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Measurement of T_1 relaxation time of osteochondral specimens using VFA-SWIFT

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Abstract

Purpose—To evaluate the feasibility of SWIFT with variable flip angle (VFA) for measurement of T_1 relaxation time in Gd-agarose-phantoms and osteochondral specimens, including regions of very short T_2^* , and compare with T_1 measured using standard methods.

Methods— T_1 s of agarose phantoms with variable concentration of Gd-DTPA²⁻ and nine pairs of native and trypsin-treated bovine cartilage-bone specimens were measured. For specimens, VFA-SWIFT, inversion recovery (IR) fast spin echo (FSE) and saturation recovery FSE were used. For phantoms, additionally spectroscopic IR was used. Differences and agreement between the methods were assessed using non-parametric Wilcoxon and Kruskal-Wallis tests and intra-class correlation.

Results—The different T_1 mapping methods agreed well in the phantoms. VFA-SWIFT allowed reliable measurement of T_1 in the osteochondral specimens, including regions where FSE-based methods failed. The T_1 s measured by VFA-SWIFT were shifted towards shorter values in specimens. However, the measurements correlated significantly (highest correlation VFA-SWIFT vs. FSE was $r=0.966$). SNR efficiency was generally highest for SWIFT, especially in the subchondral bone.

Conclusion—Feasibility of measuring T_1 relaxation time using VFA-SWIFT in osteochondral specimens and phantoms was demonstrated. A shift towards shorter T_1 s was observed for VFA-SWIFT in specimens, reflecting the higher sensitivity of SWIFT to short T_2^* spins.

Keywords

T_1 relaxation; SWIFT; variable flip angle; cartilage; bone; Gd-DTPA²⁻

Introduction

The inherent information associated with T_1 relaxation times of tissues with extremely fast relaxing spins, such as parts of the musculoskeletal system or the lungs has been unavailable or difficult to measure. A swift and accurate three-dimensional (3-D) method for determining longitudinal relaxation time T_1 in all biological tissues, including those with extremely fast relaxing spins is highly desirable in a number of applications. Examples of applications include quantification of the accumulation of contrast agent into tissue in the delayed gadolinium enhanced magnetic resonance imaging of cartilage (dGEMRIC) technique (1), dynamic contrast enhanced (DCE) MRI (2), and a number of other quantitative measurements that require knowledge of the spin-lattice relaxation time T_1 (3). The T_1 relaxation times may differ within or between normal tissues (4,5) as well as provide significant information on disease processes. Diseases such as osteoarthritis (5,6), heart (7), liver (8) and brain disorders (3) manifest altered T_1 relaxation times of the affected tissues, promoting the use of quantitative measurement of relaxation properties.

Despite the obvious drawbacks in scanning time, standard inversion recovery (IR) and saturation recovery (SR) techniques for the measurement of T_1 relaxation time remain among the primary methods and are generally considered the “gold standard”. However, several other, typically faster methods have been introduced. Two of the most common techniques are Look-Locker (9) and variable flip angle (VFA) (10) techniques and their imaging implementations (11–14). Look-Locker is based on sampling the whole relaxation curve after inversion and VFA techniques rely on measuring the flip angle dependent signal at two or more different flip angles in a spoiled steady state. These methods allow rapid and reasonably accurate 3-D quantification of T_1 , but are, however, still limited by their acquisition delay (TE, echo time) in detection of the spin pools with very short T_2 / T_2^* relaxation times.

A number of tissues, such as cortical bone, lung parenchyma, tendons, menisci as well as the deep and calcified layers of articular cartilage are difficult to characterize using conventional pulse sequences due to the extremely short apparent transverse relaxation times (T_{2s} / T_2^* s) and signal decay in these tissues (15–20). To overcome this limitation, ultra short echo time (UTE) techniques have been recently applied for T_1 mapping in cortical bone, tendon and deep parts of articular cartilage (17,19,21). These methods have demonstrated significant potential for new findings making the previously undetected pools of short T_2 spins accessible (22); the full range of applications is yet to be determined.

Sweep imaging with Fourier transformation (SWIFT) is an emerging technique capable of capturing signal from the most rapidly decaying spin pools (23,24). Similar to UTE, SWIFT has contrast that depends on proton density and T_1 relaxation time of the imaged object (23). SWIFT differs from UTE techniques mainly by its use of RF frequency sweeping with constant gradient instead of gradient ramping for k-space encoding (23,25,26). Since the fully ramped radially ordered readout gradient is applied simultaneously with the high bandwidth gapped excitation pulse, SWIFT is inherently a 3-D method. The sensitivity to extremely short T_2 and the 3-D measurement geometry make SWIFT an attractive option for a number of situations where volumetric T_1 mapping is desirable, especially in context of

tissues that have limited or no detectable signal with conventional sequences. A recent study reported application of SWIFT with variable flip angles for measurement of T_1 relaxation time of aqueous suspensions of iron oxide nanoparticles (27).

