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Transverse relaxation mechanisms in articular cartilage

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Abstract

Relaxation rates in the rotating frame ($R_{1\rho}$) and spin–spin relaxation rates (R_2) were measured in articular cartilage at various orientations of cartilage layer to the static magnetic field (B_0), at various spin locking field strengths and at two different static magnetic field strengths. It was found that $R_{1\rho}$ in the deep radial zone depended on the orientation of specimens in the magnet and decreased with increasing the spin locking field strength. In contrast, $R_{1\rho}$ values in the transitional zone were nearly independent of the specimen orientation and the spin locking field strength. Measurements of the same specimens at 2.95 and 7.05 T showed an increase of $R_{1\rho}$ and most R_2 values with increasing B_0. The inverse B_0 dependence of some R_2 values was probably due to a multicomponent character of the transverse magnetization decay. The experiments revealed that the dominant $T_{1\rho}$ and T_2 relaxation mechanism at $B_0 \leqslant 3$ T is a dipolar interaction due to slow anisotropic motion of water molecules in the collagen matrix. On average, the contribution of scalar relaxation due to rapid proton exchange in femoral head cartilage at 2.95 T is about 6% or less of the total $R_{1\rho}$ at the spin locking field of 1000 Hz.

Keywords: $T_{1\rho}$ and T_2 relaxation; Dipolar relaxation mechanism; Scalar relaxation mechanism; Articular cartilage

1. Introduction

It is believed that early degenerative disease of articular cartilage is associated with a loss of proteoglycans. Proteoglycans are responsible for the elasticity and stiffness of this tissue and their depletion makes cartilage prone to mechanical damage.

Although magnetic resonance imaging is one of the most common modalities used for the cartilage examination, detection of biochemical disorders in the early stages of cartilage degeneration, when the cartilage layer is still mechanically intact, is difficult. The difficulties relate to the fact that none of the parameters usually used to control the contrast in MR images, in particular native and contrast-enhanced T_1 and T_2 relaxation times, proton density or, less frequently, T_2* and magnetization transfer, are sensitive and specific enough to detect the loss of proteoglycans in the early stages of degeneration.

Several MR techniques have been reported which seem to be feasible for detecting the proteoglycan loss in articular cartilage. The delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) depends on the fact that proteoglycans contain a lot of negatively charged side groups. Thus, the negatively charged gadolinium complex ion is expelled more efficiently from a normal cartilage tissue than from the cartilage depleted of proteoglycans [1]. Sodium MRI detects the proteoglycan-depleted regions through a decreased sodium concentration in affected cartilage [2]. The decrease in the concentration of Na^+ ions is related to the lower number of negatively charged groups in proteoglycan-depleted cartilage.

Relaxation time in the rotating frame ($T_{1\rho}$) was reported to be a sensitive marker of the loss of proteoglycans in articular cartilage. An increase in $T_{1\rho}$ values in bovine patellae with decreasing proteoglycan concen-

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tration was observed at 1.5 T [3], at 2 T [4], and at 4 T [5–7]. On the other hand, Menezes et al. [8,9] found no correlation of the cartilage $T_{1\rho}$ with proteoglycan concentration.

The relation between $T_{1\rho}$ and the amount of proteoglycans has not yet been explained. In fact, $T_{1\rho}$ is a measure of longitudinal relaxation in a very weak magnetic field. Thus, low frequency relaxation contributions may be effective in this relaxation process. It has been shown that the transverse (T_2) relaxation in cartilage is dominated by dipolar interaction [10] due to anisotropic motion of water molecules in a fibrous collagen network. The same dominant relaxation mechanism was identified for the relaxation in the rotating frame [11]. However, other low frequency relaxation mechanisms might contribute substantially to the overall relaxation in the rotating frame. Duvvuri et al. [12] suggested that proton exchange between chemically shifted NH and OH groups of proteoglycans and the tissue water (a mechanism of scalar relaxation) might be an important relaxation mechanism in normal and pathological articular cartilage and could be responsible for the increase of $T_{1\rho}$ with decreasing amount of proteoglycans. The contribution of the chemical exchange to the relaxation rate in the rotating frame can be expressed as [13,14]

