Found in translation: the dependence of oxygen uptake kinetics on O₂ delivery and O₂ utilization

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That the rate of pulmonary oxygen uptake (V̇O₂) does not immediately increase in response to a step increase in work rate, resulting in the so-called “oxygen deficit,” is one of the oldest and most controversial observations in exercise physiology. Relatively little controversy emanates from the description of the V̇O₂ kinetics: that the “fast” or “primary” component is exponential in character, that a “slow component” emerges at work rates above the lactate threshold, and that the origin of both components resides within the exercising muscle is not disputed (11). However, the mechanisms underpinning these transient V̇O₂ responses are subject to considerable and often heated debate. Part of the reason this debate persists is that it has until recently been difficult to directly associate measurements made at the mouth with mechanisms within the muscle. As a result, the fundamental challenge that the field of V̇O₂ kinetics presents will be familiar to all exercise physiologists: to what extent do physiological inferences derived from whole body measurements (at the mouth and/or in the systemic circulation) translate to (and from) physiological processes occurring within the myocytes and microcirculation?

It is first important to note that, when narrow limits of statistical confidence are provided by the appropriate sampling and averaging of V̇O₂ kinetics data, the transient pulmonary V̇O₂ signal during whole body exercise in healthy participants reflects the muscle V̇O₂ kinetics (11). The muscle V̇O₂ kinetics, in turn, is coupled by mitochondrial creatine kinase to the dynamics of high-energy phosphate metabolism in the cell (10): the time course of phosphocreatine (PCr) degradation has been shown to be functionally identical to the simultaneously measured V̇O₂ response (6). In addition, a slow component in pulmonary V̇O₂ is mirrored by a slow component in PCr degradation (7). Broadly speaking, therefore, what is measured at the mouth (taking account of appropriate transport delays) closely reflects energetic events occurring within the exercising muscle. However, the extent to which the kinetics of V̇O₂ is determined by O₂ delivery to the cell, or by a lag in O₂ utilization by the cell, remains the principal issue of debate. As might be expected, the problems associated with the translation of experimental findings from the cell and adjacent capillaries to the muscle and further to the whole body provide a major source of controversy. In addition, the degree to which O₂ delivery influences the V̇O₂ response is crucially dependent on the experimental design. Factors such as body orientation, exercise intensity, exercise mode, and contractile regime may shift the locus of control toward or away from O₂ delivery (6). The dependence of O₂ uptake kinetics on O₂ delivery is exponential in character, that a “slow component” emerges at work rates above the lactate threshold, and that the origin of both components resides within the exercising muscle is not disputed (11). However, the mechanisms underpinning these transient V̇O₂ responses are subject to considerable and often heated debate. Part of the reason this debate persists is that it has until recently been difficult to directly associate measurements made at the mouth with mechanisms within the muscle. As a result, the fundamental challenge that the field of V̇O₂ kinetics presents will be familiar to all exercise physiologists: to what extent do physiological inferences derived from whole body measurements (at the mouth and/or in the systemic circulation) translate to (and from) physiological processes occurring within the myocytes and microcirculation?

Recently, the view has been expressed that the O₂ delivery/utilization debate is a false dichotomy. A more realistic view of this issue is that there is a “tipping point” in the relationship between the speed of the V̇O₂ kinetics (expressed using the primary V̇O₂ time constant) and muscle O₂ delivery (Fig. 1; Ref. 5). To the left of this tipping point, the kinetics is undeniably O₂ delivery dependent, whereas to the right of the tipping point, the kinetics is determined by O₂ utilization. In this context, specific human populations and/or experimental conditions may occupy distinct and predictable positions on the continuum. For example, the kinetics of well-conditioned young subjects performing upright cycle exercise might not become O₂ delivery dependent even at work rates that elicit the maximum V̇O₂ (5). Crucially, attempting to increase O₂ delivery by breathing hyperoxic inspirates does not discernibly speed the V̇O₂ kinetics (e.g., 12), which seems to provide compelling evidence in favor of an intracellular locus of control. In contrast, older humans, particularly those possessing chronic cardiovascular, respiratory, and/or muscular pathologies, may be consistently positioned to the left of the tipping point, although interventions designed to reduce O₂ delivery have been shown to slow the V̇O₂ kinetics, implying that healthy humans lie close to, or even “straddle” the tipping point. Interventions that increase O₂ delivery usually do not speed the kinetics, consistent with a right-shift away from the tipping point. The work of Davies et al. (1) provides indirect evidence that cardiovascular adjustments may be necessary to prevent a slowing of V̇O₂ kinetics following exercise-induced muscle damage. See text for further details.
tipping point (i.e., O₂ delivery dependent; 5), and hence therapeutic strategies to improve muscle O₂ delivery may enhance exercise tolerance by speeding VO₂ kinetics.

