Pulmonary O_2 Uptake during Exercise: Conflating Muscular and Cardiovascular Responses

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ABSTRACT

WHIPP, B. J., S. A. WARD, and H. B. ROSSITER. Pulmonary O_2 Uptake during Exercise: Conflating Muscular and Cardiovascular Responses. *Med. Sci. Sports Exerc*., Vol. 37, No. 9, pp. 1574–1585, 2005. For moderate-intensity exercise (below lactate threshold, θ_L), muscle O_2 consumption ($\dot{Q}O_2$) kinetics are expressed in a first-order phase 2 (or fundamental) pulmonary O_2 uptake ($\dot{V}O_2$) response: $d\dot{V}O_2/dt \cdot \tau + \Delta\dot{V}O_{2(t)} = \Delta\dot{V}O_{2(ss)}$; where $\Delta\dot{V}O_{2(ss)}$ is the steady-state $\dot{V}O_2$ increment, and τ the $\dot{V}O_2$ time constant (which is within approximately 10% of $\tau\dot{Q}O_2$). A likely source of $\dot{Q}O_2$ control in this intensity domain is ADP-mediated, for which intramuscular phosphocreatine (PCr) may serve as a proxy variable. Whether, in reality, this behavior reflects the operation of a single homogeneous compartment is unclear, however; a multicompartment structure comprised of units having a similar $\Delta\dot{V}O_{2(ss)}$ but with widely varying τ can also yield a "well-fit" exponential response with an apparent single τ. In support of this is the inverse (although poorly predictive) correlation between τ and both θ_L and $\dot{V}O_{2max}$. Above θ_L, the fundamental $\dot{V}O_2$ kinetics are supplemented with a delayed, slowly developing component that can set $\dot{V}O_2$ on a trajectory towards $\dot{V}O_{2max}$, and that has complex temporal- and intensity-related kinetics. This $\dot{V}O_2$ slow component is also demonstrable in [PCr], suggesting that the decreased efficiency above θ_L predominantly reflects a high phosphate cost of force production rather than a high O_2 cost of phosphate production. In addition, the oxygen deficit for the slow component is more likely to reflect a progressive shifting of $\Delta\dot{V}O_{2(ss)}$ rather than a single $\Delta\dot{V}O_{2(ss)}$ having a single τ. **Key Words:** MUSCLE OXYGEN CONSUMPTION, FEEDBACK CONTROL, ^{31}P-MR SPECTROSCOPY, KINETICS

The ability to develop high levels of aerobic energy transfer, and develop them rapidly, is the *sine qua non* of successful performance in most athletic and many occupational activities. Whereas the magnitude and time course of muscle O_2 consumption ($\dot{Q}O_2$) is reflected in that of pulmonary O_2 uptake ($\dot{V}O_2$), there is a necessary dissociation between them in the transient or nonsteady state. But this does not mean that useful, and possibly important, information regarding the characteristics and control of muscles' aerobic energy transfer cannot be determined from what is commonly termed "oxygen uptake kinetics." The time course of $\dot{V}O_2$ during exercise may be considered to be the vented expression of its immanent utilization—readily quantifiable, but delayed by the influence of the intervening vascular bed, and modified by the utilization of the body O_2 stores.

It has been supposed that, as O_2 is utilized from the body gas stores during the transient (manifest as a reduction in mixed venous O_2 content, $C\bar{v}O_2$), there *must* be an obligatory slowing of the $\dot{V}O_2$ kinetics relative to those of the skeletal muscle. That this is *not* necessarily so is a consequence of $\dot{V}O_2$ during the transient being determined by two separate but interrelated mechanisms:

Increased pulmonary blood flow ($\dot{Q}_P$) itself, during the phase in which alterations of muscle venous composition do not yet influence gas exchange at the lung. This is the phase of "cardiodynamic" gas exchange ("phase 1," φ1) (4,27,47); φ1 is thus a period of time, and not a pattern of response.

The subsequent reduction of $C\bar{v}O_2$ (as a result of increased O_2 extraction in the contracting muscles) supplementing the continuing cardiodynamic component to yield the "phase 2" (φ2) response. The onset of φ2 is delayed as a result of the vascular transit delay between the exercising muscles and the pulmonary capillaries (some 15–20 s).

The φ1 and φ2 responses sum to give the steady-state or "phase 3" (φ3) response.

As shown in Figure 1 there are, consequently, two conditions in which $\dot{V}O_2$ would have exactly the same temporal profile as $\dot{Q}O_2$:

(a) If muscle blood flow ($\dot{Q}$) were to increase in precise proportion to $\dot{Q}O_2$ (Fig. 1A). In this case, as there would be no decrease in muscle-venous O_2 content ($CvO_2 = CaO_2 - \dot{Q}O_2/\dot{Q}$), the entire $\dot{V}O_2$ response would reflect cardiodynamic mediation and hence there would be no φ2 in the response.

(b) If $\dot{Q}$ were actually not to change (i.e., assuming the available O_2 stores to be sufficiently large to entirely support $\dot{V}O_2$) (Fig. 1B). In this case, there would be no increase in $\dot{V}O_2$ throughout the φ1 duration and the entire subsequent $\dot{V}O_2$ response would be determined by the more markedly reduced $C\bar{v}O_2$.

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Submitted for publication January 2005.
Accepted for publication April 2005.

0195-9131/05/3709-1574/0
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DOI: 10.1249/01.mss.0000177476.63356.22

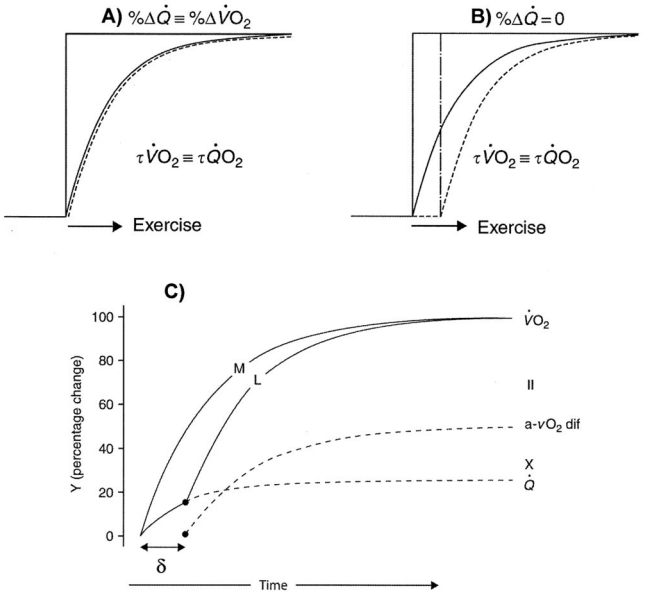

FIGURE 1—*Above*. Schematic demonstrating two hypothetical conditions in which the time constants (τ) for the muscle $\dot{Q}O_2$ (*solid line*) and $\dot{V}O_2$ (*dashed line*) responses to a moderate square-wave increase of work rate could be equal. *Panel A*: muscle and pulmonary blood flow ($\dot{Q}$) increase with the same kinetics as $\dot{Q}O_2$. *Panel B*: there is no increase in muscle and pulmonary blood flow ($\dot{Q}$). See text for further details. *Below*. *Panel C*: Schematic demonstrating the contribution of $\dot{Q}$ and arterio-venous O_2 content difference ($C(a\text{-}\bar{v})O_2$) to the observed $\dot{V}O_2$ response (L) kinetics (i.e., Fick principle), relative to muscle $\dot{Q}O_2$ (M) kinetics. This is intermediate between the hypothetical responses presented in Panels A and B, with both φ1 and φ2 components being evident, and the latter occurring with a delay (δ) that reflects the arrival of O_2-extracted blood at the lung. See text for further details. (From: B. J. Whipp and H. B. Rossiter (2005). The kinetics of oxygen uptake: physiological inferences from the parameters. In: A. M. Jones and D. C. Poole (Eds.). *Oxygen Uptake Kinetics in Sport, Exercise and Medicine*. Routledge, London, pp. 62–94).

The observed $\dot{V}O_2$ response is intermediate, however, with a cardiodynamic phase preceding the φ2 component, as schematized in Figure 1C and shown for an actual subject in Figure 2A. During φ2 in this situation, a particular arterio-venous O_2 content difference ($C(a\text{-}v)O_2$) expressed at a particular time at the muscle will, when subsequently expressed at the lung, be associated with a higher $\dot{Q}$—which will contribute further to the ongoing $\dot{V}O_2$ increase. This results in the φ2 time course of $\dot{V}O_2$ being similar ($\leq$ approximately 10%) to that of muscle $\dot{Q}O_2$ and in extreme conditions could even be faster (4).

The overall difference between the temporal profile of muscle $\dot{Q}O_2$ and that of $\dot{V}O_2$ reflects the O_2 utilization from the body's O_2 stores (Fig. 1B and 1C). The delta term (δ) in Figures 1 and 2B represents the time taken for the altered O_2 concentration in the venous effluent from the exercising musculature to influence the O_2 concentration in the mixed-venous blood entering the pulmonary capillary bed. Note here that this only represents the muscle-to-lung transit time if the muscle-venous O_2 content begins to decrease in concert with exercise onset. This delay is signaled at the lung by the respiratory exchange ratio (R) beginning to decrease (reflecting the, predominantly intramuscular, storage of CO_2) and end-tidal PCO_2 beginning to increase and end tidal PO_2 beginning to decrease as a result of the altered mixed-venous gas partial pressures (47). This delay therefore has a physiological equivalent—the other "delays" that emerge from conventional exponential fitting strategies (e.g., as shown in Fig. 2) do not.

