

Editorial for "Quantitative Assessment of Peripheral Oxidative Metabolism with a new Dynamic ^1H MRI: a Pilot Study in People with and without Diabetes Mellitus"

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The usefulness of phosphorus magnetic resonance spectroscopy (^{31}P MRS) in studying skeletal muscle metabolism lies in its ability to quantify some key quantities (notably the cytosolic concentrations of phosphocreatine (PCr), inorganic phosphate and ADP, cytosolic pH and free energy of ATP hydrolysis (ΔG_{ATP})) whose dynamic responses to muscle contraction can yield information about oxidative and glycolytic ATP synthesis, contractile efficiency and cellular acid-base physiology *in vivo* which is hard to obtain any other way (1, 2). One well-established application is the use of post-exercise PCr recovery kinetics to assess mitochondrial ATP synthesis (1, 3). A paper in this issue (4) demonstrates the feasibility of a CEST ^1H imaging approach to this which avoids some serious practical limitations of ^{31}P MRS.

Why is this needed? ^{31}P MRS is constrained by low signal-to-noise and the consequent trade-off between temporal and spatial resolution. Pulse-acquire sequences with surface-coil localization can work for large muscles like quadriceps (5), but in general it is important to distinguish muscles with different metabolic properties. Single-voxel ^{31}P MRS techniques allow this, but at the price of separate exercise acquisitions for each volume of interest (6). A 3D imaging approach would clearly be useful, but this is impractical for full-spectrum ^{31}P acquisition. However, for assessing mitochondrial function (and also contractile efficiency (1)), PCr is the most informative metabolite; accordingly, spectrally selective imaging methods allow PCr recovery measurements across the whole calf to assess mitochondrial function in several muscles at once (7, 8). Nevertheless, scanners with multinuclear capability and ^{31}P coils are not common. The present paper's ^1H imaging-based approach avoids this major limitation (4): the authors implemented CEST MRI in a clinical 3T system, using a single-shot RARE sequence to quantify post-exercise PCr recovery in calf muscle (distinguishing medial gastrocnemius and soleus) of 7 individuals with type 2 diabetes (T2DM) and 7 control subjects.

What can we learn from PCr recovery kinetics? During exercise [PCr] decreases as the creatine kinase system buffers the transient mismatch between glycolytic and oxidative ATP supply and the ATP demand of contraction; once contraction stops, PCr resynthesis depends solely on oxidative (mitochondrial) ATP synthesis (1); furthermore, after moderate-intensity exercise with little glycolytic ATP synthesis and consequent cellular acidification (1), PCr recovery follows mono-exponential kinetics, whose rate constant (k) reflects what is variously called 'mitochondrial capacity' (3) or 'oxidative capacity' (or here 'mitochondrial index' (4), calculated from the recovery time constant τ ($= 1/k$)). Physiologically, this mitochondrial capacity depends on several factors, including muscle mitochondrial density, activity of respiratory chain components and key enzymes of fat and carbohydrate oxidation, and the structural capillarity and functional blood flow responses which govern vascular supply of O_2 (2, 3). All of these factors may change with ageing, training state, disease and therapy, and in this lies the usefulness of post-exercise PCr recovery as a biomarker of these changes, whether by classical ^{31}P MRS (2), by selective ^{31}P imaging (8), or now CEST MRI (4). Some technical points are still debated. In all models of the regulation of oxidative ATP synthesis, k after non-acidifying exercise is a relative measure of mitochondrial capacity, i.e they are roughly proportional (3). Furthermore, $k \times [PCr]_{RESTING}$ (or, as here, $[PCr]_{RESTING}/\tau$ (4)) is a plausible absolute measure of mitochondrial capacity, although this claim is model-dependent, and more complex ^{31}P MRS-based measures involve putative feedback signals such as [ADP] or ΔG_{ATP} which are not accessible by CEST (or by selective ^{31}P imaging) (1, 3). None yield demonstrably exact measures of maximum oxidative ATP synthesis rate, although as surrogates they correlate in expected ways with invasive measurements (3). The simplest and most robust marker of mitochondrial capacity is the k of PCr recovery after moderate-intensity exercise (or, inversely, τ or $t_{1/2} = 2.303 \times \tau$) (2).

Using this approach the authors found slow PCr recovery (τ was larger, so k was smaller) in T2DM patients compared to controls (4); this indicates a functional impairment of mitochondrial ATP synthesis, which other studies show is likely to be physiologically multifactorial (9). Making parallel MRI measurements of muscle blood flow, they found correlations with τ only in controls, where perfusion differences therefore seem to contribute to variation in mitochondrial function (4). They describe the lack of such correlation in the T2DM patients as a decoupling of metabolism from perfusion (4). If not an artifact of relatively small sample size, this decoupling is best thought of relative: in T2DM other factors, such as reduction in mitochondrial numbers or components (9), appear dominant. This interesting result merits further investigation in larger samples. In any case, the main importance of this study is to demonstrate the feasibility of this method of studying muscle mitochondrial function in a clinical scanner, on clinical subjects (4).

References

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