Detection of Exercised Induced Changes in Creatine Level in Human Calf Muscles through CEST: A Preliminary Study

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Introduction:

Phosphocreatine (PCr) along with Cr and adenosine-triphophate (ATP) provide major energy reservoirs in the biological system. Creatine kinase (CK) catalyzes the reversible reaction between PCr and Cr. Muscle exercise leads to a decrease in PCr signals, which corresponds to an increase in Cr and inorganic phosphate (Pi), whereas the recovery time is characterized by a mono-exponential increase in PCr. There are numerous reports on the muscle bioenergetics impairment in various muscle myopathies, injuries and various other disorders involving muscle weakness[1-3]. ^{31}P Magnetic resonance spectroscopy (MRS) has been extensively used to investigate non-invasively the energy metabolism and CK kinetics in the human muscle[1-4]. Using the ^{1}HMRS it is not possible to observe the change in free Cr level as it measures sum of PCr and Cr. Recently, It has been shown that Cr shows concentration dependent chemical exchange saturation transfer (CEST) (CrEST) effect between its amine proton (-NH2) and bulk water protons[5]. Using the endogenous CrEST technique the change in [Cr] *in-vivo* can be monitored at high spatial resolution. In the current study, our objectives were to (i) determine the sensitivity advantage of CrEST over single voxel spectroscopy (SVS) at 7T and (ii) map the change in Cr level at high resolution in calf muscles through CrEST in response to mild exercise.

Materials and Methods:

***Phantom Imaging*:** In order to determine sensitivity of CrEST over ^{1}HMRS, SVS point resolved spectroscopy (PRESS) water suppressed spectrum (TR=10 s, TE=16 ms, 16 averages) from 10 mM Cr was acquired. The water ^{1}H resonance spectra for the same voxel were obtained while saturating at ±1.8ppm. The saturation parameters were: a pulse train with saturation pulse amplitude (B_{1rms}) of 155 Hz and a total duration of 1s was used with 10 Hanning windowed rectangular pulses of 99.8 ms duration each with a 0.2 ms delay between them.

CEST imaging from Cr (10), PCr (15mM), and ATP (10mM) solutions (pH=7.0) were performed on 7T Siemens whole-body scanner (Siemens Medical Solutions, Malvern, PA). CEST images were acquired using the same saturation parameters as described above. The other sequence parameters were: slice thickness =10mm, TR=5.6ms, TE=2.7 ms, field of view=100*100mm^2, matrix=192*192, and one saturation pulse and 64 acquired segments at every 10s.

***In vivo Imaging of Human Calf Muscles*:**

CEST images from a normal human calf muscle were performed on 7T under an Institutional Review Board approved protocol. To change the Cr level in calf muscles repeated plantar flexion was performed in magnet by depressing a nonmagnetic exercise pedal. A series of CEST images were obtained before and after exercise at B_{1rms} of 63 Hz and 1 second saturation duration. The B_0 and B_1 maps were also gathered. The CrEST contrast was calculated at ±1.8ppm by normalizing with 20ppm signal using the equation- $CEST=100*[(S_{-ve}-S_{+ve})/S_0]$, where S_{-ve}, S_{+ve} and S_0 are the B_0 corrected MR signals at -1.8ppm, +1.8ppm and 20ppm respectively. The CEST contrast was further corrected for any B_1 inhomogeneity[6].

Results and Discussion:

With the experimental parameters used, the actual sensitivity of CEST realizable experimentally is ~1500 times higher than ^{1}H MRS (Fig 1). This sensitivity amplification should make it feasible to detect relatively small changes in Cr levels at high resolution (voxel size of 0.02 cc). Figure 2 shows the high resolution CEST map from Cr, PCr and ATP phantoms at 1.8ppm. No appreciable contribution from PCr and ATP is observed to CrEST, this could be probably due to the slower exchange rate of PCr and ATP. Figure 3 shows the high resolution CrEST map from a healthy volunteer before and after exercise. After exercise an increase in CrEST contrast was observed in each calf muscles, which returned to baseline following relaxation (Fig 3, 4). These results indicate that high resolution imaging of Cr is possible without any contamination from PCr. The change in the Cr concentration following exercise can be monitored through CrEST. This technique may provide an opportunity to map any alteration in the [Cr] and creatine kinase reactions at high spatial resolution in the muscle. However, quantification of Cr changes using CrEST may be affected by exercise induced changes in pH and T_2 relaxation times. Water T_2 relaxation maps and 31-MRS acquired before and after exercise would enable one to isolate these effects from that of Cr. Further studies in these lines are currently in progress in our department.

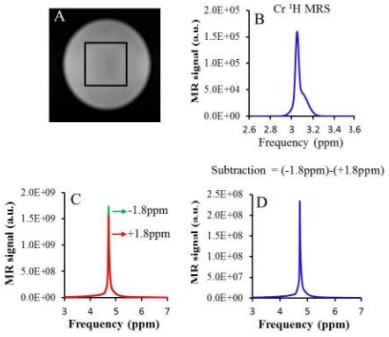

Figure 1: A. Image showing the single voxel localization from a bottle of 10 mM creatine. B. ^{1}H MRS PRESS water suppressed spectrum from the single voxel shown in the image A. The measured amplitude of Cr peak at 3.02 ppm is 1.5 × 10^5 units. C. Water ^{1}H resonance spectra obtained while saturating at ±1.8ppm as well as their difference spectrum. The difference spectrum is 2.3 × 10^8 units. With experimental parameters used, the actual sensitivity of CrEST is ~ 1500 times higher than ^{1}H MRS.

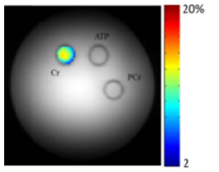

Figure 2: Shows the CEST map from Cr, PCr, and ATP at 1.8ppm. Predominant CEST contrast was observed from Cr.

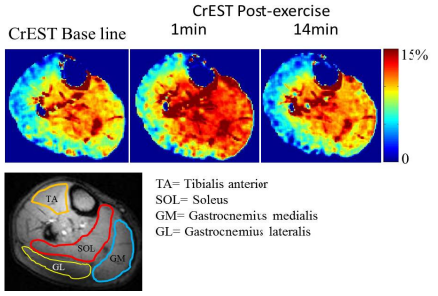

Figure 3: CrEST maps from a normal human calf muscles before and after mild exercise. An increase in CrEST contrast was observed immediately after exercise in each calf muscles followed by decrease in CrEST contrast and reach back to the baseline during time course.

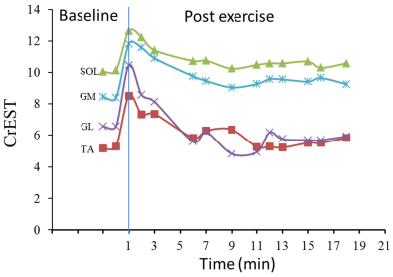

Figure 4: Graphs show the post-exercise change in CrEST contrast (%) in each calf muscles.

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