Three Dimensional Mapping of the Creatine Kinase Reaction Rate in Muscles of the Lower Leg

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TARGET AUDIENCE: People who study muscle physiology, muscle bioenergetics and metabolism, and people interested in multinuclear MRI. **PURPOSE**: The aim of this study was to develop and implement a novel 3D imaging sequence that maps the kinetics of creatine kinase enzyme reaction (CK), a major energy transducing reaction involving adenosine triphosphate (ATP) and phosphocreatine (PCr), in the lower leg muscles of healthy subjects and patients with type 2-diabetis mellitus (T2DM) at relatively high spatial resolution, within experimental times that can be well tolerated by patients. Previous ^{31}P-MRS studies have employed small surface coils and used unlocalized or single voxel sequences. Therefore, very little is known about the spatial localization of metabolic properties in diseases. **METHODS**: We recruited five healthy volunteers (three male and two female, 30.4 ± 4.0 years of age), and two male T2DM patients. They were all scanned on a 7T MRI system (Siemens Medical Solutions, Erlangen, Germany) using a dual-tuned ^{31}P/^{1}H quadrature transmit-receive knee coil (Rapid MRI, Ohio) with 18 cm inner diameter and 20 cm length. We obtained images using a spectrally selective 3D-TSE sequence described previously[1], which we modified by adding a magnetization transfer (MT) module comprised of a train of 40 Gaussian pulses, each with 100 ms duration and 360° nominal flip angle. We obtained three 3D-imaging data sets, one without irradiation, and a pair of images on which MT preparation was applied on the γ-ATP resonance (-2.48 ppm, M_z) and the mirrored side relative to PCr (+2.48 ppm, M_0). All 3D-data sets had field-of-view (FOV) of 220 x 220 x 200 mm, acquisition matrix size of 48 x 48 x 8, yielding a nominal voxel size of 0.52 mL, with TR of 12 s. We modified the imaging sequence further to include an inversion recovery module to measure T_1 relaxation of PCr while saturating γ-ATP. We evaluated the efficiency of the γ-ATP saturation module using unlocalized ^{31}P-MRS (Fig.1). We calculated the pseudo-first order rate, k_{CK} (forward direction) of the phosphorus exchange between PCr and γ-ATP in six lower leg muscles using the following equation: $k_{CK} = (1-M_z/M_0)/T_1$, and the metabolic fluxes of the reaction (V_{CK}) from the product of k_{CK} and PCr concentration. We measured absolute concentration of PCr by acquiring images of phantoms with known Pi concentration in a separate scan (substitution method). **RESULTS**: The mean and standard deviation k_{CK} and V_{CK} in different lower leg muscles of the healthy volunteers were measured: In the tibialis anterior: $k_{CK} = 0.23 \pm 0.03$ s^{-1}, $V_{CK} = 7.25 \pm 0.74$ mM s^{-1}. In the tibialis posterior: $k_{CK} = 0.26 \pm 0.02$ s^{-1}, $V_{CK} = 7.93 \pm 0.76$ mM s^{-1}. In the peroneus muscle: $k_{CK} = 0.26 \pm 0.04$ s^{-1}, $V_{CK} = 8.03 \pm 1.23$ mM s^{-1}. In the soleus muscle: $k_{CK} = 0.27 \pm 0.02$ s^{-1}, $V_{CK} = 7.78 \pm 0.67$ mM s^{-1}. In the gastrocnemius lateral: $k_{CK} = 0.29 \pm 0.02$ s^{-1}, $V_{CK} = 8.91 \pm 0.42$ mM s^{-1}. In the gastrocnemius medial (GM): $k_{CK} = 0.27 \pm 0.01$ s^{-1}, $V_{CK} = 8.42 \pm 0.48$ mM s^{-1}. Images from a healthy volunteer and a T2DM patient are shown in Fig.2. In a specific area of this patient's GM, the CK reaction rate is significantly lower (~ 0.18 s^{-1}) compared to the rest of the muscles of the lower leg, where the reaction rate is within the limits of the healthy volunteers (0.22 - 0.25 s^{-1}). **DISCUSSION**: The results of this work demonstrate that quantitative mapping of the kinetics of the CK reaction can be achieved in the entire volume of skeletal muscle at relatively high spatial resolution using a spectrally selective imaging sequence. Our results are in close agreement with unlocalized or single voxel localized ^{31}P-MRS MT measurements reported elsewhere[2,3]. Having a tool to study those spatial heterogeneities can improve our understanding of patterns of disease presentation and propagation, thus allowing us to longitudinally track the effectiveness of interventions. In the case of T2DM patients, our method detected decreased CK rates in some of the muscles, while the CK reaction rates in the rest of the lower leg muscles were within the range of the healthy volunteers. These results suggest that spatial mapping of metabolic turnover rates may identify regions of skeletal muscle affected by pathology that have remained undetected with single voxel acquisitions. **CONCLUSION**: 3D-mapping of the CK forward reaction rates and metabolic fluxes can be achieved in skeletal muscle, which can bring new insights into differential localization and the way patterns of muscle bioenergetics are affected by several diseases. **REFERENCES**: 1. Parasoglou P, Xia D, Regatte RR. Spectrally selective 3D TSE imaging of phosphocreatine in the human calf muscle at 3 T. Magn Reson Med 2012; DOI: 10.1002/mrm.24288. 2. Valkovic L, Chmelik M, Kukurova IJ, *et al.* Time-resolved phosphorous magnetization transfer of the human calf muscle at 3 T and 7 T: A feasibility study. Eur J Radiol 2011; DOI: 10.1016/j.ejrad.2011.09.024. 3. Bottomley PA, Ouwerkerk R, Lee RF, Weiss RG. Four-angle saturation transfer (FAST) method for measuring creatine kinase reaction rates in vivo. Magn Reson Med 2002;47(5):850-863.

