# Feasibility of in vivo CEST Imaging of Creatine (CrCEST) at 3T

Catherine DeBrosse[1], Feliks Kogan[1], Mohammad Haris[1], Anup Singh[1], Kejia Cai[1], Ravi Prakash Reddy Nanga[1], Hari Hariharan[1], and Ravinder Reddy[1]
[1]*Center for Magnetic Resonance and Optical Imaging, Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania, United States*

**Introduction**: The aliphatic protons of free creatine and Phosphocreatine (PCr) have the same chemical shifts and it is rather difficult to measure their individual contributions to the observed proton magnetic resonance spectrum ($^1$HMRS). While $^{31}$P MRS enables the determination of PCr it is not suitable for measuring free creatine. One of the unique features of CrCEST[2] is that it measures free creatine signal in vivo, which is difficult to obtain from either $^1$HMRS or $^{31}$P MRS. By measuring changes in metabolites such as creatine, treatment of various metabolic disorders can be studied. The CrCEST effect has been used for spatial and temporal mapping of creatine changes in skeletal muscle at 7T.[3] However, ultra high field scanners are still not widely available and they are currently limited for clinical research only. In order for rapid clinical translation, it is important to characterize the CrCEST effect at lower fields. In this work, we demonstrate the feasibility of imaging Cr at 3T in skeletal muscle using CrCEST and discuss potential advantages and disadvantages compared to 7T.

**Methods**: Imaging experiments were performed using an 8-channel $^1$H knee coil on a 3T whole body scanner (Siemens Medical Systems, Erlangen, Germany). In order to optimize imaging parameters, CrCEST maps of the lower leg were acquired at varying saturation amplitude and pulse duration. Baseline imaging of human subjects was performed for 2 minutes, followed by 2 minutes of mild plantar flexion exercise and 8 minutes of post-exercise imaging. Plantar flexion exercise was performed using an MR-compatible, pneumatically controlled foot pedal. CrCEST images were acquired on healthy volunteers at 3T using a saturation pulse of 500 ms and a $B1_{rms}$ of 93 Hz (2.25μT) and imaging parameters: slice thickness = 8 mm, flip angle = 10°, TR = 5.6 ms, TE = 2.7 ms, field of view = 140 x 140 mm$^2$, matrix size = 128 x 128. Image processing was performed using in-house MATLAB scripts. $B_0$ and $B_1$ maps were used to generate corrected CEST images as described previously[4]. CrCEST contrast was computed by subtracting the normalized magnetization signal at the Cr proton frequency (Δω = +1.8 ppm), from the magnetization at the corresponding reference frequency symmetrically at the opposite side of the water resonance (-Δω), according to the following equation.[4]

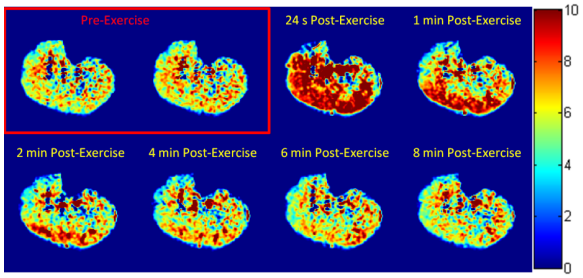


**Figure 1**: $CrCEST_{asym}$ maps before and after exercise at 3T

$$CEST_{asym}(\Delta\omega) = \frac{M_{ref}(-\Delta\omega) - M_{ref}(+\Delta\omega)}{M_{ref}(-\Delta\omega)}$$

$CEST_{asym}$ changes in individual muscle groups pre and post-exercise were determined by overlaying $CEST_{asym}$ maps onto manually segmented anatomic images. $^{31}$P MRS was performed with a 7-cm diameter $^1$H/$^{31}$P dual tuned surface coil using an unlocalized free induction decay (fid) sequence with the following parameters: number of points = 512, averages = 5, and TR = 2.4 s. $^{31}$P MRS Spectra were phased and baseline corrected and fitted using nonlinear least squares method with Gaussian functions.

