High Field Strength 7T MSK Imaging: Technical Challenges

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1 Introduction

MRI of articular cartilage is becoming an increasingly useful tool for the assessment and monitoring of articular cartilage injury and degeneration. It is an excellent non-invasive research instrument and there is considerable potential for expansion of the role of MRI in clinical applications, especially for very high fields and the use of dedicated sequences. MRI techniques have been well described to evaluate morphologically articular cartilage and allow visualization of the cartilage surface, as well as its internal structure, thickness, volume and the adjacent subchondral region. In addition, several new techniques and the use of very high fields allow detection of biochemical changes that precede the morphological degeneration in cartilage.

2 MR techniques to asses biochemical properties of cartilage

The delayed gadolinium-enhanced MRI of cartilage **(dGEMRIC)** technique is based on the fact that GAG contains negatively charged side chains which lead to an inverse proportionality in the distribution of the negatively charged contrast agent molecules with respect to the concentration of GAG. Consequently, T_1 which is determined by the Gd-DTPA^{2-} concentration becomes a specific measure of tissue GAG concentration. The value of this technique and the possible clinical application has been repeatedly reported (1-6). Drawbacks of this technique are the necessity of a double dose of MR contrast agent which is now under critical review since systemic nephrogenic fibrosis was reported as a possible complication of standard MR contrast agents (7). Furthermore the delay between i.v. contrast administration and MR examination, necessary for full penetration of cartilage by the contrast agent, and the relatively time-consuming T1 mapping techniques (despite new developments which help to reduce scan time) complicate the examination procedure, lowers the patient compliance and is therefore less attractive for clinical application.

Relaxation time in the rotating frame ($T_1\rho$) has been reported to be a sensitive marker for the loss of proteoglycans in articular cartilage (8-10). $T_1\rho$ is a time constant that characterizes magnetic relaxation of spins under the influence of a radiofrequency field that is parallel to the spin magnetization. The resulting contrast is sensitive to the low frequency interactions between water molecules and their local macromolecular environment, such as GAG and collagen, which are the main constituents of the extracellular matrix in cartilage. Changes of $T_1\rho$ were observed in cartilage plugs chemically or enzymatically depleted of GAG but not in collagenase-treated tissue (11,12). In addition, it was reported that the dominant $T_1\rho$ and T_2 relaxation mechanism at $B_0 < 3T$ is dipolar interaction due to slow anisotropic motion of the water molecules in the collagen matrix.

Diffusion Weighted Imaging (DWI) is based on molecular motion that is influenced by intra and extra-cellular barriers. Consequently, it is possible to estimate biochemical structure and architecture of the tissue by measuring molecular movement (13,14). When based on spin-echo (SE) sequences, DWI is relatively insensitive to susceptibility effects, but diffusion weighted SE sequences require acquisition times that cannot be readily applied in clinical practice, and are very sensitive to bulk motion. Echo planar imaging (EPI)-based diffusion sequences are the current gold standard of DWI in neurological applications, but these suffer from image distortions (susceptibility artifacts) and from limitations in contrast and resolution (due to the long echo times required). Both renders them impracticable for imaging tissues with short T2, such as cartilage and muscles. Alternatively, diffusion imaging can be performed using steady state free precession sequences (SSFP) which provide diffusion weighting at relatively short echo times (15). This is achieved by the application of a mono-polar diffusion sensitizing gradient, which leads to a diffusion weighting of consecutive echoes (spin echoes, stimulated echoes and higher order echoes) under steady-state conditions. For the assessment of diffusion weighted images in articular cartilage, a three-dimensional steady state diffusion technique, called PSIF has been used. In order to assess diffusional behaviour of the cartilage semiquantitatively, the diffusion sequence protocol should consist of two immediately consecutive measurements with zero (0), and 75 $mT*ms*m^{-1}$ monopolar diffusion gradient moments for DWI, but identical imaging parameters. For evaluation, the quotient image (non-diffusion weighted / diffusion-weighted image) is calculated on a pixel-by-pixel basis. The feasibility of diffusion-weighted PSIF imaging after matrix-associated chondrocyte transplantation was demonstrated in vivo (16). The drawback of this technique is the semiquantitative character, since the b-values and diffusion weighting depend on several tissue and scanner parameters.