In a study in the *Journal of Applied Physiology*, Davies et al. (1) report the results of experiments that illustrate the utility of the tipping point concept. These authors demonstrated that eccentric exercise resulting in severe muscle damage did not alter the primary VO₂ kinetics, as also reported by Schneider et al. (8). These findings are surprising, since it has been demonstrated that such damage also severely disrupts the microvasculature and thus compromises the matching of O₂ delivery to O₂ demand [in effect, left-shifting (reducing) O₂ delivery; Fig. 1], which would be expected to result in the VO₂ kinetics being slowed (3). A possible conclusion, therefore, is that the VO₂ time course is independent of O₂ delivery. However, Davies et al. (1) also provide novel evidence that the kinetics of near-infrared spectroscopy (NIRS)-derived deoxygenated hemoglobin (HHb) was slowed at the onset of exercise with muscle damage. This could occur if muscle blood flow had been increased in an attempt to increase microvascular VO₂ to maintain O₂ flux to the active myocytes. Thus the work of Davies et al. (1) suggests that to preserve VO₂ kinetics during severe-intensity exercise following muscle damage, compensatory cardiovascular adjustments must occur. This work provides an excellent example of the power of integrative and translational physiology: taking measurements at the whole body and muscle levels simultaneously and paying heed to known physiology from other experimental models, Davies et al. (1) have reconciled previously disparate findings and suggested new avenues of inquiry.

In measuring variables related to the matching of O₂ delivery and O₂ utilization, Davies et al. (1) raise important physiological questions and suggest how answers might be sought. One avenue of investigation concerns whether muscle blood flow kinetics is altered by prior muscle damage as would be predicted from their results. Interestingly, recent calculations based on measurements of HHb and VO₂ kinetics suggest that capillary blood flow dynamics may be considerably slower than those measured in the conduit artery (2), and the effect of muscle damage on capillary blood flow kinetics in humans is also unknown. Thus, where the preservation of VO₂ kinetics by cardiovascular adjustments occurs begs the question, at which functional level(s) might these adjustments occur?

Returning to the tipping point concept, the data presented by Davies et al. (1) suggest that their subjects’ VO₂ kinetics may have been positioned close to the tipping point itself. However, the “position” of a subject in relation to the tipping point is, in itself, a simplified view of the physiology. Heterogeneities in perfusion and metabolism, accentuated by inter- and intraindividual variations in fiber type and capillary distribution, imply that the position is perhaps better expressed not as a point but as a distribution. But how wide should this distribution be to reflect these heterogeneities? Perhaps most importantly, how should the relationship between VO₂ kinetics and O₂ delivery be presented to most accurately reflect the underlying physiology? At present, the tipping point concept is intended only to illustrate the dependence of primary VO₂ time constant on O₂ delivery. Yet it is known that muscles containing predominantly type II fibers evidence slower kinetics of PCr degradation than those containing predominantly type I fibers (4). These fiber-specific responses may influence the VO₂ kinetics at high work rates even if O₂ delivery is adequate. If we are to generate hypotheses using the tipping point concept, then the model should take account of these findings also. Perhaps what is needed is a diagram analogous to that presented by Wagner (9) to describe the interplay between convective and diffusive O₂ delivery in determining the maximal VO₂ (9).

In summary, the study of Davies et al. (1) highlights the benefits of adopting integrative and translational approaches to investigate the energetics of whole body exercise. This investigation also significantly strengthens the rationale for considering the contributions of O₂ delivery and O₂ utilization to the control of VO₂ kinetics in light of the tipping point concept.

REFERENCES