The aim of the present work was to apply SWIFT with variable flip angles for the measurement of T_1 relaxation times in biological specimens with varying relaxation properties. The hypothesis of this study is that this setup allows measurement of T_1 for a broader range of spin populations as compared to the conventional spin echo techniques. To test this hypothesis, T_1 relaxation times were measured in a set of Gd-DTPA²⁻-doped agarose phantoms and further in trypsin-treated and intact cartilage-bone specimens using SWIFT, and compared to T_1 relaxation times as determined using different conventional techniques. An osteochondral tissue model with enzymatic treatment, both in the presence and absence of gadopentetate (Gd-DTPA²⁻) was used due to its wide range of T_1 relaxation times (~ 400 – 2000 ms (6)) as well as T_2 relaxation times (~ 1 – 80 ms (6,28)).

Methods

Phantoms

For phantom measurements, Gadolinium-doped agarose (2%-weight) in saline with different concentrations (0, 0.05, 0.1, 0.25, 0.5, 1.0 and 2.0 mM) of gadopentetate dimeglumine (Gd-DTPA²⁻, Magnevist, Bayer Schering Pharma, Berlin, Germany) were prepared. The Gd-agarose liquids were injected in to 5-mm NMR tubes before cooling into gel.

Specimens and enzymatic treatment

Bovine knee joints ($n = 9$) were obtained from the local abattoir (Atria Oyj, Kuopio, Finland) and specimens were harvested. In total, 18 samples ($n = 9 + 9$, osteochondral plugs, diameter = 7 mm) were prepared, two adjacent samples from lateroproximal parts of the patellae. One specimen from each pair was digested for 2.5 hours in 1 mg/mL trypsin (Sigma-Aldrich, St. Louis, MO, USA. Trypsin treatment primarily affects cartilage proteoglycans, cleaving the molecules and altering the properties of the specimens; treatment was specifically utilized to alter the relaxation times of the specimens.) at 37°C while the other sample remained in phosphate buffered saline (PBS) containing enzyme inhibitors (5 mM EDTA (VWR International LLC, West Chester, PA, USA) and 5 mM Benzamidine HCl (Sigma-Aldrich)). After the treatment, the samples were stored frozen at -20°C, acknowledging potential changes in the MRI characteristics of the specimens (29,30). Prior to the measurements samples were thawed in a water bath at room temperature, and after the MRI measurement they were rinsed with fresh PBS and frozen again. A subset ($n = 3 + 3$) of the samples was subjected to another thaw-freeze cycle and an extra measurement; the subset was immersed in 1.0 mM gadopentetate solution for 24 hours and re-measured again using a subset of the same protocol.

MRI measurements

The phantom tubes were individually scanned spectroscopically and simultaneously with imaging sequences. The scans were conducted at 9.4 T, using Agilent VnmrJ software version 3.1 and a quadrature volume transmit/receive radio frequency (RF) coil (Millipede,

Varian NMR Systems, Palo Alto, CA, USA). The T_1 relaxation times of the tubes were measured using inversion recovery sequence with TR of 12 s, 22 inversion times logarithmically spaced between 1.56 ms and 7.8 s, receiver bandwidth of 312.5 kHz with 20 000 points acquired. T_1 measurements with imaging scans were conducted using 1) saturation recovery fast spin echo (FSE) with an effective echo time of 5.0 ms, 2) saturation recovery FSE with effective echo time of 15.0 ms, 3) inversion recovery FSE with an effective echo time of 5.0 ms and 4) with VFA-SWIFT sequence. Relevant imaging sequence parameters for T_1 measurements are listed in Table 1. In addition to T_1 measurements, the T_2 relaxation times of the phantoms were measured using spin-echo prepared FSE, using 10 logarithmically spaced echo times between 7 and 120 ms.

Due to logistical reasons, the MR imaging experiments of the specimens were conducted with slightly different hardware, at 9.4 T (Oxford Instruments Plc, Witney, UK), coupled to a Varian console (VnmrJ 2.3A, Varian Inc., Palo Alto, CA, USA) using a 19 mm quadrature volume RF transmit/receive coil (RAPID Biomedical GmbH, Rimpf, Germany). The samples were immersed in perfluoro polyether (Fomblin®, Solvay Solexis, Milan, Italy) inside a PTFE (Teflon™) test tube with the normals of the articular surfaces along B_0 , at the center of the RF coil. T_1 relaxation times were measured using four different sequences: 1) saturation recovery fast spin echo (FSE) with an effective echo time of 5.0 ms (FSE_{TE5}), 2) saturation recovery FSE with an echo time of 15.0 ms (FSE_{TE15}), 3) inversion recovery FSE with an effective echo time of 5.0 ms and TR of 5.6 s (IR-FSE) and 4) with VFA-SWIFT sequence with an effective echo time of ~ 16 μ s (23). The two effective echo times, 5 and 15 ms were chosen for FSE as the shortest reasonably achievable TE and as a clearly longer, yet reasonable TE for the specimens. For SWIFT, a gapped HS1 pulse (24) was used for excitation, 96 000 views in 32 spirals with 3 averages and 256 complex points were acquired at 62.5 kHz bandwidth using a TR of 5.1 ms for each flip angle (23). Before the first spatial encoding, 1024 dummy projections were applied (duration = 1024 * TR = 5.22 s) and before each spiral, additional 32 dummy projections were applied to ensure steady state. After the 24-hour immersion in gadopentetate, the subset of specimens was scanned again using FSE_{TE5} and VFA-SWIFT sequences. Other relevant parameters of the sequences are presented in Table 1.

