Advanced MR Methods at Ultra-high Field (7 Tesla) for Clinical Musculoskeletal Applications

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Abstract. *This presentation provides an overview of the initial clinical results of musculoskeletal studies performed at 7 Tesla, with special focus on sodium imaging, new techniques such as chemical exchange saturation transfer (CEST) and T_2* imaging, and multinuclear MR spectroscopy. Sodium imaging was clinically used at 7 Tesla in the evaluation of patients after cartilage repair procedures because it enables to monitor the GAG content, which is crucial for cartilage function, in non-invasive fashion. Sodium imaging and T_2* mapping allow insights into the ultra-structural composition of the Achilles tendon and help detect early stages of disease. Chemical exchange saturation transfer was, for the first time, successfully applied in the clinical set-up at 7 Tesla in patients after cartilage repair surgery. The potential of phosphorus MR spectroscopy in muscle was demonstrated in a comparison study between 3 and 7 Tesla, with higher spectral resolution and significantly shorter data acquisition times at 7 Tesla. Presented initial clinical studies demonstrate the potential of ultra-high field MR at 7 Tesla, with the advantage of significantly improved sensitivity for other nuclei, such as ^{23}Na (sodium) and ^{31}P (phosphorus). The application of non-proton imaging and spectroscopy provides new insights into physiology of healthy and diseased musculoskeletal tissues, particularly cartilage, tendons, and muscles.*

Keywords: 7 Tesla, Sodium MRI, gagCEST, T_2 Mapping, Phosphorus MR Spectroscopy, Musculoskeletal Radiology, MR Clinical Studies*

1. Introduction

By the end of the 1990s, high-field MRI at 3 Tesla had become the benchmark for routine clinical applications, as well as for clinical MRI research. The next important step was taken in the early 2000s and involved increasing the MRI field strength by another factor of approximately two, up to the 7 Tesla. During the last several years, the number of finalized installations or installations under preparation has increased to about 40 (0.2% of the currently installed MR systems). This rapid increase indicates the growing interest in ultra-high-field MRI in the bio-imaging community, brought to the fore by promising results with regard to morphological detail, as well as functional imaging capability.

Most clinical MR research centers operating at 7 Tesla primarily focus on neuroradiological applications, with only a few sites performing whole-body clinical research at 7 Tesla. This is because of the limited availability of suitable transmit/receive coils for 7 Tesla, the higher B_0 and B_1 heterogeneity related to the ultra-high field, as well as safety issues, particularly about 22 times higher specific absorption rate at 7 Tesla compared to 3 Tesla.

This presentation provides an overview of the initial clinical results of musculoskeletal studies performed at 7 Tesla, with a special focus on sodium imaging, new techniques such as

chemical exchange saturation transfer (CEST) and T_2* imaging, as well as multinuclear metabolic imaging or MR spectroscopy (MRS) in tissues such as cartilage, tendons, and muscles.

2. Subject and Methods

Sodium MRI at 7 Tesla - Sodium Imaging of Cartilage and Cartilage Repair

Proton MRI at ultra-high-field (7 Tesla and above) MR systems poses various challenges, including radiofrequency power deposition, increased chemical shift, susceptibility artifacts, homogeneity of RF coils, and changes in relaxation times, compared to lower-field clinical MR systems. These problems are much less pronounced in nuclei with a low gyromagnetic ratio, such as sodium (^{23}Na). However, a 3.8-fold smaller gyromagnetic ratio, a lower resonance frequency (^{23}Na: 78.6 MHz vs. ^{1}H: 297.2 MHz), a significantly shorter T_2 relaxation time, and a lower concentration of sodium nuclei (^{23}Na: 300 mM vs. ^{1}H: 110 M) result in sodium MR signal in articular cartilage that is 1/4,000–1/5,000 smaller than the proton MR signal. In order to achieve sufficiently high SNR (SNR>15), sodium MRI requires longer measurement times (15–40 min) and results in low-resolution images. Ultra-high-field MR systems can provide higher intrinsic ^{23}Na SNR and/or higher spatial/temporal resolution and improved contrast in the image [1, 2]. The MR relaxation properties of sodium nuclei in biological systems are dominated by quadrupolar interactions and result in very short longitudinal (T_1) and transverse relaxation (T_2) times. Due to the short T_1 of sodium, rapid averaging can be used in sodium MRI in order to improve the SNR in image. Many recent studies on sodium MRI of articular cartilage at 7 Tesla have used MR techniques with non-Cartesian k-space trajectories, such as 3D radial [3-7] or 3D cones [2], which enable ultra-short echo time (UTE) acquisition.