$$R_{1\rho,\mathrm{sc}} = 4\pi^2 p_\mathrm{A} p_\mathrm{B} (\nu_\mathrm{A} - \nu_\mathrm{B})^2 \frac{\tau_\mathrm{ex}}{1 + \omega_1^2 \tau_\mathrm{ex}^2}, \quad (1)$$

where p_A and $p_\mathrm{B} = 1 - p_\mathrm{A}$ are the mole fractions of hydrogen in the states A and B (e.g., –OH and H_2O), ν_A and ν_B are its resonance frequencies in these states, and $(\tau_\mathrm{ex})^{-1} = k_\mathrm{AB} + k_\mathrm{BA}$ is the sum of the rate constants of the forward and reverse reactions. Eq. (1) is valid if

$$|\nu_\mathrm{A} - \nu_\mathrm{B}|\tau_\mathrm{ex} \ll 1. \quad (2)$$

A feasible way of identifying relative contributions of various relaxation mechanisms in articular cartilage is to measure $T_{1\rho}$ relaxation times under different experimental conditions in different regions of the cartilage layer, i.e., in its deep portion with radial orientation of collagen fibers and in the intermediate portion with variable orientation of collagen fibers, respectively. Neglecting the contribution of high frequency processes, the dipolar relaxation contribution to the transverse (T_2) relaxation should be independent of the static magnetic field B_0 [15]. The dipolar contribution to the relaxation in the rotating frame depends on the amplitude of the spin locking field, $\gamma B_1 = \omega_1 = 2\pi\nu_1$, however, it should be also independent of B_0. On the other hand, the chemical exchange contribution to both T_2 and $T_{1\rho}$ is independent of the specimen orientation and is proportional to the square of the frequency difference between exchanging sites, and thus increases quadratically with B_0.

In this study we attempted to evaluate the relative importance of various relaxation mechanisms, in particular of dipolar and scalar relaxation, to the T_2 and $T_{1\rho}$ relaxation in articular cartilage by measuring the relaxation times at different amplitudes of the spin locking field ($T_{1\rho}$ dispersion), at different orientations of the specimens in the magnetic field, and at different static magnetic field strengths, namely at approximately 3 and 7 T. Knowledge of the relaxation mechanisms can clarify the role of the $T_{1\rho}$ relaxation time in monitoring proteoglycan depletion in articular cartilage.

2. Experimental

Seven human cartilage-bone specimens, one from the femoral condyle and six from femoral heads, were obtained from patients who had undergone knee and hip joint replacement, respectively. The specimens were approximately 14 mm × 5 mm × 5 mm in size, contained pieces of cartilage with grossly normal appearance, were wrapped tightly in polyethylene film and were stored in a humid atmosphere at about 0 °C. For the measurements, they were fixed in a covered plastic tube in the desired position, i.e., with the normal to the cartilage surface about 55°, about 0° and about 90° relative to B_0. Surfaces of the specimens were usually curved and they were not necessarily parallel with surfaces of subchondral bone. In addition, orientation of the collagen fibers in the radial cartilage zone might deviate from the ideal perpendicular orientation to the surface of the subchondral bone in various anatomical locations. Thus, the angles given above are only approximate and their estimated error limits are ±10°.

The experiments were performed at 23 °C. The specimens were measured in random order at 2.95 and at 7.05 T. The stability of one of the specimens was tested by repeated measurements of $T_{1\rho}$ at 2.95 T and the spin locking field of 1000 Hz after another 7 days of storing the specimen at 0 °C, and after another 6 months of keeping the specimen at −18 °C. The results of these measurements did not significantly differ from those measured on the fresh specimen.

