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**MAGNETIC
RESONANCE
IMAGING****Skeletal muscle mitochondrial function cannot be properly inferred from PCr resynthesis without taking pH changes into account**

To the Editor:

We have read with much interest the paper recently published by Khushu et al. regarding the impaired muscle metabolism in hypothyroid patients [1]. Although the results of this investigation are of potential interest, we are actually concerned about the utilization of the phosphocreatine recovery rate constant (kPCr) as a simple index of mitochondrial function and the corresponding conclusions regarding the impact of hypothyroidism on muscle metabolism during exercise. The real issue is actually to clearly determine whether one can infer about mitochondrial function on the basis of PCr rate constants measurements.

During recovery from exercise, PCr is resynthesized purely as a consequence of oxidative adenosine triphosphate (ATP) synthesis [2], and measurements of the kPCr have been used in order 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 actually well acknowledged that kPCr is inversely 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 Khushu et al. study, cytosolic pH was found to be significantly lower after a 6-min constant-load plantar flexion exercise in hypothyroid patients compared to controls (6.95 ± 0.02 vs. 7.02 ± 0.06 , respectively). Therefore, the conclusions of an altered mitochondrial function in hypothyroid patients [1] on the single basis of kPCr measurements have to be interpreted cautiously. Of note, several kinetic parameters are commonly used to describe PCr changes during exercise-to-recovery transition, including kPCr, the initial rate of PCr recovery (ViPCr) and the maximum aerobic capacity (Q_{max}) [4]. These three parameters characterizing PCr resynthesis are correlated to oxidative capacity. However, in contrast to kPCr, ViPCr and Q_{max} are insensitive to exercise intensity and end-of-exercise metabolic conditions [3]. On that basis, ViPCr and Q_{max} should be considered as additional indices to compare the postexercise 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. These additional parameters were considered in some previously published studies which investigated in vivo mitochondrial function from childhood to young and/or late adulthood [5,6]. In contrast, these parameters were not taken into account in other studies which 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]. In the Khushu et al. study, the Q_{max} calculation was oversimplified as the product of kPCr and the resting [PCr], as previously described [9]. This oversimplification is actually derived from the calculation of the ViPCr from an exponential fitting. In that case, ViPCr is represented by the product of kPCr and the amount of PCr consumed at the end of exercise. On that basis, a few authors have calculated Q_{max} similarly to ViPCr, with the amount of PCr consumed being replaced by the resting [PCr]. Although mathematically plausible, this calculation is not supported by any control model, and the corresponding Q_{max} is devoid of any enzymatic meaning, as it is the case for the calculation of Q_{max} using ADP within a Michaelis–Menten framework. This method is then largely questionable because it ignores the commonly accepted theory considering adenosine diphosphate as a key regulator of oxidative ATP synthesis [10]. In addition, with such an approximate calculation, Q_{max} becomes strongly dependent on kPCr and/or [PCr] measured at rest. In their study, Khushu et al. [1] reported no significant difference in the resting [PCr] values between hypothyroid patients and controls (43.6 ± 0.8 vs. 42.0 ± 1.0 mmol kg^{-1} , respectively). Given that the resting [PCr] values were similar, the corresponding calculated Q_{max} values were lower in hypothyroid patients than in controls on the single basis of lower kPCr measurements in hypothyroid patients. Consequently, this result should be interpreted with caution.

Overall, it is of utmost importance to keep in mind that one cannot simply infer on 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 then pay attention to these methodological inaccuracies which might hedge data interpretation and confound the corresponding conclusions.

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