the kinetics of $\dot{V}O_2$ and HR depend on the starting point for exercise and on the magnitude of the step increase in work rate. In control theory, if a single rate-limiting step regulated the response, it would be anticipated that the time constant should be independent of starting point or magnitude. The fact that $\dot{V}O_2$ and HR kinetics changed in parallel suggests a link between these variables. It is well established that HR response in the rest-to-exercise transition is controlled by a nonlinear mechanism with rapid PNS withdrawal followed by slower SNS activation. Under these conditions, it appears that the nonlinear response of $\dot{V}O_2$ is a function of the nonlinear response of HR (5).

It is often argued that the lack of a statistically significant change in τ for $\dot{V}O_2$ between, for example, the rest-to–moderate exercise transition versus the rest-to–heavy exercise transition is evidence that the same controlling mechanism might operate over a wide range of exercise demands. In the recent study of Scheuermann et al. (13), τ for exercise below lactate threshold was 20.4 ± 10.5 s, whereas for exercise above lactate threshold, τ was 28.2 ± 13.1 s. However, this 40% increase in mean value was not statistically significant. It remains to be determined what magnitude of change is required to be physiologically significant.

In an effort to understand our ability to detect differences in metabolic control at the onset of exercise, we created a simulation that incorporates the following conditions (Figure 3). First, O_2-independent metabolic factors that establish oxidative phosphorylation were assumed to rise with τ of 30 s. Second, in the early adaptive phase, it was assumed that sufficient O_2 was supplied due to the actions of the muscle pump and the rapid increase in HR and blood flow. Third, it was assumed that the delivery of O_2 required additional feedback control acting to achieve vasodilation to match O_2 supply to demand with a τ of 36 s. Construction of the curve in Figure 3 allowed for increase in $\dot{V}O_2$ with the rapid metabolic τ of 30 s for the first 30 s of exercise, followed by the slower O_2 transport τ of 36 s from 30 s to steady state. Simulated breath-by-breath data were created from this curve by assuming 15 breaths/min and random variation in $\dot{V}O_2$ of ± 50 mL/min. Curve fitting of these simulated data points with a single exponential function found τ to be 30.7 s, a value obviously closer to the rapid τ of metabolism that persisted for only the first 30 s of exercise. It would be statistically impossible to justify application of a higher-order model, although it is quite probable that metabolic control is more complex than described by a single exponential. The effect on metabolism of shifting to this slower response during the feedback control portion of blood flow adaptation was that the O_2 deficit increased by 192 mL O_2 (difference between heavy and thin lines in Figure 3). If we assume 10 kg of active muscle during cycling exercise, this is equivalent to ≈ 5 mmol/kg additional depletion of muscle PCr (where 192 mL O_2 = 8.4 mmol O_2 = 51 mmol high-energy phosphate). Alternatively, if the O_2 deficit were accounted for entirely by lactate accumulation, this would be equivalent to 1.7 mmol/kg in 10 kg of active muscle, assuming that none of this lactate diffused out of the cells or was subsequently metabolized. This simulation shows how a physiologically significant change in metabolic control would probably not be detected by simple measurements of $\dot{V}O_2$ kinetics.

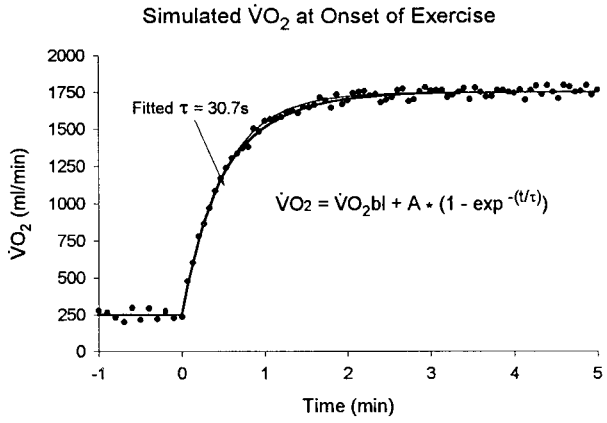

Figure 3. $\dot{V}O_2$ at the onset of exercise has been simulated by monoexponential response as shown, where $\dot{V}O_2$bl is baseline, A is amplitude above baseline, and τ is time constant. Heavy solid line represents simulation with τ = 30 s from 0 to 0.5 min and then τ = 36 s from 0.5 to 5 min. Also shown is the continued response with τ = 30 s (thin solid line visible from ≈ 0.5 to 2 min). Simulated breath-by-breath data are represented by the individual filled dots, assuming 15 breaths/min during exercise with a randomly generated range from the heavy solid prediction line of ± 50 mL/min. Standard curve fitting was performed to these simulated data with a resultant τ = 30.7 s.