SWIFT images were acquired and reconstructed using CMRRpack written in VnmrJ (Agilent Technologies, Santa Clara, CA, USA) and LabVIEW (National Instruments, Austin, TX, USA) and Matlab (MATLAB R2011b, MathWorks, Natick, MA, USA) (<http://www.cmrr.umn.edu/swift/>) (23,24). For a better comparison, the intensity images of the inherently 3-D SWIFT sequence were re-calculated in the same 2-D imaging slice that was used in the FSE-based sequences using Matlab. Re-slicing was done by rotating the 3-D volume according to the slice positioning parameters (always in increments of 90 degrees, avoiding oblique re-slicing), averaging over 1 mm thickness and then resampling (using *imresize* in Matlab) and cropping the slice to the same in-plane resolution that was used for FSE-based sequences. For phantom experiments, averaging over a thickness of 4 mm matching FSE slice was done.

For imaging experiments, T_1 relaxation times were fitted pixel-by-pixel to the intensity images using mono-exponential two-parameter fitting for saturation recovery and three-

parameter fitting for inversion recovery with non-linear fitting. Spectroscopic T_1 relaxation times were fit using the maximum signal intensity of the spectra and the same three-parameter mono-exponential fitting as for imaging experiments. VFA-SWIFT T_1 relaxation times were fitted using pixel-by-pixel fitting using the Ernst equation (23). In specimens, relaxation time profiles over the depth of cartilage were calculated by averaging 1-mm wide columns from the articular surface to the cartilage-bone interface. Furthermore, for assessing region-wise relaxation times, sub-regions from the profiles were averaged corresponding to the histological collagenous zones (superficial zone of 5%, transitional zone of 20% and radial zone of 75% relative depth (31)). Additionally a region of interest (ROI) was defined in the subchondral bone. Signal to noise ratios (SNRs) were calculated for each of the source data images for each sequence in two separate hand-drawn ROIs consisting of bulk cartilage (i.e. a high signal region) and subchondral bone plate (a low signal region). SNR was calculated by taking the ratio of the mean of the signal intensities in a given ROI and the standard deviation of the signal of a ROI from the background. For comparison between the sequences, the SNR values were adjusted by dividing with the square root of the scan time effectively required to acquire the data (thus accounting for the differences in resolution and imaging time), termed SNR efficiency here. Finally, the SNR efficiency values were averaged over all the samples, treated and non-treated, excluding the data acquired after gadopentetate immersion. All the fitting and data analysis was performed in Matlab

Statistical analyses

To compare the different T_1 measurements methods, Pearson's correlation coefficients were calculated between the T_1 values measured for the phantoms. To evaluate the agreement between the methods, intra-class correlation coefficients were calculated between the methods. To test the differences in the measured relaxation times of the specimens between SWIFT and FSE-based sequences, the relaxation times were compared pair-by-pair, point-by-point, using Wilcoxon's signed rank test over the whole depth of the cartilage. Differences between the SNR efficiencies of the various measurements were evaluated using the Kruskal-Wallis test. Since meaningful statistical comparison was not possible between individual source images' SNRs due to different acquisition parameters, the differences were assessed after grouping the values for all the individual source images for the given measurement technique. For the average regional values, Wilcoxon's signed rank test was also applied. To further investigate the differences and concurrences between the methods, Pearson's linear correlation coefficients and intra-class correlation coefficients between the measured T_1 values of the specimens were also calculated. All the statistical analyses were performed in Matlab.

Results

The measured T_1 relaxation times of the gadopentetate-doped phantoms demonstrated the agreement of the methods (Table 2, Table 3). Pearson's correlation coefficients further indicated very strong and significant correlation between each of the different measurement methods, with p-values smaller than 0.0001 for each correlation. The intra-class correlation coefficients were all near one, indicating very strong agreement between the methods (Table

3). The T_2 relaxation times of the phantoms were between 32.8 ms (highest Gd-DTPA²⁻ concentration) and 71.2 ms, a range easily detectable for FSE.

Fitting of the T_1 relaxation times using the different methods was generally reliable in the area of cartilage, as exemplified in the fitting curves for single-point ROIs in one specimen (Figure 1). The fitting residuals (second norm of the difference between the fit and measured data), normalized with the maximum of the signal were on the same order for each of the methods in the two chosen data points in superficial and deep layers of articular cartilage (Figure 1).

