Point:Counterpoint: The kinetics of oxygen uptake during muscular exercise do/do not manifest time-delayed phases

POINT: THE KINETICS OF OXYGEN UPTAKE DURING MUSCULAR EXERCISE DO MANIFEST TIME-DELAYED PHASES

Modeling a physiological system’s response to a stressor, such as muscular exercise, demands more than a mathematically adequate characterization of its transient response profile: adequacy and appropriateness are not synonymous. The model constituents should be reflective of the system’s physiological features, with implications for both its control mechanisms and providing testable hypotheses for their confirmation or not.

As muscle oxygen consumption ($Q_{O2}$) has been demonstrated to be under the dominant feedback control of enzymatic processes linked to high-energy phosphate use (6, 11, 27), exponentiality inheres in its response to a change in work rate (WR) (13), most simply for moderate-intensity exercise. And so it has been demonstrated to be, both inferentially by the intramuscular phosphocreatine profile (19) and from direct determination of muscle blood flow ($Q_{M}$) and its arteriovenous $O_2$ content difference (7)—despite the formidable difficulties of directly demonstrating this with precision, among which is the muscle-effluent delay to the sampling site varying as $Q_{M}$ changes (1) and the likely small quantitative consequence of the Fick equation not being rigorous in the non-steady state.

But there is no such a priori expectation for the rate at which pulmonary oxygen uptake ($V_{O2}$) increases during exercise. For the muscle, a flow increase alone will not, of itself, increase $Q_{O2}$ except for the extremely small storage effect as its $P_{O2}$ increases—unless the muscle is already flow limited. In contrast, the lung inflow ($Q_{p}$) has a reduced $O_2$ content ($C_{O2}$); this is raised to arterial level during the pulmonary-capillary transit, necessitating a flow-dependent $V_{O2}$ increase even if $C_{O2}$ remains constant (10). This is clearly evident in the $V_{O2}$ profile during the transient of a step-increase in WR, especially from rest (23; Fig. 1, top).

Subsequently, however, the influence of the decreasing muscle-venous $O_2$ content results in a decrease in $C_{O2}$ at a time dependent on the vascular transit delay between the sites. The $V_{O2}$ response therefore conflates the influence of $Q_{p}$ and that of $C_{O2}$ into, what is termed, its phase I and its subsequent and dominant first-order component [at all but very low WRs (21)] of the non-steady-state response (phase II) to the steady state (phase III). It is therefore hard to see how the assertion that $V_{O2}$ kinetics has a delayed component during moderate exercise can be seriously challenged.

But the concern under consideration is more related to whether, for higher intensity exercise, the $V_{O2}$ response has a subsequent component of delayed origin superimposed on a fundamental first-order kinetic response. The simplest answer is that “there certainly seems to be”! And, if not, is there compelling contradictory evidence? The presence of a slow phase of delayed onset is often evident even by inspection (4, 16; Fig. 1, middle). In other cases, its onset is most clearly established by a “simple” monoenzymatic characterization of the entire transient being no longer justifiable. The “best-fit” characterization of the response requires an additional component, the onset of which (its “delay") merges onto the still-rising phase of the fundamental (5, 14) typically after one-and-a-half to two-and-a-half minutes (although see Ref. 12) with an amplitude that correlates highly with the proportion of type 2 fibers (3, 9). This $V_{O2}$ “slow” component, as typically charac-

Fig. 1. Top: time course of the pulmonary $O_2$ uptake ($V_{O2}$) response from rest to a constant moderate-intensity work rate demonstrating the phases of the response (from Ref. 23). Middle: as for top, except the work rate is of heavy intensity (from Ref. 4). Bottom: time course of the $O_2$ response to an incremental ($\times$) and a step-decremental ($\bigcirc$) ramp [modified, by the addition of the steady-state relationship (solid symbols), from Ref. 24].

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terized [for discussion, see Whipp and Rossiter (22)], can be of considerable relative amplitude and large time constant (e.g., Refs. 5, 14, 25). One might expect the presence of a component of such magnitude throughout the transient to distort the phase II monoeXponential—it does not seem to (4, 14, 26)! And so, if the component is neither apparent nor discernible as a statistically justifiable component throughout the entire phase II, at least by best-fit multiexponential summing, then one seems compelled either to accept the conclusion that it is not there or the less-than-satisfying conclusion that it is there but cannot be seen! Furthermore, that the slow phase is a different component of the response is suggested by the demonstration that a sufficiently recent bout of high-intensity priming exercise can reduce its magnitude with no discernible effect on the fundamental component (5, 17). Of course, there are additional nonlocomotor components of the VO2 response expressed without delay, including those of ventilatory and cardiae work. But the dominant component of the slow phase originates in the locomotor muscles (18, 22); it is this which is at issue.

Considerations of superposition also prove to be instructive. If instead of considering the profile of VO2 response to a constant WR one considers its response to a constant rate-of-change of WR (an incremental ramp), then the expected lagged-linear response, with a slope equal to that of the steady-state requirement, is evident throughout the moderate-intensity domain (24; Fig. 1, bottom). However, for ramp durations of 8–12 min (and in some cases even longer), this behavior is also maintained throughout the heavy- and very heavy intensity domains (Fig. 1, bottom). It is as if the slow phase of the kinetics is not, or is not yet, contributory. The response to more-prolonged ramps (8) or small-step increments (25, 29), however, remains consistent with first-order kinetics throughout the moderate-intensity range but one for which the response profile backs away from simple linearity at higher intensities—as if a delayed component is now supplementing the underlying process only in the heavy- and very heavy intensity domains. But, if we also consider the response to a decremental ramp, instituted immediately from a step to the highest WR achieved on the incremental ramp, then an entirely different response is evident (Fig 1, bottom). In this case the VO2 response increases to a value appreciably greater than “expected” for the particular WR, based on the incremental ramp kinetics, and which subsequently decreases with a markedly steeper slope—as if the high WR fiber type recruitment profile uses units with high energy cost of force production.