FITTING STRATEGIES

The available evidence strongly suggests that $\dot{Q}O_2$ is determined by intracellular control mechanisms linked enzymatically to changes in the high-energy phosphate pool, rather than, except possibly at very high work rates, being blood flow– or "O_2 delivery"–dependent (the reader is referred to the work of Hughson and his associates (42) for a different perspective on this matter). The $\dot{Q}O_2$ response consequently manifests first-order kinetics:

$$\tau \cdot d\dot{Q}O_2/dt + \Delta\dot{Q}O_{2(t)} = \Delta\dot{Q}O_{2(ss)} \quad [1]$$

where $\Delta\dot{Q}O_{2(ss)}$ is the incremental steady-state or asymptotic response, $\Delta\dot{Q}O_{2(t)}$ is the $\dot{Q}O_2$ increment at time t, and τ is the time constant. For a square-wave work-rate (WR) forcing, the time course of the response may consequently be characterized as (28):

$$\Delta\dot{Q}O_{2(t)} = \Delta\dot{Q}O_{2(ss)} \cdot (1 - e^{-t/\tau}) \quad [2]$$

It has, until recently, been taken as an article of faith that there is no delay term in this profile. There are, however, reports that $\dot{Q}O_2$ does not begin to increase in concert with the increase in work rate (3), a fascinating observation when considered in the light of no apparent delay in the reduction of the intramuscular phosphocreatine (PCr) concentration (Figs. 3 and 4) (29,35,36). Being so crucial to understanding the control of oxidative phosphorylation during exercise, this is likely to prove a fertile topic for further investigation.

The initial exercise-induced increase in $\dot{Q}$ can reasonably be assumed to be manifest essentially instantaneously as an increased $\dot{Q}_P$. The proportional $\dot{Q}_P$ increase will only differ from that of $\dot{Q}$ because of exercise-induced alterations in: (a) the intervening venous vascular volume between the muscles and lung—which accounts for the larger amplitude of the φ1 $\dot{V}O_2$ response when starting exercise in the upright posture from rest versus a background of "unloaded" pedaling (47) or versus rest-to-work transitions in the supine posture (44); and (b) the proportional perfusion to nonexercising tissues and organs, which is on average small (37). The muscle-to-lung vascular transit delay is reflective of the capacitance-to-conductance ratio of the intervening vascular pool. The consequence is that the simple monoexponential increase in $\dot{Q}O_2$ is transformed into a more complex two-component increase in $\dot{V}O_2$ at the lungs:

$$\Delta\dot{V}O_{2(t)} = \Delta\dot{V}O_{2(ss)} \cdot (1 - e^{-(t-\delta/\tau)}) \quad [3]$$

where $\Delta\dot{V}O_{2(ss)}$ is the steady-state increment or asymptotic response at the lung, $\Delta\dot{V}O_{2(t)}$ is the $\dot{V}O_2$ increment at time t, and δ is a delay term that is a consequence of (but not necessarily equal to) the limb-to-lung vascular transit time (47), with a value that is highly dependent on the model-fitting strategy (see below).

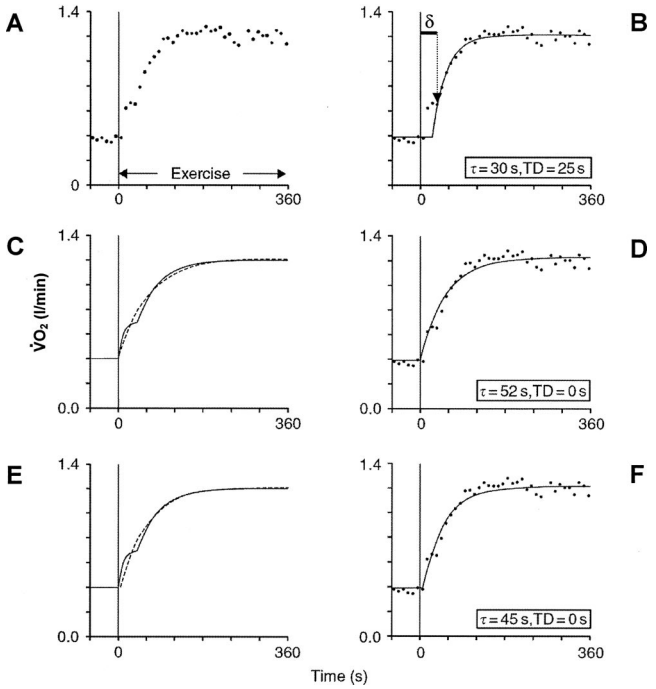

FIGURE 2—Model-fitting strategies for the $\dot{V}O_2$ response to a moderate square-wave increase of work rate. *Panel A*: a measured $\dot{V}O_2$ response. *Panel B*: the same $\dot{V}O_2$ response, fit to a monoexponential constrained to the $\varphi 2$ component, which yielded estimates for τ and δ (*solid bar*) of 30 and 25 s, respectively. *Panel C*: schematic of a measured $\dot{V}O_2$ response (c.f. *Panels A and B*), showing the $\varphi 1$ and $\varphi 2$ components (*solid line*), and the resulting "best-fit" exponential to the entire $\dot{V}O_2$ response (*dashed line*), with the fit being constrained to start at exercise onset (i.e., $\delta = 0$). *Panel D:* application of the *Panel C* fitting strategy to the measured response, yielding a longer τ (52 s) than for the fitting strategy depicted in *Panel B*. *Panel E*: schematic of the measured $\dot{V}O_2$ response (*solid line*), and the resulting "best-fit" exponential to the entire $\dot{V}O_2$ response (*dashed line*), but with the fit not constrained to start at exercise onset. *Panel F:* application of the *Panel E* fitting strategy to the measured response, yielding a τ (45 s) longer than for the fitting strategy depicted in *Panel B* but shorter than for that depicted in *Panel D*; δ (7 s) is also intermediate. See text for further details. (From: B. J. Whipp and H. B. Rossiter (2005). The kinetics of oxygen uptake: physiological inferences from the parameters. In: A. M. Jones and D. C. Poole (Eds.). *Oxygen Uptake Kinetics in Sport, Exercise and Medicine*. Routledge, London, pp. 62–94).

As the magnitude and time course of $\dot{V}O_2$ during $\varphi 1$ is proportionally coupled to the change in pulmonary blood flow (12), Sietsema et al. (39) have successfully used the $\varphi 1$ change in $\dot{V}O_2$ during constant-load exercise as an index of the adequacy of cardiac function.

The subsequent $\tau\dot{V}O_2$, when "isolated" to the actual $\varphi 2$ component, has been shown to be within approximately 10% of $\tau\dot{Q}O_2$. This has been demonstrated both by modeling the influences of plausible differences in on-transient $\dot{Q}_P$ profiles and venous capacitance volumes (4) and also by direct analysis of the time course of $\dot{V}O_2$ in concert with that of $\dot{Q}O_2$ using high-density determinations of the variables in the Fick equation [$\dot{V}O_2 = \dot{Q}\cdot(CaO_2 - CvO_2)$]. However, there are a number of assumptions regarding this application of the Fick equation, especially during the nonsteady state, some of which remain to be justified (e.g., the influence of regional flow-induced changes in the weighting of the venous concentrations from the "muscle" and "other" vascular beds on the final mixed-venous value) and the latter approach presents formidable technical challenges—especially in, but not limited to, humans:

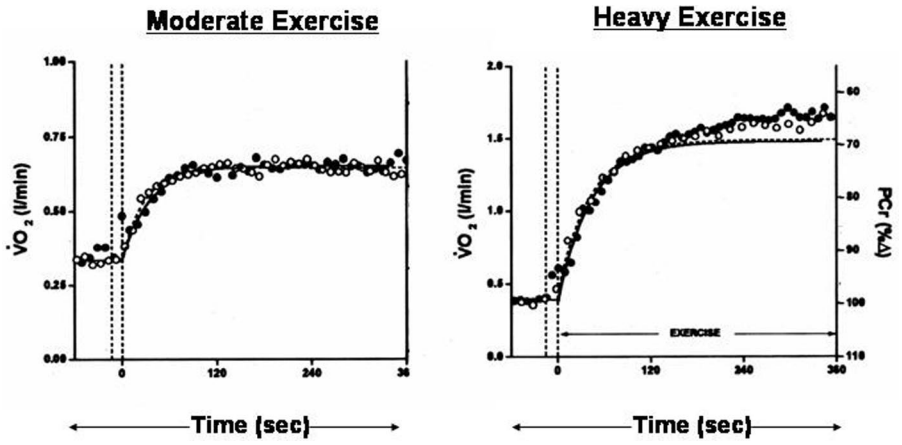

FIGURE 3—An example of the simultaneously determined $\dot{V}O_2$ (●) and [PCr] (○) responses to moderate (*left*) and heavy (*right*) square-wave knee-extensor exercise, showing the superimposed monoexponential best fit to the $\varphi 2$ and fundamental components, respectively. To facilitate kinetic comparisons, the [PCr] scale has been inverted and normalized to that of the $\dot{V}O_2$ response.