O_2 AND METABOLIC CONTROL

To maintain the ATP concentration at the onset of exercise, the creatine kinase reaction and glycolysis are rapidly activated, whereas oxidative phosphorylation increases more slowly. Oxidative metabolism involves multiple steps in the transfer of energy from the electrons of fuel molecules to coenzymes (e.g., NAD) and then to O_2 to accomplish the phosphorylation of ADP to ATP. The equation described by Chance is helpful in understanding this coupling.

$$6ADP + 6Pi + O_2 + 2NADH + 2H^+ \rightarrow$$
$$6ATP + 2NAD^+ + 2H_2O$$

Thus, a molecule of O_2 is reduced to two molecules of water by the transfer of four electrons from 2 NADH. It is possible at the onset of exercise that the limitation to the rise in oxidative phosphorylation depends on the availability of ADP initially, but this quickly changes to a limitation based on one or more of the other substrates. For example, the provision of substrate NADH depends on the availability of acetyl CoA to feed into the TCA cycle as well as NAD^+, which is a substrate for three dehydrogenase reactions in the cycle. Moreover, in a rested muscle, allosteric inhibition of three TCA cycle enzymes by elevated NADH levels plus a low content of matrix calcium ensures that the TCA cycle is functioning at a low rate. With the onset of muscle contraction, the availability of ADP for ATP synthesis leads to NADH oxidation, an increase in NAD^+, and stimulation of the TCA cycle. Further activation of the TCA cycle follows an increase in intramitochondrial calcium that increases the activity of two TCA cycle enzymes and acetyl coenzyme A formation from pyruvate. Finally, the availability of O_2 as the substrate for cytochrome *c* oxidase may become limiting when myoglobin-bound O_2 decreases below a threshold level (1,15).

The majority of literature that has considered the regulators of metabolic control at the onset of exercise have failed to consider the potential role of O_2 as a modulator (15). The reason for this seems to arise from the observations that the critical P_{O_2} to sustain maximal rate of oxidative phosphorylation under conditions of optimal substrate is $\approx$ 0.5 mm Hg. However, Wilson and, later, Arthur (1) and Connett (for details, see Tschakovsky and Hughson [15]) clearly demonstrated that submaximal flux rates through oxidative phosphorylation can be sustained across a range of P_{O_2} values but that the other substrates (see equation A) must alter their concentrations to do so. To illustrate this concept, Figure 4 shows how a given metabolic flux rate can be sustained under conditions of saturating P_{O_2} and reduced P_{O_2}. To achieve the desired flux rate with reduced P_{O_2}, it might be necessary to increase the concentrations of NADH (redox potential) and ADP (phosphorylation potential), contributing to nonlinearity of metabolic control and delay in the adaptation to steady state.

Evidence from exercising human muscle indicates that manipulations of intracellular P_{O_2} by the breathing of high and low O_2 gas mixtures is sufficient to modify the muscle concentration of PCr during constant-load exercise (3). Of critical importance are the observations via proton magnetic resonance spectroscopy that reveal an intracellular P_{O_2} that stabilizes in the range of 3 to 5 mm Hg *within 20 s of exercise onset* even during relatively low-intensity exercise (11). These data are entirely consistent with O_2 consumption being limited by the relative rates of adjustment in metabolic controllers and O_2 supply. Thus, the theoretical considerations of O_2 interactions with metabolic control (see Tschakovsky and Hughson [15]) are consistent with the modification of phosphorylation potential required to achieve the same rate of ATP synthesis via oxidative phosphorylation under conditions of variable intracellular P_{O_2} (see Figure 4). Alterations in total utilization of PCr in hypoxic or hyperoxic exercise must be accompanied by corresponding changes in $\dot{V}_{O_2}$ kinetics and probably also in the contribution to ATP supply from glycolysis (15).

