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RESEARCH ARTICLE

THE SLOW COMPONENT OF O_2 UPTAKE KINETICS DURING HEAVY EXERCISE

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ABSTRACT

During constant-load exercise of moderate intensity, pulmonary O_2 uptake (VO_2) is characterized by two temporal response components. The first occurs during the transit delay from the exercising limbs and is mediated predominantly by increased pulmonary blood flow. Thereafter, this response is supplemented by the influence of increased O_2 extraction, causing VO_2 to increase mono-exponentially to its steady state, with a time constant that does not vary appreciably with work rate, at this intensity. At work rates that engender a lactic acidosis, however, an additional slow phase of VO_2 is superimposed upon the underlying kinetics: this is of delayed onset and prolongs the time to steady state over the range within which the increases in blood lactate and $[H^+]$ stabilize or ever decrease (heavy exercise). At higher work rates (severe exercise), a steady state is unattainable, with the VO_2 trajectory resulting in VO_2 max progressively earlier the higher the work rate: it is therefore a fundamental determinant of exercise tolerance. Although the kinetic features of this slow VO_2 component (other than its delay) remain tobe determined, current evidence suggests that it is manifest predominantly in the exercising limbs, with the recruitment profile and metabolic features of fast-twitch fiber activation being the major contributor.

INTRODUCTION

The ability to sustain muscular exercise is dependent in large part on the body's ability to transport oxygen from the atmosphere to be used as the terminal oxidant in the mitochondrial electron transport chain. The time course of pulmonary O_2 uptake (VO_2) at high work rates, therefore, is probably the best overall index of the adequacy of the functioning of both the systemic O_2 transport chain and the mitochondrial electron transport chain, which are linked at cytochrome oxidase. It is perhaps surprising, therefore, that such relatively little attention has been paid both to characterizing then onsteady-state profiles of VO_2 and considering the physiological control inferences that may be drawn from these response profiles. I shall therefore consider what is currently known about the effects of exercise intensity on the response dynamics of VO_2 with respect to the gains, time constants, and delays of the various components of the response and their implications for the gas-exchange control-with special reference to the slow component of the VO_2 response during heavy-intensity exercise. However, the characterization of this slow component is, perhaps, best considered as a modification or distortion of the "fundamental" kinetics. The responses to moderate exercise (e.g., Fig. 1) may therefore be used as the frame of reference for the altered profiles at higher work rates.

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Characterizing the response

Techniques of control system theory have proved invaluable with respect to establishing the parameters of the VO_2 response to muscular exercise, and consequently allowing physiological model equivalents to be established (Barstow *et al.,* 1990; Cerretelli and Di Prampero 1987; Hughson and Morrissey 1982; Lamarra *et al.,* 1987; Paterson and Whipp 1991; Wasserman *et al.,* 1991; Whipp *et al.,* 1982). Such approaches presently rely upon interpretations of the VO_2 response profile with respect to a particular workrate forcing. But in order to gain a better understanding of the control, I need first to characterize the time course of VO_2 change with respect to its putative stimuli. These stimuli may well be different in different intensity domains of exercise. Within a given intensity domain, different temporal components of the VO_2 response to constant-load exercise can be identified (Yoshida 1990), each with different underlying determinants. These temporal components can be characterized as: (a) the early, usually rapid, response ("phase I",QI); (b) the slower, exponential increase ("phase II" Ø II); and, if attained, (c) the steady state ("phase III" Ø III).

Moderate exercise

The range of work rates within which there is not a sustained metabolic (lactic) academia (Wasserman *et al.,* 1987) may be considered to be of moderate intensity (although Hughson and his associates (Hughson *et al.,* 1988; Krough and Lindhard

1913) and Dennis *et al.* (1989) dispute the existence of such a region). Pulmonary VO_2 is determined by the amount of partially reduced hemoglobin that enters the pulmonary capillary bed per unit time. This, in turn, is determined by two separate but, as described below, related variables; (a) pulmonary blood flow (Qp), considered here to equal the total cardiac output (Qt) – except for those conditions where they are dissociated by, for example, cardiac pathology (Wasserman 1987); and (b) the mixed venous O_2 content($C\bar{v}O_2$).

