Possible Mechanisms of Oxygen Uptake Kinetics

Michael L. WALSH

School of Kinesiology, Simon Fraser University,
Burnaby, B.C., V5A 1S6, Canada

The \( \dot{V}O_2 \) response to a step change in work rate resembles a first order exponential function. This suggests that a single site of the many which link ATP demand to \( \dot{V}O_2 \) is limiting. The location of this site is controversial. Some authors suggest that \( O_2 \) delivery regulates the \( \dot{V}O_2 \) response. Others have suggested that peripheral mechanisms within the active muscle regulate \( O_2 \) consumption. The evidence supporting each hypothesis is reviewed. It is concluded that \( O_2 \) delivery sets the initial parameters and peripheral mechanisms then regulate \( O_2 \) utilization within the bounds initially established by delivery mechanisms.

Key words: \( O_2 \)-Kinetics, Exercise

When a step increase in work rate is the forcing function, the \( \dot{V}O_2 \) response rises exponentially from baseline to steady state (Fig. 1). It is amazing that the \( \dot{V}O_2 \) response appears as a linear function of work rate and displays first order exponential kinetics in spite of a multitude of intervening complex steps between input and output.

One possible reason for this simple first order \( \dot{V}O_2 \) response is that perhaps only one of the steps is rate limiting. This concept is supported by numerous authors, but controversy arises over which step is limiting. Some investigators suggest that \( O_2 \) delivery to the working muscle is the rate-limiting step (Hughson, 1990) whereas others suggest that the ability of the active muscle to utilize \( O_2 \) is rate limiting (Whipp and Mahler, 1980). Simply stated, are \( \dot{V}O_2 \) kinetics regulated centrally (i.e., by transport mechanisms) or peripherally (i.e., by diffusive mechanisms)?

To assume that only one step is limiting the \( \dot{V}O_2 \) response implies other steps are not limiting and thus there is only a single exponential component of the \( \dot{V}O_2 \) response. It is possible however that more than one physiological process or step may be limiting \( \dot{V}O_2 \) kinetics and from this a sigmoidal-shaped \( \dot{V}O_2 \) response to a step work forcing function would be expected (Jones, 1973). Rarely, however has such a \( \dot{V}O_2 \) response been documented. Whipp and Mahler (1980) report a sigmoidal response to a step change in work rate from unloaded pedalling to a work rate above the anaerobic threshold. Cerretelli

Fig. 1 The \( \dot{V}O_2 \) response to a step change in work rate resembles a single order exponential function.
et al. (1977) also recorded such a response for arm cranking. One reason for the rarity of this sigmoidal-shaped \( \dot{V}O_2 \) response is that it may be masked by the phase 1 response.

**Evidence Concerning Central Limitations to \( \dot{V}O_2 \) Kinetics**

Three methods are commonly used to identify the site(s) limiting the \( \dot{V}O_2 \) response to a work rate stimulus. One approach is to identify the physiological compartment with the same response characteristics as the \( \dot{V}O_2 \) response. Another approach is to modify a process involved in the body's regulation of \( O_2 \) utilization and observe the effect produced on the \( \dot{V}O_2 \) response. These two approaches involve acute observations. A third approach is by a chronic intervention. For instance, it is known that training induces a faster \( \dot{V}O_2 \) response whether the \( \dot{V}O_2 \) response is compared at the same absolute (Cerretelli et al., 1979; Hickson et al., 1978) or at the same relative work rate (Hickson et al., 1978). Such chronic studies may correlate a change in \( \dot{V}O_2 \) tau, induced by training or detraining, to a change in another variable measured concurrently.

When the rate of response of an \( O_2 \) delivery process is compared to the rate of \( \dot{V}O_2 \) response to a change in work rate, the \( O_2 \) delivery mechanism is usually determined to be faster. Cardiac output (Ceretelli et al., 1966; Davies et al., 1972; De Cort et al., 1991; Eriksen et al., 1990; Gruca et al., 1990; Shindell et al., 1977) and HR (Davies et al., 1972; Linnarsson, 1974) each display a faster kinetics than \( \dot{V}O_2 \) at the onset of exercise.