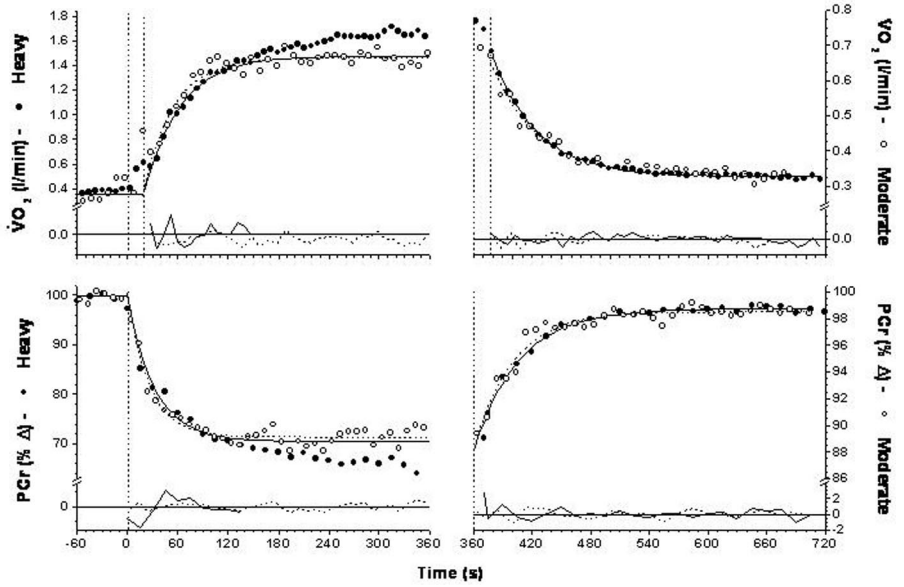

FIGURE 4—An example of the simultaneously determined $\dot{V}O_2$ (*upper panels*) and [PCr] (*lower panels*) responses to moderate (○) and heavy (●) square-wave knee-extensor exercise; on-transient (*left*), off-transient (*right*). Superimposed are the corresponding monoexponential best fit to the $\varphi 2$ (moderate) and fundamental (heavy) components (with residuals), respectively. To facilitate kinetic comparisons, the moderate and heavy responses have been normalized to the respective fundamental amplitudes. (From: H. B. Rossiter, S. A. Ward, J. M. Kowalchuk, F. A. Howe, J. R. Griffiths, and B. J. Whipp (2002). Dynamic asymmetry of phosphocreatine concentration and O_2 uptake between the on- and off-transients of moderate- and high-intensity exercise in humans. *J. Physiol. (Lond.)* 541: 991–1002).

(a) the technique is highly invasive;

(b) the sampling site may not capture all of the exercising musculature;

(c) appropriate temporal alignment of the rapidly changing $\dot{Q}$ with CvO_2 at the downstream sampling site is by no means straightforward; and

(d) $\dot{Q}O_2$ is only approximated as the product of the mean regional blood flow and the mean $C(a\text{-}v)O_2$ over the sampling period. It is properly determined as the flow-weighted integral of $C(a\text{-}v)O_2$—appropriately corrected for the varying transit delay to the sampling site.

In practice, there have been two approaches to "isolating" the $\varphi 2$ component:

(a) Treating the $\varphi 1$ response as if it were itself exponential and characterizing the entire nonsteady response for moderate exercise with a six-parameter model, that is, two delay terms (although one is fixed at the time of exercise onset), two time constants, and two proportional gains: $\dot{V}O_{2(t)}$

$$\dot{V}O_{2(t)} = A1 \cdot (1 - e^{-(t-\delta 1)/\tau 1}) + A2 \cdot (1 - e^{-(t-\delta 2)/\tau 2}) \quad [4]$$

where A is the steady-state $\dot{V}O_2$ response, and the subscripts 1 and 2 refer to $\varphi 1$ and $\varphi 2$, respectively (5).

(b) Others prefer to delete the $\varphi 1$ component by constraining the fitting window for the parameter estimation to start at a time after the exercise onset sufficient to ensure that only the $\varphi 2$ component is considered (30,47). This is based upon the reasoning that: (a) there is no sufficiently sound evidence to support the exponentiality of the $\varphi 1$ component and (b) that the asymptote of the actual $\varphi 1$ response is larger than the value attained at the time of the $\varphi 1$–$\varphi 2$ transition (Fig. 1C). The concern with this deletion method is that starting the fit before $\varphi 2$ has begun will allow a $\varphi 1$ contribution to distort the goodness of fit—starting somewhat later will only reduce the amount of data used for the exponential fit. A period of 20 s has been used as the effective compromise.

Consequently, up to an approximately 10% degree of uncertainty, the $\varphi 2$ $\tau\dot{V}O_2$ may be used as a proxy function for $\tau\dot{Q}O_2$ (Figs. 2B and 3). We stress "up to" here, as the values could in fact be the same in some circumstances—but one cannot, at present, "know" with certainty.

Fitting the entire $\dot{V}O_2$ data set with a simple "τ plus δ" model (Fig. 2F) will result in a less accurate reflection of the actual time course of $\dot{V}O_2$, with a τ that is longer than for the $\varphi 2$ fit (Fig. 2B) and a δ that is shorter than that of the actual $\varphi 1$–$\varphi 2$ transition. The sum of τ and δ for this model has been termed the "mean response time" (MRT) or the "effective" time constant (τ'). When the exponential (Fig. 2D) is fixed to begin at time zero ($\delta = 0$), the estimated τ is even longer and in fact equivalent to the MRT or the τ' for the previous model fit.

INTENSITY DOMAINS

Both the contour and the gain of the $\dot{V}O_2$ response (i.e., $\Delta\dot{V}O_2/\Delta WR$) and by inference those of $\dot{Q}O_2$, are intensity-dependent. Although there is, to date, no generally accepted definition of intensity, the available evidence makes it clear that the $\%\dot{V}O_{2max}$, despite still being the most widely used index, is *not* a justifiable functional definition. This is because the parameters that partition the range of potential work rates into clusters of common response characteristics (i.e., the lactate threshold (θ_L), the "critical power" (CP) and

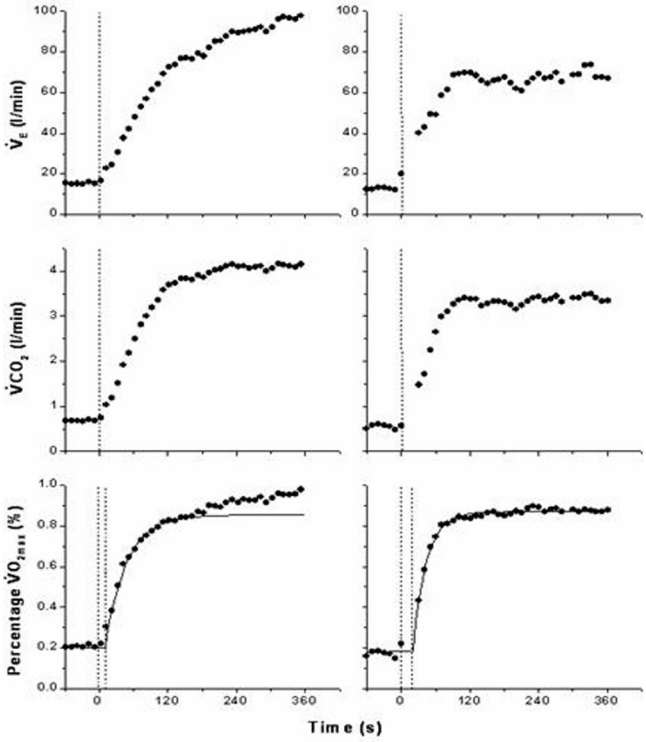

FIGURE 5—$\dot{V}O_2$, CO_2 output ($\dot{V}CO_2$), and ventilatory ($\dot{V}_E$) responses to square-wave exercise in two subjects exercising at the same $\%\dot{V}O_{2max}$. Note the marked $\dot{V}O_2$ slow component in the left-hand subject, and its absence in the right-hand subject.

$\dot{V}O_{2max}$), have highly variable relationships among each other in different subjects. Consequently, assigning intensity domains on the basis of a single parameter, such as a given percentage of $\dot{V}O_{2max}$ (or of $\%\theta_L$), can result in markedly different physiological stress characteristics in different subjects at what would appear to be the same work intensity, as shown in Figure 5. And, naturally, merging such responses in different subjects into a single average or "ostensibly characteristic" response can be misleading with respect to their control inferences. A particular exercise intensity should, we argue, be characterized by a common physiological stress profile.

Assigning exercise intensity on the basis of the profiles of muscle metabolic and pulmonary gas exchange response to constant-load exercise, however, largely overcomes these concerns. For example, if the WR range for which there is no sustained metabolic acidosis, with its associated increase in arterial blood [lactate] ([lactate]a) and decrease in pH (pHa) (i.e., below θ_L), is considered to be of common intensity, moderate for example, then a common set of response characteristics will be evident (e.g., Fig. 6). Similarly, if the range of higher WR within which there is a sustained metabolic acidosis with increased [lactate]a and decreased pHa, but which, with time, may either stabilize to a constant level or even revert back towards baseline is considered to be of common intensity, e.g. heavy, this also yields a characteristic response profile (e.g., Figure 6). Above this, there is a WR region in which the increase in [lactate]a and the decline in pHa do not stabilize, but rather develop progressively to the limit of tolerance (very heavy). The parameter that has classically been used to partition the heavy and very heavy–intensity domains is the critical power (reviewed in (30,48)), which some (but not all) investigators report to match closely the power equivalent of the "maximum lactate steady state" (MLSS); others, however, have suggested that CP may slightly exceed the power output at MLSS (for discussion, see (21)). As will be described below, significant kinetic dislocations in the $\dot{V}O_2$ contour are introduced by both θ_L and CP (and/or MLSS). Furthermore, we find it useful, as discussed below, to consider an additional intensity domain (severe) for those high work rates for which the steady-state requirement for the fundamental $\dot{V}O_2$ response component is greater than the subject's $\dot{V}O_{2max}$.

MODERATE EXERCISE

In response to moderate square-wave exercise ($<\theta_L$) following the initial $\varphi 1$ component, the normally more-dominant $\varphi 2$ or "fundamental" τ of $\dot{V}O_2$ ($\varphi 2\ \tau\dot{V}O_2$) is typically of the order of 30–40 s in healthy young individuals, tending to be smaller in endurance-trained individuals (18) and to be appreciably larger in elderly sedentary individuals (2) and in patients with pulmonary and cardiovascular disease (39). Consequently, whereas τ is inversely correlated with both θ_L and $\dot{V}O_{2max}$, the associated confidence limits are wide, and hence τ is poorly predictive of these parameters (48).