T_1 relaxation times measured with the different techniques demonstrated qualitative (Figure 2), as well as quantitative differences (see below). Relaxation time maps qualitatively revealed the differences in the measured relaxation time, as well as in the success of the fitting procedure: in regions where the signal level equaled the noise level fitting was not attempted (presented in black color). All of the FSE based methods demonstrated such locations, mostly in the region of the subchondral bone plate but also within the cartilage, where the fitting either failed or signal was determined too low for fitting. However, with VFA-SWIFT, the T_1 was easily fitted in the same locations, as indicated by the smooth T_1 relaxation time map.

Depth-wise relaxation time profiles averaged over the sample groups (non-treated, $n = 9$ and treated, $n = 9$) revealed differences in the apparent T_1 relaxation times measured by the different sequences (Figure 3). Within the group of non-treated samples, T_1 relaxation time as measured by VFA-SWIFT was significantly shorter ($P < 0.01$) throughout most of the depth of cartilage compared to FSE-based measurement (Figure 3a). The difference between VFA-SWIFT and FSE_{TE15} could not be determined in the deeper part of cartilage where the fitting was unreliable for FSE_{TE15} and caused significant variation. In the same region, the difference between VFA-SWIFT and IR-FSE was non-significant. For trypsin-treated samples, the findings were similar; however, the failing of T_1 fitting for FSE_{TE15} was even more pronounced (Figure 3b).

In the sample subset ($n = 3+3$) equilibrated in gadopentetate for 24 hours, T_1 relaxation time was measured using only VFA-SWIFT and FSE_{TE5}. A clear difference was observed in the T_1 relaxation times between treated and non-treated, as measured by either FSE_{TE5} or VFA-SWIFT in approximately 70% of the tissue from surface towards bone interface (Figure 3c). In the deepest 30% of the cartilage the standard deviations were higher and the relaxation times between treated and non-treated were close to each other. Due to the small number of samples in this subset, no statistical comparison was performed. A representative case of Safranin-O-stained microscopy slices of the treated and non-treated specimen are shown along with T_1 relaxation time profiles (Figure 3d); the reduction in stain indicating loss of proteoglycans was also reflected in the T_1 relaxation time profiles after equilibration in gadopentetate.

Signal to noise ratios were calculated in two regions that raised interest in the relaxation time maps: the bulk of the cartilage and in the region of the subchondral bone plate. The SNR efficiencies of the source-images (i.e. different TR, TI or flip angle) were compared

after normalizing to the square root of the total time required obtaining the images. Statistical comparison of the average SNR efficiencies over all the individual source images revealed significant differences between the methods (Table 4). The benefit of the shorter echo times was clearly demonstrated especially in the low-signal region of the subchondral bone. Furthermore, difference in the SNR efficiency between the FSE-based methods followed the difference in the respective echo times, and a significant difference to SNR efficiency of SWIFT was noted (Table 4). In the cartilage region, the SNR efficiency of FSE_{TE5} was on average approximately 70% of that of SWIFT (Table 4).

The distributions of the T_1 relaxation times in full-cartilage ROIs in treated and non-treated samples demonstrated differences between the methods (Figure 4). Bi-modal distributions were observed in both sample groups using FSE-based methods, whereas a more uniform distribution was evident in the SWIFT-measured T_1 s. Similar to the relaxation time profiles in Fig. 3ab, a shift towards shorter T_1 relaxation times was seen at a shorter effective echo time.

There were significant and strong correlations between the T_1 relaxation times measured by different methods, but also deviation from and scatter about the line of identity (Figure 5). The strongest correlation was observed between FSE_{TE5} and IR-FSE with coefficient $r = 0.981$, $P < 0.001$ (Figure 5a). Regardless of the absolute differences in the measured relaxation times, each of the FSE-based methods correlated significantly with VFA-SWIFT-measured T_1 with correlation coefficients $r = 0.812$, $P < 0.001$ (FSE_{TE5}, data *without* gadopentetate), $r = 0.650$, $P < 0.001$ (FSE_{TE15}) and $r = 0.802$, $P < 0.001$ (IR-FSE). By including the data after the gadopentetate immersion (shorter T_1 relaxation times), the correlation between FSE_{TE5} and VFA-SWIFT improved slightly ($r = 0.966$, $P < 0.001$) (Figure 5b). Significant correlations were also observed between FSE using long echo time (TE = 15 ms) and the other FSE-based methods ($r = 0.801$, $P < 0.001$ and $r = 0.782$, $P < 0.001$ for FSE_{TE5} and IR-FSE, respectively). For FSE_{TE15}, ill-fitting data points had to be removed before correlation analysis (ie. data points corresponding to T_1 values of 0 s or > 100 s, which amounted to 6.3% of the data points). A systematic trend towards shorter T_1 relaxation times was observed for VFA-SWIFT. Deviation from the line of identity was further demonstrated by the intra-class correlation; the coefficients were 0.272 and 0.465 between VFA-SWIFT and FSE_{TE5} or IR-FSE, respectively, indicating poor to fair agreement. After including the data with gadopentetate, the intra-class correlation coefficient between FSE_{TE5} and VFA-SWIFT increased to 0.827, indicating very strong agreement.

