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

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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 3T 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 3T 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.

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Keywords

CEST; $T_{1\rho}$; $R_{1\rho}$ dispersion; Articular cartilage

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 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 3T, 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 3.0T 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 $180 \times 146 \text{ mm}^2$, pixel size $0.5 \times 0.5 \text{ mm}^2$, slice thickness 4mm. 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 $\alpha_x = 90^\circ$) 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 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=3300ms/10ms, TSE factor=15, NEX=1, bandwidth=233.7Hz/pixel. Five TSLs [= 2ms, 22ms, 42ms, 62ms, 82ms] were combined into a single scan for $T_{1\rho}$ calculations, resulting in a total scan time of 5min16sec. 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 following:

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

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]:

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

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 w_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]:

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

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):

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

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

In order to investigate local variations of $R_{1\rho}$ dispersion, cartilage from the lateral to medial side of the articulation was further subdivided into a few small regions. For each subregion, the dispersion curve was extracted and its first order derivative was then obtained. The inflection point of the dispersion curve and the exchange rate k_{ex} can be determined using the equation above. In addition, to evaluate the $R_{1\rho}$ change of a dispersion curve, the $R_{1\rho}$ difference between two selected FSLs (one was 100 Hz corresponding to the higher part of the dispersion curve, and another was 350Hz within the tail of the curve) was measured. All the data processing was based on custom Matlab (version R2013a) scripts.

3. Results

Fig. 2 shows one subject's knee structural image, as well as the corresponding color maps of $T_{1\rho}$ and $R_{1\rho}$ overlaid on the articular cartilage region.

Fig. 3A displays the $R_{1\rho}$ dispersion curves over the entire cartilage region for all six subjects. Marked $R_{1\rho}$ dispersion is observed within the spin-locking frequency range of 0-550Hz, although there are some local variations in the data estimates. Fig. 3B shows the subdivision of the cartilage: articular cartilage from the lateral to medial sides was subdivided into four regions: with one region (#3) centered upon the patellar ridge and femur trochlear groove, from which to the medial side was considered a region (#4), and to the lateral side was further subdivided into two regions (#1 and #2).

Fig. 4 shows an example of one subregion's dispersion curve and its first derivative. Spin-locking frequency at the inflection point, which corresponds to the minimum of the first

derivative curve, is $FSL_{ip} = \frac{w_{ip}}{2\pi} = 196.7$ Hz, so the estimated average exchange rate is $k_{ex} = 1986$ Hz using Eq. (4).

Table 1 summarizes the exchange rates over the subregions for all six subjects, which are also plotted in Fig. 5A. It is seen that the k_{ex} values are within the range of 882 – 2868 Hz, but larger variations are observed in the cartilage as age increases. For example, the absolute k_{ex} variations of the two oldest subjects are 1084Hz (71y) and 989Hz (52y) respectively, while those of the two youngest subjects are only 64Hz (24y) and 88Hz (29y). In Fig. 5B, $R_{1\rho}$ changes between two FSLs of the dispersion curve, i.e. $R_{1\rho} = R_{1\rho}(FSL:100Hz) - R_{1\rho}(FSL:350Hz)$, was plotted for all the subregions of the six subjects.

4. Discussion

Cartilage extracellular matrix consists predominately of water, the remainder being collagen fibers and proteoglycan molecules, in which proteoglycan is of particular interest for its GAG content. Early stages of cartilage matrix breakdown include the loss of proteoglycans, changes in water content, and molecular-level changes in collagen [20]. However, such early changes are often not detected by conventional MRI techniques, such as T_1 -, T_2 -, or proton density-weighted imaging. On the other hand, the biochemical environment of cartilage matrix includes a large concentration of amide (NH+), hydroxyl (–OH), and amine protons (–NH₂) that exchange with bulk water, which therefore provides an opportunity using exchange-sensitive MRI techniques to detect changes in cartilage composition before morphologic changes occur. Previous methods to detect biochemical markers within cartilage have included quantitative T_2 mapping, $T_{1\rho}$ imaging, CEST (chemical exchange saturation transfer) imaging, sodium imaging as well as dGEMRIC (delayed Gadolinium-enhanced MRI of cartilage). The dGEMRIC technique has been used to infer GAG distributions in cartilage in clinical studies [21,22], but it requires the administration of a contrast agent (a gadolinium chelate) and may be limited to certain subjects. While both quantitative T_2 and $T_{1\rho}$ values are potentially non-invasive biomarkers of cartilage degeneration, they have been reported to provide complementary information [23,24], with $T_{1\rho}$ values being more sensitive to the proteoglycan content, and T_2 mapping to water and collagen content [2,4]. As such, $T_{1\rho}$ relaxation may be a more sensitive indicator than T_2 for early cartilage degeneration detection [25].

Changes in the cartilage matrix environment, such as the loss of GAG, may be reflected in measurements of $T_{1\rho}$, especially at high fields when exchange contributes significantly to relaxation. $R_{1\rho}$ dispersion can in principle provide more complete characterization of tissue composition and the biochemical changes associated with pathology. Most tissues show little dispersion even at 3T, but where there are significant populations of exchanging protons such as proteoglycan hydroxyls, the dispersion of $R_{1\rho}$ may be dominated by exchange effects. Our data show that exchange processes are detectable within cartilage and the kinetics of that exchange can be measured. Changes in these exchange contributions are expected if there are alterations in the concentrations of exchangeable species or in the exchange rate, caused by changes in pH or other effects.