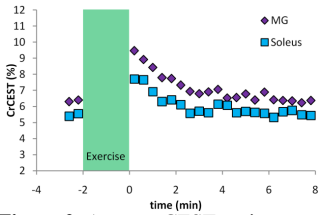


**Figure 2**: Average $CEST_{asym}$ in soleus and gastrocnemius muscles before and after exercise at 3T

**Results and Discussion**: The optimal saturation parameters for CrCEST at 3T were determined to be a $B1_{rms}$ of 93 Hz (2.25μT) and saturation duration of 500 ms. Figure 1 shows $CrCEST_{asym}$ maps generated before and after plantar flexion exercise at 3T. During exercise, there is an increase in creatine levels, resulting in higher $CrCEST_{asym}$, which then recovers to basal value. The average $CEST_{asym}$ in the soleus and medial gastrocnemius muscles at baseline and following exercise is plotted as function of time in figure 2. Following exercise, an increase in $CEST_{asym}$ of 2.2% in the soleus muscle, and 3% in the medial gastrocnemius muscle over baseline values was observed.

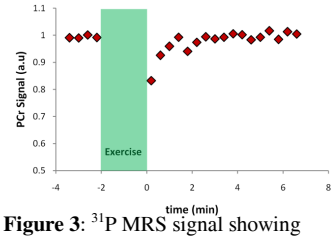


**Figure 3**: $^{31}$P MRS signal showing baseline PCr, and recovery of PCr after exercise at 3T

These post-exercise increases then exponentially recovered to baseline levels. In order to validate the observed increase in creatine, $^{31}$P MRS was performed to observe changes in PCr. The concentrations of PCr and Cr are tightly coupled in the creatine kinase reaction. In order to maintain ATP levels during exercise, PCr is depleted leading to an increase in Cr concentration. This is seen in figure 3, in which the $^{31}$P MRS PCr peak signal is plotted vs. time, showing a decrease in PCr signal following exercise, which exponentially recovers back to baseline values. We did not observe any measurable changes in either water $T_2$ nor in magnetization transfer ratio (MTR) (data not shown). There are several challenges to translating CrCEST technique from 7T to 3T. At 3T, the chemical shift (Δω) between Cr amine protons and free water protons is smaller. This leads in increased direct water saturation at 3T as saturation of Cr labile protons is less selective. This greatly decreases the signal-to-noise ratio (SNR). To address the decrease in SNR to some extent, a larger slice thickness was used in this study. Another consequence of increased direct water saturation is that the $B_1$ that gives the optimal $CrCEST_{asym}$ is lower at 3T than at 7T. This decreases the labile proton saturation efficiency, which similarly decreases $CrCEST_{asym}$. However, the optimal exchange rate of Cr amine protons lends itself to CEST imaging at lower fields. With the parameters used in this study, the dynamic range of $CrCEST_{asym}$ values of skeletal muscle in the lower leg was approximately half of that observed at 7T. There are also some advantages to CrCEST imaging at 3T. $T_1$ relaxation times are shorter at lower fields. As the repetition time between saturation pulses (Shot TR) is directly correlated to the $T_1$ (Shot TR~5*$T_1$), this allows for increased temporal resolution. This is significant for translation of this method to studies of muscle energetics, which have a time course on the order of 30 seconds to a few minutes. Similarly, higher $T_2$ of skeletal muscle at 3T also leads to lower direct water saturation. Additionally, the widespread availability and clinical applicability of 3T scanners will allow this method to be advanced and translated into clinical applications more rapidly.

**Conclusion**: This work has demonstrated the feasibility of in vivo CrCEST imaging on routine clinical scanners (3T). It has the potential to clinically advance this method, which could enhance research into conditions such as heart and renal failure, and other secondary complications of metabolic disorders.

**References**: [1] Sherry et al. *Annu. Rev. Biomed. Eng*. 10(2008): 391–411 [2] Haris et al. *NMR Biomed*. 25(2012): 1305-09 [3] Haris et al. *Proc. Intl. Mag. Reson. Med*. 2012:2342 [4] Haris et al. *NeuroImage* 54(2010): 2079-85