Regional average T_1 values (Figure 6) demonstrated statistically significant difference when comparing the VFA-SWIFT measurement with all the other methods (for FSE_{TE15}, large variation in the deep cartilage prevented reliable assessment). In the ROIs consisting of the subchondral bone plate VFA-SWIFT showed shorter T_1 relaxation times as compared to FSE-based measurements (Figure 6).

Discussion

In the present study, the feasibility of measurement of T_1 relaxation time capturing the full spectrum of relaxing spins, including those with extremely short T_2 / T_2^* relaxation times in

articular cartilage and subchondral bone was investigated using the SWIFT sequence. The measurement proved feasible in this model system and correlated significantly with standard inversion recovery and saturation recovery methods. In the Gd-agarose phantoms with a T_2 range easily detectable by FSE, a good agreement between the methods was noted; only in the non-doped phantom with longest T_1 , VFA-SWIFT measured shorter relaxation time than the other methods. In specimens, measurement of T_1 relaxation time with VFA-SWIFT was more robust in regions with short T_2 and low signal as compared with conventional FSE methods, as was expected due to lack of signal. It was noted, that the SNR efficiency of SWIFT was superior in typical regions of low signal, such as subchondral bone, and allowed for robust estimation of the T_1 relaxation time also in these regions where FSE-based sequences may fail.

Articular cartilage is among the tissues that have T_2 relaxation times ranging from approximately 80 ms down to one millisecond or less (15,16). Moreover, the subchondral bone, especially the thin cortical bone plate, has extremely short T_2^* values in the sub-millisecond range (32) and is generally invisible with conventional pulse sequences. These short T_2^* values result in poor signal-to-noise ratios with conventional MRI and also hinder the accuracy of quantitative measurements using them. The results indicated that VFA-SWIFT could be used for 3-D measurement of T_1 relaxation time in articular cartilage, as well as in the subchondral bone. Although the use of dGEMRIC has recently received criticism due to the necessity of using gadopentetate contrast agent, recently associated with cases of nephrogenic systemic fibrosis (33,34), it has been established to correlate well with cartilage degeneration (1,6,35). Furthermore, in the clinical setup, the possibility of reliably acquiring full three-dimensional T_1 data in reasonable time could alleviate the limitations related to anisotropic resolution of imaging only few slices and significantly aid in evaluating the same regions in follow-up studies. In other situations, where 3-D volume is not required, however, time saving with 2-D slices over inherent 3-D volumetric acquisitions could be beneficial. As has already been demonstrated in UTE studies (17), as well as in a recent study on VFA-SWIFT (27), there are applications where sensitivity to extremely short T_2 / T_2^* is also required; this indicates that measurement of T_1 relaxation time with VFA-SWIFT, with improvements in scanning time via optimization of the sequence and parameters is also likely to have further use in demanding situations, such as compact bone or teeth (36) or in presence of SPIOs (27,37).

While the specimens of our study do not represent such extremes of rapid T_2^* relaxation as high concentrations of SPIOs for example, they do include regions of very short T_2 / T_2^* . T_1 relaxation time values measured for the bovine specimens are in line with the T_1 relaxation times reported in literature for approximately the same field strength (6,38,39). The effect of the trypsin treatment was observed in native T_1 , as measured by FSE-based methods, within approximately 50 to 60% of the tissue depth starting from the articular surface. A small subset of samples was subjected to gadopentetate immersion (dGEMRIC) and similarly changes were noted between treated and non-treated samples. After equilibration in gadopentetate, the difference in T_1 between treated and non-treated was also evident in VFA-SWIFT-measured T_1 . In all cases, the change in T_1 relaxation times can be attributed to the approximate depth of cartilage affected by the enzyme. The specimens equilibrated in gadopentetate were subjected to an additional freeze-thaw cycle. This extra

cycle, as well as the initial storage period at -20°C may have altered the relaxation characteristics of the specimens (29,30), however differences induced in native T_1 relaxation times over a scanning session, i.e. between the different measurement methods are assumed to be negligible.