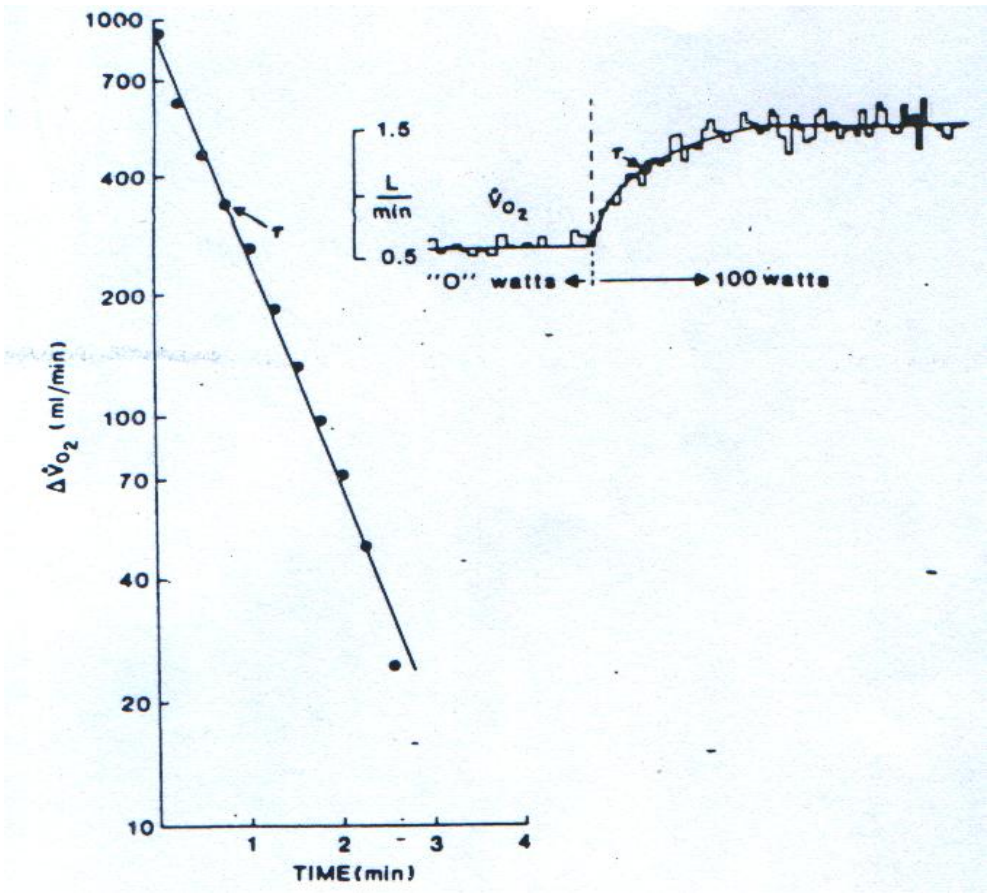

Figure 1. Right: Time course of the breath-by-breath O_2 uptake (VO_2) response to a single about of moderate constant-load exercise. Left: Semilogarithmic display showing that the response is well described by a monoexponmential process (reproduced from Whipp, B. J. and M. Mahler. Dynamics of pulmonary gas exchange during exercise. In: Pulmonary Gas Exchange, Vol. II, J. B. West (Ed.) New York, Academic Press, 1980. pp. 33-96, with permission).

Although the increase in VO_2 is equal to the increase in the mean rate of muscle O_2 utilization (QO_2) in the steady state, it is dissociated from muscle QO_2 in the no steady state. This occurs: (a) temporarily, as a result of the muscle-to-lung transit delay; (b) in magnitude, as a result of the muscles utilization of stored O_2 (i.e., as a muscle venous and subsequently mixed venous O_2 content decrease, there is a reduction of tissue PO_2 in the contracting units and possibly a small contribution of oxymyoglobin desaturation (P_{50} is approximately 5 mm Hg) in those fibers that have myoglobin); and (c) in its rate of change, as any given value for the arteriovenous O_2 content difference, C (a-$\bar{v}$) O_2, established at the muscle level will be associated with a higher blood flow when it is expressed at the lung. That is, the cardiac output will have increased during the transit delay. This is schematized in Fig. 2, which demonstrates that the time constant for VO_2 will be exactly equal to that of QO_2 if (a) the proportional change in muscle blood flow exactly matches that of its O_2 utilization rate, or (b) if muscle blood flow does not change at all (Fig. 2b) (but there are sufficient local stores to sustain the aerobic exchange). The more physiological response is shown in Fig. 2c. Note that the O_2 concentration in the venous effluent from the contracting muscle ($CV(m)O_2$) will be determined by the change in the ratio between QO_2 and the muscle blood flow (Qm):

$Cv(m)O_2 = CaO_2 – (QO_2/Qm)$.(1). The increase in Qm will be reflected virtually instantaneously in an increased Qp. The fidelity of the response magnitude of Qp with respect to Qm will depend only on the changes in the mean blood flow in the remaining vascular beds (thought to be small at these work rates (9)) and any changes in the volume of the intervening venous pool. The influence of the altered Cv (m) O_2 onCv O_2 will, in contrast, be delayed. The simple mono-exponential increase in QO_2 is there foretrans formed into a more complex two-component increase in VO_2, but with a time constant that will be similar to that of muscle QO_2. This is based upon the results of Barstow *et al.* (1990), who modeled the relationship between the QO_2 time constant (T) and the subsequent VO_2 time constant as a function of different Qt time courses. They concluded that ${}_TVO_2$ is likely to be less than 10% different from ${}_TQO_2$ (as schematized in Fig. 2c), over a wide range of Qt

changes. There will therefore be a component of gas exchange (ØI) between the steady states of rest and of exercise (ØIII) – or between two different work rates – which is dominated by changes in Qp (ØI), as first described by Krogh and Lind hard (Lamarra *et al.,* 1983), and a subsequent component (ØII) in which the exchange is supplemented by the influence of the altered Cv (m) O_2 on $C\bar{v}\ O_2$ (Yoshida 1990). Note, however, that in Figure 2a we have the interesting phenomenon of the response having no ØII component!