Cardiac output is one of several factors contributing to \( O_2 \) delivery to working muscle. The amount of \( O_2 \) transported by arterial blood to the systemic system is also dependent on the hemoglobin concentration (\( (Hb) : \text{gm}\cdot\text{ml}^{-1} \)) and the degree to which the hemoglobin is saturated with \( O_2 \) (\( \text{SaO}_2 : \text{fractional percent} \)). The constant 1.37 is the amount of \( O_2 \) that binds to hemoglobin (\( \text{ml}\cdot\text{gm}^{-1} \))

\[ \dot{V}O_2 = \dot{Q} \cdot (\text{Hb}) \cdot \text{SaO}_2 \cdot 1.37 \]

The transport of \( O_2 \) (\( \dot{V}O_2 : \text{ml}\cdot\text{min}^{-1} \)) to muscle rather than \( \dot{Q} \) (\( \text{l}\cdot\text{min}^{-1} \)) has been suggested as a regulated variable (Saltin et al., 1986). Thus an alteration in one parameter determining \( \dot{V}O_2 \) may be compensated by an offsetting change in another parameter.

Raynaud et al. (1973) demonstrated that \( O_2 \) delivery to exercising muscle (i.e., \( \dot{Q} \cdot \text{arterial} \ (O_2) \)) has a faster response than \( \dot{V}O_2 \) measured at the mouth. Additionally, these authors demonstrated that the amount of \( O_2 \) returning to the lungs (i.e., \( \dot{Q} \cdot \text{venous} \ (O_2) \)) is higher during the first 40s of exercise. These observations suggest that the rate limiting step in \( \dot{V}O_2 \) kinetics is \( O_2 \) extraction by the working muscle.

The effects of redistribution of blood flow further indicate that \( \dot{V}O_2 \) is more important than \( \dot{Q} \) in determining the \( \dot{V}O_2 \) response. During supine cycle ergometry, femoral artery blood flow has a similar time constant as \( \dot{Q} \) (~10 s) (Eriksen et al., 1990). Moreover, the calculated increase in femoral artery blood flow exceeds that of cardiac output indicating a significant redistribution of blood flow during light supine exercise humans.

The muscle capillary bed is a logical site to consider as the locus of \( \dot{V}O_2 \) kinetic regulation. It is here that the \( O_2 \) in the blood is unloaded to the cell. Much of the discussion on the possible regulation of \( \dot{V}O_2 \) kinetics by \( \dot{Q} \) kinetics assumes or implies that a change in blood flow to the capillary bed is similar to the change in \( \dot{Q} \) at exercise onset. However, when the gracilis muscle is stimulated electrically in an anesthetized dog, skeletal capillary blood flow triples within 5 s (Honig et al., 1980). This is an order of magnitude faster than the response of the heart rate. In addition, the capillary blood hematocrit increases during stimulation (Klitzman and Duling, 1979). The time course of this latter effect has not been reported. However, it appears that convection of \( O_2 \) in the capillaries occurs at a much faster rate
than the \( \dot{V}O_2 \) response and thus cannot be considered as the mechanism regulating \( \dot{V}O_2 \) kinetics.

Strong support of a central limitation of \( \dot{V}O_2 \) kinetics is evidenced by studies which have acutely altered an \( O_2 \) delivery process. In most studies of this nature there is a corresponding change in the \( \dot{V}O_2 \) kinetic response. The administration of a beta-adrenergic antagonist slows both the heart rate and \( \dot{V}O_2 \) response to a step increase in work rate (Petersen et al., 1983). \( \dot{V}O_2 \) kinetics are also slowed by reducing the inspired fraction of \( O_2 \) (Linnarsson, 1974; Murphy et al., 1989).

Cuffing the non-exercising limbs is thought to augment blood flow to the exercising limbs. As predicted from the central limitation hypothesis, such a manipulation is associated with a faster \( \dot{V}O_2 \) response to a step increase in work rate (Hughson and Inman, 1986).

If the capillary bed is the locus of \( \dot{V}O_2 \) kinetic regulation then it is to be expected that factors which influence unloading of \( O_2 \) to muscle will affect \( \dot{V}O_2 \) tau. Training has been reported to augment the Bohr effect (Braumann et al., 1982). As such, part of the influence of a faster \( \dot{V}O_2 \) response with training may come from the Bohr effect. However, acute alteration in the Bohr effect by oral ingestion of ammonium bicarbonate and ammonium chloride to increase and decrease blood pH, respectively, does not affect \( \dot{V}O_2 \) tau significantly when a person exercises at a work rate equivalent to 75% of the anaerobic threshold (Oren et al., 1982).

Muscle capillarity is enhanced by training. Since blood flow to a muscle does not change with endurance training, an increase in the capillary to muscle fibre ratio will prolong the blood capillary transit time thereby augmenting \( O_2 \) unloading. Additionally, greater capillarity will reduce the capillary-to-mitochondrion \( PO_2 \) gradient required for a given \( O_2 \) flux from the capillary to the mitochondrion because the radial diffusion distance will be less. Correspondence between a faster \( \dot{V}O_2 \) response induced by training and the time course of augmented capillarity has not been investigated.

