Creatine concentration in human calf muscle at 7T with AREX

Eugenia Rerich[1], Moritz Zaiss[1], Johannes Windschuh[1], Patrick Schünke[1], and Peter Bachert[1]
[1]*German Cancer Research Center, Heidelberg, Baden-Württemberg, Germany*

Target Audience: Researchers and physicians who are interested in CEST-MRI, MR spectroscopy, creatine metabolism

Purpose:

Creatine (Cr) plays an important role in cellular energy metabolism and storage [1]. By ^{1}H MRS only the total Cr can be detected and a full validation of metabolic changes is only possible by including ^{31}P spectroscopy. Recently, Kogan et al. [2] demonstrated a CEST-based technique to measure free Cr changes in muscle of subjects performing mild exercise prior to CEST-MRI. In our study we carried out a similar experiment but with pulsed steady-state CEST. The newly introduced evaluation method *AREX* [3, 4] yielded a signal free of concomitant effects and therefore allowed a linear concentration calibration and quantification of Cr in human calf muscle. This study also represents a validation of AREX in the intermediate exchange regime.

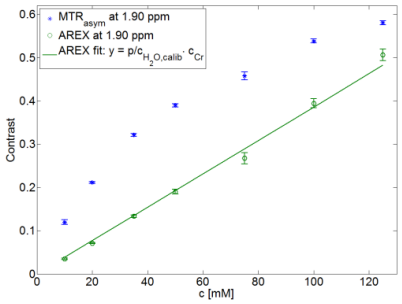
Materials & Methods:

We employed a multi-phantom set of different Cr concentrations (10, 20, 35, 50, 75, 100 and 125 mM) at $\mathrm{pH} = 7.15$ and $\mathrm{T} = 37°\mathrm{C}$ in PBS on a 7T whole body MRI scanner (MAGNETOM 7T; Siemens Healthcare, Erlangen, Germany) using a 2-D gradient echo sequence and a 28-channel Tx/Rx ^{1}H knee coil. The saturation pulse train was 10 s long consisting of a series of 100 ms Gaussian-shaped RF pulses with 100 ms interpulse delay. The Z-spectra acquisition was performed from -4.0 to 4.0 ppm with a step size of 0.2 ppm. Eight different $\mathrm{B_1}$ amplitudes were applied: 1.17, 1.36, 1.56, 1.75, 1.94, 2.33, 2.72, 3.11 and 3.50 µT. The imaging parameters were: $\mathrm{TR} = 6.9$ ms; $\mathrm{TE} = 3.36$ ms; field of view, 180 mm^2; matrix, 128×128; in-plane resolution, $1.4 \times 1.4 \times 5$ mm^3; flip angle, $10°$. For the *in vivo* study five healthy volunteers were examined with CEST (40 Gaussian-shaped RF pulses with $\mathrm{t_p} = 100$ ms and $\mathrm{DC} = 50$ %). The $\mathrm{B_1}$ amplitudes were 1.01 µT, 1.65 µT and 2.10 µT. These images were used for $\mathrm{B_1}$ correction and Z-spectra stacks at 1.17 µT and 1.75 µT were generated. Frequency offsets were distributed around the CEST pool: ± 1.3 ppm to ± 2.5 ppm in steps of 0.2 ppm. The imaging parameters were: $\mathrm{TR} = 7.4$ ms; $\mathrm{TE} = 3.94$ ms; field of view, 180 mm^2; matrix, 128×128; in-plane resolution, $1.4 \times 1.4 \times 5$ mm^3; flip angle, $10°$. Additionally to the CEST measurements at rest the protocol was repeated after muscle exercise. A magnetic resonance-compatible foot pedal was used. The slice position (FoV) did not change during exercise. All Z-spectra were $\mathrm{B_0}$-corrected employing a WASSR map [5]. $\mathrm{B_1}$ mapping was realized by a prepared GRE sequence ($\mathrm{TE} = 2.42$ ms; $\mathrm{TR} = 5$ s; 5 shots; field of view, 180 mm^2; matrix, 128×128; in-plane resolution, $1.4 \times 1.4 \times 5$ mm^3; flip angle, $8°$). Z-spectra B_1 correction was done using the method of Windschuh et al. [6].

To correct for spillover, MT and $\mathrm{T_1}$ the inverse metric [4] was used: $\mathrm{AREX} = \frac{\left(\frac{1}{\mathrm{Z}(1.9\ \mathrm{ppm})} - \frac{1}{\mathrm{Z}(-1.9\ \mathrm{ppm})}\right)}{\mathrm{T_1}}$. The required $\mathrm{T_1}$ map was obtained by a fit of $\mathrm{T_1}$-weighted MR images acquired by a saturation recovery gradient echo sequence with 22 recovery times between 250 ms and 7.5 s for *in vitro* studies and 11 contrasts at recovery times between 500 ms and 5.5 s for the *in vivo* measurements. We compared the results with the conventional asymmetry analysis with 1.9 ppm as label frequency and the opposite frequency as a reference $\mathrm{MTR_{asym}} = \mathrm{Z}(-1.9\ \mathrm{ppm}) - \mathrm{Z}(1.9\ \mathrm{ppm})$.

