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REPLY

Reply to: The rate of PCr resynthesis is not a reliable index of skeletal muscle oxidative capacity

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Dear Editor,

In our study on the calf muscles of children and adults, we used ^{31}P-MRS to examine energy metabolism during and after high-intense intervals of plantar flexion exercise (Kappenstein et al. 2013). Energy metabolism was studied to find reasons to support why children commonly recover faster from similar intense exercise than adults. After exercise, PCr levels in children were significantly higher than in adults. During final recovery, following the last bout of exercise, the individual time courses of PCr were fitted by an exponential function. PCr recovery is commonly accepted to reflect oxidative ATP formation by mitochondria. The time constants of the exponential time course of PCr recovery (τPCr given in ms) are commonly used to characterise the actual mitochondrial function. Moreover, τPCr can be calculated directly from the time course of PCr peak intensities in ^{31}P-MR spectra without using any assumption on not measured variables and without using models. In children, τPCr was borderline smaller than in adults. In children, PCr recovery was not only faster because it started at higher PCr levels but also it seems that the functional capacity of oxidative ATP formation was borderline higher in children than in adults.

Ratel et al. proposed in their letter, the additional calculation of the initial rates in PCr recovery (ViPCr given in mmol/l cell water/min) and the maximum aerobic capacity (Q_{max} given in mmol/l cell water/min). Actually, Ratel et al. cited publications referring to the maximum capacity of mitochondrial ATP formation (V_{max} given in mmol/l cell water/min), which is calculated using simplified models of the control of mitochondrial ATP formation by the concentrations of ADP. They argued that calculating ViPCr and V_{max} would be essential for an accurate characterisation of mitochondrial ATP formation in skeletal muscle. With all due respect, we decided not to calculate these two variables for testing the main hypothesis of our study. ViPCr (%/min) is only the ratio of DeltaPCr and τPCr. PCr at the end of exercise was higher and τPCr was only borderline lower in children compared with adults. It is trivial that ViPCr was lower in children. ViPCr did not provide further information. The calculation of absolute values requires a calibration of per cent values on the assumption that [ATP] was 8.2 mmol/l cell water which ignores the natural variation of this value. The calculation of V_{max} uses a large number of variables partially based on assumptions and partially derived from actually measured ^{31}P-MRS data. In the literature V_{max} has been frequently calculated for testing models on the regulation of the energy metabolism.

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However, V_{max} cannot count as a valid result of ^{31}P-MRS data evaluation.

It is well-known that in many subjects the time constant of PCr recovery increases when PCr decreases to very low levels during contraction. This phenomenon does not fit to the mono-exponential time course of PCr recovery and hints at an additional mechanism that initially inhibits PCr recovery after deep depletion. Bendahan et al. in (1990), found correlations between the time constant of PCr recovery and pH at the end of exercise, or the pH minimum during subsequent recovery. Unfortunately Bendahan et al. as well as other research groups confirming this correlation, run into the correlation-trap and concluded that low cytosolic pH values may somehow inhibit the oxidative phosphorylation and the subsequent transphosphorylation from ATP to Cr by the two CKs. However, the paradox of PCr recovery was also found in patients with McArdle disease who start PCr recovery at alkaline pH values (Zange et al. 2003). Low pH values should increase—not decrease the rate of oxphos, because they increase the H^+ gradient driving the mitochondrial ATP synthesis. The CKs always keep their reaction close to equilibrium. This is commonly accepted and become the major prerequisite for all model calculations made on ^{31}P-MRS data. Therefore, pH affects the equilibrium of the CKs but it should not have relevant effects on the reaction velocities. The pH minimum during recovery is caused by the recovery of PCr. If the acidosis was inhibiting PCr recovery, the processes of PCr recovery would inhibit itself and the time course would not be an exponential rise to maximum. Ratel et al. mentioned the so-called robustness of modelled V_{max} values against low pH levels. This robustness results by a large portion from the calculation of ADP concentration, which uses the CK equilibrium including H^+.

Recent literature suggests that during recovery from exercise starting at low levels of PCr, the rate of oxidative phosphorylation is likely not determined by [ADP] and [Pi] but by the rate of mitochondrial oxygen supply. We described this issue in the discussion section of our article.

In conclusion, we think that τPCr is a robust and direct ^{31}P-MRS variable describing the functional capacity of oxidative ATP formation and therefore, we are not in agreement with the suggestions from Ratel et al. (i.e., a calculation of ViPCr and V_{max}). We agree that V_{max} theoretically better than τPCr represents mitochondrial density in muscle fibres, although is the result of a modelling process. In our study we did not aim on modelling, as we were interested in the actual metabolic behaviour of muscle in response to high-intense interval exercise. Moreover, a comparison of V_{max} in two different groups always includes a discussion about the validity and comparability of the large number of assumed variables used for the calculation of V_{max}.

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