pH Dependence of gagCEST at 7T

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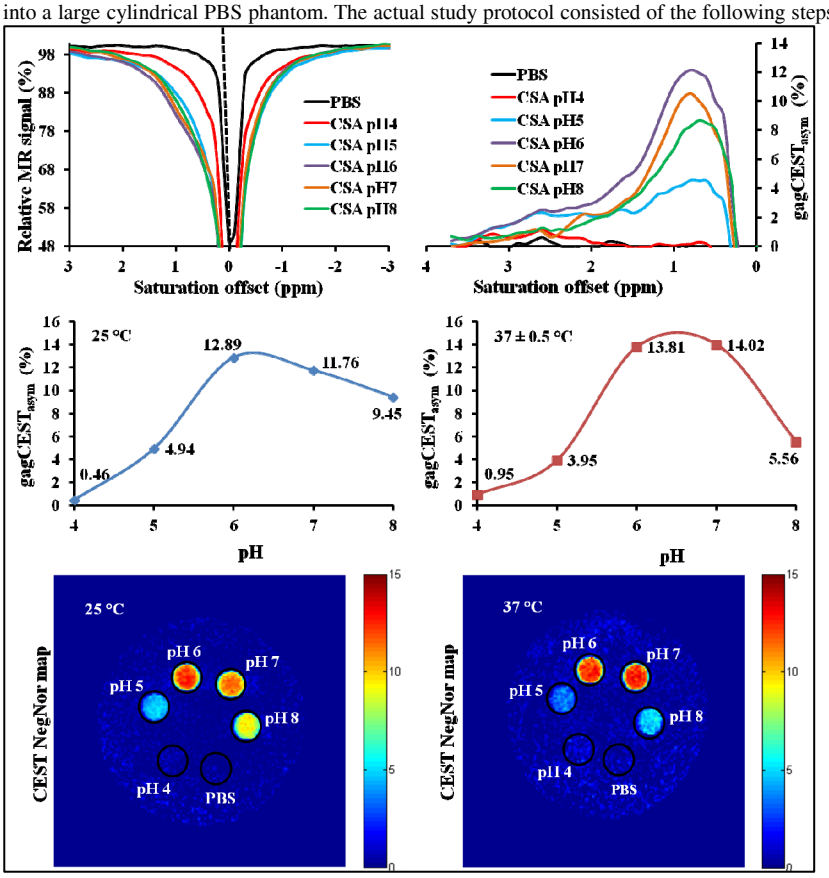
INTRODUCTION: Osteoarthritis (OA) is one of the major debilitating joint diseases of the musculoskeletal system affecting a large population worldwide. The initiating event of OA is thought to be predominantly due to loss of proteoglycans (PG) from the tissue (1). Recently, it has been shown that chemical exchange saturation transfer (CEST) of labile –OH protons on glycosaminoglycans (GAG) with bulk water leads to a significant reduction of bulk water magnetization creating "gagCEST" (2), which potentially can be used as a diagnostic method at 7T for early OA. While the B_0 inhomogeneity and direct saturation effects, on the accuracy of the computed CEST values (3-5) as well as optimal saturation pulse parameters for obtaining maximum gagCEST on human cartilage at 7T have been previously reported (6), there are no studies reporting the sensitivity of gagCEST on pH changes. This is important, as there have been studies reporting a significant drop in pH (7.1±0.4 in normals; 6.2±0.9 in Grade 1, 5.7±1.0 in Grade 2, 5.5±1 in Grade 3 cartilage surfaces) in knee cartilage of OA subjects (7). Therefore, in this study we have performed the gagCEST experiments on 5% chondroitin sulfate A (CSA; from bovine trachea; Sigma Aldrich) phantoms with varying pH (pH4, 5, 6, 7 and 8) and determined the sensitivity of gagCEST towards the pH changes at two different temperatures.