Additional support for the control of $\varphi 2$ $\dot{V}O_2$ in moderate exercise involving a first-order control process (e.g., involving intramuscular [ADP] feedback) is provided by the on–off symmetry for square-wave exercise at this intensity (27,30) (Fig. 6). That is, a first-order process is one whose kinetic parameters (e.g., gain and τ) are independent of the magnitude and format of the input-forcing function. For example, the gain of the $\dot{V}O_2$–WR relationship during the linear phase of ramp-incremental exercise is equal to that for the steady states of moderate square-wave exercise (i.e., approximately 10 $mL \cdot min^{-1} \cdot W^{-1}$). Interestingly, the observation that $\tau\dot{V}O_2$ for a given WR increment in the high end of the moderate-intensity domain is longer than for the same WR increment at the low end (9) (with multiple WR transitions being utilized to confer a sufficiently high signal-noise characteristic) suggests a different or modulated control process that may no longer conform to first-order behavior. The precise control mechanism(s) remain to be elucidated, however.

A "well-fit" monoexponential $\dot{V}O_2$ response should not, however, necessarily suggest the operation of a single metabolic "compartment." Numerous compartments having a wide range of τ can also sum to characterize a "well-fit" monoexponential for the overall $\dot{V}O_2$ response. Using a 10-compartment model with widely varying individual τ (20–65 s) as an example, the summed $\dot{V}O_2$ response was shown (9) to differ from a pure monoexponential only subtly—hardly, if at all, discernible with even a small component of breath-to-breath noise.

The apparent kinetic τ could, therefore, be concealing evidence of variations of muscle metabolic function at the

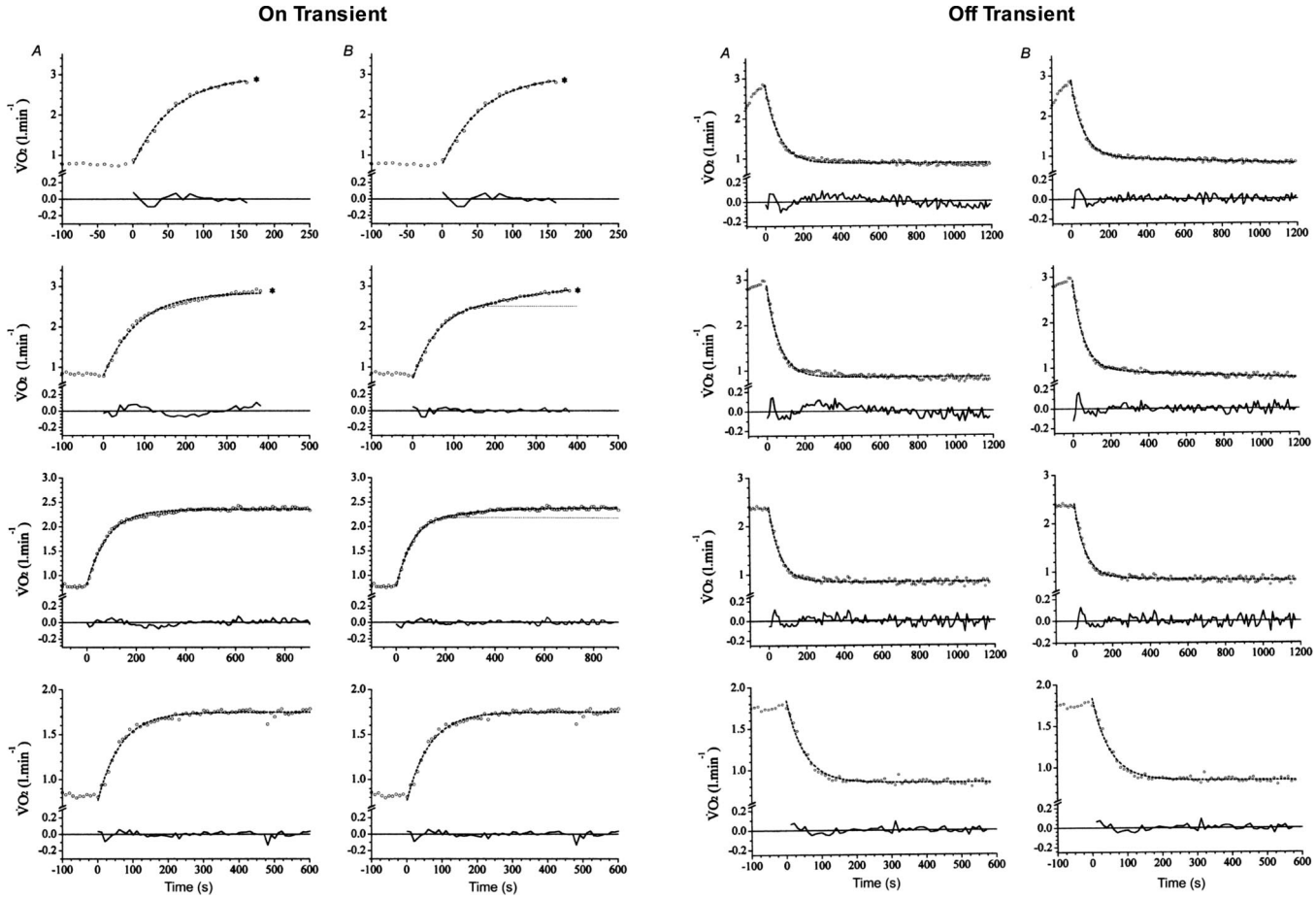

FIGURE 6—An example of the on-transient (*left*) and off-transient (*right*) $\dot{V}O_2$ responses to severe (*top*), very heavy, heavy, and moderate (*bottom*) square-wave cycle-ergometer exercise, showing superimposed best-fits (with residuals) to a monoexponential or a double exponential model. Asterisk indicates point of fatigue. See text for further details. (Modified from: F. Özyener, H. B. Rossiter, S. A. Ward, and B. J. Whipp (2001). Influence of exercise intensity on the on- and off-transient kinetics of pulmonary oxygen uptake in humans. *J. Physiol. (Lond.)* 533: 891–902).

same time it is revealing its modally representative behavior. Consider, for example, two subjects with ostensibly the same overall τ but with one having a narrow distribution and the other a wide distribution of regional τ. The metabolic demands in the long-τ units of the more widely distributed model would require increased supplemental regional energy transfer from anaerobic mechanisms. This could plausibly yield different regional θ_L and, consequently, a different $\dot{V}O_{2max}$, despite the same average $\tau\dot{Q}O_2$. Indeed this heterogeneous function may be the mechanism behind the finding that τ is not consistently constant over all intensity domains. Typically, the fundamental τ has been found to be similar between moderate and severe exercise (30), likely reflecting a relatively homogeneous muscle metabolic profile and/or recruitment of bioenergetically similar motor units. However, subjects having muscle fibers that express a wide range of τ values (i.e., as opposed to a narrow range) may show a tendency to increase τ as work rate increases (6); however, the underlying mechanism(s) is currently not clear.

There is a growing body of evidence that humans do manifest such heterogeneities of metabolism during muscular exercise. Using magnetic resonance (MR) imaging, Prior et al. (33) demonstrated wide regional variations in muscle T_2 relaxation time during exercise—considered to reflect regional muscle recruitment. Similarly, regional MR imaging of the quadriceps during high-intensity exercise in humans has revealed marked regional differences in [PCr] and [Pi], and also in the chemical shift between the PCr and Pi peaks—evidence of regional variations in intramuscular pH and metabolic "stress" (48). The issue of distributed metabolic function under conditions for which uniformity is assumed is of concern because the mean response of a group of muscles or even a particular muscle, as determined for example by ^{31}P-MR spectroscopy or from a femoral-venous blood sample, is likely to mask important regional variations; a single muscle-biopsy sample from an individual muscle may be similarly concerning.

The $\dot{V}O_2$ response kinetics also impact on considerations of the O_2 deficit (O_2def). As the total O_2 requirement of a given WR can be assumed to be ($\Delta\dot{V}O_{2(ss)}\cdot t$), the corresponding O_2def may be quantified as:

$$O_2\text{def} = (\Delta\dot{V}O_{2(ss)} \cdot t) - \Delta\dot{V}O_{2(ss)}\int_0^t (1 - e^{-t/\tau'})dt \qquad [5]$$

where t is the exercise duration. As t becomes appreciably greater than τ', this yields the following simplification:

$$O_2\text{def} = \Delta\dot{V}O_{2(ss)} \cdot \tau' \qquad [6]$$

It is important to emphasize, however, that the τ' value used in the O_2def computation is not the $\varphi 2$ τ nor even the $\varphi 2$ $(\tau + \delta)$, but rather is the τ value that derives from the best-fit exponential applied for the entire nonsteady-state $\dot{V}O_2$ data set (i.e., including $\varphi 1$), with the delay term (δ) either set to zero (i.e., corresponding to exercise onset) or estimated from the least-squares fit using a single $(\tau + \delta)$ model (47). Thus, for a given WR in the moderate-intensity domain, and therefore $\Delta\dot{V}O_{2(ss)}$, the O_2def increases as a linear function of τ'. Hence, the O_2def will be larger in a sedentary individual with slow $\dot{V}O_2$ kinetics than in one who is active, exercising at the same WR. The importance of the $\dot{V}O_2$ mean response time becomes evident when considering, for example, a typical subject exercising at 100 W on a cycle ergometer. The O_2def at a τ' of 60 s would be expected to be approximately 1 L; a value approximately equivalent to the entire phosphocreatine stores of 10 kg of active muscle. Were τ' to decrease to the normal range of approximately 20 to 40 s, this value of anaerobic energy provision would be reduced by between 30 and 60%.

The O_2def at a given moderate WR may therefore be computed from the product of the required $\Delta\dot{V}O_{2(ss)}$, and the effective time constant or mean response time determined either from the monoexponential fit from time zero (Fig. 2D) or from $(\tau + \delta)$ when the $\dot{V}O_2$ fit is not constrained (Fig. 2F). It should be emphasized, however, that the τ obtained from this latter model does not provide an accurate characterization of the actual $\varphi 2$ $\dot{V}O_2$ response, and that, from a physiological viewpoint, the δ term is entirely factitious. Indeed, if the $\dot{V}O_2$ kinetics are very slow and the $\varphi 1$ response is particularly prominent, this delay can be negative—suggesting a $\dot{V}O_2$ response that has preceded the actual start of the exercise. But interestingly, erroneous values for both τ and δ with respect to mechanism sum in this instance to provide an appropriate value for a physiological construct, that is, for O_2 deficit computation.

