Detection of Glycosaminoglycans using Positive CEST approach

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Introduction

CEST contrast employs *C*hemical *E*xchange *S*aturation *T*ransfer to generate contrast in MRI images. It is based on the selective presaturation of the small pool of exchanging protons and can be switched "on" and "off" using suitable RF irradiation (1). Recently, CEST was applied to detect glycosaminoclycans (GAGs) in articular cartilage and intervertebral disc. This method was called gagCEST (2). In gagCEST –OH or –NH groups, present in GAG were pre-saturated, and the CEST contrast was shown to correlate with tissue degeneration.

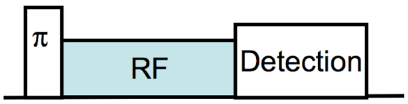

Figure 1. *A schematic of the RF sequence employed to generate positive CEST scheme. "Detection" box corresponds to 90^0 pulse and FID acquisition in case of spectroscopic measurements, or to an imaging sequence (e.g. Spin Echo) in the imaging experiments.*

The standard CEST approach results in the *negative* contrast, i.e. the signal is decreased due to the presence of the RF saturation. Recently, an alternative approach was introduced -- positive CEST (pCEST) that results in the *positive* contrast, i.e. the signal is increased when exchanging groups are pre-saturated (3). Similar to the CEST scheme, PCEST scheme employs selective pre-saturation of the exchanging group. This saturation results in shortening of the apparent relaxation time, $T_{1(app)}$ (4) when RF is applied on the resonance frequency of the exchanging pool. The schematic of the sequence is given in Fig.1: an inversion pulse is applied, and the magnetization is recovering to the steady-state under the frequency-selective saturation RF. Similar to CEST, the saturation is applied either at the frequency of the exchanging group (RF ON) or at the frequency symmetrical w.r.t the bulk water frequency (RF OFF). The timing of the saturation is chosen to NULL the signal when the RF is OFF. Hence, the pCEST scheme results in substantial suppression of the background signal. Due to the shortening of the apparent relaxation time the signal is increased and is positive when the RF is ON.

Here we present preliminary results evaluating the application of pCEST to GAG detection and comparing the positive gagCEST (gagpCEST) with the standard gagCEST.

Materials and Methods

The experiments were performed using vertical bore 8.5T Bruker system (Bruker-Biospin Inc., Billerica, MA) equipped with a 10mm volume proton coil. For the relaxation measurements, inversion and RF saturation were applied prior to 90^0 detection pulse (Fig.1). For the imaging experiments a pCEST preparation was used with spin echo detection: 15mmx15mm FOV, TR/TE 15000/12ms, 64x64 matrix size, 4mm slice thickness, 1 NEX. The RF saturation intensity was 3 μT.

Results and Discussion

To verify the applicability of the technique, we have conducted a series of measurements in solutions of 5% GAG in PBS. The apparent relaxation rate $R_{1(app)}=1/T_{1(app)}$ was measured using inversion recovery as a function of the frequency of the saturation pulse while keeping the RF intensity constant at 3μT. When the frequency of the saturating RF is equal to the frequency of the exchanging –OH pool (RF ON), $R_{1(app)}$ increases. The results agree well with the Z-spectra (Fig. 2). The increase in apparent relaxation ($\Delta R_{1(app)}(1ppm)=R_{1(app)}(1ppm)-R_{1(app)}(-1ppm)$ for –OH protons or analogous $\Delta R_{1(app)}(3.2ppm)$ for -NH) depends on the exchange parameters, as well as on the RF intensity. Here saturation at the –OH frequency resulted in $\Delta R_{1(app)}(1ppm)\sim0.4sec^{-1}$, or, in relative terms, 40% decrease in relaxation times. These data indicate that the frequency-selective apparent relaxation changes can be utilized for the identification of GAG.

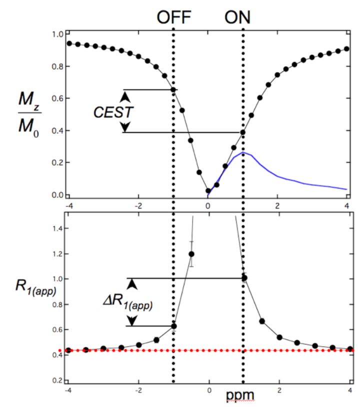

Figure 2. *Z-Spectra (top panel) and $R_{1(app)}$ vs RF off-resonance (bottom panel) for 5% GAG solution. The red horizontal line at the bottom panel indicates R_1 in the absence of irradiation. The blue line at the top panel shows CEST asymmetry.*

For pCEST imaging, the time after the inversion pulse (TI) is adjusted to null the signal with the RF OFF (TI_{null}). TI is adjusted for a particular RF OFF frequency, (symmetrical to RF ON frequency) and RF intensity. Here the TI_{null} is 1.28 sec. In essence, by adjusting TI to null the signal when RF OFF, TI is adjusted to the apparent relaxation time containing contributions from all mechanisms (i.e, dipolar interactions, fast exchange), but not CEST (which is only present when the frequency is ON). When RF is switched to the ON frequency, keeping the TI_{null}, the signal becomes small and positive due to apparent shortening of the relaxation times because of the saturation transfer. In the absence of chemical exchange the signal would still be null. With exchange effects, occurring at ON frequency, the signal is small and positive.

Fig.3 displays images obtained using pCEST in 5% GAG solution. The difference images were obtained using slightly different formulas accounting for the negative or positive nature of the contrast: (OFF-ON) for CEST and (ON-OFF) for pCEST. The background suppression obtained using a positive CEST scheme is good, with only the edge of the phantom visible, due to the susceptibility distortions at the edges. In comparison, standard CEST results in an inhomogenous image, probably due to B_0 and B_1 imperfections.

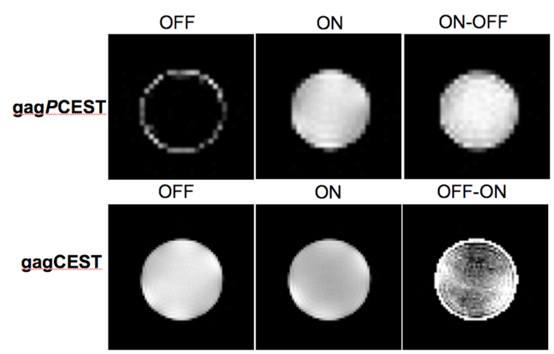

Figure 3. *Images of phantoms containing 5% GAG in PBS, obtained using gagPCEST (upper row) and gagCEST (bottom row) schemes. RF OFF is at -1ppm; RF ON is at +1ppm relative to the bulk water.*

Conclusions

The results presented here show the potential of pCEST to image GAG specifically. Work is in progress to verify the scheme in suspensions containing cartilage constituents (GAG and collagen I), as well as in *ex-vivo* samples of bovine nasal cartilage.

References

1. Ward K,*et.al. J Magn Reson* 2000;143:79; **2.** Ling W,*et.al. PNAS* 2008; 105:2266; **3.** Vinogradov E,*et.al.*, ISMRM 2009; **4.** Baguet E,*et.al. J Magn Reson* 1997;128:149.