Correlation of Exercise Induced Changes in Cr CEST and 31P MRS in Human Calf Muscles

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Introduction: Creatine (Cr) plays an essential role in the storage and transmission of phosphate-bound energy. During exercise, phosphocreatine (PCr) is depleted to maintain the adenosine triphosphate (ATP) supply leading to an increase Cr concentration. ^{31}P Magnetic Resonance Spectroscopy (MRS) is able to relay information about the concentrations of PCr, Pi, as well as muscle pH and has been used extensively to study oxidative metabolism of skeletal muscle(1). ^{31}P MRS been applied to studies of bioenergetic impairment in various muscle impairments as well as in cardiac energetics. However, ^{31}P MRS, like all spectroscopy techniques, suffers from poor spatial resolution as well as low sensitivity due the low gyromagnetic ratio of ^{31}P. Chemical exchange saturation transfer (CEST) is new sensitivity enhancement mechanism that can indirectly detect metabolite content based on exchange-related properties(2). Recently it has been shown that Cr exhibits a concentration dependent CEST effect between its amine (-NH_2) and bulk water protons(3) and that this CEST effect can be isolated from the other metabolites of the creatine kinase reaction (PCr, ATP, ADP). This technique allows for the monitoring of Cr concentration changes with high spatial resolution. In this work, we demonstrated the potential of measuring the CEST effect from Cr (CrCEST) in spatial mapping of free creatine in exercised muscle.

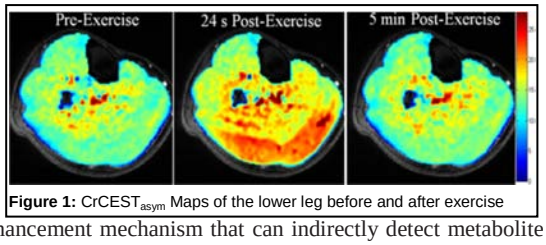

Figure 1: CrCEST$_{asym}$ Maps of the lower leg before and after exercise

Methods: All imaging experiments were performed on a 7T whole body scanner (Siemens Medical Systems, Erlangen, Germany) under an approved Institutional Review Board protocol. An MR compatible pneumatically controlled foot pedal was used for plantar flexion exercise with a 28 channel ^{1}H knee coil utilized for proton imaging and a custom built 7 cm diameter ^{31}P transmit/receive surface coil was used for ^{31}P MRS. CEST, T_2, MTR and ^{31}P MRS acquisitions of the calf were performed at 7T on healthy volunteers (n=8, 5 male, 3 female, ages 19-30) with various activity levels (sedentary to active). For each methodology, baseline imaging was performed for 2 minutes, followed by 2 minutes of mild plantar flexion exercise and then 8 minutes of post exercise imaging. CEST images were acquired with a 500 ms long saturation pulse consisting of a series of 100 ms Hanning windowed saturation pulses and a B_{1rms} of 123 Hz (2.9 μT) followed by a FLASH readout. Water saturation shift reference (WASSR) images and B_1 maps were collected, as described previously (4,5), for all CEST studies before and after exercise to correct for B_0 and B_1 inhomogeneities. CrCEST asymmetry was calculated using the B_0 corrected signal intensity at ±1.8 ppm, the chemical shift of Cr amine protons, using the equation: $CEST_{asym} = [(S_{-\Delta\omega} - S_{+\Delta\omega})/S_{-\Delta\omega}]$. ^{31}P MRS spectra were acquired using an unlocalized free induction decay (fid) sequence. ^{31}P MRS Spectra were phased and baseline corrected and fitted using nonlinear squares methods with Gaussian functions.

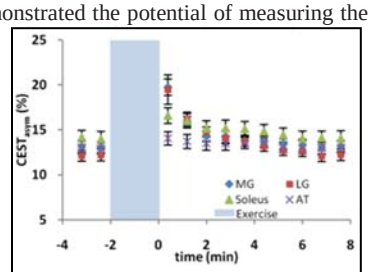

Figure 2: Average CrCEST$_{asym}$ vs. time in muscles segmented from anatomical images