Results and Discussion:

As was shown for slow [4] and for intermediate exchange of Cr protons [7] AREX corrects spillover and MT effects and removes $\mathrm{T_1}$-compensated influences. Evaluation with AREX is also applicable *in vivo* after pulsed steady-state measurements. In contrast to $\mathrm{MTR_{asym}}$ it is linearly dependent on the concentration (Fig. 1) and allows Cr-concentration calibration $\mathrm{c_{Cr}} = 258.92 \cdot \mathrm{AREX}$. Based on the water proton content (77 % [8, 9]) in muscle the CEST-based Cr mapping is given by the AREX signal and the relation $\mathrm{c_{Cr,muscle}} = 258.92 \cdot \mathrm{AREX} \cdot 0.77$. The Cr concentrations pre- and post-exercise differ significantly (Fig. 2). The results for one volunteer are in table 1. The Cr concentration changes were in the same range for all subjects. The strained muscles during our plantar flexion exercise are the gastrocnemius, the anterior tibialis and the fibularis longus. The soleus muscle showed no activity during the exercise.



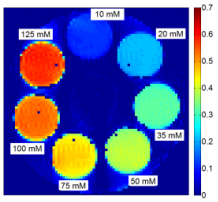


Figure 1: CEST contrast as a function of Cr concentration employing the multi-phantom set ($\mathrm{MTR_{asym}}$-map at 1.90 ppm is to the right of the graph). AREX (green circles) yields a linear dependence on the Cr concentration which is not the case with $\mathrm{MTR_{asym}}$ (blue stars). The linear fit (solid green) yields $\mathrm{AREX}(\mathrm{c_{Cr}}) = 0.003862 \cdot \mathrm{c_{Cr}}$. Hence, the calibration equation for creatine concentration is $\mathrm{c_{Cr}}(\mathrm{AREX}) = 258.92 \cdot \mathrm{AREX}$..

Muscle type	LG	MG	Soleus	FL
Cr c [mM] at rest	21.20 ± 6.03	17.97 ± 4.55	18.83 ± 4.36	27.78 ± 9.25
Cr c [mM] during exercise	26.52 ± 5.69	24.96 ± 6.04	21.06 ± 7.19	32.21 ± 10.48

Table 1: Volunteer #1: Cr concentration pre- and post-exercise in lateral gastrocnemius (LG), medial gastrocnemius (MG), Soleus and fibularis longus (FL).

Conclusion:

We introduced a simple method to determine Cr concentrations *in vivo* which is proportional to the *AREX* contrast being free of spillover, MT and T_1 influences. This allows for future applications of Cr CEST in muscle diseases. This evaluation can be applied to CEST studies in other tissues.

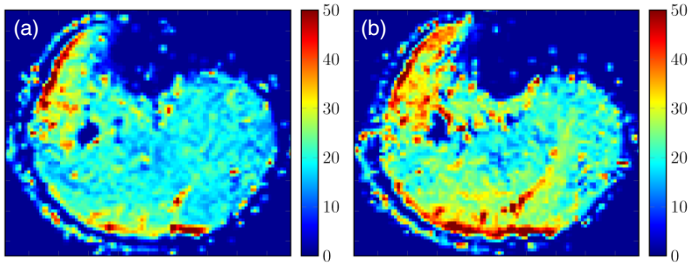


Figure 2: Transversal Cr-images of the calf muscle of volunteer #1. With **AREX** and the calibration function one can generate Cr concentration maps which show an increase of Cr content in gastrocnemius, in musculus tivialis anterior and fibularis longus after exercise (b).

References:

[1] Chance, B. et al., J Biol Chem. 1955 Nov;217(1):409-27.
[2] Kogan F. et al., Magn Reson Med. 2014 Jan;71(1):164-72
[3] Zaiss M. et al., NMR Biomed. 2013 May;26(5):507-18
[4] Zaiss M. et al., NMR Biomed. 2014 Mar;27(3):240-52
[5] Kim M. et al., Magn Reson Med. 2009 Jun;61(6):1441-50
[6] Windschuh, J. et al., ISMRM & ESMRMB (Electronic Poster 3303, 2014)
[7] Rerich, E. et al., ISMRM & ESMRMB (Electronic Poster 3302, 2014)
[8] Bergström, J. et al., J Appl Physiol. 1971 Jan;30(1)
[9] Sjøgaard, G. et al., Am J Physiol. 1982 Sep;243(3):R271-80