The magnitude of the O_2 deficit is thus linked to both the O_2 equivalent of the total energy demands of the task and the kinetics of $\dot{V}O_2$, which in turn can be viewed in terms of the convective fluxes for alveolar ventilation ($\dot{V}_A$) and cardiac output ($\dot{Q}_T$) through the corresponding Fick equations:

$$\dot{V}O_2 = \dot{V}_A \cdot (F_IO_2 - F_AO_2) = \dot{Q}_T \cdot (C(a - \bar{v})O_2) \quad [7]$$

where $(F_IO_2 - F_AO_2)$ is the inspired-alveolar O_2 fractional concentration difference, and whence $F_AO_2 = F_IO_2 - \dot{V}_A/\dot{V}O_2$ for O_2 uptake into the lung from the atmosphere, and $CaO_2 = C\bar{v}O_2 + (\dot{V}O_2/\dot{Q}_T)$ for O_2 uptake across the lung into the blood. The $\dot{V}O_2$ terms in these two latter relationships will only be equal, however, if there is no change in the amount of O_2 stored in the lung. As end-expiratory lung volume (EELV) has been shown to decrease by approximately 500 mL (27) throughout the on-transient of exercise in normal subjects (and can actually increase by at least this much in patients with chronic obstructive lung disease), several groups have developed algorithms designed to correct the $\dot{V}O_2$ transient for the associated change in lung O_2 stores (7,11,17,41,45). The basic premise, based upon the pioneering work of Auchincloss et al. (1) is that the amount of O_2 in the lung (VO_2) at a particular time or a particular lung volume (V_A) is given by:

$$VO_2 = V_A \cdot F_AO_2 \quad [8]$$

where V_A has traditionally been determined as the functional residual capacity (FRC); that is, the EELV at which the chest wall musculature is relaxed and sufficient time has elapsed for thoracic equilibrium to be reestablished from the prior inspiration.

On the next breath, VO_2 will change if EELV increases $(V_A + \Delta V_A)$ or decreases $(V_A - \Delta V_A)$, that is:

$$VO_2 = (V_A \pm \Delta V_A) \cdot (F_AO_2 \pm \Delta F_AO_2) \quad [9]$$

which, on expansion, gives:

$$VO_2 = (V_A \cdot F_AO_2) \pm (V_A \cdot \Delta F_AO_2) \pm (\Delta V_A \cdot F_AO_2) \pm (\Delta V_A \cdot F_AO_2) \quad [10]$$

As the final term is considered to be disappearingly small, the difference in VO_2 between the breaths (ΔVO_2) is given by:

$$\Delta VO_2 = (V_A \cdot \Delta F_AO_2) \pm (\Delta V_A \cdot F_AO_2) \quad [11]$$

F_AO_2 and ΔF_AO_2 can be directly measured, and ΔV_A readily computed with the assumption of N_2 balance over the breath (note that at the end of the breath, all the gas in the lung is considered to be alveolar)—that is, when more N_2 is exhaled than was inhaled on the breath, the "extra" is a result of a decrease of EELV (now *not* equal to the FRC). This leaves V_A to be known. Although this can be measured by body plethysmography or by gas dilution techniques before exercise, it rarely is—although predictions can be used for normal subjects.

In an attempt to overcome potential inaccuracies in $\tau\dot{V}O_2$ for the uptake across the alveolar-capillary bed consequent to an inappropriate value being assumed for V_A, Grønlund et al. (17) conceived an astute solution. If the measurement of VO_2 were to be between two points on successive breaths at which F_AO_2 were the same, then the first term in equation 11 would disappear as ΔF_AO_2 would be zero. Cautero et al. (11) have recently asserted that this be considered the gold-standard method for considerations of $\dot{V}O_2$ kinetics during exercise. There are concerns, however. First, the method would benefit from independent validation. Secondly, it demands a redefinition of what is meant by a "breath," which carries with it implications for the estimation of $\tau\dot{V}O_2$. For example, as the slope of the alveolar phase of F_AO_2 increases throughout $\varphi 1$ and $\varphi 2$ (40), then a particular reference intrabreath F_AO_2 may be attained earlier in the expirate; this would result in an erroneous breathing frequency for the breath—or, at least, one that is different from that of the conventional breath. Furthermore, if, as is not uncommon, the subject hyperventilates during the exercise transient, the entire alveolar F_AO_2 profile will be increased, possibly to a level for which there is *no* point in the profile that matches the reference value for the prior breath.

However, as shown in Figure 4 of Cautero et al. (11), when FRC is correctly set, in what they term the "Auchin-

closs" method, there is naturally no error in the estimated $\tau\dot{V}O_2$—assuming, of course, that the EELV change is accurately determined. There is, however, an error that increases as a linear function of decreased FRC estimation: a 50% error in FRC appears to lead to a 10–12% error in the estimated $\tau\dot{V}O_2$, whereas a 10% error in FRC appears to lead to a 2–3% error in $\tau\dot{V}O_2$. Cautero et al. (11) therefore provide a useful reminder that when the Auchincloss et al. (1)—Beaver et al. (7) algorithms are used, FRC should be determined (and in the same "posture" as for the exercise test) or closely estimated for appropriate kinetic analysis of $\dot{V}O_2$ transients.

Changes in $\dot{V}_A$ and $\dot{Q}$ do not seem to contribute to the normal control of O_2 utilization. For example, the $\varphi 2$ $\dot{V}O_2$ kinetics for a given WR increment were not affected by a fourfold experimental alteration of the associated ventilatory time constant in the anesthetized dog—a finding not unexpected when arterial PO_2 provides a "saturation" that operates on the "flat" part of the oxy–hemoglobin (Hb) dissociation curve. Similarly (also in the anesthetized dog), experimentally elevating muscle $\dot{Q}$ at rest to the steady-state exercise level had no discernible effect on $\dot{Q}O_2$ kinetics (despite an O_2 availability apparently in excess of demand) for a subsequent moderate exercise bout and, interestingly, also in most of the individual study animals at high WR; the group mean response, however, was reduced. These results support the earlier assertions of Mahler (28) and Whipp and Mahler (46) that $\dot{Q}O_2$ kinetics are determined largely, if not exclusively, by intracellular mechanisms.

The mechanism(s) controlling intramuscular $\dot{Q}O_2$ during moderate exercise has been proposed to be mediated via closed-loop feedback via, for example, creatine kinase catalyzed PCr kinetics, induced by changes in intramuscular [creatine], [ADP] and/or the phosphorylation potential (i.e., [ATP]/[ADP]·[Pi]) (29). The role of PCr turnover in $\dot{Q}O_2$ control has been investigated in humans using ^{31}P-MR spectroscopy, simultaneously with $\dot{V}O_2$ (35). Support for an involvement of PCr (either directly or as a proxy) derives from both studies on human skeletal muscle mitochondria and the demonstration that the τ of [PCr] decline and that of the $\varphi 2$ $\dot{V}O_2$ increase are closely correlated (Figs. 3 and 4) (35).

Whereas the fundamental $\tau\dot{V}O_2$ has been demonstrated to be increased experimentally by prior β-adrenergic blockade and by hypoxia (42), prior high-intensity exercise (10,13,25), muscle warming (23), and hyperoxia (42) have proved ineffective in reducing the fundamental τ. A speeding has been demonstrated, however, for both forearm exercise in humans, consequent to a speeding of its $\dot{Q}$ response, by a prior calf ischemic exercise (31), and by blocking the mitochondrial influence of nitric oxide (using L-NAME) in the horse (22) and more recently in humans (20).

Feedforward control schemes (with respect to ATP resynthesis) have also been proposed and are clearly distinct from feedback control from, for example, intramuscular phosphates (see above). Here, intracellular [Ca^{2+}] has been proposed to serve as a putative "trigger" (19) for the increase in the rate of oxidative phosphorylation. A feedforward mechanism that constrains substrate provision (H^+, e^-) to the mitochondrial electron transport chain has also been suggested. Thus, the pyruvate dehydrogenase complex functions as a variable "stenosis" to the overall flux (16) and could theoretically control the rate of oxidative phosphorylation by controlling the provision of oxidizable substrate. Whereas the pyruvate dehydrogenase complex has been demonstrated to limit the rate of substrate entry into the mitochondrion, several recent studies in humans, using pharmacological intervention (via dichloroacetate administration) in an attempt to relieve this putative stenosis, were unable to demonstrate a speeding of $\dot{V}O_2$ kinetics (for discussion, see chapters 7 and 9 in (21)).

SUPRA-θ_L EXERCISE

Above θ_L, $\dot{V}O_2$ kinetics become more complex (5,27,30,32,48) (Figs. 3, 4, and 6). The difference between the "expected" steady-state $\dot{V}O_2$ value (i.e., projected from the sub-θ_L $\dot{V}O_2$–WR relationship) and the actual $\dot{V}O_2$ achieved in the quasisteady state is positive for the supra-θ_L WR range at which the steady-state projection is less than the subject's $\dot{V}O_{2max}$. As a consequence, the overall steady-state gain ($\Delta\dot{V}O_{2(ss)}/\Delta WR$) can be markedly increased from the normal 9–11 $mL \cdot min^{-1} \cdot W^{-1}$ to values of 14 $mL \cdot min^{-1} \cdot W^{-1}$ or more (30,48). The additional increment in $\dot{V}O_2$ has been termed "excess" $\dot{V}O_2$ ($\dot{V}O_{2(xs)}$). This has been shown to be the result of a "slow component" ($\dot{V}O_{2(sc)}$), which *appears to be* of delayed origin and which is superimposed on that of the fundamental component. The use of "drift" for this component seems less than suitable; as previously pointed out by Gaesser and Poole (14), the word (according to Webster's) connotes moving "in a random or casual way; to become carried along subject to no guidance or control." But, regardless of the terminology, the attainment of a $\dot{V}O_2$ steady state is appreciably delayed in the heavy-intensity domain, by as much as 10–15 min (5,30,32,48).