The 2.95 T scanner was a MEDSPEC-DBX whole body tomograph (Bruker, Ettlingen, Germany) equipped with a 200 mT/m microimaging gradient system and a 35 mm inner diameter resonator. The T_2 relaxation times were obtained from a series of six single spin echo images obtained with a repetition time (TR) of 1.5 s, a FOV of 30 mm, a slice thickness of 1.7 mm, a matrix size of 128 × 96 and 1 or 2 averages. The $T_{1\rho}$-weighted images were achieved using a magnetization preparation spin locking pulse sequence [4] followed by a gradient echo sequence with TR = 1.5 s and an echo time (TE) of 3 ms, using the same geometrical parameters and the same number of averages. The ranges of TE in the T_2 measurements and the spin locking times in the $T_{1\rho}$ measurements were identical, in three specimens from 6

to 30 or 35 ms and in the remaining specimens from 10 to 80 ms. The spin locking field amplitudes in frequency units, ν_1, were calibrated in a separate pulse-and-acquire experiment, based on the lengths of rectangular pulses necessary to produce on-resonance inversion of magnetization.

The 7.05 T scanner was a Bruker AM 300 WB spectrometer equipped with a microimaging accessory. The maximum available gradient strength was 400 mT/m and the maximum ν_1 was 1000 Hz. Single spin echo images were measured using a slice thickness of 1.5 mm, a FOV of 20 mm, a matrix size of 128×128 and 2 averages. The repetition time and the ranges of echo and spin locking times were the same as for 2.95 T. The quality of the gradient echo images was poor at this field. Hence, magnetization prepared by the spin locking sequence was visualized by the spin echo sequence having the same parameters as used for the T_2 measurement, and the echo time of 10.8 ms. The length of the echo time in the imaging part of the protocol has no noticeable effect on the calculated $T_{1\rho}$ relaxation times. This was confirmed by repetition of two of these measurements using a smaller matrix size of 64×64 and a TE of 6.8 ms. Due to technical limitations of the 7.05 T scanner, only the $T_{1\rho}$ value at $\nu_1 = 1000$ Hz was measured. In all spin locking experiments, care was taken to adjust the spin locking frequency exactly on water resonance.

As illustrated in Fig. 1, regions of interest were outlined manually for each specimen in such a way that they comprised areas of the shortest relaxation time in the deep part of the cartilage layer, and the areas of the longest relaxation time in its superficial part. Since no experimental verification of orientation of the collagen fibers was available, the region of interest in the transitional zone could also contain portions of cartilage with slightly anisotropic angular distribution the fibers. Thus, some degree of orientation dependence can also be expected in the transitional zone.

For all series of images, the T_2 and $T_{1\rho}$ relaxation times were calculated using the Image Sequence Analysis tool included in the Paravision version 2.1.1 software package provided by the scanner manufacturer. Relaxation times were obtained by fitting mean signal intensities from the regions of interest to the equation

$$M(\tau) = A + B\exp(-\tau/T), \tag{3}$$

where τ is TE or the spin locking time, respectively, A is the mean of the absolute noise level taken from an empty region of the image, and B and T are fitted parameters.

3. Results

To obtain consistent results, almost identical measurement protocols at both magnetic fields B_0 and the same method of calculating relaxation times were used. Since the contributions of various relaxation mechanisms to the total relaxation rate are assumed to be additive, it is practical to consider relaxation rates ($R_2 = 1/T_2, R_{1\rho} = 1/T_{1\rho}$) rather than relaxation times. The series of R_2 and $R_{1\rho}$ relaxation rates obtained at 2.95 T in radial and transitional zones of the femoral condyle and one of the femoral head specimens, at different orientations of the specimens with respect to the static magnetic field and at different values of ν_1, are shown in Figs. 2 and 3. The relaxation rates obtained at the same orientations and ν_1 but at two different B_0 fields are summarized in Tables 1 and 2. The $R_{1\rho}$ relaxation rates at 2.95 T in the deep radial zone depended on the orientation of the cartilage specimens in the magnet and decreased with increasing spin locking field strength (Figs. 2A and 3A). The maximum dispersion was found at the angle of 0° and the minimum dispersion at 55°, whilst intermediate values were found at the angle of 90°. In contrast, the $R_{1\rho}$ values (except $R_2 = R_{1\rho}$ at $\nu_1 = 0$) in the transitional zone were nearly independent of the specimen orientation and the spin locking