**Peripheral Regulation of Oxygen Kinetics**

A peripheral site of regulation of muscle cell \( O_2 \) utilization (\( \dot{Q}O_2 \)) can be justified on a conceptual basis. In a muscle cell, it is the contractile activity that determines the rate of energy utilization and production. Thus contractile activity determines \( O_2 \) consumption. It is not the supply of \( O_2 \) to the muscle which regulates ATP production and contractile activity. Intuitively, locating control of \( O_2 \) utilization at the site where the ATP demand is occurring is a better design in terms of coupling ATP demand to \( O_2 \) utilization. The \( Km \) of \( O_2 \) for mitochondrial respiration is well below the \( O_2 \) level in muscle tissue indicating an excess of \( O_2 \) is present. From this standpoint, it appears that a mechanism peripheral to supply regulates \( O_2 \) utilization (Gollnick and Hodgson, 1986). If the \( O_2 \) supply is limiting then one would expect a higher rate of glycolysis, a higher respiratory exchange ratio, and a lower venous \( PO_2 \) value than is commonly observed at rest or at a moderate work rate.

There has been infrequent support for a peripheral locus regulating \( \dot{V}O_2 \) kinetics when whole body metabolism has been studied. This is due in part to a greater degree of difficulty in conducting such research and perhaps to a misinterpretation of previous studies supportive of a central locus for \( \dot{V}O_2 \) kinetic regulation.

A step in the process of justifying a peripheral locus for \( \dot{V}O_2 \) kinetic regulation is identification of a rate limiting modulator. Many regulators have been proposed (Balaban, 1990; Mahler 1980) but it is beyond the scope of this paper to review oxidative control mechanisms. However, to be more precise on many concepts relating muscle metabolism to \( O_2 \) regulation, the creatine phosphate shuttle hypothesis will be used as to represent a peripheral locus regulator. This hypothesis has been investigated in preparations ranging from mitochondrial fragments...
to whole body metabolism and the change in muscle creatine phosphate concentration is proportional to the change in work rate.

The creatine phosphate shuttle hypothesis indicates that the concentration gradients of creatine phosphate (CP) and creatine (C) between the mitochondrion and the myofibrils combine to drive the rate of mitochondrial ATP production.

During a step increase in work rate, there is an instantaneous decrease in (CP) and increase in (C) at the actin-myosin locus (Fig. 2). The increase in (C) at the actin-myosin site will increase the flux of C to the mitochondrion. The increased presentation of C to the mitochondrion will increase the generation of high energy phosphate and hence O₂ utilization. This will reduce the PO₂ at the mitochondrion resulting in a larger O₂ pressure gradient between the blood and the mitochondrion. This will increase the O₂ flux into the cell. The reduced (CP) at the actin-myosin site will augment shuttling of CP generated at the mitochondrion to the actin-myosin locus. In this process, the error signal between the current C, CP, and O₂ concentration gradients and those demanded in the steady state will become less as steady state is approached. The rate of change of the concentration gradients will be proportional to the error signal and thus be exponential in character.

As indicated earlier, the regulator(s) of O₂ utilization should have a similar time course to that of O₂ utilization itself. Both NMR studies on humans during exercise (Challis et al., 1987; Meyer, 1988, 1989; Meyer et al., 1986; Mole et al., 1985) and muscle biopsy studies from electrically stimulated frog muscle (Mahler, 1985), indicate the kinetics of CP reduction at the start of exercise are similar to that of oxidative metabolism.

The existence of a cellular regulator for O₂ consumption implies that the change in the regulator during exercise should be linearly related to the change in O₂ utilisation. Data from stimulated in vivo frog muscle (Mahler, 1985), in situ rat muscle (Meyer, 1988) and dog muscle (Connett and Honig, 1989), and exercising human muscle (Linnarsson et al., 1974) have confirmed this. If there is no CP depletion, there is no O₂ flux; similarly if there is 100 % CP depletion there is 100 % or maximal O₂ flux. The linear relation of CP depletion with increasing muscle oxygen consumption (VO₂), indicates a 50 % depletion may account for a 50 % O₂ flux. If the capacity of O₂ flux from the capillary to the muscle cell is changed (e. g., varying the FVo₂), the relation of CP depletion to oxygen consumption should not change. A 0 % CP depletion still induces 0 % O₂ flux; a 50 % CP depletion will still induce a 50 % VO₂ max; and a 100 % CP depletion induces 100 % of the possible O₂ flux. Expressed another way, the maximal concentration and gradient change for C and CP will induce the maximal possible O₂ flux into the muscle cell.