Sodium (^{23}Na) MR imaging has been described as a new technique for cartilage imaging (17, 18). According to the similar principle as described for dGEMRIC imaging, positive sodium ions are attracted by the negative fixed charged density (FCD) of the side chains of GAG. These electrostatic forces are responsible for a direct relationship between the local sodium concentration and FCD, and research has shown sodium imaging to be sensitive to small changes in GAG concentration (19, 20). The MR sensitivity for ^{23}Na is only 9.2% of the ^{1}H MR sensitivity, and the in vivo concentration is ~360 times lower than the in vivo water proton concentration. The combination of these factors results in a ^{23}Na signal which is approximately 4000 times smaller than the ^{1}H signal. In addition, the very short T2 relaxation time of ^{23}Na leads to a further reduction in signal intensity.

Recent advances in magnet technology, improved gradient performance, multi coil RF technology (parallel receive as well as transmit) may make sodium MRI clinically feasible on high fields systems. There is strong evidence that an ultra-high field 7T-MRI system will further improve sensitivity, specificity, and spatial and temporal resolution.

Although sodium MRI has high specificity and does not require any exogenous contrast agent, it does require special hardware capabilities (multinuclear), specialized RF coils (transmit/receive) and likely 3D-ultra short TE sequences.

Chemical Exchange Saturation Transfer (CEST) imaging

Balaban and his colleagues were the first to demonstrate that chemical exchange between labile protons of low concentration solutes and bulk water protons provides a sensitivity enhancement scheme known as CEST (21, 22). After this initial work on small solutes, Zhou et. al. showed that endogenous mobile proteins and peptides at very low concentration in biological tissue could also be detected via the bulk water signal (23). When saturation is applied at a particular frequency far from the water resonance, this saturation is transferred rapidly between solid-like matrix (rigid collagen) and free bulk water. Therefore, two possible molecular mechanisms are responsible for MT. The first pathway is through-space dipolar coupling from: 1) protons of the immobilized macromolecular phase, 2) protons of hydration water on the macromolecular surface, and 3) protons of the unbound bulk water. The second pathway is through the protons of some side groups (e.g –NH, -NH_2, -OH etc), which mix with water protons via fast chemical exchange. Interestingly, both proteoglycans and collagen macromolecules have exchangeable amide protons (~100mM) that exchange with bulk water. In addition, each proteoglycans unit also has three -OH protons (~300mM) that rapidly exchange with bulk water. Similarly, collagen has exchangeable amine protons (-NH_2). Recently Ling et. al. extensively studied and identified the potential metabolites in the cartilage via ^{1}H and ^{13}C one and two dimensional NMR spectroscopy as well as CEST methods (24). Furthermore, feasibility of the CEST method was also demonstrated in model systems, bovine cartilage and an in vivo human volunteer on a 3T clinical scanner (25) and 7T scanner (26).

6 References

1. Bashir, A., et al., Nondestructive imaging of human cartilage glycosaminoglycan concentration by MRI. Magn Reson Med, 1999. 41(5): p. 857-65.
2. Burstein, D., et al., Protocol issues for delayed Gd(DTPA)(2-)-enhanced MRI (dGEMRIC) for clinical evaluation of articular cartilage. Magn Reson Med, 2001. 45(1): p. 36-41.
3. McKenzie, C.A., et al., Three-dimensional delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at 1.5T and 3.0T. J Magn Reson Imaging, 2006. 24(4): p. 928-33.
4. Kimelman, T., et al., Three-dimensional T1 mapping for dGEMRIC at 3.0 T using the Look Locker method. Invest Radiol, 2006. 41(2): p. 198-203.
5. Bashir A, Gray ML, Burstein D. Gd-$DTPA^{2-}$ as a measure of cartilage degradation. Magnetic Resonance in Medicine 1996; 36: 665-673.
6. Bashir A, Gray ML, Boutin RD, Burstein D. Glycosaminoglycan in articular cartilage: in vivo assessment with delayed $Gd(DTPA)^{2-}$-enhanced MR imaging. Radiology 1997; 205: 551-558.
7. Ersoy H, Rybicki FJ. Biochemical safety profiles of gadolinium-based extracellular contrast agents and nephrogenic systemic fibrosis. Journal of Magnetic Resonance Imaging 2007; 26: 1190-1197.
8. Regatte RR, Akella SV, Wheaton AJ, Lech G, Borthakur A, Kneeland JB, et al. 3D-T1rho-relaxation mapping of articular cartilage: in vivo assessment of early degenerative changes in symptomatic osteoarthritic subjects. Acad Radiol 2004; 11: 741-749.
9. Akella SV, Regatte RR, Gougoutas AJ, Borthakur A, Shapiro EM, Kneeland JB, et al. Proteoglycan-induced changes in T1rho-relaxation of articular cartilage at 4T
10. Regatte RR, Akella SV, Lonner JH, Kneeland JB, Reddy R. T1rho relaxation mapping in human osteoarthritis (OA) cartilage: comparison of T1rho with T2. J Magn Reson Imaging 2006; 23: 547-553.