However, is the $\dot{V}O_2$ slow phase actually delayed at all—and if so, by how much? Although it can be discerned emerging from the fundamental component at the time of the apparent delay, the degree of "overlap" between the confidence limits of the (usually continuing) fundamental $\varphi 2$ component at that time and the slow component itself is considerable. There is, consequently, doubt about "when" the $\dot{V}O_{2(sc)}$ is manifest. And because there is no convincing mechanistic evidence that the $\dot{V}O_{2(sc)}$ is intrinsically monoexponential, "back extrapolation" based on the assumption of exponentiality is not justified. The τ and δ for the $\dot{V}O_{2(sc)}$ should, at present, therefore be considered parameters of convenience, rather than control parameters having physiological equivalents.

Interestingly, it has been consistently demonstrated that the fundamental $\dot{V}O_2$ component remains well described as an exponential (despite the elevated [lactate]a) with a τ and projected asymptotic gain similar to that of moderate exercise (5,10,30,48). Although some (6) have demonstrated that the fundamental τ may increase at intensity domains above moderate, this is not consistently the case (30). It is

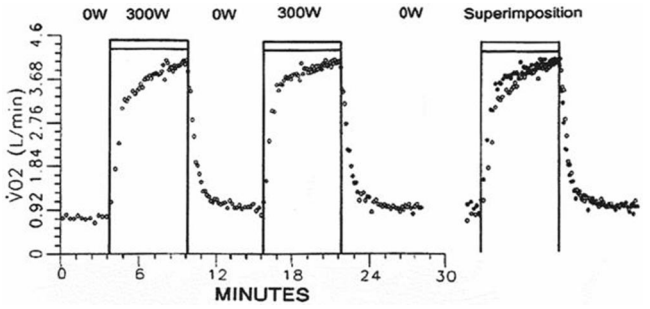

FIGURE 7—*Left:* an example of the $\dot{V}O_2$ response to two successive 6-min bouts of high-intensity square-wave cycle-ergometer exercise. *Right:* the bout 1 and 2 responses are superimposed, to illustrate the speeded kinetics on bout 2. (From: A. Gerbino, S. A. Ward, and B. J. Whipp (1996). Effects of prior exercise on pulmonary gas-exchange kinetics during high-intensity exercise in humans. *J. Appl. Physiol.* 80: 99–107).

thought that an increase in τ at supra-θ_L intensities may represent the manifestation of putatively slower kinetics of fast-twitch muscle fibers, which are only recruited at these higher intensities. Although this suggestion has yet to be conclusively verified, it may be the reason why some subjects show an increase in τ at higher intensities and others do not. Similarly puzzling are reports that the fundamental gain has been variously reported to be: similar over a wide range of work rates (5,30); to increase at increasing work rates (9); or to decrease with increasing fast-twitch fiber involvement (6). These discrepancies may reflect interindividual differences in factors such as the involved muscle fiber types, muscle recruitment patterns, kinetic profiles of the recruited musculature, and the degree to which portions of muscle with slow kinetics can "dilute" the predominant signal coming from recruited slow-twitch fibers. Whereas the $\dot{V}O_2$ on-transient characteristics in the heavy domain are different from those of moderate exercise, the $\dot{V}O_2$ off-transient features remain well described by a monoexponential function (albeit with slightly slower kinetics than for moderate exercise (30)), that is, there is on–off dynamic asymmetry (see Figs. 4, 6, and 7). This, we argue below, may provide an important clue to interpreting the kinetics of the $\dot{V}O_2$ slow component.

For work rates above the subject's CP (i.e., very-heavy–intensity exercise), the $\dot{V}O_{2(sc)}$ sets $\dot{V}O_2$ on a trajectory to or towards $\dot{V}O_{2max}$, with fatigue ensuing as, or soon after, the $\dot{V}O_{2max}$ is attained (14): the higher the WR, the shorter its tolerable duration. Billat and her associates (8), however, have demonstrated that subjects (certain ones, and at certain particular work rates in this domain, presumably) may not be able to sustain exercise at this intensity sufficiently long to reach their $\dot{V}O_{2max}$—suggestive of a different, or at least a proportionally more contributory, mechanism limiting the exercise tolerance. At this intensity, the off-transient $\dot{V}O_2$ response also requires an additional exponential component (Fig. 6) for adequate characterization (30). And as any metabolic "compartments" recruited during the exercise will be operative at the cessation of the work, regardless of when they were recruited, there should be no delay term similar to that for the on-transient.

For severe-intensity exercise, the tolerable duration of the work becomes so truncated that the $\dot{V}O_{2(sc)}$ either has had insufficient time in which to develop or that it has only developed to a stage where it is not discernable from these techniques. Whereas the on-transient $\dot{V}O_2$ can be adequately fit by a single exponential at this intensity (Fig. 6) with a τ not dissimilar to that for moderate-intensity exercise (despite the often meager amount of data, for the model fit, which makes projection of the asymptotic $\dot{V}O_2$ gain less certain), the $\dot{V}O_2$ off-transient still requires a double exponential structure for adequate fitting (30).

The origin of the $\dot{V}O_{2(sc)}$ mediation appears to be, or to be greatly predominant in the exercising muscles themselves. Poole et al. (32) were able to demonstrate that more than 80% of the $\dot{V}O_{2(sc)}$ was attributable to the progressive slow component in the lower-limb $\dot{Q}O_2$. Furthermore, the $\dot{V}O_{2(sc)}$ has been shown to be accompanied by a similar slow component of intramuscular [PCr] decline (35) (Figs. 3 and 4). This argues strongly that the determinant (or at least the dominant component) of the $\dot{V}O_{2(sc)}$ reflects a high phosphate cost of force production rather than a high O_2 cost of phosphate production (consistent with suggestions of Bangsbo et al. (3), who used "direct" measures during severe-intensity exercise). A range of putative mediators have been proposed, including:

(a) *Lactate-stimulated metabolism*. However, the demonstration of a, seemingly typical, slow phase of the $\dot{V}O_2$ kinetics in patients with myophosphorylase deficiency (McArdle's Syndrome) argues against a significant role (34).

(b) *Acid-base status.* Zoladz et al. (49) have reported that the prior induction of a metabolic acidosis by ammonium chloride ingestion increased the magnitude of the $\dot{V}O_{2(sc)}$; the effects of metabolic alkalosis resulting from sodium bicarbonate ingestion, however, are more contentious, with both reductions (50) and increases (24) in τ $\dot{V}O_2$ having been demonstrated.

(c) *Progressive Bohr shift effect*. A more specific effect of the metabolic acidosis enhancing off-loading of O_2 from Hb via the Bohr effect (i.e., maintaining a high capillary PO_2) has also been suggested (43). However, why this would lead to $\dot{V}O_2$ increasing to levels greater than those appropriate for the normal gain is not at all clear.

(d) *Increased cardiac and ventilatory muscle work*. While naturally contributing to an extra O_2 cost, such a component (as argued below) would also be expected to be manifest at the off-transient with similar kinetics, which is not the case (see above).

(e) *Increased levels of circulating catecholamines and/or increased muscle temperature*. Neither appears to be to be significantly contributory, as they do not induce a discernible increase in $\dot{V}O_{2(sc)}$ when experimentally increased in humans, even with a greater hyperpnea.

(f) *Extra upper body work, such as more forceful pulling on the handle bars during cycling*. This may well contribute, especially in some subjects, although the presence of the $\dot{V}O_{2(sc)}$ during both treadmill exercise and knee-extensor

exercise is not consistent with its being the exclusive mechanism of the nonleg component.

(g) *Serial recruitment of additional, presumably type II muscle fibers having a high $\dot{V}O_2$ gain (26).* Interestingly, however, Barstow et al. (6) reported that the $\dot{V}O_2$ gain at high work rate is an inverse, rather than a direct, function of the proportion of type II fibers during cycle ergometry in humans. Clearly, much remains to be resolved about the causes and consequences of the slow phase of $\dot{V}O_2$ during exercise.

There are pitfalls to interpreting the exponential characterization of the $\dot{V}O_{2(sc)}$ in the same sense as for moderate exercise. While it properly rules out taking the final asymptotic projection (and decisively not just the final value) as the single frame of reference for the O_2 deficit computation (Fig. 8, upper panel), it could imply that the deficit be thought of as comprising two separate compartments: one reflecting the $A \cdot \tau'$ of the fundamental component and summing with the $A \cdot \tau'$ of the slow component, as depicted in Figure 8 (middle panel). At first sight, this may appear to represent an improvement over the "traditional" approach for O_2def quantification (Fig. 8, upper panel). However, it bears a heavy burden of assumption; that is, at any time during the slow phase, $\dot{V}O_2$ has an exponential trajectory towards a final $\dot{V}O_2$ asymptote. This implies the abrupt recruitment of a new compartment with relatively uniform metabolic characteristics at the onset of the slow phase. However, this is not the only model structure that will result in a well-fit apparently monoexponential response to $\dot{V}O_{2(sc)}$. Consider one multicompartment example (Fig. 8, lower panel) that has a single τ (other models could have compartments with differing τ, to similar effect) but with a progressively increasing gain. The interesting feature of this model is that the actual underlying τ of the individual metabolic units generating this phase could be appreciably faster than that of the apparent τ estimated from a fit to the $\dot{V}O_{2(sc)}$ data. For example, in the model in Figure 8 (lower panel) we set the fundamental τ to be 30 s, and the "real" slow-phase τ arbitrarily at 45 s. However, in this case, the gain term was not constant; rather, it increased progressively, with the time course shown by the solid dots. The result is that the changing gain and the relatively fast kinetics conflate to yield a well-fit monoexponential response, but with an apparent τ of 250 s—the actual time constants and gain profile of the slow phase naturally remain to be determined. The consequence of this different model approach is that the O_2 deficit for the slow phase will be appreciably smaller than for the procedures used in Figure 8 (upper and middle panels). Highly confident parameter estimation is therefore a necessary, but not sufficient, feature of an appropriate model of the $\dot{V}O_{2(sc)}$—especially when physiological inferences are being drawn. Were the $\dot{V}O_{2(sc)}$ to be the result of a model consistent with the recruitment of a metabolic compartment having a single (and high) asymptotic gain and slow τ (6,22), as expressed in equation 12:

$$\dot{V}O_{2(t)} = A_1 \cdot (1 - e^{-(t-\delta_1)/\tau_1}) + A_2 \cdot (1 - e^{-(t-\delta_2)/\tau_2}) + A_3 \cdot (1 - e^{-(t-\delta_3)/\tau_3}) \quad [12]$$