A recent publication reported two major T_2 components, with corresponding different T_1 s for cortical bone specimens: bound water was found to have a T_1 of approximately 357 ms whereas more mobile pore water had a T_1 of about 551 ms (32). More significantly, the resulting net average T_1 for cortical bone in that study was approximately 412 ms. Another publication reported bi-component T_2^* relaxation also for articular cartilage with short (bound) T_2^* fractions reaching 21.2% in deep layers of cartilage (40). A recent study utilizing UTE reported T_1 relaxation time of the calcified zone of cartilage to be approximately 304 ms (41). A study using 2-D T_1 – T_2 relaxation spectroscopy demonstrated different T_1 s for different T_2 s in human cartilage; more specifically, at approximately 2.3 Tesla (100 MHz), T_1 peaks between 118 – 388 ms were reported for T_2 s of approximately 3 – 12 ms, at about 10% of the total intensity (42). Together these suggest that pools of differing T_1 exist in articular cartilage, especially in the deep layers as well. In our study, the T_1 relaxation time measured with FSE-based methods appeared longer at longer effective echo times (FSE_{TE5} vs. FSE_{TE15}), suggesting a T_2 -dependent pool of T_1 s as a potential source of differences in the observed T_1 s. A statistically significant reduction in the T_1 relaxation time measured with VFA-SWIFT was observed as compared to the FSE-based methods. The FSE measurements suggest that altering the detectable pool of spins, i.e. spins with different T_2 relaxation times, also the detected range of T_1 s is affected. Indeed, although there was a strong correlation between the measured T_1 relaxation times, the intra-class correlation coefficients indicated that the agreement between FSE-based and VFA-SWIFT-measured T_1 s was poor to fair – until adding the data points with Gd-DTPA²⁻. The results are concordant with the earlier reports: the VFA-SWIFT-measured T_1 , with its drastically shorter effective echo time was shifted towards shorter relaxation times, likely due to inclusion of signal from shorter T_2 spins (likely with associated shorter T_1 s) (32,42,43), while signal from long T_2 spins dominated the FSE-based measurements. The T_1 relaxation time distributions suggested a shift towards shorter detected T_1 relaxation times; this is specifically true for the region of the subchondral bone as seen in the data of Figure 6, in line with the previous study on cortical bone (32). In the phantoms, with a range of T_2 s easily detectable for FSE, the measured T_1 relaxation times were almost exactly the same for VFA-SWIFT, FSE-based measurements and spectroscopic inversion recovery, a result very similar to the previous VFA-SWIFT study investigating aqueous iron oxide nanoparticles (27). Magnetization transfer (MT) could also affect the different measured T_1 s in tissue specimens; however, the agarose phantoms would be expected to exhibit MT effects as well, yet no significant differences were observed between the measured T_1 s, further suggesting the possibility of short T_2 spins affecting the T_1 measurements in tissue specimens. The only point of difference was the phantom with no Gd-DTPA²⁻ added and longest measured T_1 , which was markedly shorter as measured by VFA-SWIFT compared to the other methods. A possible explanation for the difference in the T_1 of the non-doped phantom (the longest measured T_1) is insufficient coverage of the smallest flip angles, resulting in suboptimal fitting of the data.

In general the SNR efficiency of SWIFT was equal to, or greater than that of the FSE-based methods. While the SNR efficiency values were normalized with the scan time required for the same volume and are thus comparable, the scan time of the VFA-SWIFT was notably longer than those of the FSE-based methods in the present study; however providing vastly more data at the same time. In the region of the subchondral bone plate, known to have significantly shorter T_2^* relaxation times than cartilage and soft tissues in general, the SNR efficiency of SWIFT was significantly better compared to any of the conventional FSE measurements. In cartilage, the SNR efficiency of SWIFT was approximately equal to that of FSE_{TE5} with the source image of longest TRs and not vastly different from IR-FSE either (see online supplemental material). On average, the SNR efficiency of FSE_{TE5} was approximately 70% of that of SWIFT (see Table 4). It should be noted that the slight smoothing resulting from the resampling of the SWIFT source images artificially increased the SNR values by approximately 5% compared to the non-resampled images. However, for all data necessary for T_1 measurement, the grouped SNR efficiency was statistically different from SWIFT for both sequences. As a result of the poor SNR, the fitting of T_1 relaxation time in the deep tissue was unstable for FSE with the echo time of 15 ms.

Regardless of the demonstrated feasibility of measuring T_1 with VFA-SWIFT, there are several limitations in the present study. First and perhaps foremost is the lack of direct comparison to UTE; or variable flip angle SPGR –based methods. UTE sequence was not available at the time of the measurements; instead, FSE-based standard methods were chosen as a well-known gold-standard measurement of T_1 relaxation time. For articular cartilage this choice is generally valid, however in the case of short T_2^* spins, FSE may be presumed not to perform adequately. Previous studies have, however, shown the agreement between VFA-SPGR and FSE methods (14,44), as well as between VFA-SWIFT and VFA-SPGR in phantoms (27). Secondly, the choice of flip angle ranges and other imaging parameters will affect the observed signal as well as the reliability of the fitting. However, due to the inherent variation of T_1 in cartilage the selection of imaging parameters for generating T_1 weighting will always be a compromise and a range of flip angles should be preferentially covered. The estimation of T_1 relaxation time from the Ernst equation (23,45) is sensitive to B_1 homogeneity (i.e. precise knowledge of the flip angles). A simulation (data not shown) using a range of T_1 values and the same SWIFT acquisition parameters as in the experimental part of the study indicated an error in T_1 of approximately $\pm 20\%$ for an error of $\pm 10\%$ in the flip angle. However, the RF power calibration was very carefully performed for each scan and a high quality homogeneous volume coil was used (generally variation of less than 1% in B_1 is observed for similar specimens). If the actual flip angle would be lower than the assumed, the estimation of T_1 would result in relaxation time values smaller than actual. While potential of B_1 inhomogeneity could affect the T_1 measured using VFA-SWIFT, it could not explain the relative differences observed between the different methods in cartilage and in the region of subchondral bone. Instead, these changes may be ascribed to the differences in detected spin pools by VFA-SWIFT and FSE-based methods. A factor potentially affecting T_1 measurement of spins with extremely short T_2/T_2^* s is T_2/T_2^* decay during the pulse (46); however with the gapped SWIFT acquisition the effective echo time was in the order of 16 μ s (23) and considered to result in negligible decay in the specimens of the present study.