11. Pakin SK, Schweitzer ME, Regatte RR. 3D-T1rho quantitation of patellar cartilage at 3.0T. J Magn Reson Imaging 2006; 24: 1357-1363.
12. Regatte RR, Akella SV, Borthakur A, Kneeland JB, Reddy R. In vivo proton MR three-dimensional T1rho mapping of human articular cartilage: initial experience. Radiology 2003; 229: 269-274.
13. Miller KL, Hargreaves BA, Gold GE, Pauly JM. Steady-state diffusion-weighted imaging of in vivo knee cartilage. Magnetic Resonance in Medicine 2004; 51: 394-398.
14. Glaser C. New techniques for cartilage imaging: T2 relaxation time and diffusion-weighted MR imaging. Radiologic Clinics of North America 2005; 43: 641-653.
15. Deoni, S.C., T.M. Peters, and B.K. Rutt, Quantitative diffusion imaging with steady-state free precession. Magn Reson Med, 2004. 51(2): p. 428-33.
16. Mamisch, T.C., et al., Steady-state diffusion imaging for MR in-vivo evaluation of reparative cartilage after matrix-associated autologous chondrocyte transplantation at 3 tesla-Preliminary results. Eur J Radiol, 2008. 65(1): p. 72-9.
17. Reddy R, Li SC, Noyszewski EA, Kneeland JB, Leigh JS. In vivo sodium multiple quantum spectroscopy of human articular cartilage. Magnetic Resonance in Medicine 1997; 38: 207-214.
18. Reddy R, Shinnar M, Wang Z, Leigh JS. Multiple-quantum filters of spin-3/2 with pulses of arbitrary flip angle. Journal of Magnetic Resonance 1994; B104: 148-152.
19. Ling W, Regatte RR, Schweitzer ME, Jerschow A. Behavior of ordered sodium in enzymatically depleted cartilage tissue. Magn Reson Med 2006; 56: 1151-1155.
20. Navon G, Werrmann JG, Maron R, Cohen SM. 31P NMR and triple quantum filtered 23Na NMR studies of the effects of inhibition of Na+/H+ exchange on intracellular
21. Guivel-Scharen V, Sinnwell T, Wolff SD, Balaban RS. Detection of proton chemical exchange between metabolites and water in biological tissues. J Magn Reson 1998; 133: 36-45.
22. Ward KM, Balaban RS. Determination of pH using water protons and chemical exchange dependent saturation transfer (CEST). Magn Reson Med 2000; 44: 799-802.
23. Zhou J, Wilson DA, Sun PZ, Klaus JA, Van Zijl PC. Quantitative description of proton exchange processes between water and endogenous and exogenous agents for WEX, CEST, and APT experiments. Magn Reson Med 2004; 51: 945-952.
24. Ling W, Regatte RR, Schweitzer ME, Jerschow A. Characterization of bovine patellar cartilage by NMR. NMR Biomed 2007.
25. Ling W, Regatte RR, Navon G, Jerschow A. Assessment of glycosaminoglycan concentration in vivo by chemical exchange-dependent saturation transfer (gagCEST). Proc Natl Acad Sci USA 2008.
26. Krusche-Mandl I, Schmitt B, Zak L, Apprich S, Aldrian S, Juras V, Friedrich KM, Marlovits S, Weber M, Trattnig S. Long-term results 8 years after autologous osteochondral transplantation: 7 T gagCEST and sodium magnetic resonance imaging with morphological and clinical correlation. Osteoarthritis Cartilage. 2012 May;20(5):357-63