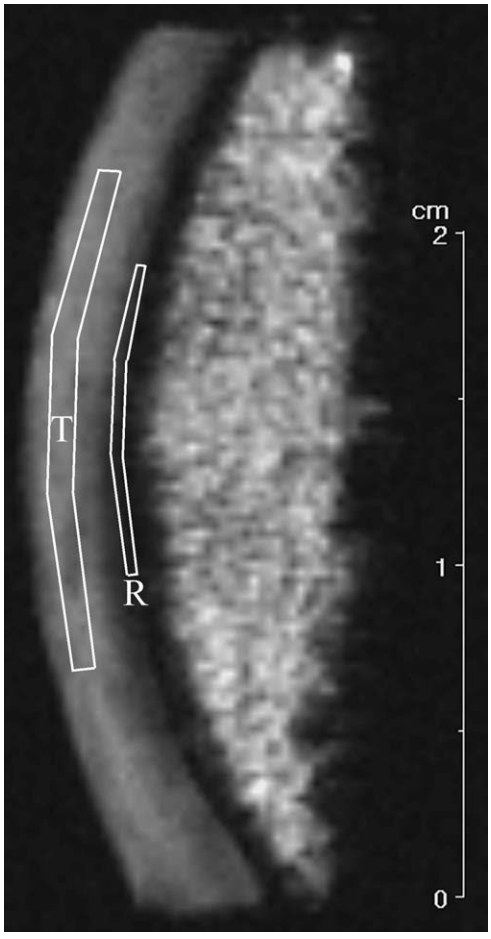

Fig. 1. A 7.05 T spin echo (TE = 10.8 ms) image of the cartilage-bone specimen from femoral condyle with selected regions of interest in the radial zone (R) and the transitional zone (T) of articular cartilage.

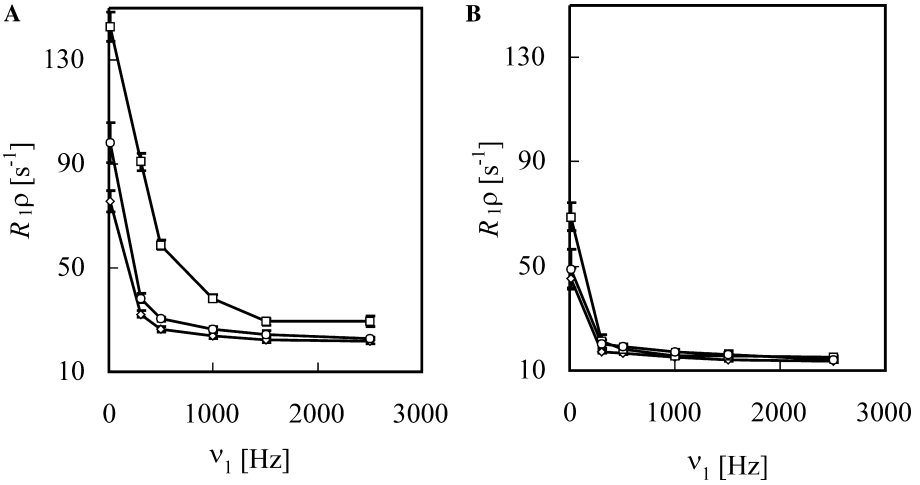

Fig. 2. Spin locking field dependence of $R_{1\rho}$ relaxation rates in the radial (A) and transitional (B) zones of cartilage from the femoral condyle ($R_2 = R_{1\rho}$ at $\nu_1 = 0$) at 2.95 T. Values obtained in the specimen orientated at angles of 55°, 0°, and 90° are denoted by diamonds, squares, and circles, respectively. The error bars denote standard errors of the calculated relaxation rates.