And so, the issue is not simply a mathematical quibble over fitting strategies but one with significant physiological implications. A characterization of the high-intensity VO2 response kinetics that does not consider a delay in the slow phase onset necessitates the process be established from the onset rather than one subsequently resulting from the contractile-energetic consequence(s) of fatigue, mediated, for example, by mechanisms linked to a sufficient increase of intracellular inorganic phosphate—a close kinetic correlate of the VO2 response profile, including its slow phase (20). Maintaining force production would necessitate additional motor units to be recruited and/or a decrease in the contractile efficiency of the operational pool (1), i.e., that will not be manifest until this fatigue begins to be expressed, at some time after exercise onset. The current literature addressing this issue provides evidence that is both confirmatory and contradictory [e.g. Refs. 16, 28 and see also Poole and Jones for discussion (17)]—we await decisive resolution.

In conclusion, while we cannot definitively rule out the possibility that a shallow-contoured sigmoidal component, for example, operates throughout the high-intensity transient, there seems to be no sufficient justification to rule it in. But the debate under consideration is useful, as it is “... imperative to be absolutely clear that one’s equations make strict and accurate sense. However, it is equally important not to be insensitive to 'things going on behind the scenes' which may ultimately lead to deeper insights” (15).

REFERENCES
COUNTERPOINT: THE KINETICS OF OXYGEN UPTAKE DURING MUSCULAR EXERCISE DO NOT MANIFEST TIME-DELAYED PHASES

The existence of time-delayed phases (1) is not supported by oxygen uptake kinetics data. Despite many attempts for a number of years, no convincing physiological mechanism for such behavior has been proven to exist. The reason is that these time-delayed phases are a figment of the incorrect treatment of the data and the overly simple curve fitting of the, usually, averaged data. The reported problems regarding high levels of uncertainty in TD2 or insufficient clarity in the drop in the pulmonary gas exchange ratio, R, defining TD1 are due to trying to fit time-delayed phases to data with no such features. Due to the poor data handling and curve fitting the time constant is also physiologically irrelevant.

Breath-by-breath recordings exhibit spontaneous fluctuations (18). A number of different algorithms with different assumptions are therefore used to estimate the breath-by-breath VO2, resulting in notable differences observable throughout the whole on/off transient, most extremely so in the initial response (16). These algorithms can also affect the three-phase curve parameters estimates (9, 13). Breath-by-breath variability may have biological significance (5) as nonlinear systems such as those governing the respiratory and circulatory functions can produce signals that look like random noise but are in fact not stochastic (3, 11, 14, 15, 21). Therefore part of what is attributed to noise can contain inherent features and vital information (30). For example, in both constant and free-paced 10,000-m runs the VO2 (and HR) has a scaling exponent above 0.5, the value for white noise (4).

Noise reduction is commonly achieved via ensemble averaging the responses of multiple supposedly identical exercise bouts (17). This is only justified when the noise is Gaussian and stochastic (26) and the basic response pattern of each bout is identical, which in general is not the case (2, 20). To support this procedure (17, 20) it is often quoted as showing that the noise is white. These papers however do not provide sufficient proof of the noise’s whiteness for the whole on/off transient at any intensity, as only the steady states at rest or during the last 2 min (120 s is a very short sample size) of non-slow component data are analyzed. In contrast more modern studies show that some breath-by-breath algorithms produce data with non-white noise (4, 7, 9), hence averaging several repetitions can be methodologically unjustified (9). Also due to variation in parameter values on repeated testing days it is debatable whether ensemble averaging is an accurate method (2). Parameter variability is also reported, especially in the time constants (19). Differences between bouts, when ensemble averaged, can produce features not found in the raw unaveraged time series for a single bout of exercise (30). Therefore a model that is fit to the features of averaged data is not necessarily a good model of the raw unaveraged data of a single exercise bout [in which features such as time-delayed phases cannot be observed due to the high-frequency signal oscillations (5, 23)]. A curve without time-delayed phases (22–25, 28–30) can fit the data perfectly well. If the data for a single bout of exercise is instead filtered using a low-pass filter or a moving average with sufficient high n (30) or a more sophisticated nonlinear curve smoothing techniques (15) then the curve obtained will provide the basic response pattern for that bout of exercise. The basic response pattern is what should be modeled, not the average, which in general is a different curve (30).

The phase 1/2 components are intertwined, complicating the TD1 interpretation (26). In theory, the start of phase 2 (i.e., TD1) should be triggered by a fall in the pulmonary gas exchange ratio (R = VCO2/VO2), however, “this decrease is often not sufficiently clear for this purpose and a value of at least 20 s is commonly used” (26). Many researchers try to improve the phase 2 fit by constraining the fitting window to start some time after the exercise onset (26). As there exists a high degree of interdependency in the parameters (16), arbitrarily cutting data affects all the parameter values. As a result τ2 will be dependent on the amount of data removed, making it of limited use physiologically. For the phase 1 and slow component, the best fit to the data can result in unphysiologically large values of the amplitude and/or time constant (16). It is debatable therefore whether the exponential is a good model for these phases (8, 12, 26). The determination of both the phase 2 asymptote and TD2 is highly uncertain and via dependency, this can dramatically affect the parameter values and confidence, possibly causing an unacceptable reduction in the τ2 confidence (26).

Slow kinetics can easily be observed to exist by inspection, what is not certain however is the existence of a time-delayed slow component, nor has a physiological mechanism been proven (26). Slow kinetics emerge from the background noise after a time period, however, crucially this does not imply the