**Reply to Korzeniewski: Muscle Bioenergetic System Properties as Common Mechanisms of V̇O2 On-Kinetics and Critical Power**

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We thank Professor Korzeniewski for his letter and the opportunity to discuss further the development of concepts for an integrated understanding of the physiology that limits exercise tolerance. As we presented in the section of our review titled “V̇O2 kinetics and the O2 deficit” (1), evidence supports that V̇O2 kinetics (and its fundamental phase 2 time constant, τV̇O2) are a consequence of the intracellular bioenergetic system properties, dependent on variables including oxidative phosphorylation (OXPHOS) activity, each step-activation intensity (ESA), O2 and metabolite concentrations. Therefore, we agree with Professor Korzeniewski’s statement that V̇O2 kinetics are an “epiphenomenon of the kinetic properties of the system” (2), and presented it as such in our manuscript. With knowledge of this recognized hierarchy, we would like to highlight that V̇O2 kinetics are a far more accessible variable to “assay” these lumped system properties non-invasively. With appropriate recognition of assumptions, such as the influence of circulatory dynamics (3), pulmonary V̇O2 kinetics are a close proxy of muscle V̇O2 kinetics (4,5), providing a non-invasive window on the overall status of the muscle bioenergetics system. In our review we gathered the evidence testing the hypothesis that interventions modifying V̇O2 kinetics (representing muscle bioenergetic system properties) also modify CP; we believe the weight of current evidence supports this hypothesis, and is also consistent with computer simulations of the bioenergetics system, as highlighted in Professor Korzeniewski’s correspondence (Table 1 in Korzeniewski & Rossiter, 6).

The quantitative “Pi double-threshold” mechanism, discussed in our review and formalized by Korzeniewski and Rossiter (6,7) provides new insight into these complex system behaviors. We would like to take this opportunity to emphasize (as the original authors do) that the critical [Pi] mechanism is a proxy variable in the computer simulations representing many, potentially diverse, mechanisms that initiate a loss of efficiency in contracting muscles (increased [Pi], [ADP], [H+], reactive oxygen species, Ca2+ sensitivity, extracellular [K+]; among other candidates). Despite these recognized assumptions, the critical [Pi] represents an O2-deficit-related phenomenon, initiating a loss of work efficiency from which CP emerges as a property of the entire bioenergetics system. This is the new piece of the puzzle that provides a bridge from historical efforts to associate the O2-deficit with exercise tolerance, to the current hypothesis that common mechanisms in the bioenergetics system determine both V̇O2 kinetics and CP. We attempted to summarize this in our conclusion where we stated that fast V̇O2 kinetics are associated with improved metabolic stability, lesser metabolite accumulation and greater CP. Expanding on the general causal chain during rest-to-work transitions, as outlined in Professor Korzeniewski’s letter, ATP breakdown at the cross-bridge leads to accumulation of Pi and ADP that interacts with the instantaneous OXPHOS activity to cause an increase in V̇O2. Iteratively, this then mediates how much further Pi and ADP will increase; these interactions will determine both V̇O2 kinetics and CP. In the trained state, adapted bioenergetics system variables, such as, but not limited to, greater OXPHOS activity and ESA result in faster τV̇O2 and an increase in CP consequent to these system adaptations allowing improved metabolic stability; hence the title of our review “Bioenergetic Mechanisms *Linking* V̇O2 Kinetics and Exercise Tolerance”. Future investigations to test these hypotheses with experimental studies *in vivo* will undoubtedly lead to a more complete and unified understanding of the mechanisms that determine exercise intolerance.

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