TECHNICAL ASPECTS

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TARGET AUDIENCE

Basic and clinical researchers aiming to perform successful qMRI studies of articular cartilage.

OBJECTIVES

Several quantitative MRI (qMRI) mapping techniques are utilized as biomarkers for biochemical composition and structure of articular cartilage (1). Various technical aspects, however, affect the quality and reliability of qMRI data and interpretation. The objective of this talk is to address these factors both at general level and with regard to particular qMRI techniques in order to aid the researcher to pursue successful *in vitro* and *in vivo* experiments.

METHODS: GENERAL PRE-REQUISITES FOR SUCCESSFUL MEASUREMENT

The pre-requisites for any quantitative MRI measurements is a homogeneous B0 field, a coil setup yielding the intended flip angle and sufficient signal-to-noise ratio (SNR), and an appropriate scheme for data fitting.

Water-protein interactions occur at different timescales with different degree of binding (2). Consequently, qMRI parameters such as T1 relaxation time are dependent on the field strength used (3-5). Thus, the absolute relaxation time values at different field strength may not be directly comparable and could, essentially, probe different proton pools. Relaxation times are also dependent on the measurement temperature (2).

SNR of the experiment as well as the flip angle may vary between coils. For example, T2 relaxation times from articular cartilage is reported to vary between different type of coils and is dependent on image SNR (6,7). The accuracy of rotating magnetization to a particular flip angle can be improved by using adiabatic radiofrequency (RF) pulses even when the B1 field is inhomogeneous (8).

Computation of qMRI parameters always requires fitting of experimental data into a known equation. The method of fitting will affect the computed values. For example, the approach to pursue T2 relaxation time fitting (linear, nonlinear, weighted) causes bias of different order of magnitude (9). Noise-corrected fitting methods can further improve the estimation of relaxation times in articular cartilage (10). Multiple relaxing proton populations are present in cartilage and thus multi-exponential fitting may be required when acquisition delays are sufficiently short (11). When using commercial software it

is important to know, and evaluate if necessary, how the fitting and analysis is actually performed.

In vivo use of different qMRI techniques involves various considerations. Due to the finite thickness of cartilage high imaging resolution is desirable. Fast sequences are preferred when various qMRI parameters are mapped as well as to minimize patient motion. Correction for patient motion may be necessary. Automatic or manual coregistration of imaged slices is necessary in follow-up studies. Standardized analysis schemes would improve the comparison of results between different studies. A quality assurance protocol and regular phantom measurements are desirable for longitudinal qMRI studies (12). Unfortunately, not all sequences for mapping qMRI parameters are readily available for clinical systems.

METHODS: TECHNIQUE-SPECIFIC CONSIDERATIONS

T2 relaxation time mapping is one of the most popular qMRI techniques applied for evaluation of articular cartilage. T2 in cartilage is dependent on collagen content, collagen orientation and tissue hydration (1). The orientation of the collagen fibrils with respect to the B0 field considerably affects the measured relaxation time values, the so-called *magic angle effect*. Consequently, cartilage at different depth has a different T2 value. Thus, it is meaningful to evaluate different tissue zones separately. For *in vitro* experiments depth-wise profiles can be evaluated (13), while for *in vivo* imaging one is usually limited to dividing the tissue into superficial and deep halves (14). Due to both the magic angle effect as well as the topographical variation in biochemical composition of cartilage, different areas of different articular surfaces should be separately evaluated (14,15). Averaging relaxation times at different joint surfaces and depths is likely to decrease the sensitivity of qMRI techniques. Data may be affected by a non-ideal slice profile and stimulated echoes (16). Currently, the major MRI vendors provide clinical tools for T2 mapping of cartilage.

