Hyperpolarized ^{13}C-acetate for the detection of metabolic response of the heart to a stress protocol

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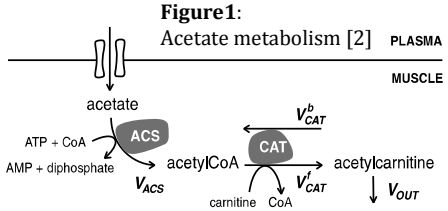
Introduction:
Acetate metabolism plays an important role particularly in myocardial cells [1]. The carboxylate molecule is taken up into the cytosol and gets converted to Acetyl-Carnitine (ALCAR) via Acetyl Coenzyme A (Fig. 1). Hyperpolarized MRS using [1-13C]acetate gives the ability to differentiate between normal and pathological metabolic rates. Specifically the conversion of [1-13C]acetate to [1-13C]ALCAR can be a negative marker for viability of myocardial cells and disorders like cardiomyopathy as it occurs in ischemia [1,5] or as a positive marker for changes of fatty acid metabolism in diabetes mellitus. The bottleneck of the proposed method on a clinical MR-scanner is the low SNR of the ALCAR-signal. To adress this problem a stress protocol, previously developed for ^{11}C-acetate-PET [6] was applied in order to enhance the myocardial acetate consumption. Furthermore a SNR-optimized spectro-spatial pulse sequence was designed. The aim of this study was to investigate the increase of ALCAR-production under stress in the short time scale of a hyperpolarized MRS experiment in respect to the ALCAR-to-Acetate ratios in the rat heart.

Figure1:
Acetate metabolism [2]



Methods:
A spectro-spatial rf-pulse was used to exploit the magnetization efficiently, acquiring the ALCAR signal with a higher flip-angle (20°) than acetate (5°) (Fig. 2). The pulse was designed to be short (8 sub-lobes, duration 15,5ms, isodelay 7ms) [4], in order to minimize the T2*-decay during the pulse, therefore allowing a residual excitation of acetate during the ALCAR acquisition (Fig. 3). A slice of 12mm, containing the whole heart was excited. The measurement started with the injection of acetate, the alternating excitations on the two frequencies had a repetition time of 5s for each. The flip angle corrected signal intensities of each species for 60s after injection were summed up after Rice correction of each spectrum, finally the total signal-ratio was calculated.
For the preparation of the substrate, [1-13C]acetate sodium salt (4.5 M) was dissolved in glycerol doped with 30mM OXO63 radical and 1.6mM of Dotarem®. This was polarized in a 3.35T Hypersense DNP polarizer for 75 min. A 120mM acetate solution was injected into the rat tail vein inside the MR-scanner (dose 5ml/kg). All in vivo studies were performed on healthy Sprague-Dawley male rats (n = 6) on a 3T GE HDx system equipped with a dual-tuned ^{1}H-^{13}C-volume coil. Each animal underwent two MRI sessions: One prior to Dobutamine treatment (control) and one after infusion of Dobutamine (5µg/min/kg for 2min; 10µg/min/kg for 2 min; 20µg/min/kg for 9 min) [6].

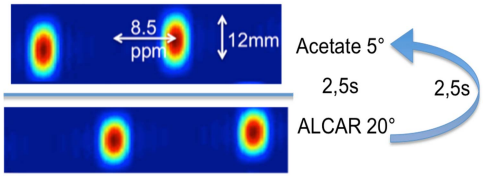


Figure2:
Pulse sequence: Alternating excitation of Ac and ALCAR with different flip-angles using a spectrospatial pulse

