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Chemical exchange in knee cartilage assessed by $R_{1\rho}$ ($1/T_{1\rho}$) dispersion at 3 T

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ABSTRACT

Purpose: To quantify the characteristics of proton chemical exchange in knee cartilage *in vivo* by $R_{1\rho}$ dispersion analysis.
Materials and methods: Six healthy subjects (one female and five males, age range 24 to 71 y) underwent $T_{1\rho}$ imaging of knee cartilage on a 3 T MRI scanner. Quantitative estimates of $R_{1\rho}$ ($=1/T_{1\rho}$) were made using 5 different spin-lock durations for each of 12 different spin-lock amplitudes over the range 0 to 550 Hz. When the variations of $R_{1\rho}$ with spin-locking strength (the $R_{1\rho}$ dispersion) are dominated by chemical exchange contributions, $R_{1\rho}$ dispersion curves can be analyzed to derive quantitative characteristics of the exchange and provide information on tissue composition. In this work, *in vivo* $R_{1\rho}$ dispersion of human knee articular cartilage at 3 T was analyzed, and the exchange rates of protons between water and macromolecular hydroxyls (mainly in glycosaminoglycans) were estimated based on a theoretical model.
Results: $R_{1\rho}$ values showed marked dispersion in articular cartilage and varied by approximately 50% between low and high values of the locking field, a change much greater than in surrounding tissues, consistent with greater contributions from chemical exchange. From the theoretical model, the exchange rates in cartilage were estimated to be in the range of 1.0–3.0 kHz, and varied within the tissue. Variations within a single knee appear to be larger with increasing age.
Conclusion: $R_{1\rho}$ dispersion analysis may provide more specific information for studying cartilage biochemical composition and form the basis for quantitative evaluation of cartilage disorders.

1. Introduction

Cartilage is an avascular connective tissue structure composed of one cell type (chondrocyte), surrounded by a large extracellular matrix [1,2]. Chondrocytes control the synthesis and composition of the extracellular matrix, which is functionally responsible for the biomechanical properties of cartilage. For this reason, interest in the extracellular matrix has stimulated several approaches for early detection of cartilage degradation due to normal aging, or more importantly, due to osteoarthritis (OA). Osteoarthritis is one of the major health concerns affecting adults, and its risk for causing disability is as great as that of cardiovascular disease [3].

$T_{1\rho}$ sensitive imaging has shown promise for the detection of biochemical changes in the extracellular matrix, and has been previously used to evaluate cartilage in healthy and osteoarthritic subjects [4–6]. However, the origins of contrast in $T_{1\rho}$-weighted imaging have not been unambiguously validated, and the contributions of different potential mechanisms at different field strengths has been a question of some debate [7–9]. Although other mechanisms such as residual dipolar effects may contribute, conclusions from computer simulations, theory and experimental measurements strongly support the role of chemical exchange between water and hydroxyl protons (mainly in glycosaminoglycans) as major contributions to $R_{1\rho}$ ($=1/T_{1\rho}$) at higher fields [10–12]. Previous imaging studies have usually used only a single value of the locking field amplitude to report values of $T_{1\rho}$. The contributions to relaxation from chemical exchange at high fields can be partially reduced in the presence of stronger locking fields, so that the value of $T_{1\rho}$ depends on the choice of experimental parameters. The variation of $R_{1\rho}$ with spin-locking field strength, known as $R_{1\rho}$ dispersion, can then provide quantitative information relevant to chemical and diffusive exchange [8,10,11,13], and therefore can in principle provide a more complete characterization of tissue composition and alterations associated with pathology. In spite of this, only very few $R_{1\rho}$ (or $T_{1\rho}$) dispersion studies in biological tissues have been reported previously, and mostly these have been at lower magnetic field strengths [14,15] where exchange effects are much less important. At higher fields, $R_{1\rho}$ dispersion may be modeled

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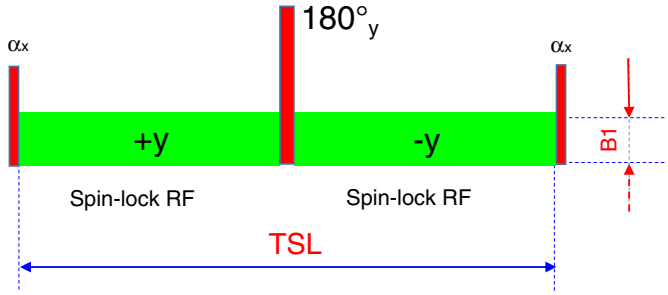

Fig. 1. B0 and B1 insensitive composite pulse for $T1_\rho$ weighted imaging. Magnetization is tipped a flip angle α_x (90° and duration 0.5 ms, in this paper) about x axis by the first pulse then nutates about the effective field for time TSL/2. The 180° refocusing pulse (duration 1 ms) is applied about the y axis to flip the magnetization and is then followed by another spin-locking pulse (TSL/2) with phase reversed, resulting in a total spin-locking time TSL. Finally, the $T1_\rho$-prepared magnetization is turned back to –z axis by the second α_x pulse, and the residual transverse magnetization is spoiled. Note that the image could still suffer certain artifacts when the 180° pulse is imperfect. The $T1_\rho$-prepared signal can be acquired with a routine acquisition scheme, such as TSE.

in terms of chemically exchanging protons so that information on specific constituents and pH can be derived [12,16].