The two temporal components of the transient response in pulmonary gas exchange clearly, but only when the confounding influence of breath – to – breath "noise" is removed (Linnarsson 1974), or sufficiently minimized by averaging several repetitions of a particular increment in work rate (Miyamoto *et al.,* 1983; Yoshida 1990); with single transitions they are difficult to dicirminate.

Whip *et al*. (Yoshida 1990)). But to estimate the O_2 deficit appropriately the VO_2 change in Φ1 must be included in the fit either by fitting the entire no steady state response and "forcing" the exponential to being at time zero ("model 1": Whip *et al.* (Yoshida 1990) or to fit the best exponential – plus – delay to the data ("model 2": Whip and Ward (1980). It should be noted that the delay derived from the latter strategy (i.e. the "effective" delay) has no physiological meaning-unlike the delay that ends at the onset of phase II (i.e. the "real" or physiological delay). Furthermore the model 1 τ is numerically equal to the sum of the model 2 τ plus delay, each being equivalent to what has been termed the mean response time (MRT) of the response (Paterson and Whipp 1991) τVO_2 does not vary appreciably between work rates of different amplitudes in this intensity domain or of initial baselines (Lamarra *et al.,* 1987; Whipp and Ward 1993; Whipp *et al.,* 1982; Yoshida 1990) (although the latter point is disputed (Funk *et al.,* 1990; Hughson *et al.,* 1987).

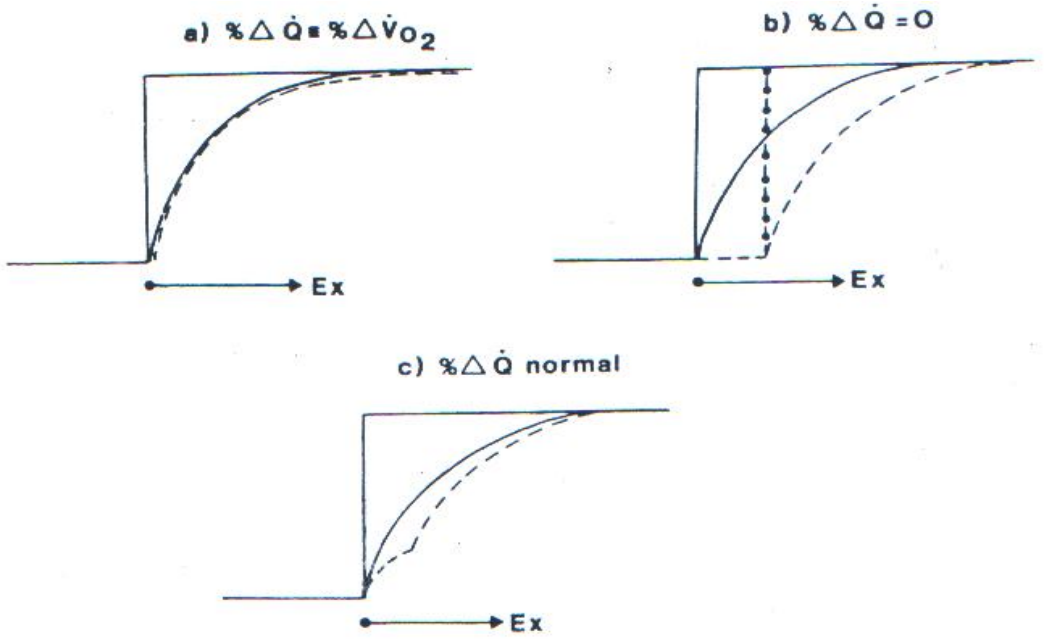

Figure 2. Schematic to illustrate the influence of the time course of pulmonary blood flow (Q) on the kinetics of the pulmonary O_2 uptake (VO_2) response (*dotted lines*) to moderate, constant-load exercise. The kinetics of the corresponding muscle O_2 consumption (QO_2) response (*solid lines*) are shown for comparison. See text for further details

For constant load (i.e., square wave) exercise of moderate intensity (i.e., below)the lactate threshold (T_{lac}), the muscle QO_2 response is mono exponential as it is controlled by the dynamics of the phosphate pool turnover. The precise nature of the control mechanism, however, remains the topic of debate. Excellent reviews of the various control schemes are available in the literature (Clause 1976; Gaesser *et al.,* 1992; Lamarra *et al.,* 1987). The consequence is a mono exponential response in the time course of pulmonary VO_2 with a similar time constant (τ), but only after a delay (δ) that reflects tissue-to-lung transit time VO_2, however, does increase during the delay component, chiefly, as a result of the increase in Qp, as schematized in Fig 2C. It should be noted that different strategies for considering the delay component can markedly influence the value for the best fit τ to the VO_2 response. The most appropriate Φ11 τVO_2 for estimating τVO_2 is when the VO_2 change during Φ1 is neglected in the curve fit ("model 3") That is, the early transient rise in blood lactate (Chance *et al.,* 1985) that is not uncommon at these work rates does not seen to influence the response discernibly. Furthermore, the off-transient. VO_2 time constant is not appreciably different from that at the on-transient (Hansen *et al.,* 1988; Lamarra *et al.,* 1987), despite lactate having typically returned to resting levels before the recovery component.