Delayed gadolinium enhanced MRI of cartilage (dGEMRIC) is a technique sensitive to the cartilage glycosaminoglycans (GAGs) of proteoglycans. Typically, T1 relaxation time is measured 60-120min after intravenous injection of Gd-DTPA(2-), also known as the *dGEMRIC index* (17). Gd-DTPA(2-) is assumed to distribute in inverse relation to the fixed charge density of GAGs in cartilage. When post-contrast T1 is only measured it is assumed that the pre-contrast T1 relaxation time (T1,pre) remains constant throughout the tissue and between subjects. There are contradicting views on whether the additional measurement of T1,pre and computing $\Delta R1$ (i.e. $1/T1Gd - 1/T1,pre$) would make the dGEMRIC experiment more sensitive to cartilage degeneration (18-20). Furthermore, since contrast agent is administered per patient weight, overweight increases the absolute concentration of contrast agent in cartilage, and correction is for BMI is required when there is considerable variation between BMI of subjects (21). While dGEMRIC is well validated *in vitro* (22,23), in the *in vivo* environment other factors besides GAG content, such as pharmacokinetics, affect contrast agent distribution in cartilage (24-26). For faster T1 mapping of cartilage new sequences have been validated and applied (27,28).

T1ρ relaxation, i.e. T1 relaxation in the rotating frame, utilizes a spin-locking field enabling the assessment of very slow molecular motion. For cartilage, T1ρ is sensitive to the GAG content (29,30). Due to SAR considerations, clinical implementation of the technique requires the use of low spin-lock fields that may not adequately lock the spins. T1ρ is also dependent on residual dipolar interaction from the collagen network (31), and its dependence on collagen network orientation appears to increase with

decreasing spin-lock fields (32). Traditionally, the spin-lock field is generated using a continuous-wave (CW) radiofrequency pulse. Alternatively, adiabatic pulses can be used in order to sensitize the method to a broader range of slow molecular motions as compared to CW methods (33). Besides T1ρ, new rotating-frame techniques namely adiabatic T2ρ and RAFF (relaxation along fictitious field) have been recently introduced and show promise for sensitive detection of cartilage degeneration (33-35).

Na-MRI enables the quantitation of sodium content in cartilage. This is essentially a reliable measure of cartilage GAGs since each negative charge associated with GAGs attract a sodium ion (36,37). For clinical implementation of sodium MRI specialized hardware is required due to the difference in resonance frequencies as compared to protons. Other limitations of Na-MRI include lower SNR, and consequently, low resolution images. Nonetheless, it is feasible for cartilage imaging on 7T human systems (38). For reliable results the measured sodium signal has to be calibrated and corrected for B1 inhomogeneity as well as for T1 and T2* relaxation which are short for sodium (39).

Diffusion weighted imaging (DWI) can be used to quantify water diffusion. The principal direction of water diffusion can be determined using diffusion tensor imaging (DTI). DTI of articular cartilage is feasible (40), and the techniques can be applied *in vivo* (41). The application of the method for articular cartilage is challenged by the relatively low degree of diffusion anisotropy as compared to, *eg.* the brain white matter. Since DWI is essentially a measurement of proton motion, patient movement is a potential source of error.

Chemical exchange saturation transfer (CEST) is a method to study the exchange between bulk water and macromolecules (42). In CEST, exchangeable protons bound to macromolecules are saturated, followed by saturation transfer to the free water pool. CEST contrast is evaluated by studying the asymmetry of the *z*-spectrum. For articular cartilage, the CEST contrast arises from the exchange between protons of free water protons and –NH or –OH groups of GAG macromolecules (43). The method is suitable for cartilage GAG quantitation, hence the name *gagCEST* for the particular application for cartilage. For a successful CEST experiment the signal separation between bulk water and macromolecule resonances has to be sufficient, and thus the technique benefits from using ultra-high fields (44). Correction for B0 inhomogeneity is crucial for successful quantitation of spectral asymmetry (45).

CONCLUSIONS

Accounting for general and method-specific aspects, as discussed above, will help one in pursuing successful experiments and correctly interpret qMRI data from articular cartilage.

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