Optimization of pulsed-gagCEST at 3.0T

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Introduction: Chemical exchange saturation transfer (CEST) is recognized as a technique for obtaining contrast from certain molecules based on their chemical exchange with water protons. Specifically, gagCEST uses the –OH (and to a lesser extent –NH) groups to produce an endogenous contrast from tissues containing glycosaminoglycan (GAG). The potential applications include studies of articular cartilage and intervertebral disc degeneration. A majority of the work reported so far relied on *ex-vivo* studies using narrow-bore high field scanners (4.7T-11.7T) [1-3]. *In-vivo* results were also reported [3-4], but, so far, to a lesser extent. There are specific challenges associated with transferring gagCEST to clinical scanners, arising from the decreased field strength of clinical scanners (3.0T) and SAR and hardware limitations on saturation. In particular, the –OH groups that undergo saturation in gagCEST are located relatively close to water resonance, at +0.9 to +1.9 ppm, i.e. +114 to +242 Hz at 3.0T, thus making experiments particularly sensitive to direct RF saturation and B_0 homogeneities. With these complications in mind, we undertook a systematic optimization procedure aimed at generating reliable and reproducible gagCEST maps. As a first step *ex-vivo* samples were used to establish that comparable CEST effects distinguishing degenerated from non-degenerated samples could be obtained on the 3T clinical scanner. The results were compared with gagCEST obtained using a high field (4.7T) scanner as "gold standard". Previously, Sun et al. compared the use of pulsed-CEST imaging with the more standard continuous-wave (CW) saturation for amide proton transfer [5]. The pulsed-CEST scheme not only gave a contrast similar to that from CW-CEST, but it also addressed SAR and hardware limitations for CW-CEST on clinical scanners. Recently, pulsed-CEST was used to assess GAG concentrations *in vivo* [3]. Here, we look at optimization of pulsed-CEST to obtain the maximum gagCEST contrast at 3.0T. Specifically, experiments were carried out to differentiate samples of normal bovine nasal cartilage (BNC) from BNC degraded with trypsin [6] and Z-spectra from pulsed-CEST were simulated using a two-pool model [7].

Materials: Tissue was obtained from a local butcher. To achieve degradation some samples were treated with trypsin for a prolonged period of time. Trypsin removes GAGs, ultimately leaving only a collagen matrix. Samples of normal and degraded BNC were placed in a tube filled with Fluorinert™ (3M, St Paul MN).

Methods: All experiments were carried out on a clinical 3.0T MR system (Signa EXCITE, GE Healthcare) with a transmit-receive knee coil. Due to scanner limitations, 5 pulses with a maximum length of 50ms each were implemented. The pulses were separated by crusher gradients to spoil any transverse magnetization. A B_1 in the order of the chemical exchange rate [8] was selected, which for GAG results in ~1.5μT. This B_1 also provided minimal direct saturation of the liquid pool. With the prescribed settings, 4 established pulse shapes were evaluated: block, Fermi, gauss, and half-sinc (i.e. sinc pulse with no lobes). As such, the peak value for B_1 was altered to maintain an equivalent RF power of 1.5μT for 50ms CW irradiation [5]. The shapes were incorporated prior to a gradient-echo acquisition. Data were collected for offset frequencies in the RF saturation pulses of 600 to -600Hz in increments of -50Hz. Additional imaging parameters were: FA=30°; FOV=6.4x6.4cm; matrix=64x64; TE/TR=4.6/500ms. Correction of B_0 inhomogeneities was conducted based on Z-spectra minima ± 3σ, where σ is the standard deviation in the noise. The gagCEST maps were produced by integration of the Z-spectrum between 120 and 240Hz (0.9 to 1.9ppm, where OH groups resonate) and its subtraction from the value integrated over the same range upfield. To confirm any difference between degraded and normal BNC and validate the 3.0T protocol, CEST data were also obtained on a 4.7T horizontal bore small animal scanner (Bruker BioSpec, Billerica MA), using 5x50ms gauss-shaped pulses followed by a fast spin-echo acquisition: FOV=6.0x6.0cm; matrix=64x64; TE/TR=12/500ms. The two-pool exchange model between water and GAG was simulated in MATLAB (R2008a, Mathworks, Natick MA) with T_{1a}/T_{2a} = 3.0/2.0s for water, T_{1b}/T_{2b} ≈ 1.24/0.04s for GAG and a chemical exchange rate for –OH of ~$10^3 s^{-1}$.