τVO_2 and δ are best analyzed using impulse or square wave forcing (Krebs and Kornberg 1957; Miyamoto *et al.,* 1983; Poole (1991). Pseudo-random binary sequences (Hughson and Morrissey 1982) and sinusoids (Casaburi *et al.,* 1978) yield a single value for both on – and off – transient responses; ramps are not useful in this regard.

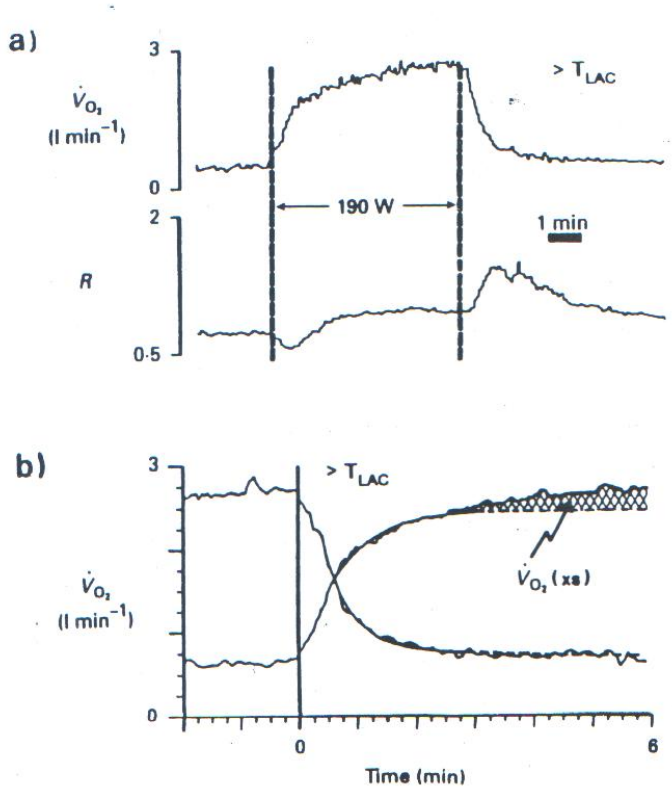

Figure 3. (a) Breath-by-breath responses of O2 uptake (VO_2) and respiratory exchange ratio (R) to a single 6-min bout of constant-load work above T_{LAC}, with on- and off-transients to "O" W. (b) Averaged breath-by=breath responses (*N=4*) of VO_2 in a single subject to and from a 6-min bout of constant-load work above T_{LAC} (190 W). Super imposed on the VO_2 responses are the monoexponential fits to the early component of the response (*solid lines*), with the *dashed extension* being the remainder of the monoexponential fit to the entire 6 min. *Vertical lines* indicate onset and cessation of work (modified form Paterson, D. H. and B. J Whipp. Asymmertries of oxygen uptake transients at the on- and off-set of heavy exercise on humans. *J.Physiol. (Lond.)* 443:575-586, 1991)

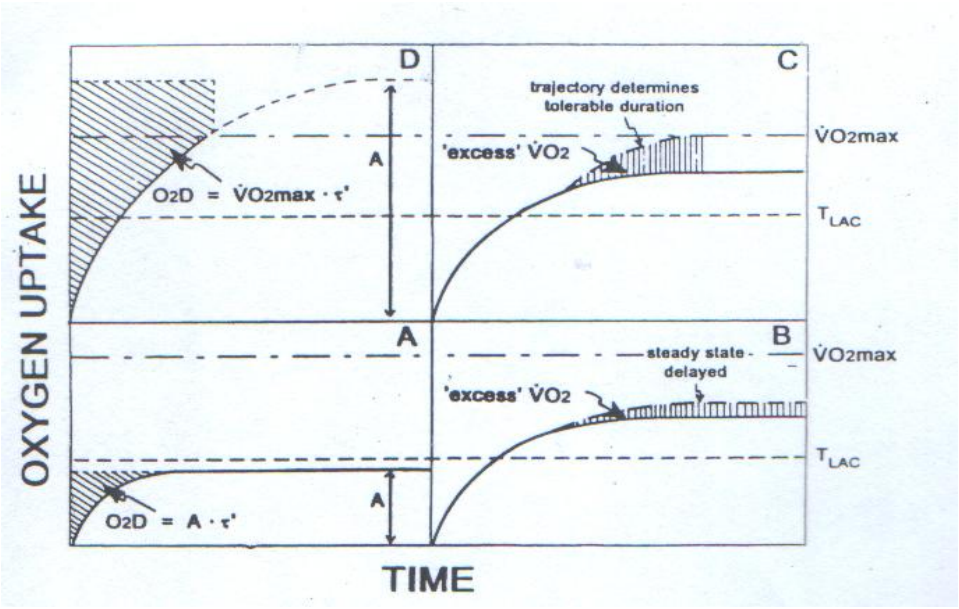

Figure 4. Schematic representation of the O_2 uptake (VO_2) response to constant-load exercise at different work intensities. (A) Below the lactate threshold (T_{LAC}); (B) above T_{LAC}, with VO_2 reaching a steady state but with a delayed time course; (C) above T_{LAC}, but with a component of "excess" VO_2 that leads VO_2 to attain the maximum VO_2 (VO_{2max}); and (D) a supramaximal work rate where fatigue occurs so rapidly that the excess VO_2 component has not had time to develop discernibly, O_2D represents the calculable O_2 deficit. The time scales on each panel are not mean to be the same: this allows the VO_2 contours to be visualized more clearly. (modified form Whipp, B. J. and S. A. Ward. Pulmonary gas exchange kinetics during exercise: physiological inferences of model order and parameters. *J. Therm. Biol.*, 18:599-604, 1993, with permission)