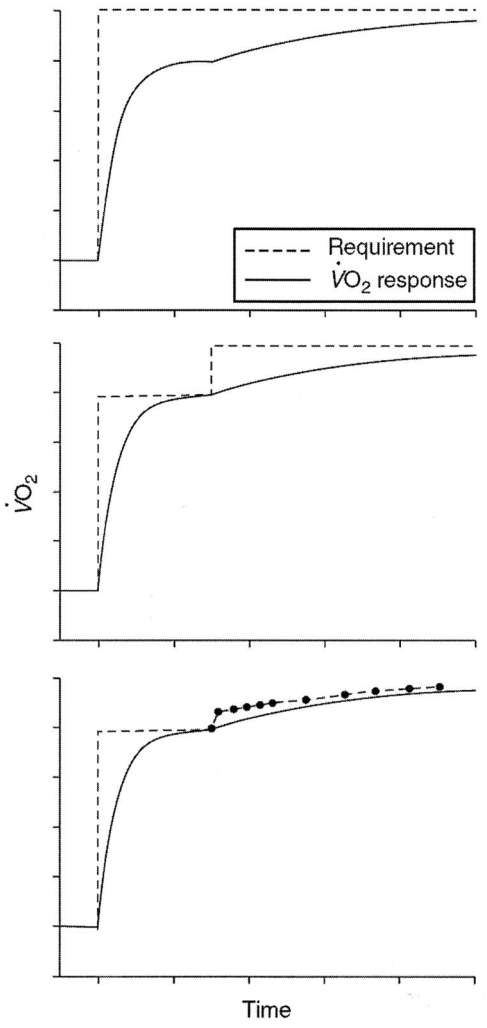

FIGURE 8—Models for computing the O_2 deficit (*dashed contour*) during supra-θ_L square-wave exercise. *Upper*: "traditional" approach, which assumes that the end-exercise or asymptotic $\dot{V}O_2$ represents the O_2 equivalent of the energy requirement throughout the entire work bout (i.e., a single abruptly recruited compartment with relatively uniform metabolic characteristics). *Middle:* partitioning the deficit into "fundamental" and "slow-component" portions, each with relatively uniform metabolic characteristics and abruptly recruited. *Lower*: as for middle panel, but with the "slow-component" portion being characterized via a series of sequentially recruited metabolic units with progressively increasing $\dot{V}O_2$ response gain, but a similar and relatively fast time constant (τ; e.g., 45 s); the slow-component region is well fit by a monoexponential, but with an estimated τ (e.g., 250 s) appreciably slower than the single-unit τ, and its O_2 deficit being appreciably smaller than those predicted by models A and B. See text for further details. (From: B. J. Whipp, and H. B. Rossiter (2005). The kinetics of oxygen uptake: physiological inferences from the parameters. In: A.M. Jones and D. C. Poole (Eds.). *Oxygen Uptake Kinetics in Sport, Exercise and Medicine*. Routledge, London, pp. 62–94).

then its influence should be apparent also at the off-transient. These $\dot{V}O_2$ on–off kinetic asymmetries thus seem more consistent with continued recruitment of additional contractile units throughout the slow phase (38) with the $\dot{V}O_2$ gain factor expressed as a variable rather than as a constant throughout the slow phase. Parameter estimation, and model discrimination, therefore, should be kindred features of kinetic analysis. This leads to an entirely different

model structure with different implications for the control of the $\dot{V}O_{2(sc)}$.

Clues to the $\dot{V}O_{2(sc)}$ control process may be discerned from supra-θ_L experiments in which: (a) the overall on-transient $\dot{V}O_2$ kinetics are speeded, and (b) the increases in [lactate]a and $[H^+]$a is reduced (10,15,25) (Fig. 7), when the exercise is recently preceded by an identical "priming" bout of supra-θ_L exercise. Gerbino et al. (15) reported that $\dot{V}O_{2(sc)}$ was reduced by the priming exercise (subsequently confirmed by Burnley et al. (10) and Koppo and Bouckaert (25)). Gerbino et al. (15) also suggested, however, that the fundamental $\tau\dot{V}O_2$ was speeded. This was based on evidence that such a high-intensity priming bout does not speed the VO_2 kinetics of a subsequent sub-θ_L bout (10,15) and that the $\dot{V}O_2$ gain ($\Delta\dot{V}O_2/\Delta WR$) of the fundamental component for a single bout of supra-θ_L exercise does not differ from that of sub-θ_L exercise despite the developing metabolic acidosis. But as shown in equation 1, with reference to the fundamental component, the demonstrably faster the rate of $\dot{V}O_2$ change at a given $\dot{V}O_2$ can be explained either by a shorter τ and/or a larger asymptotic $\dot{V}O_2$ value. Using the higher confidence averaged responses of several like transitions in each subject, Burnley et al. (10), Koppo and Bouckaert (25), and Endo et al. (13) were able to show that the fundamental $\tau\dot{V}O_2$ was actually unaltered by the priming exercise; it was the asymptotic $\dot{V}O_2$ that was increased. This and the work of Cautero et al. (11), prove to be useful reminders that all the model assumptions properly require experimental justification. Interestingly, however, for high-intensity knee-extension exercise, a high-intensity priming bout speeded both the fundamental $\tau\dot{V}O_2$ and its associated fundamental τ[PCr]. Why the effect differs with the mode of the exercise, or possibly with the muscle mass recruited, remains to be determined.

CONCLUSION

Pulmonary $\dot{V}O_2$ kinetics during muscular exercise should be considered among the important sources of information accessible from the body surface (the lung being an invagination of the surface), including, for example, the ECG, rales, and body temperature, which provide indices of the adequacy of physiological system functioning. Whereas the parameters of the $\dot{V}O_2$ response provide accessible estimates of those in muscle (i.e., until they can be readily established within sufficiently narrow confidence limits in the muscles themselves), a range of model structures capable of yielding the response should be considered in light of the most plausible physiological equivalents for the estimated parameters. A challenging example of this is establishing the magnitude of the O_2 deficit for the slow component of the $\dot{V}O_2$ kinetics at high work rates, as it is almost certainly not the O_2 utilization itself, but the consequences of the nonaerobic components of the energy transfer, that lead to fatigue. The trajectory of $\dot{V}O_2$ and related acid-base variables to, or towards, their limiting levels therefore set the tolerable performance limits. Deconvoluting the overall kinetic features into their component parts can lead to testable hypotheses regarding the physiological mechanisms controlling and, potentially, limiting oxidative phosphorylation and, hence, can provide clues to the physiological determinants of exercise tolerance.

HBR is a Wellcome Trust (UK) International Prize Traveling Research Fellow (#064898).

REFERENCES

1. Auchincloss, J. H., Jr., R. Gilbert, and G. H. Baule. Effect of ventilation on oxygentransfer during early exercise. *J. Appl. Physiol.* 21:810–818, 1966.
2. Babcock, M. A., D. H. Paterson, D. A. Cunningham, and J. R. Dickinson. Exercise on-transient gas exchange kinetics are slowed as a function of age. *Med. Sci. Sports Exerc.* 26:440–446, 1994.
3. Bangsbo, J., P. Krustrup, J. Gonzalez-Alonso, and B. Saltin. ATP production and efficiency of human skeletal muscle during intense exercise: effect of previous exercise. *Am. J. Physiol. Endocrinol. Metab.* 280:E956–964, 2001.
4. Barstow, T. J., N. Lamarra, N., and B. J. Whipp. Modulation of muscle and pulmonary O_2 uptakes by circulatory dynamics during exercise. *J. Appl. Physiol.* 68:979–989, 1990.
5. Barstow, T. J., and P. A. Molé. Linear and non-linear characteristics of oxygen uptake kinetics during heavy exercise. *J. Appl. Physiol.* 71:2099–2106, 1991.
6. Barstow, T. J., A. M. Jones, P. H. Nguyen, and R. Casaburi. Influence of muscle fiber type and pedal frequency on oxygen uptake kinetics of heavy exercise. *J. Appl. Physiol.* 81:1642–1650, 1996.
7. Beaver, W., N. Lamarra, and K. Wasserman. Breath-by-breath measurement of true alveolar gas exchange. *Appl. J. Physiol.: Respir. Environ. Exer. Physiol.* 51:1662–1675, 1981.
8. Billat, V. L., R. Richard, V. M. Binsse, J. P. Koralsztein, and P. Haouzi. The $\dot{V}O_2$ slow component for severe exercise depends on type of exercise and is not correlated with time to fatigue. *J. Appl. Physiol.* 85:2118–2124, 1998.
9. Brittain, C. J., H. B. Rossiter, J. M. Kowalchuk, and B. J. Whipp. Effect of prior metabolic rate on the kinetics of oxygen uptake during moderate-intensity exercise. *Eur. J. Appl. Physiol.* 86:125–134, 2001.
10. Burnley, M., A. M. Jones, H. Carter, and J. H. Doust. Effects of prior heavy exercise on phase II pulmonary oxygen uptake kinetics during heavy exercise. *J. Appl. Physiol.* 89:1387–1396, 2000.
11. Cautero, M., P. E. Di Prampero, and C. Capelli. New acquisitions in the assessment of breath-by-breath alveolar gas transfer in humans. *Eur. J. Appl. Physiol.* 90:231–241, 2004.
12. Cummin, A. R. C., V. I. Tyawe, and K. B. Saunders. Ventilation and cardiac output during the onset of exercise and during voluntary hyperventilation in humans. *J. Physiol.* 370:567–583, 1986.
13. Endo, M., S. Usui, Y. Fukuoka, A. Miura, H. B. Rossiter, and Y. Fukuba. Effects of priming exercise intensity on the dynamic linearity of the pulmonary $\dot{V}O_2$ response during heavy exercise. *Eur. J. Appl. Physiol.* 91:545–554, 2004.
14. Gaesser, G., and D. C. Poole. The slow component of oxygen uptake kinetics in humans. *Exerc. Sport Sci. Rev.* 24:35–71, 1996.
15. Gerbino, A., S. A. Ward, and B. J. Whipp. Effects of prior exercise on pulmonary gas-exchange kinetics during high-intensity exercise in humans. *J. Appl. Physiol.* 80:99–107, 1996.
16. Greenhaff, P. L., S. P. Campbell-O'Sullivan, D. Constantin-Teodosiu, S. M. Pouchera, P. A. Roberts, and J. A. Timmons. An acetyl group deficit limits mitochondrial ATP production at the onset of exercise. *Biochem. Soc. Trans.* 30:275–280, 2002.
17. Grønlund, L. A new method for breath-to-breath determination of oxygen flux across the alveolar membrane. *Eur. J. Appl. Physiol.* 52:167–172, 1984.
18. Hagberg, J. M., R. C. Hickson, A. A. Ehsani, and J. O. Holloszy.