Prediction of the relation of (CP) to % VO₂ max has not been specifically investigated. However, there are some incidental data to support this concept. Linnarsson et al. (1974) exercised subjects in a barometric chamber at ambient pressures of 0.68, 1.00, and 1.40 ATA. Corresponding maximal O₂ uptake at each pressure was 3.38, 3.91, and 4.34 l·min⁻¹, respectively. For each ambient pressure con-
dition, submaximal work at 147 W produced a \( \dot{V}O_2 \) corresponding to 62, 53, and 49 % of \( \dot{V}O_2 \) max, respectively. Phosphagen depletion at \( \dot{V}O_2 \) max was about 18 mmol·kg\(^{-1}\) for all conditions. Expressing the phosphagen depletion values as a percentage of maximal phosphagen depletion results in 60, 54, and 44 % depletion, respectively (Fig. 3). These values are very similar to the % \( \dot{V}O_2 \) max of the submaximal work rate. This suggests that even when the maximal rate of \( O_2 \) flux is altered, a linear depen-

dence of \( \dot{Q}_O_2 \) on phosphagen depletion is maintained.

Evidence presented in this section so far indicates a strong relation between a change in a potential regulator of \( O_2 \) utilization such as creatine and the rate of \( O_2 \) utilisation. There is an equally strong relation between a regulator of \( O_2 \) utilization and the \( P_O_2 \) of muscle and arterial blood. In human subjects performing foot ergometry, the relation of (CP) with intramuscular \( P_O_2 \) is linear throughout a range from rest to fatigue (Bylund-Fellenuis et al., 1981). As \( O_2 \) delivery (and arterial \( P_O_2 \)) to a hind-limb preparation is reduced there is a concomitant reduction in muscle (CP)/(Pi) at rest and during exercise (Gutierrez et al., 1989; Idstrom et al., 1985; Idstrom et al., 1986).

Emphasis on the stronger relation of oxygen kinetics with percent \( \dot{V}O_2 \) max rather than absolute \( \dot{V}O_2 \) max is not a new concept in exercise physiology. Clausen (1977) stressed the same effect for the relation of sympathetic outflow to the heart and peripheral resistance during exercise. In addition, the lactate threshold, measured against against absolute \( \dot{V}O_2 \), is reduced in hypoxia. However, on a percent \( \dot{V}O_2 \) max basis, hypoxia does not change the lactate threshold (Yoshida et al., 1987). One implication of this is that the lactate threshold is related more to the percent change in the cellular modulator of \( \dot{Q}_O_2 \) rather than to an absolute change in the modulator of \( O_2 \) utilisation.

An example of a subject exercising on a cycle ergometer may clarify this concept. Assume that a subject is working at 100 W and is at steady state. The change in the concentration gradients of C and CP has already been established to generate the \( O_2 \) flux and the rate of high energy phosphate production demanded by the work rate. If there is a reduction in \( F_iO_2 \), this will decrease the \( O_2 \) pressure gradient between the blood and the mitochondrion. Thus the \( O_2 \) flux into the cell will be reduced. Since the work rate has not changed the demand rate for high energy phosphates has not changed. The reduced \( O_2 \) flux will decrease mitochondrial high energy phosphate production. This will cause a reduction in (CP) and an increase in (C) similar to that occurring for a step increase in work rate discussed previously. The increase in (C) at the mitochondrial site will increase \( O_2 \) utilization at the mitochondrion resulting in a reduced \( P_O_2 \) at this locus. The reduced \( P_O_2 \) increases the pressure gradient of \( O_2 \) between the mitochondrion and the blood thereby compensating for its initial reduction when \( F_iO_2 \) was reduced. The concentrations of C and CP have now changed. There is a greater depletion of CP in the more hypoxic condition. The \( O_2 \) flux remains the same in the steady state under each \( F_iO_2 \) condition. Since \( \dot{V}O_2 \) max is reduced in the hypoxic condition, a greater percentage of potential \( O_2 \) flux occurs to meet the energetic requirement.
and the relation between CP depletion and percent
O₂ flux is maintained. The increase in [C] during
hypoxia means there is more substrate available for
glycolysis. Thus glycolytic flux will increase and
decrease the proportion of fat to carbohydrate
utilisation.