In response to square-wave exercise in this domain, therefore, the $\dot{V}O_2$ responses are sufficiently well characterized by a simple exponential (Hughson *et al.,* 1987; Paterson and Whipp 1991; Whipp *et al.,* 1982; Yoshida 1990) of the form:

$$\dot{V}O_2(t) = \Delta\dot{V}O_2(SS)(1 - e^{-(t-\delta/\tau)}) \quad \ldots\ldots\ldots\ldots(2)$$

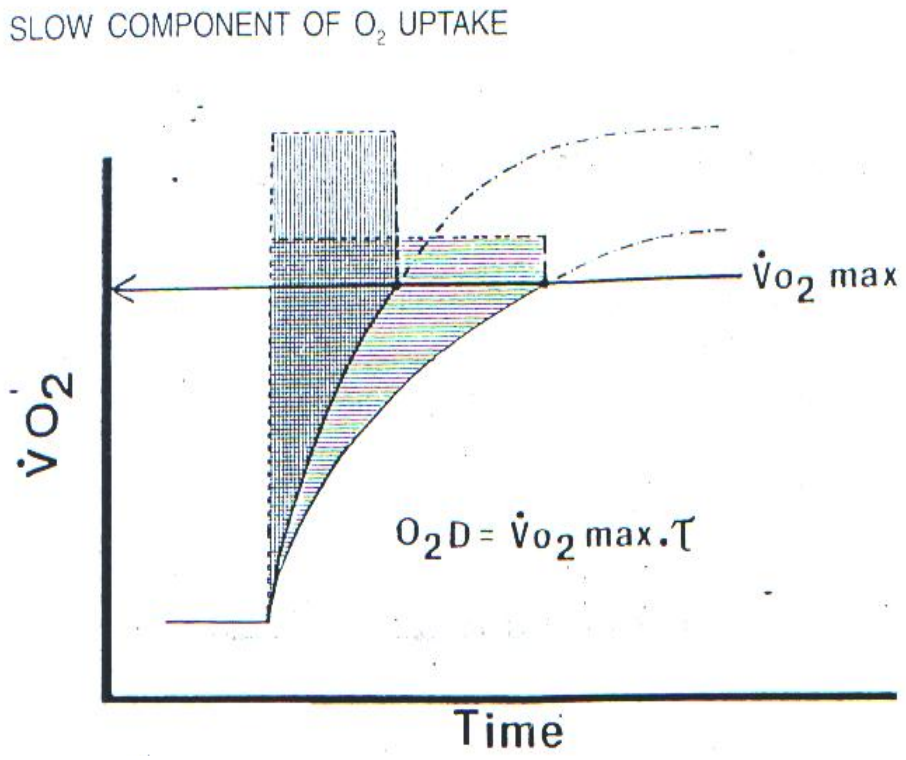

Figure 5. Schematic of the time course of the O_2 uptake (VO_2) response to constant-load exercise at an intensity equivalent to panel D in Figure 4. The shaded areas represent the O_2 deficit. See text for further details

Although more complex formulations of the transient VO_2 responses to constant – load exercise, such as:

$$\Delta Y(t) = \Delta Y(SS) \cdot (1 + b)/(1 + be^{-t/\tau}) \quad \ldots\ldots\ldots\ldots\ldots\ldots(3)$$

Or

$$\Delta Y(t) = ae^{-be-t/\tau} \quad \ldots\ldots\ldots\ldots\ldots\ldots(4)$$

(Where a and b are constants) can characterize the actual response with adequate goodness – of – fit, i.e., an appropriate exponential component that is preceded by an early delay – like deflection, these formulations are not justified physiologically. Although they may meet the parameter estimation criteria, they fail with respect to the demands of model discrimination. This is because the actual physiological response is determined by two discrete mechanisms – with a relatively abrupt demarcation between them. The responses should therefore be treated as such.

Heavy exercise

Above the lactate threshold, the VO_2 response becomes appreciably more complex (Barstow and Mole 1991; Paterson And Whipp 1991; Poole *et al.,* 1991; Rowell 1971), with both time – and amplitude – based non-linearities of response. For example, it is well known that the steady – state increment in VO_2 (ΔVO_2 (SS) during square-wave exercise below T_{lac} increases as a linear function of work rate ($\dot{W}$), i.e., ΔVO_2 (SS) / $\Delta\dot{W} = K \simeq 10 ml.min^{-1}$. W. In contrast, a steady state of VO_2 is either delayed or unattainable for work rates above T_{lac}. Even when VO_2 does eventually stabilize, however (or when its asymptotic value is estimated), ΔVO_2 (SS) / $\Delta\dot{W}$ is markedly increased; the increase being a function of both ($\dot{W}$ - T_{lac}) and time: values of 13 ml. Min^{-1}. W are not uncommon during tests of 10 – 15 minutes duration (Hesser *et al.,* 1977; Rowell *et al.,* 1971; Whipp and Mahler 1980). The difference between the actual VO_2 achieved in the quasi – steady state and the steady – state value projected from the sub – T_{lac} VO_2 - $\dot{W}$ relationship was shown by Whip and Mahler (1993) to be positive for work rates above T_{lac}; naturally, this is only the case up to work rates at which the steady state projection is less than the subjects VO_2 max. This additional increment in VO_2 may, for convenience, be termed "excess" VO_2 (VO_2 (XS)). It is important to recognize, however, that this VO_2 (XS) is a result of a slow component of the VO_2 kinetics which is superimposed upon the early VO_2response (Fig. 3). Furthermore, this superimposed component is of delayed onset, beginning some minutes into the test (Barstow and Mole 1991; Poole *et al.,* 1991; Whipp and Ward 1993).