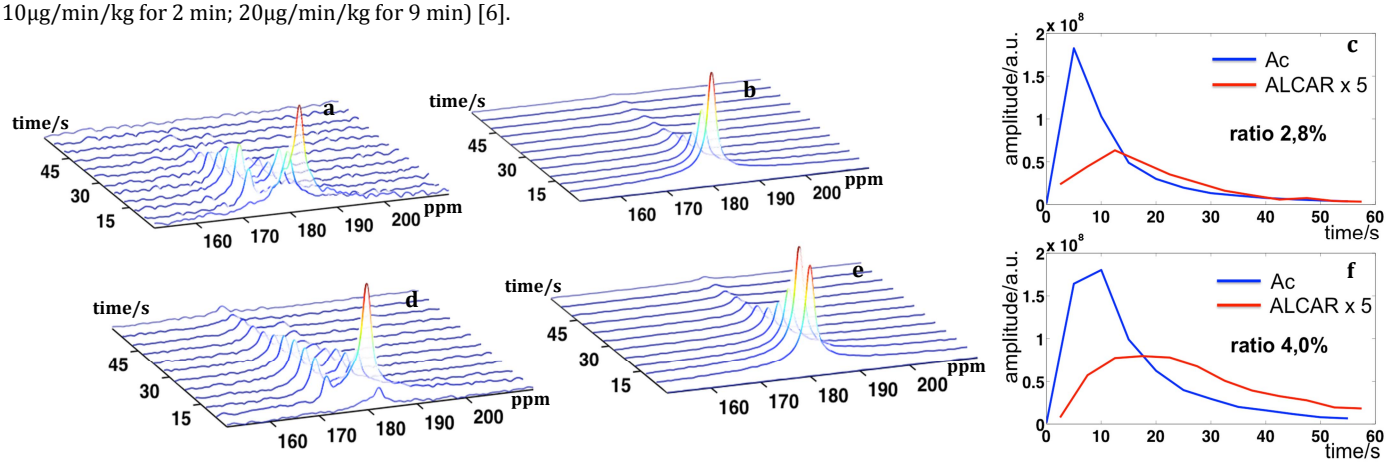


Figure 3.: Upper row: Without dobutamine. Signal evolution after 20° ALCAR- (a) and 5° acetate- (b) excitation. The timecourse of both signals is shown in (c). Lower row: After dobutamine infusion. ALCAR- (d) and acetate- (e) excitation and comparison (f).

Results and Discussion:
In Fig. 3 an exemplary dataset is shown, the ALCAR-signal increases after dobutamine injection, especially at later timepoints (after 30s). In the 20° ALCAR-acquisition a residual excitation of acetate is visible, but the signals can clearly be separated at every timepoint. Furthermore the acetate signal after dobutamine infusion is higher at later timepoints as well, confirming the increased uptake into the myocardium. A significant increase of the ALCAR/Acetate ratio was shown consistently over the datasets (Fig. 4). Without stress protocol the average ratio was 3,41%±1,04% after dobutamine administration it increased to 5,49%±1,44%. Both results (more acetate signal in the heart slice and a higher conversion rate) lead to an increase of the ALCAR-SNR opening a longer time-window for more detailed observations of this metabolic system in the heart.

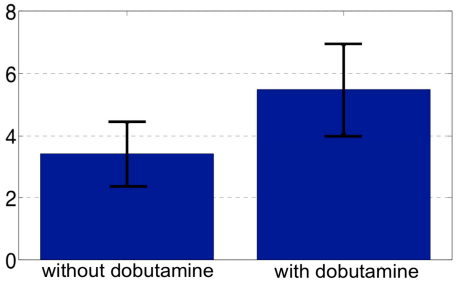


Figure 4:
Increase of the ALCAR/Acetate ratio under stress (error bars: Standard deviation)

Conclusion:
The increase of the ALCAR-signal after hyperpolarized acetate administration by inducing myocardial stress with dobutamine was shown with an optimized spsp-pulse sequence in rats. The conversion ratio as well as the SNR of the carnitine improved after stress induction. The higher SNR of ALCAR can be exploited for further investigation of cardiac acetate metabolism and can be particularly helpful for imaging studies.

[1] Jensen et al., JBC 2010; [2] Bastiaansen et al., BBA 2013; [3] Bastiaansen et al., ISMRM 2012; [4] Schulte et al. MRM 2012; [5] Lionetti et al., Cardiovascular Research 2011; [6] E. Crnteauet al. Nuclear Med. And Biob. 2012

Acknowledgements
Funding from BMBF 13CMMR grant number 01EZ1114