RESPONSE TO COUNTERPOINT

Grassi (2) suggests that $\dot{V}_{O_2}$ on-kinetics might be limited by O_2 availability for work rates above, but not below, VT (typically $\approx$ 65% $\dot{V}_{O_2}$peak). However, the major evidence for that comes from isolated canine gracilis muscle (2) or other animal preparations. The canine muscle preparation has resting blood flow that is $\approx$ 10-fold greater than that in human muscle, in addition to greater oxidative enzyme concentrations. In contrast, when small human muscle groups are examined (e.g., calf muscle [3,11] or forearm [6]), there is evidence that (a) intramuscular P_{O_2} is $\approx$ 3 to 5 mm Hg across a wide range of exercise intensities, (b) muscle [PCr] depletion is affected by hypoxia and hyperoxia, and (c) muscle $\dot{V}_{O_2}$ and blood flow kinetics are correlated. This latter observation also seems to apply to the onset of leg cycling in the experiments of Grassi et al. (2), where time to 63% response for leg blood flow and muscle $\dot{V}_{O_2}$ were highly correlated. It is critically important here to consider beyond the first 15 s of exercise mentioned by Grassi (2). Although excess O_2 delivery might occur in the very early stages of exercise, oxidative metabolism continues to adapt over the

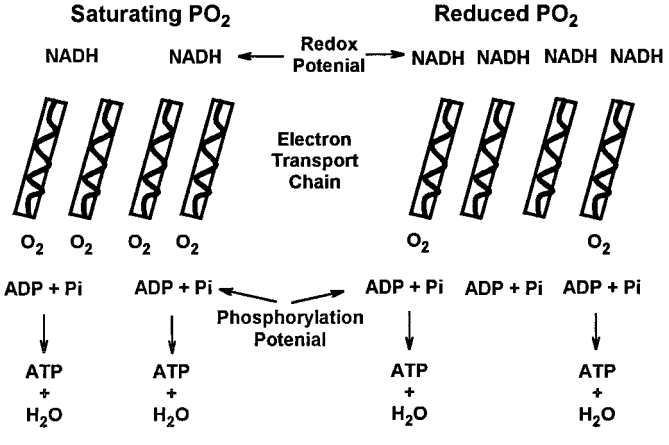

Figure 4. Schematic illustrating the interactions between substrates and flux rate through the electron transport chain. Under nonsaturating conditions of P_{O_2}, the redox potential and phosphorylation potential must be increased (note greater number of NADH and ADP plus Pi, respectively) to sustain the required rate of ATP production.

first 2 to 3 min of exercise even below VT, as shown in the simulation of Figure 3.

The suggestion by Grassi (2) that increased substrate availability at the onset of exercise after the activation of pyruvate dehydrogenase with dichloroacetate will increase $\dot{V}O_2$ kinetics is a complex issue. As indicated above and considered previously in detail (9,15), metabolic control is related to the interaction of the substrates of oxidative phosphorylation. Therefore, it is to be expected that the activation of pyruvate dehydrogenase will alter metabolism by changing substrate concentrations (9), which will in turn interact with O_2 to establish metabolic control, possibly with accelerated $\dot{V}O_2$ kinetics. This would prove only that in the presence of altered concentrations of substrates, oxidative metabolism might adapt at a different rate.

CONCLUSIONS

Precise regulation of O_2 supply to match the metabolic demand at the onset of exercise can be achieved only through the superposition of feedback control on the partially effective feed forward mechanisms. During the transition to steady state, intracellular PO_2 is reduced to $\approx$ 3 to 5 mm Hg within 20 s across a wide range of exercise intensities under normoxic conditions (11). These observations taken together with results showing that muscle PCr is depleted more or less in hypoxic and hyperoxic exercise, respectively (3), show that phosphorylation potential must be adjusted to maintain oxidative metabolism. A necessary consequence of this interaction between PO_2 and metabolism is that $\dot{V}O_2$ kinetics must be affected (15). Our simulation of $\dot{V}O_2$ at the onset of exercise (Figure 3) clearly demonstrated that metabolism can be altered in a physiologically significant manner by small changes in O_2 delivery but that gas exchange methods might not be able to detect a difference in $\dot{V}O_2$ kinetics. Thus, the O_2 delivery and metabolic control hypothesis is consistent with the spectrum of data measured under conditions of normal or altered arterial O_2 content across a wide range of exercise tasks in healthy humans.

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