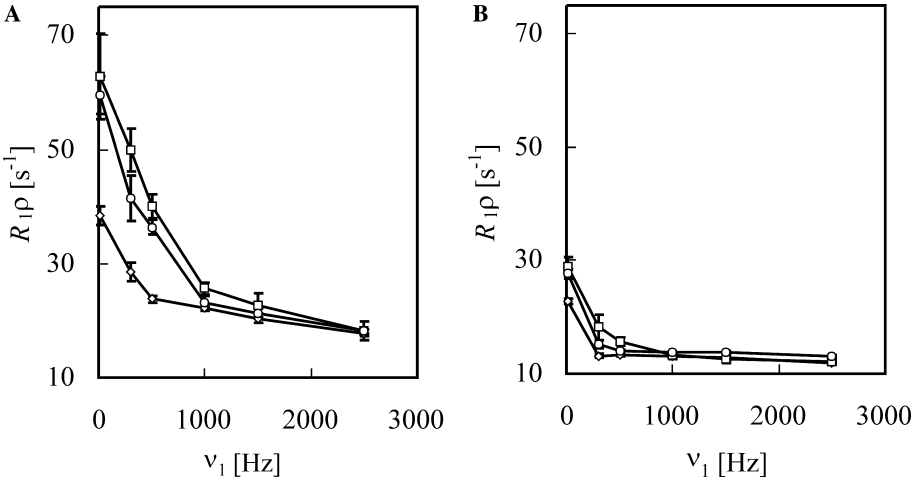

Fig. 3. Spin locking field dependence of $R_{1\rho}$ relaxation rates in the radial (A) and transitional (B) zones of cartilage from the femoral head at 2.95 T. Values obtained at angles of 55°, 0°, and 90° are denoted by diamonds, squares, and circles, respectively.

Table 1
Orientation and B_0 field dependence of R_2 and $R_{1\rho}$ at $\nu_1 = 1000$ Hz (in s^{-1}, ±standard error) observed in radial and transitional zones of cartilage from femoral condyle

Zone, orientation	R_2		$R_{1\rho}$		$R_{1\rho,sc}$	
	2.95 T	7.05 T	2.95 T	7.05 T	2.95 T	7.05 T
Radial, 55°	77 ± 4	80 ± 5	23.8 ± 1.1	38 ± 4	3.4 ± 1.5[a]	19.2 ± 8.7[a]
Radial, 0°	143 ± 6	114 ± 5	38.5 ± 1.0	48 ± 3	12%[b]	42%[b]
Radial, 90°	98 ± 11	97 ± 4	26.3 ± 0.8	50 ± 4		
Transitional, 55°	45 ± 4	25.6 ± 1.3	15.2 ± 0.6	25.0 ± 3.4	1.8 ± 0.2[a]	10.3 ± 1.3[a]
Transitional, 0°	69 ± 5	31.2 ± 1.1	15.9 ± 0.4	24.4 ± 3.0	11%[b]	42%[b]
Transitional, 90°	49 ± 7	26.3 ± 1.1	17.2 ± 1.0	25.0 ± 3.2		

[a] A mean value for all orientation of the specimen.
[b] $R_{1\rho,sc}/R_\rho$, i.e., the relative contribution of the scalar relaxation mechanism to the mean total relaxation rate in the corresponding cartilage zone.

field strength (Figs. 2B and 3B). The trends of $R_{1\rho}$ relaxation rates observed in other femoral head specimens were similar to those given in Fig. 3. However, with regard to various anatomic locations and/or possible pathological changes the ranges of the relaxation rates varied among the specimens.