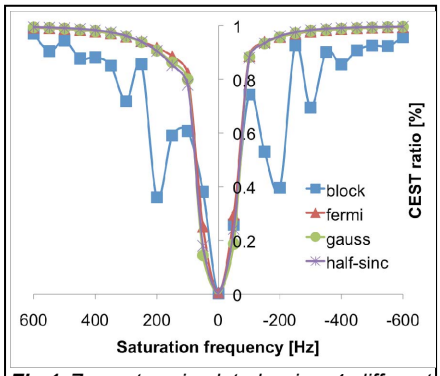

Fig.1 *Z-spectra simulated using 4 different pulse shapes for contrast due to gagCEST (120-240Hz).*

Results & Discussion: Figure 1 shows the simulated Z-spectra using the 4 different pulse shapes. Pulsed-CEST with the block shape produces a sinc-like shaped Z-spectrum with multiple sidelobes, due to its sinc profile in the frequency domain (Fig.1, squares). The Z-spectrum from the Fermi pulse shows the narrowest minimum, which might reflect a reduction in RF spill over (Fig.1, triangles). Within the expected range for a gagCEST effect of +0.9 to +1.9ppm, the greatest decrease occurs for the gauss and half-sinc shapes (Fig.1, circles and stars, respectively). Figure 2 shows experimental results obtained using the same shapes. The block pulse shows a strong CEST effect from the fully trypsinized sample: clearly an erroneous effect reflecting the sinc-shaped Z-spectrum found in simulation. For all other pulses the CEST effect in normal BNC is greater than in the fully trypsinized sample, as expected, since virtually no GAG is left in the degraded BNC. The greatest CEST effect was obtained using the gauss pulse. A comparable contrast difference is seen from the gagCEST parameter maps using data acquired at 4.7T (Fig.2e). ROI analysis confirms the visual assessment: the greatest gagCEST effect in normal BNC obtained using gauss shape at 3.0T is equal to (5±2)%. This result is in agreement with the gagCEST effect measured at 4.7T, which is equal to (4±1)%. At the same time, gagCEST in the fully degraded sample is equal to (1±2)% and (1±1)% on 3.0T and 4.7T, respectively.

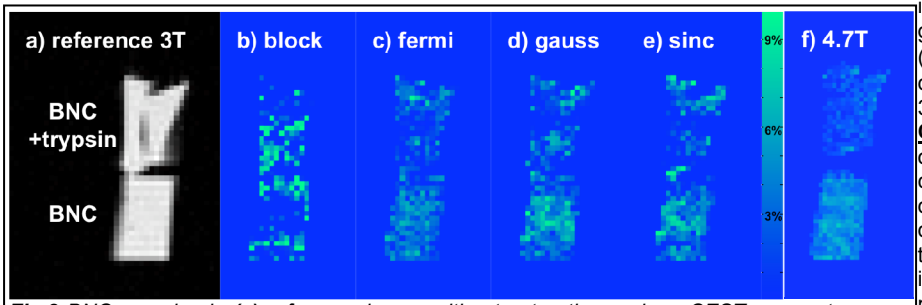

Fig.2 *BNC samples in **(a)** reference image without saturation and gagCEST parameter maps from pulsed-CEST data using **(b)** block, **(c)** Fermi, **(d)** gauss and **(e)** half-sinc pulse shapes at 3.0T, and **(f)** at 4.7T.*

Conclusions: Acquisition of CEST data has been optimized for gagCEST in cartilage at 3.0T, with any contrast confirmed at 4.7T. A successful and robust detection of the difference in gagCEST between degraded and normal BNC is taken as a first step towards contrast based on the state of cartilage. Work is in progress to expand the optimized and validated protocol to *in-vivo* studies of articular cartilage and intervertebral discs.

References: [1] Ling et al. NMR Biomed 2007:289-95. [2] Ling et al. European MSK Review 2009:Vol.4(1) [3] Ling et al. Proc Natl Acad Sci 2008:2266-70. [4] Kim et al. ISMRM 2010:539 [5] Sun et al. JMR 2005:193-200. [6] Reiter et al. MRM 2009:803-9. [7] McConnell. J Chem Phys 1958:430. [8] Woessner et al. MRM 2005:790-9.