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Response

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Dear Editor-in-Chief

We thank Drs. Murias and Paterson (4) for their interest in our work and raising two important questions about our recent publication (6) in the journal. This paper provides evidence that deoxygenated myoglobin accumulation (deoxy-Mb), assessed in the muscles of the lower leg, lags behind phosphocreatine breakdown (PCr) during moderate- and heavy-intensity plantar flexion exercise in humans (6). The first concern is whether the fitting methods used to quantify deoxy-Mb and PCr kinetics influenced the interpretation that Mb desaturation lags behind PCr breakdown. The second question is whether or not a VO_2 time constant greater than 20 s resides beyond a “tipping point” for VO_2 onset kinetics, where mitochondrial O_2 delivery becomes limiting to the kinetics of oxidative phosphorylation.

To address the first concern, naturally, we agree that selection of the appropriate fitting methods is crucial to the quantitation, statistical comparison, and interpretation of the deoxy-Mb and PCr kinetic responses. Indeed, we went to great lengths to select modeling procedures that produce model fits that best reflect the physiologic processes underlying the deoxy-Mb and PCr responses. The decision to constrain the PCr fit to begin at exercise onset was based on a feature of the underlying physiology and the data itself. Specifically, the creatine kinase reaction is extremely rapid, and thus PCr buffers the immediate energy demands of muscle contraction (1). Thus, a model that allows PCr breakdown to begin before muscle contraction commences has little physiologic justification. Furthermore, in this study, the mean time delay, using an unconstrained fit, could not be distinguished from exercise onset at 120 s (moderate, 116 ± 5 s, $p = 0.11$; heavy, 117 ± 6 s, $p = 0.18$). The deoxy-Mb response was fit as described by DeLorey et al. (2), where the onset time of deoxy-Mb increase (above the baseline fluctuations) was identified, and the kinetics were determined from a fitting window projecting forward from that point. Therefore, the

reported deoxy-Mb time constant should be free from the influence of the early delay-like phase, and should be dependent on the exponential-like region of the response.

That said, to reassure the journal's readership, here we provide a figure that better documents the group mean deoxy-Mb and PCr kinetic responses during the early transient [Figure 1; redrawn from Figure 1 in Richardson et al. (6)]. The data, averaged across all participants, clearly illustrate that the PCr kinetics are more rapid than those of Mb during both moderate- and heavy-intensity exercise and, of importance, this interpretation is unencumbered by concerns regarding fitting method selection.

In terms of the second concern raised by Drs. Murias and Paterson (4), regarding the proposed VO_2 onset kinetics tipping point, where mitochondrial O_2 delivery becomes limiting to the kinetics of oxidative phosphorylation, this certainly does provide a useful conceptual framework to examine such interactions. Murias and Paterson (5) suggest a value for the tipping point (a VO_2 time constant τ of $\sim$20 s) that delimits an O_2 delivery dependent- from an O_2 delivery independent-zone, based on a series of cycle ergometry experiments. This value is likely highly specific to: (a) the exercise modality employed (e.g. double-leg cycling, plantar flexion exercise, etc.) and (b) the relative balance between the respiratory capacity of the muscle(s) studied and the cardiovascular capacity to transport O_2 to the active muscle mass. Therefore, while we acknowledge the view that VO_2 onset kinetics appear to be O_2-delivery limited when τ VO_2 is slower than 20 s during cycling exercise in young adults (5), this does not necessarily apply to our experimental paradigm. Recognizing that the skeletal muscles from the lower limbs exhibit relatively similar mitochondrial content to the rest of the muscles employed during cycling exercise (3), the use of a small muscle mass exercise modality (single-leg plantar flexion) in our study (6) would likely have limited the influence of O_2 availability to the exercising muscle, thus shifting the tipping point to a higher value compared to a large muscle mass exercise such as cycling. Therefore, we contend that despite a calculated $\tau > 30$ s for PCr and deoxy-Mb, due to very different experimental paradigms, our finding that O_2 supply did not limit the adjustment of oxidative phosphorylation may not be an overstatement and does not necessarily conflict with the modified “tipping point” concept proposed by Murias et al. (5).

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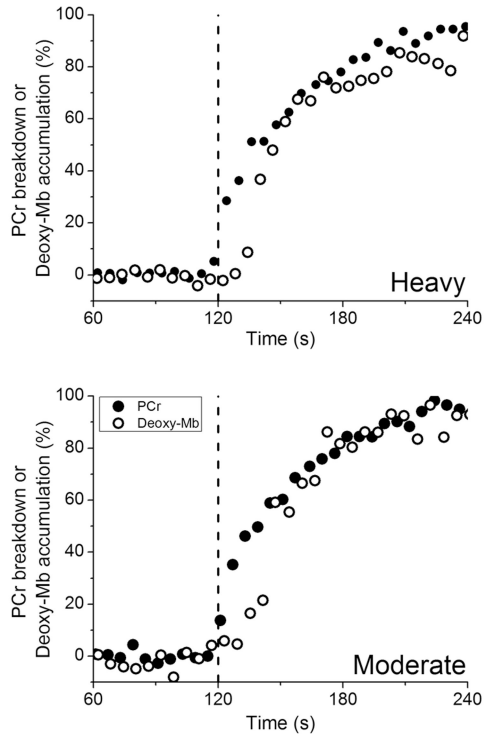

Figure 1.

Group mean (n = 6) phosphocreatine breakdown (PCr) and deoxygenated myoglobin increase (deoxy-Mb) across the rest to exercise transition for moderate (60% of the work rate associated with isolated muscle aerobic capacity) and heavy (80% peak work rate) intensity plantar flexion exercise. Data are normalized to the percentage of the end-exercise values. The figure is redrawn from Figure 1 in Richardson et al. (6) to illustrate the difference in the PCr and deoxy-Mb kinetics during first minute of contractions. Error bars are omitted for clarity [see Richardson et al. (6)].