MATERIALS AND METHODS

***Phantom Studies*:** Five samples of the 5% CSA were prepared in 10 mM phosphate buffer saline (PBS) and then the pH of the final solution was adjusted to 4, 5, 6, 7 and 8. Another sample of 10 mM PBS with pH 7 served as control. All the samples were then transferred to NMR tubes (10 mm in diameter), which were immersed into a large cylindrical PBS phantom. The actual study protocol consisted of the following steps: a localizer, WASSR (4), z-spectral or CEST acquisitions and B_1 data collection. For WASSR acquisitions, Δω range of -0.5 to +0.5 ppm with step size of 0.05 ppm was used. For z-spectrum acquisitions, Δω range of -4 to +4 ppm with step size of 0.1 ppm was used. For CEST acquisitions, Δω ranges were -1.3 to -0.7 ppm and 0.7 to 1.3 ppm with 0.1ppm steps (duration = 500 ms; $B1_{rms}$ = 2.2 μT). For WASSR acquisitions, a 0.2 s saturation pulse train (SPT) with B_{1rms} of 0.29 μT was used. For z-spectral data, a 0.5 s SPT with a B_{1rms} of 2.2 μT was used. All the acquisitions were performed on the phantoms at room temperature as well as at 37 ± 0.5 °C on 7.0T Siemens Scanner using 32 channel phased array head coil.



***Data analysis*:** All the CEST and Z-spectral data analysis was performed using in-house programs written in MATLAB. CEST effect of the solute spins (exchangeable protons of interest from metabolite) is computed generally by using the following equation: $CEST_{asym}(\Delta\omega)=100*[M_{sat}(-\Delta\omega) - M_{sat}(+\Delta\omega)]/M_{0\ldots}[1]$, where M_0 is the water magnetization without saturation, M_{sat} ($\pm\Delta\omega$) are the water magnetization obtained with saturation at a '+' or '–' $\Delta\omega$ offset of the water resonance. Thus, the CEST data (at Δω = ±1.0 ppm) or z-spectral data (typically -4.0 to +4.0 ppm) acquired were directly used to generate gagCEST maps or z-spectral asymmetry curves using Eq. [1] to get data without B_0 correction. The mean and SD of $gagCEST_{asym}$ values were calculated over the small ROI drawn on the phantom images. The $gagCEST_{asym}$ map was overlaid on off-resonance image. B_0 map was computed using WASSR data (4). Acquired CEST data (at offset frequencies, typically +0.7 to +1.3 ppm and -0.7 to -1.3 ppm) or z-spectral data (typically -4.0 to +4.0 ppm) were smoothed and interpolated using a cubic spline to generate data with a step size of 0.01 ppm. For B_0 inhomogeneity correction, each voxel data value at Δω ppm was replaced by the interpolated data value from (Δω – δω) ppm. Either z-spectral asymmetry curves or $gagCEST_{asym}$ (based on the data from ±1.0 ppm) were generated using Eq. [1].

RESULTS AND DISCUSSION: Z-spectral and gagCEST asymmetry curves from the chondroitin sulfate A phantoms showed a pH dependence varying from ~ 0 – 13% with maximum $gagCEST_{asym}$ observed with CSA phantom at pH 6 at room temperature. At 37 °C, it varied from ~0 – 14% with maximum gagCEST asymmetry observed from both the CSA phantoms with pH 6 & 7 while CSA phantom with pH 8 showed a sharp decline in its $gagCEST_{asym}$ when compared to the same phantom at room temperature. Since the preliminary data shows a clear pH dependence of the gagCEST asymmetry a finer sampling (pH 5 – 8 with increments of either 0.25 or 0.5 units) will be presented as the reported values in Grade 1-3 cartilage surfaces of OA subjects falls in the pH range of 5.5-6.2. It is well know that OA process leads to loss of [GAG] in cartilage that leads to decreased GagCEST contrast in OA cartilage. Similarly, the results from the current study show that decrease in pH due to OA may also decrease the GagCEST effect from cartilage. Since the concentration and pH changes on GagCEST are additive, it appears that the overall GagCEST measured from OA cartilage will over estimate the [GAG] loss from cartilage, which may actually increase the sensitivity of the GagCEST method. Further studies on the effect of pH changes on GagCEST in intact cartilage are currently in progress.

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