Can we simply infer mitochondrial function from PCr resynthesis after exercise in skeletal muscle?

doi:10.1038/pr.2012.67

To the Editor: We have read with much interest the paper recently published by Wells *et al.* regarding the abnormalities of muscle metabolism in adolescents with cystic fibrosis and primary ciliary dyskinesia (1). Although the results of this investigation are of potential interest, we are concerned about the utilization of the time constant of phosphocreatine recovery (τPCr) as a simple index of mitochondrial function and the corresponding conclusions regarding the impact of cystic fibrosis on muscle metabolism during exercise. The real issue is to clearly determine whether one can infer mitochondrial function on the basis of measurements of τPCr.

During recovery from exercise, phosphocreatine is resynthesized purely as a consequence of oxidative ATP synthesis (2) and measurements of the time constant of τPCr have been used to characterize mitochondrial function in a variety of conditions (3). However, several studies have clearly demonstrated that cytosolic pH has a strong influence (3). It is well acknowledged that τPCr is positively related to the extent of intracellular acidosis and PCr consumed (3). In other words, a significant intracellular acidosis and a large PCr consumption in exercising muscle would be associated with a slower PCr resynthesis (3). In the Wells *et al.* (1) study, cytosolic pH was reduced to a smaller extent after high-intensity exercise in adolescents with cystic fibrosis as compared with controls. Therefore, the magnitude of changes in muscle oxidative capacity on the simple basis of τPCr measurements could have been underestimated in patients with cystic fibrosis. Of note, several kinetic parameters are usually used to describe PCr changes during exercise-to-recovery transition, including τPCr, the initial rate of PCr recovery, and the maximum aerobic capacity (4). These three parameters characterizing PCr resynthesis are correlated to oxidative capacity. However, in contrast to τPCr, the initial rate of PCr recovery, and the maximum aerobic capacity are insensitive to exercise intensity and end-of-exercise metabolic conditions (3). On that basis, the initial rate of PCr recovery and the maximum aerobic capacity should be considered as additional indexes to compare the post-exercise PCr recovery rate and mitochondrial oxidative capacity across different populations when end-of-exercise pH and PCr concentration values are different or not taken into account. This was the case in some previously published studies that investigated *in vivo* mitochondrial function from childhood to young and/or late adulthood (5,6). In contrast, this was not the case in other studies that investigated age-related changes in mitochondrial oxidative capacity from childhood to adulthood (7) and examined the association between mitochondrial alterations and insulin sensitivity in overweight and normal-weight children (8).

Overall, it is of utmost importance to keep in mind that one cannot simply infer mitochondrial function on the basis of measurements of the rate constant of PCr resynthesis given that end-of-exercise conditions have been shown to exert a strong influence. Future studies should pay attention to these methodological inaccuracies, which might hedge data interpretation and confound the corresponding conclusions.

Editor's note: Dr Wells was offered the opportunity to respond to this letter but declined to submit a reply.

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