In future work further technical developments and optimizations will be sought. Most typically VFA techniques for T_1 measurement rely on acquiring data using only two distinct optimized flip angles (3,12,14,17,47) and it is very likely that a similar approach would work for VFA-SWIFT as well, significantly reducing the imaging time. Furthermore, signal averaging was used in the current study, but this could be removed without marked sacrifice in the image quality or SNR. Currently available two-angle VFA or Look-Locker-based sequences generally offer very favorable time efficiency, however lacking the sensitivity of SWIFT for short T_2 relaxation times.

Conclusions

It was demonstrated that VFA-SWIFT enables reliable quantification of T_1 relaxation time in an osteochondral tissue model for T_1 range of about 400 to 2000 ms. The SNR efficiency of SWIFT, after adjustment to account for differences in voxel size and imaging time, exceeded that of conventional FSE based methods, particularly in the region of the subchondral bone plate or calcified cartilage. Moreover, as SWIFT is inherently a 3-D method, the relaxation time maps obtained are three-dimensional (with isotropic resolution if desired), a significant benefit for any follow-up study or for a comprehensive assessment of a volume of a tissue, alleviating potential issues in re-aligning imaging slices. Differences in the measured T_1 relaxation times between VFA-SWIFT and conventional methods were observed, likely due to the broader pool of spins detected with SWIFT. The presented method lends itself to measurement of tissues previously undetectable and the possible applications are yet to be determined. Furthermore, the musculoskeletal system contains a multitude of tissues, such as cortical bone, entheses, tendons and ligaments with such short T_2^* relaxation times that SWIFT or a comparable ultrashort echo time technique is necessary for full visualization and assessment of relaxation properties. Other applications for T_1 mapping with VFA-SWIFT include robust 3-D measurement of T_1 relaxation time, or, similarly to the dGEMRIC technique, assessment of the concentration of contrast agents that may have a significant T_2 -shortening effect, such as ultra-small paramagnetic iron oxide nanoparticles or T_1 relaxation agents with markedly higher concentrations than typically feasible.

SNR efficiencies in two ROIs (region of subchondral bone plate and the bulk of cartilage) for each measurement and source signal image that were used for T_1 calculations. SNR efficiency was calculated by dividing the mean signal of an ROI by the standard deviation of the background signal, and further adjusted by dividing with the square root of the imaging time required for respective measurement. Acquisition parameters for each sequence are shown on the x-axis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Examples of T_1 relaxation time fitting for each of the methods in two single point ROIs in one specimen: superficial cartilage (asterisk *) and deep cartilage (circle ○). The dotted and dashed lines are the fits for superficial and deep ROIs, respectively. Residuals are second norm of the difference between the fit and the data, normalized with the maximum of the signal.

Figure 2.

T_1 relaxation time maps of representative case of treated – non-treated sample pair. Black indicates areas where SNR was insufficient for T_1 fitting (most notably present in FSE with TE = 15 ms). In the region of bone-cartilage interface (red triangle) and subchondral bone plate the T_1 fitting partially fails in all FSE based sequences.

Figure 3.

Average ($n = 9 + 9$) depth-wise T_1 relaxation times (ms) for each sequence for non-treated (a) and trypsin-treated samples (b). Solid line and symbols indicate average, shading shows $\pm$ SD. For FSE TE15, the profile breaks at locations where SNR was insufficient for T_1 fitting. Shorter T_1 relaxation times were measured using VFA-SWIFT; symbols (O, $\times$ and +) above the curves indicate locations of statistically significant difference (Wilcoxon signed-rank test, $P < 0.01$) between VFA-SWIFT and FSE TE15, TE5 or IR-FSE, respectively. A subset of samples ($n = 3 + 3$) was re-measured after 24 h immersion in 1.0 mM Gd-DTPA $^{2-}$ with FSE (TE = 5 ms) and VFA-SWIFT, demonstrating a drop in T_1 after trypsin treatment

(c). Light microscopy images of the safranin-O –stained sections indicated a small decrease in PG content with trypsin treatment (d).

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Figure 4.

Histograms of the measured relaxation times without contrast agent in full cartilage ROIs for non-treated ($n = 9$) and treated ($n = 9$) samples. Bi-modal distributions for FSE-based sequences were observed, whereas the T_1 -distribution as measured by VFA-SWIFT appeared more homogeneous.