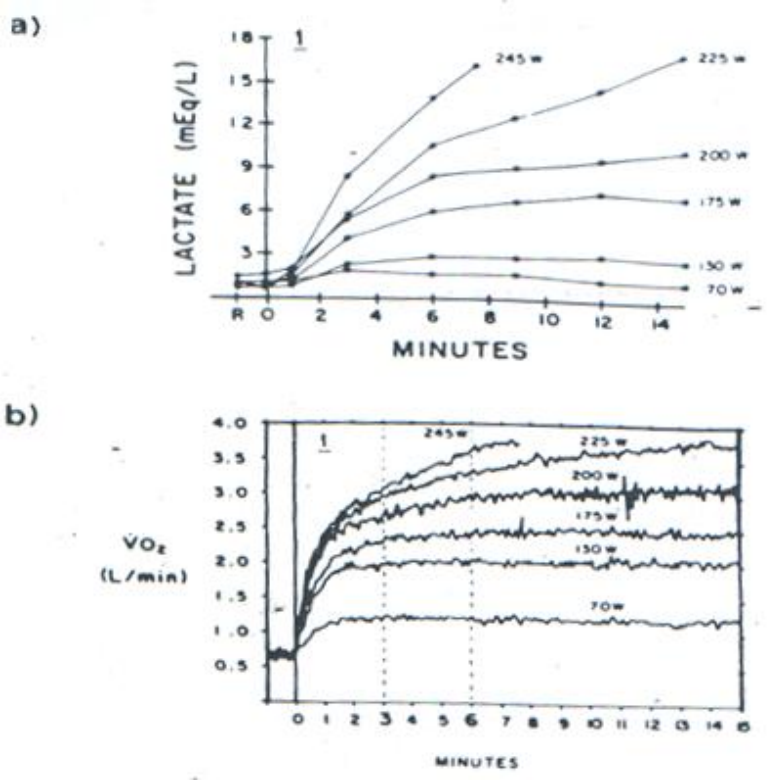

Figure 6. Temporal profiles of O_2 uptake (VO_2) and arterial blood lactate in response to six constant load exercise tests on a cycle ergometer. Test duration was either 15min or the limit of tolerance. Note that at work rates at which blood lactate continues to increase, so does VO_2 (to or toward, a maximum value) (modified from Roth, D. A., W. C. Stanley and G. A. Brooks. Induced lactacidemia does not affect most-exercise O_2 consumption. *J. Appl. Physiol.*, 65:1045-1049, 1988)

The findings of Paterson and Whipp (1991) and Barstow and Mole (1991) on the characteristics of the slow component of the VO_2 kinetics are remarkably similar in that they not only both demonstrates the slow component to be of delayed onset but also that the early component of the kinetics at these heavy work rates remains exponential and projects to a steady – state value that gives the same gain (i.e., $\Delta\dot{V}O_2/\Delta\dot{W}$ R) as for sub threshold exercise. But there is one striking, and perhaps fundamental, difference in their results: Paterson and Whipp (Poole *et al.,* 1991) found the early kinetic component to be slowed (i.e., τ was longer), whereas Barstow and Mole (1991) found it to be no different from the threshold τ. Consequently, if both τ and the gain term are in charged for the early VO_2 response to heavy exercise, then it is hard to explain an O_2 limiting component of the increased lactate concentrations at this work intensity. As the additional component is both slow and of delayed onset, its influence is virtually undetectable during ramp (Dennis *et al.,* 1992; Whipp and Ward 1990) and rapid incremental tests, or even for constant load tests in which the subject reaches the maximum VO_2 in a few minutes. When the incrementation rate is slow, however, the VO2 (XS) component does become evident as an upward concavity in the VO_2 - Wrelationship, as shown by Whipp and Mahler (1993) and Hansen *et al.* (1989).

For work rates below T_{Lac} (i.e., Fig. 4A), the O2 deficit (O_2 D) can therefore be determined as:

$$O_2D = A.\ \tau', \qquad \ldots\ldots\ldots (5)$$

Where A is the required steady – State increment in VO_2 and τ′is the "effective" time constant, or mean response time, of the VO_2 response.