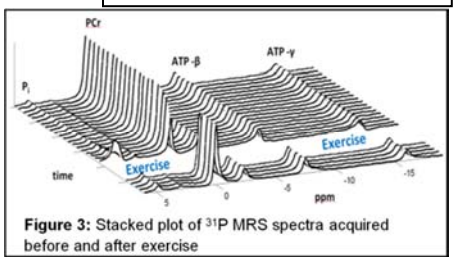

Figure 3: Stacked plot of ^{31}P MRS spectra acquired before and after exercise

Results and Discussion: Plantar flexion exercise led to an increase in the CrCEST$_{asym}$ in all subjects. Figure 1 shows CrCEST$_{asym}$ maps for the same subject before and after mild plantar flexion exercise with a temporal resolution of 48 seconds. The time dependence of the mean CrCEST$_{asym}$ for each segmented muscle group is plotted in figure 2. The post exercise CrCEST$_{asym}$ map shows that the majority of CrCEST$_{asym}$ increases were localized to the muscles of the posterior compartment of the leg responsible for plantar flexion. Whereas the CEST maps showed fairly uniform CrCEST$_{asym}$ at baseline, the first post-exercise map showed a 6.7% (±1.0%) and 7.2% (±0.8%) increase in CrCEST$_{asym}$ in the medial (MG) and lateral (LG) gastrocnemius muscles, respectively, immediately following exercise. A 2.6% (±0.9%) increase was observed in the soleus, the other major muscle of the posterior compartment. The tibialis anterior is predominantly involved in dorsiflexion and as a result, less than a 1% increase in CrCEST$_{asym}$ was observed. The CrCEST$_{asym}$ in all the muscles recovered exponentially to baseline after roughly three time points or ~2 minutes. T_2 and MTR maps for all subjects didn't show any significant differences post exercise (ΔT_2< 0.5 ms, ΔMTR < 1.0%) [data not shown].

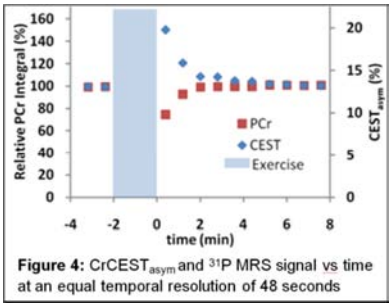

Figure 4: CrCEST$_{asym}$ and ^{31}P MRS signal vs time at an equal temporal resolution of 48 seconds

A free induction decay (fid) was used for ^{31}P MRS acquisition in the current study, and thus the signal was unlocalized. The ^{31}P MRS surface coil excitation profile showed the majority of the ^{31}P MRS signal comes from the gastrocnemius muscle with minor contributions from the soleus muscles. A stacked plot of every alternate spectra acquired is shown for subject 1 in figure 4a. A decrease in the PCr peak area following exercise is evident, which recovers back to the pre-exercise levels in about 2 minutes. The size and area of the three ATP peaks stayed constant before and after this exercise. The P_i peak increased after exercise and then quickly decayed back to baseline. No shift or splitting of the P_i peak was observed indicating that there were negligible pH changes. There was good agreement in the observed rates at which the CrCEST$_{asym}$ from a region of interest equivalent to the ^{31}P MRS coil excitation profile and the ^{31}P MRS signal recovered (fig 4).

Data from all 8 volunteers showed that there was some subject variability in regards to the level and involvement of each muscle group during exercise which was able to be detected in CrCESTasym maps. To compare the CEST$_{asym}$ and ^{31}P MRS results, the % decrease in ^{31}P MRS signal from baseline at the first integrated measurement following exercise was used to determine the decrease in PCr based on a 33 mM PCr baseline concentration(6). As the total Cr remains constant, the decrease in PCr concentration should equate to an equivalent increase in Cr concentration. Thus we can compare the change in the CEST$_{asym}$ to the Cr concentration change across all subjects (fig 5). This yields a slope of 0.84 % CrCEST$_{asym}$/mM Cr with an R^2 = 0.75.

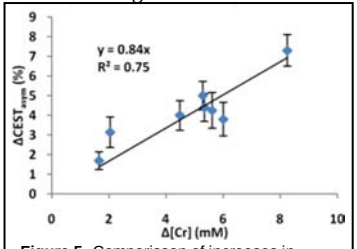

Figure 5: Comparisson of increases in CrCEST$_{asym}$ & Cr concentration following exercise across subjects

Conclusion: It is feasible to use CEST imaging to measure changes in Cr concentration in muscle following plantar flexion exercise. Further, CrCEST$_{asym}$ maps showed good spatial resolution and were able to differentiate muscle recruitment during exercise. There was good agreement in the recovery kinetics of ^{31}P MRS and CrCEST$_{asym}$ following exercise.

References: [1] Hoult et al. *Nature* 1974:285-287. [2] Wolff et al. *J. Mag. Res.* 1990:164-169. [3] Haris et al. *NMR Biomed*. 2012. [4] Kim et al. *Mag. Res. Med*. 2009:1441-1450.[5] Singh et al. *Mag. Res. Med.* 2012 [6] Kemp et al. NMR Biomed. 2007;20(6):555-565.