Transverse Relaxation Amplified by Chemical Exchange (TRACE): A New Method for Mapping Molecular Integrity of Cartilage

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Introduction: Osteoarthritis (OA), is a common joint disease, whose early stage is associated with an increase in enzymatic degradation resulting in glycosaminoglycan (GAG) depletion. There is an increase in the total water content and the total concentration of collagen (COL) remains unaltered in the earliest stages although there are generally changes in the arrangement and size of the fibers. It is well recognized that T_2 weighted image intensity is affected by spin-spin relaxation rates and this rate is increased by chemical exchange of ^{1}H protons (-OH, -NH) of macromolecules (GAG and COL) with bulk water protons as well as by static residual dipolar interaction from oriented collagen. On the other hand, the exchange contribution to the spin-spin relaxation rate can be reduced using spin locking or $T_{1\rho}$ technique. While both T_2 and $T_{1\rho}$ techniques are sensitive to macromolecular content of cartilage (1-4), with a varying degree of specificity, they both are affected by fluid contamination associated with cartilage degeneration. While the recently developed GagCEST method (5-6) is specific to GAG, as a result of substantial direct saturation of water, it has rather poor sensitivity at clinical field strengths (3T). Thus there is an unmet need for a noninvasive technique that addresses the inherent problems in the existing methods of cartilage molecular imaging. In this study, we propose a new MRI based method that directly measures the content of cartilage macromolecules (GAG and COL) with reduced contribution from elevated fluid signal during cartilage degeneration.

Materials and Methods: In MRI, spin-spin relaxation rate (R_2) is a composite phenomenon with possible contribution from free water (R_{2f}), dipolar-dipolar (R_{2dd}) and chemical exchange (R_{2ex}) based relaxation mechanisms and can be expressed by equation [1]. Spin-spin relaxation rate may be reduced using spin locking in rotating frame technique depending upon power and duration of spin lock and modified relaxation rate can be represented by equation [2]. $R_{1\rho} = R_2$ for zero spin lock amplitude and it decreases with increase in amplitude of spin lock. For small spin lock powers, as used in this study, $R_{1\rho f} \approx R_{2f}$ and $R_{1\rho dd} \approx R_{2dd}$ (assuming that the small spinlock pulse doesn't significantly affect the static dipolar interaction); however, $R_{1\rho ex} < R_{2ex}$. Let's represent the difference $R_{2ex} - R_{1\rho ex}$ by R_{ex}. Signal intensity of R_2 (=1/T_2) weighted image is given by equation [3]. Similarly, signal intensity of $R_{1\rho}$ (=1/$T_{1\rho}$) weighted image is given by equation [4]. Ratio of $T_{1\rho}$ and T_2 weighted signal (equation [5]) is defined as a new contrast Transverse Relaxation Amplified by Chemical Exchange (TRACE).

$$R_2 = R_{2f} + R_{2dd} + R_{2ex} \quad [1]$$

$$R_{1\rho} = R_{1\rho f} + R_{1\rho dd} + R_{1\rho ex} \quad [2]$$

$$S_1 = S_0 * \exp(-t.R_2),\ t = TE. \quad [3]$$

$$S_2 = S_0 * \exp(-t.R_{1\rho}),\ t = TSL. \quad [4]$$

$$TRACE = S_2/S_1 = \exp(-t.R_{ex}) \quad [5]$$

In knee cartilage chemical exchange of protons (-OH and -NH) of GAG as well as COL with bulk water protons predominately contributes to the exchange based relaxation (R_{ex}) in TRACE contrast. Therefore, TRACE contrast should serve as an index for mapping macromolecules (GAG+COL). Similar approach was used in the previously published study (7) on phantom and ex vivo data, but in that work instead of T_2 weighted imaging two spin-lock weighted images were used, which has lower sensitivity and prone to field inhomogeneities that makes it difficult to implement it in a clinical setting. The current method addresses these problems and, as shown below, it can be readily performed on human knees on clinical scanners.

MRI Experiment: All the MRI experiments were performed at 3T and 7T whole body MR scanners. Here a FLASH readout based MR pulse sequence, which can be prepared for T1ρ or T2 weighted contrast, is used. Phantom preparation: Chondroitin sulfate (CS), a sulfated GAG, was used to prepare phantoms with different amounts (0 to 6g per 100mL of PBS) at pH =7.0. For exchange effect characterization pH dependence phantoms of 5% CS in PBS with different pH (4, 5, 6, 7 and 8) were also prepared. Human subjects: MRI was performed on knee of five human subjects after obtaining consent (preapproved protocol by IRB) to participate in the study.