Similarly, for work rates> VO_{2max} (Fig. 4D) where there has not been sufficient time for the excess VO_2 component to develop and "distort the monoexponentiality, O_2 D may be determined as":

$$O_2\ D = VO_{2max}\ .\tau' \qquad \ldots\ldots\ldots\ldots\ldots\ldots (6)$$

Note that the O_2 deficit under these conditions is independent of A, but is dependent upon VO_2 max. This provides us the range of exhausting work rates for which O_2 D is constant. The fact that the O_2 deficit in this formulation, is independent of the work rate may appear to provide conceptual basis for the shape of the power-duration curve for high intensity exercise, i.e., the higher the work rate, in this domain, the more rapidly VO_2 will increase to reach the VO_2 max (as schematized in Fig. 5). However, it is the O_2 D (the entire shaded areas in Fig. 5) that is constant: for the power-duration curve to be hyperbolic, it is the shaded rectangular areas above VO_2 max in Figure 5 that must be constant. O_2 D and the rectangular areas above VO_2 max cannot both remain constant over this range of exhausting work rates. Current characterizations of the role of VO_2 kinetics in determining the shape of the power-duration curve (Yoshida *et al.,* 1982) may therefore require revision.

The O_2 deficit may not be rigorously determined, however, in the domain characterized in panels b and C of Figure 4, as the

excess VO_2 component provides an inappropriate asymptote for the early VO_2 response, even when VO_2 does attain its delayed steady state (panel B). Interestingly, as shown in Figure 3, the off-transient VO_2 response is often mono-exponential in this domain (Poole *et al.,* 1991), a finding that may prove important in elucidating the mechanism of VO_2 (XS). For example, this seems to rule out significant effect of the O_2 cost of respiratory and cardiac work and also the Q_{10} effect, each of which one would expect to be manifest in both the on – and off – transient responses.

As schematized in Figure 4B, there is a certain range of supra-T_{Lac} work rates in which a delayed steady state may eventually be reached (Quine 1975; Roston *et al.,* 1987; Rowell 1971; Whipp and Mahler 1980). However, at higher work rates a steady state is, unattainable; VO_2 continues to increase until the maximum VO_2 is attained (Quine 1975; Roston *et al.,* 1987; Rowell 1971). At these work rates, therefore, it is not possible for a subject to perform a constant work rate that provides a specific % VO_2 max, as is so commonly used as an index of work intensity. That is, subjects can only attain this % VO_2 max fleetingly; they cannot maintain it at that value. Maintaining a constant % VO_2 max would require the work rate to be reduced. Currently available evidence suggests that the highest VO_2 at which a steady state can be attained (and hence a sustainable % VO_2 max) coincides with the highest work rate at which blood (lactate) does not continue to rise (Fig. 6) and pH to fall during the course of the work (Quine 1975; Rowell 1971). Furthermore, Poole *et al.* (1975) have shown that this work rate represents the asymptote of the subject's power-duration curve.

The slow VO_2 (XS) component actually brings VO_2 to the VO_{2max} in figure 4C, resulting in exhaustion shortly thereafter. This occurs at a work rate for which the wholly aerobic component would be expected to result in a steady-state value for VO_2 that is less than VO_2 max. This slow component may therefore be considered to be a functional index of the actual fatiguing process (c.f., Quine's) "proxy function" (Roth *et al.,* 1988). That is, the more rapidly the slow component projects toward VO_2 max, the shorter will be the tolerable duration of the work rate. This consideration of the slow component of the VO_2 response differs fundamentally from the concepts currently extant regarding the determinants of the power-duration curve for exhausting exercise (Yoshida *et al.,* 1982). It does, however, have one significant benefit over these current concepts: that is, a model formulation that coheres with, rather than one that is at odds with, the actual physiological response profile. The presence of VO_2 (XS) may therefore be seen to undermine three major assumptions of models of human gas exchange during high-intensity exercise: (a) $\dot{V}O_2$ is not a linear function of $\dot{W}$(1); (b) the physiological basis of the $\dot{W}$ – duration curve having a single aerobic term (with a rapid τ of ~10-20s) is unjustified (Yoshida *et al.,* 1982); and (c) the conventional means of computing the O_2 deficit cannot be applied in this domain.

Proposed mechanisms of the slow component of vo_2 response

The mechanisms of the slower component that causes VO_2 to climb inexorably to its maximum value remain to be resolved. It has been demonstrated (39, 48), however, that the magnitude of the slow component of VO_2 can exceed 1l.min^{-1}. Both Casaburi *et al.* (1987) and Poole *et al*. (1975) have shown that the temporal characteristics of this slow component appear to be related to the magnitude and the time course of the increase in blood (lactate) (the temporal correlation with other potential mediators such as catecholamine levels, body temperature, and ventilation that training reduces both blood (lactate) and the magnitude of this "excess" VO_2 (Casaburi *et al.,* 1987; Poole *et al*., 1975). Consequently, the energetics of lactate clearance on the load to the mitochondrial hydrogen shuttle mechanism may be involved.