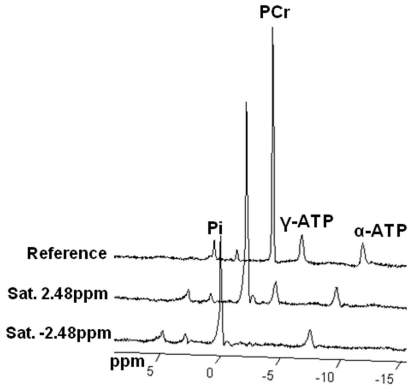

Fig. 1. γ-ATP saturation confirmed through unlocalized ^{31}P MRS of the human calf muscle. A reference spectrum collected without suppression, a control spectrum with suppression frequency at 2.48 ppm relative to PCr, and a spectrum acquired with suppression of the γ-ATP peak.

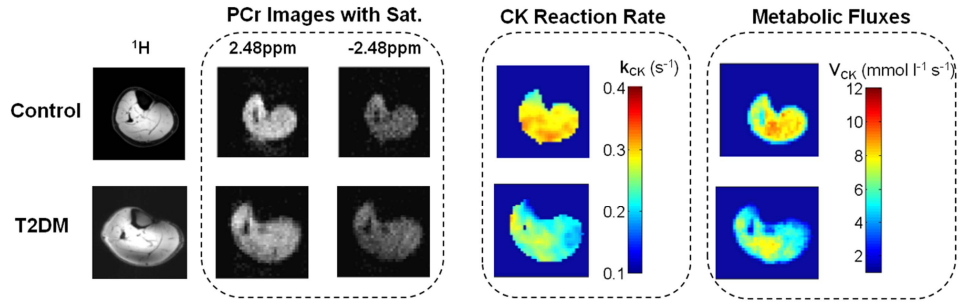

Fig. 2. Mapping of the kinetic rate (k_{CK}) of the CK reaction and the metabolic fluxes (V_{CK}) in the lower leg muscles of a healthy control (top) and a T2DM patient (bottom). From left to right, we show anatomical ^{1}H images, control PCr images acquired with the MT preparation module applied at 2.48 ppm, PCr images acquired with the MT pulse train applied on the γ-ATP peak (-2.48 ppm), CK reaction rate maps, and maps of metabolic fluxes. Muscle energy abnormalities in the GM muscle of a diabetic patient can be seen.