MRI Data acquisition: After a localizer, $T_{1\rho}$ and T_2 weighted images corresponding to different durations (TE or TSL) were obtained. For phantom MRI a 2D and for human knee MRI a 3D FLASH readout was used. Spin lock B_1 used in $T_{1\rho}$ weighted images was 700Hz.

Data processing: TRACE contrast map was generated using equation [5]. $T_{1\rho}$ and T_2 W images with TSL or TE of 40 ms for knee data and of 600ms for phantom data were used for TRACE contrast computation. In addition, for comparison, $T_{1\rho}$ and T_2 maps were also generated by fitting data to mono-exponentially decaying function.

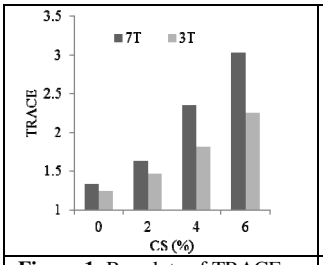

Figure 1: Bar plots of TRACE contrast from PBS phantoms with different CS concentrations in PBS at 7T and 3T.

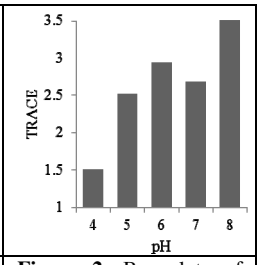

Figure 2: Bar plots of TRACE contrast from CS (5%) phantoms with different pH at 7T.

Results and Discussions: Dependence of TRACE contrast on CS concentration is shown in Fig.1. This contrast also showed dependence on static B_0 field strength (3T an 7T), which is also expected for any exchange based contrast. Note that contrast in phantom was computed at duration (TE/TSL) of 600ms and this contrast reduces with decrease in duration. TRACE contrast from CS phantoms showed pH dependence and therefore it is an exchange based contrast. However, while dependence of TRACE contrast on pH showed a complex pattern (Fig.1), it may not be significantly affected by expected changes in pH under physiological conditions (between 5 and 7). TRACE contrast maps from knee cartilage of healthy subject (Fig.3), obtained at 3T, show lower value in superficial zone of cartilage, which is consistent to reported GAG distribution in the cartilage (9, 10). Average (±SD) TRACE contrast values in healthy cartilage was 1.24±0.11. In cartilage, -OH protons of COL are also expected to contribute in addition to GAG. TRACE contrast in cartilage from subject having knee pain was much lower compared to health cartilage. Note that both T_2 and $T_{1\rho}$ values of cartilage were elevated for this subject in different amounts across cartilage. Similar to phantom data, TRACE contrast in knee cartilage was higher at 7T compared to 3T. Based upon theory of this method, the TRACE contrast will be less sensitive to fluid changes compared to T_2 and $T_{1\rho}$ contrast, and provides a direct measure of tissue macromolecular changes. In conclusion, the proposed method is simple, time efficient and yet provides quantitative index of macromolecular changes in cartilage and can be readily implemented on clinical scanners.

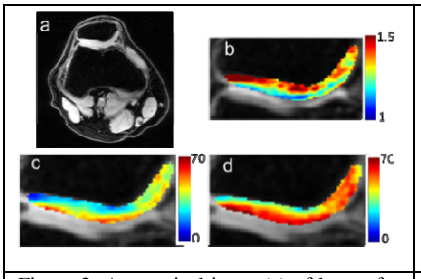

Figure 3: Anatomical image(a) of knee of a asymptomatic subject along with TRACE contrast map(b), T_2 (c), and $T_{1\rho}$ (d) maps of patellar cartilage, color overlaid on cropped anatomical image, obtained at 3T. Scales on T_2 and $T_{1\rho}$ maps are in milliseconds.

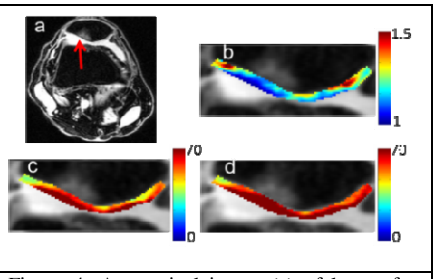

Figure 4: Anatomical image (a) of knee of a subject, with knee pain, along with TRACE map (b), T_2 (c), and $T_{1\rho}$ (d) maps of patellar cartilage, color overlaid on cropped anatomical image, obtained at 3T. The scales on T_2 and $T_{1\rho}$ maps are in milliseconds.

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