Faster adjustment to and from recovery from submaximal exercise in the trained state. *J. Appl. Physiol.* 48:218–222, 1980.
19. Hansford, R. G. Role of calcium in respiratory control. *Med. Sci. Sports Exerc.* 26:44–51, 1994.
20. Jones, A. M., D. P. Wilkerson, K. Koppo, S. Wilmshurst, and I. T. Campbell. Inhibition of nitric oxide synthase by L-NAME speeds phase II pulmonary $\dot{V}O_2$ kinetics in the transition to moderate-intensity exercise in man. *J. Physiol. (Lond.)* 552:265–272, 2003.
21. Jones, A. M., and D. C. Poole. Oxygen Uptake Kinetics in Sport, Exercise and Medicine. Routeledge: UK, 2005.
22. Kindig, C. A., P. Mcdonough, H. H. Erickson, and D. C. Poole. Effect of L-NAME on oxygen uptake kinetics during heavy-intensity exercise in the horse. *J. Appl. Physiol.* 91:891–896, 2001.
23. Koga, S. T. Shiojiri, N. Kondo, and T. J. Barstow. Effect of increased muscle temperature on oxygen uptake kinetics during exercise. *J. Appl. Physiol.* 83:1333–1338, 1997.
24. Kolkhorst, F. W., R. S. Rezende, S. S. Levy, and M. J. Buono. Effects of sodium bicarbonate on $\dot{V}O_2$ kinetics during heavy exercise. *Med. Sci. Sports Exerc.* 36:1895–1899, 2004.
25. Koppo, K., and J. Bouckaert. The effect of prior high-intensity cycling exercise on the kinetics during high-intensity cycling exercise is situated at the additional slow component. *Int. J Sports Med.* 22:21–26, 2001.
26. Krustrup, P., K. Söderlund, M. Mohr, and J. Bangsbo. The slow component of oxygen uptake during intense, sub-maximal exercise in man is associated with additional fibre recruitment. *Pflugers Arch.* 447:855–866, 2004.
27. Linnarsson, D. Dynamics of pulmonary gas exchange and heart rate changes at start and end of exercise. *Acta Physiol. Scand.* 415 (Suppl):1–68, 1974.
28. Mahler, M. First order kinetics of muscle oxygen consumption, and equivalent proportionality between $\dot{Q}O_2$ and phosphorylcreatine level. Implications for the control of respiration. *J. Gen. Physiol.* 86:135–165, 1985.
29. Meyer, R. A, and J. M. Foley. Cellular processes integrating the metabolic response to exercise. In: *Handbook of Physiology, Section 12, Exercise: Regulation and Integration of Multiple Systems, Ch.* 18, L.B. Rowell & J.T. Shepherd (Eds.). Bethesda: Amer. Physiol. Soc., 1996, pp. 841–869.
30. Özyener, F., H. B. Rossiter, S. A. Ward, and B. J. Whipp. Influence of exercise intensity on the on- and off-transient kinetics of pulmonary oxygen uptake in humans. *J. Physiol. (Lond.)* 533: 891–902, 2001.
31. Perrey, S., M. E. Tschakovsky, and R. L. Hughson. Muscle chemoreflex elevates muscle blood flow and O_2 uptake at exercise onset in nonischemic human forearm. *J. Appl. Physiol.* 91:2010–2016, 2001.
32. Poole, D. C., W. Schaffartzik, D. R. Knight, et al. Contribution of exercising legs to the slow component of oxygen uptake kinetics in humans. *J. Appl. Physiol.* 71:1245–1253, 1991.
33. Prior, B. M., J. M. Foley, R. C. Jayaraman, and R. A. Meyer. Pixel T2 distribution in functional magnetic resonance images of muscle. *J. Appl. Physiol.* 87:2107–2114, 1999.
34. Riley, M., D. P. Nicholls, A.-M. Nugent, et al. Respiratory gas exchange and metabolic responses during exercise in McArdle's disease. *J. Appl. Physiol.* 75:745–754, 1993.
35. Rossiter, H. B., S. A. Ward, J. M. Kowalchuk, F. A. Howe, J. R. Griffiths, and B. J. Whipp. Dynamic asymmetry of phosphocreatine concentration and O_2 uptake between the on- and off-transients of moderate- and high-intensity exercise in humans. *J. Physiol. (Lond.)* 541:991–1002, 2002.
36. Rossiter, H. B., S. A. Ward, F. A. Howe, J. R. Griffiths, and B. J. Whipp. Inferences for muscle energetics following exercise onset from the phosphocreatine hydrolysis profile in moderate constant-load exercise in humans. 2005 Experimental Biology meeting abstracts [on CD-ROM]. *The FASEB Journal* 19, Abstract #348.1.
37. Rowell, L. B. Human Cardiovascular Control, New York: Oxford University Press, 1993, pp 255-301.
38. Shinohara, M., and M. Moritani. Increase in neuromuscular activity and oxygen uptake during heavy exercise. *Annals Physiol. Anthropol.* 11:257–262, 1992.
39. Sietsema, K. E., D. M. Cooper, M. H. Rosove, et al. Dynamics of oxygen uptake during exercise in adults with cyanotic congenital heart disease. *Circulation* 73:1137–114, 1986.
40. Steinacker, J. M., C. Dehnert, and B. J. Whipp. Effect of exercise intensity on the changes in alveolar slopes of carbon dioxide and oxygen expiratory profiles in humans. *Eur. J. Appl. Physiol.* 85:56–61, 2001.
41. Swanson, G. D., and D. L. Sherill. A model evaluation of estimates of breath-to-breath alveolar gas exchange. *J. Appl. Physiol.* 55:1936–1941, 1983.
42. Tschakovsky, M. E., and R. L. Hughson. Interaction of factors determining oxygen uptake at the onset of exercise. *J. Appl. Physiol.* 86:1101–1113, 1999.
43. Wasserman, K., W. W. Stringer, and R. Casaburi. Is the slow component of $\dot{V}O_2$ a respiratory adaptation to anaerobiosis? *Adv. Exp. Med. Biol.* 393:187-194, 1995.
44. Weiler-Ravell, D., D. M. Cooper, B. J. Whipp, and K. Wasserman. The control of breathing at the start of exercise as influenced by posture. *J. Appl. Physiol.* 55:1460–1466, 1983.
45. Wessel, H. U., R. L. Stout, C. K. Bastanier, and M. H. Paul. Breath-by-breath variation of FRC: effect on $\dot{V}O_2$ and $\dot{V}CO_2$ measured at the mouth. *Appl. J. Physiol.: Respir. Environ.Exer. Physiol.* 46:1122–1126, 1979.
46. Whipp, B. J, and M. Mahler. Dynamics of pulmonary gas exchange during exercise. In: *Pulmonary Gas Exchange Vol. II: Organism and Environment.* J.B. West (Ed.). New York: Academic Press Inc., 1980, pp. 33–96.
47. Whipp, B. J., S. A. Ward, N. Lamarra, J. A. Davis, and K. Wasserman. Parameters of ventilatory and gas exchange dynamics during exercise. *J. Appl. Physiol.* 52:1506–1513, 1982.
48. Whipp, B. J., H. B. Rossiter, and S. A. Ward. Exertional oxygen uptake kinetics: a stamen of stamina? *Biochem. Soc. Trans.* 30: 237–247, 2002.
49. Zoladz, J., K. Duda, J. Majerczak, J. Emmerich, and J. Domanski. Pre-exercise acidification induced by ingestion of NH_4Cl increases the magnitude of the slow component of $\dot{V}O_2$ kinetics in humans. *J. Physiol. Pharm.* 49:443–455, 1998.
50. Zoladz, J. A., Z. Szkutnik, K. Duda, J. Majerczak, and B. Korzeniewski. Preexercise metabolic alkalosis induced via bicarbonate ingestion accelerates $\dot{V}O_2$ kinetics at the onset of a high-power-output exercise in humans. *J. Appl. Physiol.* 98:895–904, 2005.