All the six participants in this study show clear $R_{1\rho}$ dispersion in knee cartilage, inferring that $R_{1\rho}$ analysis could be a useful addition to existing techniques for cartilage composition analysis. The derived exchange rate from the cartilage regions is largely in a range of 1.0 – 3.0 kHz (assuming GAG chemical shift 1.0ppm). We do not have data from other similar *in vivo* studies to compare, but one previous study (in bovine cartilage samples) reported that cartilage proton exchanges from NH and OH groups to water may dominate the low-frequency (0 – 1.5 kHz) water $T_{1\rho}$ dispersion [8]. Note that in the presence of several exchanging species, a population-averaged exchange rate will determine the precise nature of the dispersions. Even then the analysis may be adapted to derive an intrinsic characteristic of the tissue that may be useful if less specific to GAG.

One potentially interesting observation from our data is that k_{ex} in cartilage appears to have greater variation as age increases, though this needs to be confirmed in a large sample.

An additional comment on current clinical practice is also warranted. $T_{1\rho}$ imaging is often performed with a relatively high locking field e.g. 500Hz. If the $R_{1\rho}$ dispersion that we report is largely the result of chemical exchange, it follows that protocols that use locking fields of 500Hz are selectively removing the contribution of exchange, and thus their sensitivity to proteoglycans. It is the difference between low and high locking fields that reflects the specific contributions of exchanging protons, not the absolute values of T_2 ($\approx$ the low field value of $T_{1\rho}$) or the value at high field. This interpretation differs from some previous conclusions about the origins of $T_{1\rho}$ effects.

It should be noted that only a small number of participants were included in this study and their ages spanned a large range (24y - 71y). In addition, the inclusion criteria were solely based on subjects' claim of no knee pain symptoms. For more accurate statistical analyses, a larger sample size, and more rigorous inclusion criteria would be preferred. In addition, some dispersion curves exhibit unexpected variations, which may reflect limitations in signal to noise, artifacts caused by imperfect RF pulses, or off-resonance effects. Nevertheless, our results demonstrate the ability to measure $R_{1\rho}$ dispersion in cartilage *in vivo* and to extract specific parameters about exchange processes. These initial results suggest that $R_{1\rho}$ dispersion analysis may serve as a promising tool for detecting early cartilage degradation prior to morphologic change and in assessing the effectiveness of treatment. In a larger population study we anticipate correlating the variation of these parameters with disease and with normal aging.

Acknowledgements

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Fig. 1.

B_0 and B_1 insensitive composite pulse for $T_{1\rho}$ weighted imaging. Magnetization is tipped a flip angle α_x (90° and duration 0.5ms, 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 1ms) 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 $T_{1\rho}$ -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 $T_{1\rho}$ -prepared signal can be acquired with a routine acquisition scheme, such as TSE.

Fig. 2.

(A) A representative structural knee slice, and (B, C) show the $T_{1\rho}$ and $R_{1\rho}$ color maps overlaid on the cartilage region, which is under a spin-locking frequency of 350Hz. The color bars indicate the value range.

Fig. 3.

(A) $R_{1\rho}$ dispersion curves based on the entire cartilage regions of the six subjects, (B) Regional subdivision of the cartilage. Four regions were defined from the lateral cartilage to medial cartilage: the lateral side was subdivided into two regions (#1 in red, and #2 in yellow), followed by a region #3 (green) centered upon the patellar ridge and the femur trochlear groove, the medial cartilage was considered a region (#4, blue).

Fig. 4.

Upper panel: representative $R_{1\rho}$ dispersion curve from a subregion of one of the subjects. Data were interpolated by a cubic polynomial to increase the smoothness of the curve. Lower panel: the first order derivative of the dispersion curve. The minimum of the derivative curve corresponds to the inflection point of the dispersion curve (as denoted by the vertical dotted line).

Fig. 5.

(A) k_{ex} changes in cartilage for all the six subjects, note that greater k_{ex} variations are observed in older subjects than in younger subjects. (B) $R_{1\rho}$ change of the dispersion curve (between FSL=100Hz and FSL=350Hz) for all the cartilage subregions of the six subjects. Age/sex information is included, M - male, F - female.

Table 1

Spin-locking frequency ($FSL_{ip} = w_{ip}/(2\pi)$, Hz) at the inflection point and the estimated exchange rate (k_{ex} , Hz) on each subregion (ROI). Chemical shift of GAG is assumed as 1.0ppm. Age/sex information is included, M - male, F - female.

	ROI#1		ROI#2		ROI#3		ROI#4	
subject index	$w_{ip}/(2\pi)$	k_{ex}	$w_{ip}/(2\pi)$	k_{ex}	$w_{ip}/(2\pi)$	k_{ex}	$w_{ip}/(2\pi)$	k_{ex}
#1(24y,M)	177.1	1754.4	176.3	1744.2	181.7	1808.7	177.2	1755.0
#2(29y,M)	172.6	1700.4	172.2	1695.6	172.9	1703.5	179.5	1783.0
#3(37y,M)	221.7	2276.9	226.7	2333.9	226.7	2333.9	224.8	2312.1
#4(41y,M)	125.3	1105.1	126.8	1125.2	133.9	1218.7	174.8	1726.9
#5(52y,F)	194.1	1955.8	187.7	1879.8	273.6	2868.1	191.3	1922.9
#6(71y,M)	180.7	1797.3	109.4	882.9	195.0	1966.4	191.0	1919.3