While $R_{1\rho}$ magnetization decay was generally exponential at both magnetic fields, a nonexponential R_2

Table 2
Orientation and B_0 field dependence of R_2 and R_ρ at $\nu_1 = 1000$ Hz observed in radial and transitional zones of articular cartilage from femoral head

Zone, orientation	R_2		$R_{1\rho}$		$R_{1\rho,sc}$	
	2.95 T	7.05 T	2.95 T	7.05 T	2.95 T	7.05 T
Radial, 55°	38 ± 2	45 ± 3	22.2 ± 0.5	22 ± 3	0.9 ± 0.8[a]	5.3 ± 4.7[a]
Radial, 0°	63 ± 8	71 ± 5	25.6 ± 1.0	33 ± 4	3.8%[b]	19%[b]
Radial, 90°	60 ± 3	78 ± 6	23.2 ± 1.1	29 ± 2		
Transitional, 55°	23 ± 1	25 ± 0.4	13.0 ± 0.3	17.2 ± 1.5	0.6 ± 0.3[a]	3.5 ± 1.8[a]
Transitional, 0°	29 ± 2	26 ± 0.5	13.3 ± 0.2	16.6 ± 0.2	4.5%[b]	22%[b]
Transitional, 90°	28 ± 1	30 ± 0.5	13.7 ± 0.2	15.0 ± 1.2		

[a] A mean value for all orientation of the specimen.
[b] $R_{1\rho,sc}/R_\rho$, i.e., the relative contribution of the scalar relaxation mechanism to the mean total relaxation rate in the corresponding cartilage zone.

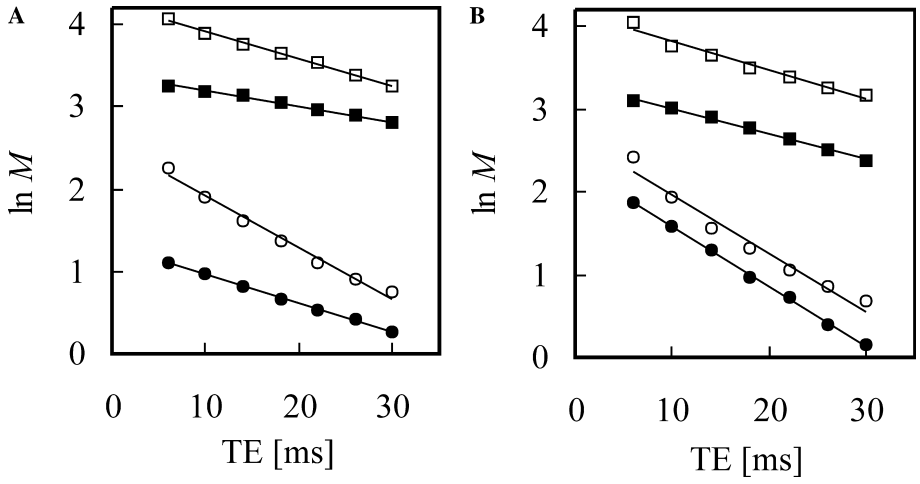

Fig. 4. T_2 decays of magnetization in the radial zone (circles) and in the transitional zone (squares) of articular cartilage from the femoral head orientated at the angle of 55° (A) and 0° (B), at 2.95 T (open symbols) and at 7.05 T (filled symbols). The data series were shifted arbitrarily along the ($\ln M$) axis.

decay of the magnetization was observed at 2.95 T which is demonstrated on semilogarithmic plots of the signal intensity versus TE observed in both zones of femoral head cartilage orientated at 55° (Fig. 4A) and 0° (Fig. 4B). The deviations from the linearity of the semilogarithmic graphs were best seen at the angle of 0° in the radial cartilage zone (open circles in Fig. 4B) while almost no deviations were observed at the angle of 55° in the transitional zone (open squares in Fig. 4A). At 7.05 T (filled symbols in Fig. 4), semilogarithmic plots of the magnetization decay were linear. It is obvious that for nonexponential decays of magnetization the T_2 values obtained using a monoexponential fit vary according to the range of echo times used for the calculation.