The energy and, hence, VO_2 cost of glycogen resynthesis from lactate in the liver is likely to be small, however (Whipp and Mahler 1980). For example, the liver is likely to be small, however (Whipp and Mahler 1980). For example, the liver would need to oxidize I MEq of lactate (Kushmerick *et al*., 1992) to provide the energy to resynthesize 6 MEq to glucogen; i.e., an O_2 cost of 3 mM. Assuming a blood lactate of 7 MEq.l^{-1}, a liver blood flow of 0.5 l. min^{-1}duringexercise and a 50% extraction of the lactate, this would only amount to approximately 17 ml.min^{-1}, i.e.,

$$\Delta \dot{V} O_2 = \frac{3mM\ of\ O_2}{7\,MEq\ of\ L^-} .7\ \frac{MEq}{1}\ of\ L^- .0.5\ extraction\ .\ 0.5\frac{1}{\min} .$$

$$22\frac{ml}{mM} = 6.5ml.\min^{-1} \qquad (7)$$

However, for skeletal muscle with a blood flow of 20l.min^{-1}, but with half of the oxidized lactate supplying ATP for muscle contraction rather than glycogen resynthesis, for example, the value could be theoretically as high as,

$$\Delta \dot{V} O_2 = 660\text{ml}\ .\min^{-1} \qquad \text{…….(8)}$$

But it should be recognized that the contracting units that are lactate – generating will, on thermodynamic grounds be unlikely to be undergoing glycogenesis from lactate, whereas those units which are not lactate – generating are unlikely to be sufficiently glycogen – depleted to constitute an available terminus for the resynthesis.

Roth *et al.* (1987) could discern no significant difference in the pattern of post-exercise VO_2 when blood (lactate) was elevated to a peak of approximately 5 mM.l^{-1} by circulatory occlusion during the work. This finding is consistent with the demonstration by Paterson and Whipp (1991) that the off-transient VO_2, kinetics (Fig. 3) were mono exponential (unlike the on-transient) at a work intensity expected to result in similar blood lactate levels. Similarly, there appears to be a sharp discontinuity in the magnitude of the VO_2 (XS) in which the magnitude is small for lactate increases up to approximately 5 MEq.l^{-1} and appreciably greater above (Whipp and Mahler 1980). It is of interest that this, in most subjects, approximates the highest sustainable lactate level. It is unlikely that lactate perse is responsible for the slow component of VO_2, however, as Poole *et al.* (1988) were not able to demonstrate a significant increase in VO_2 in response to lactate infusion into the working dog gastrocnemius.

Effects of increased body (predominantly muscle) temperature and circulating catecholamines are not likely to be quantitatively important. Rowell (Sietsema *et al.,* 1986) could show no discernible effect of 2 – 3^{o}C changes in body temperature on exercise VO_2; Gaesser *et al.* (Griffiths *et al.,* 1986) could find no significant increases in VO_2 when fourfold increases in blood epinephrine concentrations were produced by epinephrine infusions during exercise. Wasserman and his associates (Whipp 1987) have recently demonstrated an important role of the lactic acidosis in maintaining muscle-tissue PO_2 as a result of the Bohr effect, i.e., a rightward shift of the oxyhemoglobin dissociation curve. Although this is likely to be significant in causing VO_2 to increase toward its wholly aerobic value, it does not explain VO_2 actually climbing to values appreciably greater than this.

Altered proportional utilization of the malate-aspartate (M-A) andα-glycerophosphate (αGP) shuttles for transferring the NADH – linked reducing equivalents into the mitochondria could account for a component of this additional slow component of VO_2 kinetics, were the transfer via the αGP mechanism to be increased, either as a result of "saturation" of the M-A mechanism or because of its dominant use in the newly recruited Type 11b muscle fibers. Then the hydrogen transfer to intramito-chondrial FAD rather than to the M-A linked NAD would bypass one phosphorylative site and hence would require a greater QO_2 for the same ATP yield. Schantz and Henriksson (Swanson 1990) have demonstrated that the αGP mechanism is expressed to a higher degree in these relatively low – efficiency Type 11 Fibers (Davis *et al.,* 1982; Lamarra *et al.,* 1987). Further contributions to the "excess" VO_2could originate in respiratory and cardiac work and increased "extraneous" work such as pulling more forcefully on the cycle ergometer handlebars or increased swaying of the body. Study by Poole *et al*. (1990), however, have suggested that the predominant site of the "excess" VO_2 is in the exercising limbs.

This additional O_2 cost of supra T_{Lac} exercise is also evident in incremental exercise tests when the duration of each increment is relatively long (Hughson 1990; Wasserman *et al.,* 1987; Whipp and Ward 1993) and even on ramp tests with slow rates of work rate change (Henson *et al.,* 1989; Whipp *et al.,* 1981). The result is a curvilinear response of VO_2 in this region, which is concave upward, manifesting areduced work efficiency for heavy exercise – even disregarding the simultaneous anaerobic energy transfer. However, a – if not be the major contributor to the VO_2 (XS)is likely to be the high energy cost of contraction in the Type II fibers (Davis *et al.,* 1982; Lamarra *et al.,* 1987). These have been shown to be recruited proportionally more at these high work rates; they also require a large high-energy phosphate cost of force production. Whether they begin to be recruited less after training, at the same work rate that both blood lactate and the VO_2 cost of the work begin to be reduced, has not, to date, been convincingly demonstrated. In conclusion, the proportional contribution of the various potential mediators of the slow component of the VO_2 kinetics and, importantly whether the proportionality itself changes with time (i.e., each mediator may have a different time constant of response) remains to be determined, and will form the basis of the subsequent presentations.

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