Some investigators have concluded that gross
\( \dot{V}O_2 \) kinetics are regulated centrally by O₂ delivery
because a change in F_iO₂ causes an inverse change
in \( \dot{V}O_2 \) tau (Hughson, 1990; Linneråsson et al., 1974).
However, this does not disprove a hypothesis of
\( \dot{V}O_2 \) regulation at a peripheral or cellular level.
When F_iO₂ is reduced, a given absolute \( \dot{V}O_2 \) work
rate demand will require a larger O₂ gradient to be
established between the vascular compartment and
the muscle. This will take longer to establish and
thus \( \dot{Q}O_2 \) tau will be longer. From a "peripheral"
perspective, the change in F_iO₂ presets the level to
which mitochondrial PO₂ has to be reduced to in
order to establish an adequate O₂ gradient, and thus
O₂ flux, from the blood to mitochondrion for the
work rate demanded. The change in \( \dot{V}O_2 \) tau observed
when F_iO₂ is altered is therefore explained by
both the central and peripheral hypotheses of O₂
regulation.

Any explanation of the training-induced faster
\( \dot{V}O_2 \) response from a peripheral perspective, regardless
of the metabolic hypothesis that accounts for
cellular O₂ regulation, will likely incorporate the
increase in oxidative enzyme activity which also
occurs with training.

Holloszy (1967) was the first to document a
training-induced increase in oxidative enzyme activ-
ity. Holloszy also indicated that enhanced oxidative
activity would enable a given submaximal \( \dot{V}O_2 \) to
be maintained with a lower concentration of poten-
tial O₂ regulators such as ADP and Pi (Holloszy
this concept to propose that an altered energy
metabolism induced by training was due to an en-
hanced metabolic sensitivity that occurs in path-
ways which have a training-induced increase in
enzyme activity. These authors indicate that with
an augmented oxidative capacity after endurance
training, a given flux through the oxidative path-
ways can be maintained with a smaller change in
substrate concentration. As early as 1972, it was
known that muscle metabolites change less in
response to a given work rate after training (Karls-
son et al., 1972). However, it was not known if these
changes were due to an enhanced delivery of O₂ or
to a greater cellular oxidative capacity. Constable
et al. (1987) and Dudley et al. (1987) were the first to
demonstrate directly that when mitochondrial con-
tent is increased by training, a given oxidative rate
can be maintained by a smaller change in regulatory
metabolites independent of O₂ delivery.

Rather than perceive the faster training-induced
O₂ kinetics as a result of a greater activity of
enzyme, for \textit{in vivo} conditions it may be more
appropriate to view faster O₂ kinetics after training
as a reduction in diffusion distance. The end effect
is similar; instead of a lower substrate concentra-
tion maintaining a given flux with a higher enzyme
activity, a lower substrate concentration maintains
a given flux because the diffusion distance in less.
The increase in mitochondrial content with training
will reduce both the diffusion distance between the
blood and the mitochondrion and between the
myofibrils and the mitochondrion. Unfortunately,
the time course of mitochondrial changes has not
been compared with \( \dot{V}O_2 \) kinetics induced by training.

It has been briefly mentioned that glycolysis and
mitochondrial respiration compete for a common
substrate (e.g., ADP or creatine). If this is true, then
as mitochondrial respiratory power is increased
relative to glycolytic power, the \( \dot{V}O_2 \) response is
predicted to be faster in response to a step increase
in work rate. Without flux through the glycolytic
pathway there would be a major reduction in the
size of the O₂ deficit. If the O₂ deficit is reduced then
\( \dot{V}O_2 \) tau must be smaller. This is implicit in the
equation:
\[ \tau = \frac{O_2 \text{ deficit}}{\Delta \dot{V}O_2 (ss)} \]

DiPrampero et al. (1989) noted as an undocumented observation that \( \dot{V}O_2 \) kinetics are faster in subjects who had McArdle's disease than in normal adults. Children also have a lower glycolytic power (Eriksson et al., 1971) and a faster \( \dot{V}O_2 \) response than do adults (Armon et al., 1991).

This concept explains the training-induced faster \( \dot{V}O_2 \) response. With endurance training, mitochondrial oxidative power within the muscle is increased whereas glycolytic power is largely unchanged. After training, the larger relative mitochondrial oxidative power will enable respiration to compete with glycolysis more successfully for substrate. The significant relation found between the time course \( \dot{V}O_2 \) tau and the lactate threshold during training supports this concept (\( r = -0.76 \)) (Yoshida and Udo, 1991).

Acknowledgement

Supported by Natural Sciences and Engineering Research. Grant DGP0006443 to E. W. Banister, School of Kinesiology, SFU.

REFERENCES


Braumann, K.-M., Boning, D., and Trost, F., 1982: Bohr effect and slope of the oxygen dissociation curve after physical training. J. Appl. Physiol. 52, 1524-1529.


M. L. WALSH


(Received March 5, 1992)

Michael L. WALSH School of Kinesiology, Simon Fraser University, Burnaby, B. C., V5A 1S6, Canada