4. Discussion

Relaxation data measured in this study show trends that have already been reported in articular cartilage. In individual specimens, R_2 and $R_{1\rho}$ relaxation rates in the radial zone (Figs. 2A and 3A) were faster than those in the transitional zone (Figs. 2B and 3B), even under the magic angle. This finding is consistent with a number of previous R_2 studies at different field strengths in vitro [16–21] and in vivo [22,23]. A similar orientation dependence of $R_{1\rho}$ has been reported in bovine articular cartilage [11].

The fact that the relaxation in the rotating frame in the radial zone is highly efficient at the angle of the collagen fibers towards B_0 of 0°, less efficient at 90° and least efficient at the magic angle (Figs. 2A and 3A) suggests that the dominant relaxation mechanism in this zone is dipolar interaction due to slow anisotropic motion of water molecules in the collagen matrix. Despite the lack of dispersion and orientation dependence in the transitional zone (Figs. 2B and 3B), a significant contribution of the dipolar relaxation can also be expected due to the presence of variably oriented collagen fibers. However, the negligible dispersion of $R_{1\rho}$ between $\nu_1 = 300$ and 2500 Hz suggests that the components of dipolar relaxation, which are effective in the transitional zone, should have their correlation (i.e., reorientational) times shorter than those originated from densely packed fibers in the radial zone. The dominant contribution of the scalar relaxation due to exchange between OH and

NH protons with water, which has already been proposed by other authors [12], is highly improbable as it should cause significant $R_{1\rho}$ dispersion in the studied range of v_1 (cf. Eq. (1)).

The contribution of scalar relaxation to $R_{1\rho}$ can be estimated from the relaxation measurements at two different B_0 fields, i.e., at 2.95 and 7.05 T. The relaxation rates in the rotating frame at $v_1 = 1000$ Hz and at 7.05 T are slightly higher than those at 2.95 T (Tables 1 and 2). A similar but less pronounced B_0 dependence of $R_{1\rho}$ at $v_1 = 1590$ Hz, i.e., 18 s^{-1} at 9.4 T and 12 s^{-1} at 2.35 T, was recently reported in the rat brain in vivo [24]. It is reasonable to assume that the difference in the relaxation rates, $d = (R_{1\rho})_{7.05\,T} - (R_{1\rho})_{2.95\,T}$, is mainly due to scalar relaxation. Combination of the equation

$$(R_{1\rho,sc})_{7.05\,T} - (R_{1\rho,sc})_{2.95\,T} = d \tag{4}$$

and the equation

$$(R_{1\rho,sc})_{7.05\,T}/(R_{1\rho,sc})_{2.95\,T} = (v_A - v_B)^2_{7.05\,T}/(v_A - v_B)^2_{2.95\,T} = 7.05^2/2.95^2 = 5.71, \tag{5}$$

which can be derived from Eq. (1), enables calculation of the unknown quantities $(R_{1\rho,sc})_{2.95\,T}$ and $(R_{1\rho,sc})_{7.05\,T}$ as

$$(R_{1\rho,sc})_{2.95\,T} = d/4.71 \tag{6}$$

and

$$(R_{1\rho,sc})_{7.05\,T} = (5.71/4.71)d. \tag{7}$$

The calculated $R_{1\rho,sc}$ values in the transitional and radial cartilage zones of both specimens are given in Tables 1 and 2. The contributions of $R_{1\rho,sc}$ to the overall relaxation rates differ substantially not only in the radial and the transitional zone of the same specimen but also between the two specimens. This discrepancy could be due to inherent properties of the cartilage tissue, which originates from different locations. Other reasons for variability could be slight deviations in the specimen orientation in two different magnets, and errors in selecting exactly the same slice for imaging and in defining identical regions of interest at 2.95 and 7.05 T. Thus, mean values of $R_{1\rho,sc}/R_{1\rho}$ obtained on radial and transitional zones of all six measured femoral head specimens are more reliable parameters for evaluating contribution of the scalar relaxation mechanism in articular cartilage than the individual values. At 2.95 T, this parameter was calculated to be 6 and 3% in the radial and transitional zones, respectively. The corresponding values at 7.05 T were 27 and 15%. Using the quadratic dependence on the field strength, the extrapolated values of this contribution at 1.5 T would be about 2.9 and 1.1%, respectively. Thus, it seems that the scalar relaxation due to proton chemical exchange could be a relevant relaxation mechanism in the rotating frame only at the fields as high as 7 T. At 2.95 T and even at 1.5 T, which is the field strength typical for routine clinical scanners, this relaxation contribution is relatively unimportant.