In this work, *in vivo* $R_{1\rho}$ dispersion of human knee articular cartilage was studied at 3 T, and our preliminary results show pronounced $R_{1\rho}$ dispersion over practical locking fields. By analyzing the data using the Chopra model [17], proton exchange rates in cartilage were estimated to be predominately within the range of 1.0–3.0 kHz, and to vary within each subject. The exchange rates in cartilage appear to show larger variations with increasing age. To the best of our knowledge, this is the first quantitative analysis of $R_{1\rho}$ dispersion measurements in human articular cartilage *in vivo*, and may form the basis for more quantitative evaluations of cartilage disorders.

2. Materials and methods

This study was approved by the institutional review board and was HIPAA compliant. Written informed consent was obtained from all participants. Six healthy volunteers (one female and five males, ages 24–71 years) participated in this study. Imaging was performed on a Philips Achieva 3.0 T MR scanner with an eight-channel receive only knee coil (Philips Healthcare, Cleveland OH, USA). A series of T_2-weighted axial images was acquired first to locate the cartilage region of interest, with field of view 180 × 146 mm^2, pixel size 0.5 × 0.5 mm^2, slice thickness 4 mm. The subsequent $T_{1\rho}$ imaging followed this geometry. The $T_{1\rho}$ pre-pulse was implemented according to a previously established technique [18] and was designed to be relatively insensitive to B_0 and B_1 inhomogeneities. As shown in Fig. 1, this composite $T_{1\rho}$ pre-pulse includes five separate block pulses: the first hard pulse (flip angle $\alpha_x = 90°$) is applied about the x axis to tip the magnetization to the transverse plane, then followed by an on-resonance spin-locking pulse with a specific amplitude (corresponding to a specific spin-locking frequency, FSL) for one half of the spin-locking time (TSL). This is followed by a 180° refocusing pulse and a second half of the spin-locking pulse with phase reversed. Finally, the same α_x hard pulse along the x axis returns the $T_{1\rho}$-prepared magnetization to the –z axis, and then residual transverse magnetization is spoiled. The $T_{1\rho}$-weighted signal was subsequently acquired by a turbo spin echo (TSE) sequence with parameters: TR/TE = 3300 ms/10 ms, TSE factor = 15, NEX = 1, bandwidth = 233.7Hz/pixel. Five TSLs [= 2 ms, 22 ms, 42 ms, 62 ms, 82 ms] were combined into a single scan for $T_{1\rho}$ calculations, resulting in a total scan time of 5 min 16 sec. For the $R_{1\rho}$ dispersion data, the scan was repeated at different spin-locking amplitudes (frequencies) within the coil capacity and SAR limits: FSL varied from 0 Hz to 550 Hz in 50 Hz increments.

After data acquisition, a map of $T_{1\rho}$ at each spin-locking frequency was calculated by fitting the signal intensity at each pixel vs. TSL to a three-parameter mono-exponential model as follows:

$$S = S_0 exp\left(-TSL/T_{1\rho}\right) + C \tag{1}$$

where S is the acquired MR signal, S_0 is the signal intensity without locking pulse, and C is a constant. $R_{1\rho}$ maps were produced by taking the reciprocal of the $T_{1\rho}$ values. For whole cartilage analysis, an ROI (region of interest) was drawn manually on the entire articular cartilage region of the patellofemoral articulation, from which the overall $R_{1\rho}$ dispersion curve was extracted (mean cartilage $R_{1\rho}$ vs. FSL). Chopra *et al.* [17] derived an expression for $R_{1\rho}$ dispersion analysis: for a two-pool model (water pool and exchanging pool), the Chopra model can be simplified to [16]:

$$R_{1\rho} = R_2 + p_{ex}\left[R_{2ex} + \frac{k_{ex}\Delta w_0^2}{k_{ex}^2 + \Delta w_0^2 + w_1^2}\right] \tag{2}$$

where R_2 and R_{2ex} are the transverse relaxation rates of free water pool and exchanging pool (in our case of glycosaminoglycan (GAG) associated with proteoglycan molecules). Parameters p_{ex}, k_{ex} and Δw_0 denote the exchanging pool fractional population, exchange rate (from exchanging pool to water pool), and the chemical shift term respectively, and w_1 is the spin-locking field amplitude ($w_1 = 2\pi \times FSL$). Previous work from our laboratory has developed a novel approach utilizing the second derivative of the dispersion curve to measure exchange [10], which requires less data fitting and so is particularly useful in practical applications. Specifically, the minimum of the first derivative of the dispersion curve corresponds to the zero-crossing point of the second derivative, and to the inflection point of the original dispersion curve. At the inflection point, the following relationship can be derived [10]:

$$3w_1^2 = k_{ex}^2 + \Delta w_0^2, \text{i.e.}, w_1^2 = w_{ip}^2 = \frac{1}{3}\left(k_{ex}^2 + \Delta w_0^2\right) \tag{3}$$

Here $w_{ip} = 2\pi \times FSL_{ip}$ denotes the spin-locking amplitude (w_1) at the inflection point of the dispersion curve. Therefore, if the minimum of the first order derivative of the dispersion curve is identified, then the exchange rate can be simply derived according to Eq. (3):

$$k_{ex} = \sqrt{3w_{ip}^2 - \Delta w_0^2} \tag{4}$$

Here we assume that the dominant source of exchange is the hydroxyls in GAG with a chemical shift of 1.0 ppm [19], so at 3 T $\Delta w_0 = 2\pi \times 127 \times 1.0$ (Hz).