Figure 5.

Correlations between a) FSE TE5 and IR-FSE and b) between FSE TE5 and VFA-SWIFT.

For (b), data after gadopentetate immersion was also measured and is included (pool of shorter T_1 s). Solid line shows linear fit between data points and the dashed line represents the line of identity. Without the gadopentetate data, the correlation between FSE TE5 and VFA-SWIFT was $r = 0.812$, $P < 0.001$.

Figure 6.

Regional average values for each of the measurement sequences and locations. Asterisk (*) denotes statistically significant difference compared to SWIFT in each subregion ($P < 0.01$, Wilcoxon signed rank test).

Table 1

Sequences and relevant parameters used for T_1 measurements.

Sequence	Sample	Varied parameter	Effective echo time	Scan time for T_1 map (min)	Resolution
FSE _{T1E5}	Phantoms	TR = 70, 80, 100, 160, 320, 640, 1280, 2560 and 5120 ms	5 ms	6.5	4 mm slice 312.5 × 312.5 μm ² in-plane
	Specimens	TR = 80, 160, 320, 640, 1280, 2560 and 5120 ms		11.5	1 mm slice 125 × 62.5 μm ² in-plane
FSE _{T1E15}	Phantoms	TR = 70, 80, 100, 160, 320, 640, 1280, 2560 and 5120 ms	15 ms	6.5	4 mm slice 312.5 × 312.5 μm ² in-plane
	Specimens	TR = 80, 160, 320, 640, 1280, 2560 and 5120 ms		11.5	1 mm slice 125 × 62.5 μm ² in-plane
IR-FSE	Phantoms	TI = 50, 100, 200, 400, 600, 800, 1200, 1600, 2400, 3200 ms	5 ms	16.5	4 mm slice 312.5 × 312.5 μm ² in-plane
	Specimens	TI = 50, 160, 520, 1680 and 5400 ms		30	1 mm slice 125 × 62.5 μm ² in-plane
VFA-SWIFT	Phantoms	FA = 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 26, 32 degrees	~ 16 μs (=1/BW, dwell time) (23)	121 (full 3-D)	250 μm ³ isotropic
	Specimens	FA = 3, 4, 5, 6, 8, 12, 20 and 24 degrees		185.5 (full 3-D)	117 μm ³ isotropic

Table 2

T_1 relaxation times measured by each method in the Gd-doped 2%-weight agarose phantoms.

Nominal Gd- concentration (mM)	Spectroscopic inversion recovery T_1 (s)	VFA-SWIFT T_1 (s)	FSE-TE5 T_1 (s)	FSE-TE15 T_1 (s)	IR-FSE T_1 (s)
0	2.52	2.13	2.50	2.44	2.40
0.05	1.60	1.59	1.48	1.46	1.41
0.1	0.81	0.84	0.80	0.79	0.77
0.25	0.47	0.68	0.63	0.62	0.59
0.5	0.24	0.31	0.29	0.28	0.28
1	0.15	0.16	0.16	0.16	0.15
2	0.08	0.10	0.09	0.09	0.09

Table 3

Correlation coefficients and intra-class correlation coefficients between the T_1 relaxation times measured using different methods in the Gd-doped 2%-weight agarose phantoms.

	VFA-SWIFT T_1	FSE TE5 T_1	FSE TE15 T_1	IR-FSE T_1
	$r = 0.990$	$r = 0.996$	$r = 0.997$	$r = 0.997$
Spectroscopic IR T_1	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	icc: 0.980	icc: 0.996	icc: 0.995	icc: 0.994
		$r = 0.989$	$r = 0.990$	$r = 0.988$
VFA-SWIFT T_1		$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
		icc: 0.984	icc: 0.987	icc: 0.987
			$r = 1.000$	$r = 1.000$
FSE TE 5 T_1			$p < 0.0001$	$p < 0.0001$
			icc: 1.000	icc: 0.998
				$r = 1.000$
FSE TE 15 T_1				$p < 0.0001$
				icc: 0.999

Table 4

Method-averaged SNR efficiencies (i.e. divided by the square root of the scanning time to allow comparison; numbers are not *actual* SNR values) for the different T_1 measurement techniques in bulk cartilage and subchondral bone ROIs. The number of measurements for each method indicates the total number of source images for all samples.

	Bulk cartilage	Subchondral bone
FSE TE5 ^(A) (n = 126)	4.6 ± 2.1^{BCD}	1.7 ± 0.8^{BCD}
FSE TE15 ^(B) (n = 126)	2.4 ± 1.6^{AC}	1.0 ± 0.5^{AC}
SWIFT ^(C) (n = 126)	6.5 ± 1.6^{ABD}	5.0 ± 1.0^{ABD}
IR-FSE TE5 ^(D) (n = 90)	3.0 ± 1.6^{AC}	1.1 ± 0.6^{AC}

A,B,C,D Statistical difference at level $P < 0.01$, respectively, Kruskal-Wallis post-hoc test.