R_2 values are considerably higher than $R_{1\rho}$s and have significant orientation dependence both in the radial and the transitional zones (Tables 1 and 2), which indicates a substantial contribution of collagen-related dipolar interaction with structures having very slow motion. The orientation dependence of R_2 was also found in the transitional zone (see also Figs. 2B and 3B) which confirms a certain degree of anisotropy in the selected regions of interest. In contrast to the reported increase of R_2 with increasing B_0 in articular cartilage [25] and in other tissues such as brain [26] and muscle [27], a decrease of R_2 with increasing B_0 was occasionally seen, especially in the femoral condyle specimen in which signal intensities at the TE values up to 30 ms were used for calculation (Table 1). This unusual behavior is probably related to the observed multicomponent decay of the transverse magnetization (Fig. 4), which has already been reported in cartilage [16,28]. The nonexponential R_2 decay was observed at 2.95 T but not at 7.05 T, where a rapidly relaxing component is obviously no longer detectable at TE $\geqslant$ 6 ms (Fig. 4). When signal intensities obtained at longer TE (up to 80 ms) are used for the calculation of R_2 at 2.95 T, as in the specimen of the femoral head in Table 2, the rapidly relaxing component contributes little to the calculated values and the same R_2 at both magnetic fields or the expected slight increase of R_2 with B_0 is observed. A detailed analysis of components of a spatially resolved T_2 magnetization decay in articular cartilage is difficult because signal intensities for short TE values (below 10 ms) are usually not attainable with the spin echo imaging technique. Moreover, measurement of a large number of images for obtaining the shape of the magnetization decay curve is extremely time consuming.

The origin of the rapidly relaxing component of R_2, which appears to be present at 2.95 T and which is probably too short to be detected at 7.05 T, is not clear. As it seems to be B_0 dependent, it should not be a component of dipolar interaction. A significant contribution of scalar relaxation due to extremely slow chemical exchange of aqueous protons with other exchangeable ones (with the τ_{ex} well above 1/300 s) is also improbable because of the orientation dependence of this component (Fig. 4). Thus, the most plausible relaxation mechanism is diffusion of water molecules in inhomogeneous fields produced by microscopic variations in tissue susceptibility [29,30]. Such an effect is, at least partially, suppressed either by a Carr–Purcell multiple echo train [30] or by spin locking. Together with scalar relaxation, this relaxation mechanism can also contribute to the increase of $R_{1\rho}$ with increasing B_0, particularly in the highly ordered radial zone of cartilage. The calculated $R_{1\rho,sc}$ and $R_{1\rho,sc}/R_{1\rho}$ values (Tables 1 and 2) should then be conceived as their upper limits.

In summary, the dominant relaxation mechanism in the rotating frame in cartilage at B_0 about 3 T or lower seems to be dipolar interaction, in particular its component associated with oriented collagen fibers. The contribution of scalar relaxation caused by exchange of OH and NH protons with water was found to be relatively small at these fields. Thus, it is improbable that this mechanism would be responsible for the previously reported correlation between $T_{1\rho}$ and the amount of proteoglycans in cartilage. The multicomponent character of the T_2 magnetization decay might also be responsible for discrepancies between the T_2 values obtained in vitro and in vivo, using different magnetic field strengths and different measurement protocols [31].

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