Sodium MRI offers many potential clinical applications. Sodium content measured by ^{23}Na MRI has been shown to be proportional to glycosaminoglycan (GAG) content in articular cartilage [8, 9]. Sodium MRI can be used to detect early signs of cartilage degeneration or injury before morphological changes can be detected by proton MRI [10]. Sodium MRI may enable the noninvasive in vivo evaluation of disease-modifying treatments for osteoarthritis (OA) and methods for cartilage repair. Affecting millions of people, OA is the most common degenerative disease of the musculoskeletal system

Sodium Imaging of Tendons

Degeneration of the Achilles tendon leads to thickening of the tendon [11]. Tendinopathy is also accompanied by disaggregation of the microfibrillar bundles due to the greater quantities of water and proteoglycan [12]. Almost double the GAG content was observed in pathologic tendons in studies using biochemical assays [13]. In a study by Juras et al., the feasibility of sodium magnetic resonance imaging for the diagnosis of Achilles tendinopathy was investigated at ultra-high field [14]. Their cohort comprised 20 healthy volunteers with no history of pain in the Achilles tendon and 8 patients with clinical findings of chronic Achilles tendinopathy. The study found that the mean bulk sodium SNR in Achilles tendon was 4.9±2.1 in healthy control subjects and 9.3±2.3 in patients with Achilles tendinopathy. This study not only showed a statistically significant increase in sodium SNR in patients with Achilles tendinopathy, compared with healthy tendons, but also revealed abnormal sodium signal values in the whole tendon, as well as morphologically focal abnormalities with focal thickening. Sodium signal values may correspond to GAG content in the Achilles tendon, which, as shown in in vitro studies, is increased with tendinopathy.

T_2 Mapping of the Achilles Tendon at 7 Tesla*

MRI is quite frequently used for morphological evaluation of the Achilles tendon (AT). It was successfully employed to detect partial or total tendon rupture or even the degenerative

processes in the tendon tissue. Most imaging findings are related to the pathologic processes of tendon degeneration and repair progression [15]. In addition to the morphological MRI evaluation (imaged predominantly by T_2*-weighted sequences), the quantitative MRI analysis of tendon tissue may be helpful in identifying the early pathological changes in the tissue. Quantitative analysis of the relaxation or diffusion constants [such as T_1, T_2*, $T_1\rho$, and apparent diffusion coefficient (ADC)] of the AT may provide additional information about the overall condition of the tendon. On conventional high-field MR systems (1.5–3 Tesla), several parameters have been investigated as prospective markers for Achilles tendon degeneration, such as T_2* [16], $T_1\rho$ [17], ADC [18], magnetisation transfer [19], or spectroscopically, even T_2 [20]. Using spectroscopic methods, it was shown that the T_2* decay in the Achilles tendon is a multicomponent process [21]. However, with clinical sequences, it is difficult to acquire signal from the second, third, and fourth components, since these have a small component ratio. The first component has the largest ratio, but it is in the submillisecond range, and thus, can barely be acquired with conventional sequences. In general, MR imaging of rapidly relaxing tissues, such as tendons, menisci, ligaments, and bones, is rather difficult with clinical sequences. Recent developments in new hardware and sequence design allow the acquisition of a signal directly from these tissues. Moreover, ultra-high field provides a substantial increase in the SNR [1]. The 3D-UTE sequence provides the ability to detect MR signal from a large variety of rapidly relaxing tissues and materials, including tendons. Juras et al. used a 3D-UTE sequence at 7 Tesla to estimate T_2* in tendons in order to investigate the potential feasibility of using this parameter as a marker for Achilles tendinopathy [22].

Chemical Exchange Saturation Transfer (CEST) at 7 Tesla

Saturation transfer (ST) is a commonly used technique in nuclear magnetic resonance (NMR) [23] and has been proposed as a method for the direct detection of chemical exchange between bulk water protons and protons bound to solutes [24]. The resultant MR imaging scheme is referred to as CEST MRI [25, 26]. The basic principle of CEST imaging is a reduction in bulk water MR signal after off-resonant spins are selectively pre-saturated by radiofrequency (RF) irradiation and then undergo chemical exchange with bulk water protons [27]. The hydroxyl and amide protons of glycosaminoglycans (GAG) provide exchange properties that render them principally suited for CEST experiments [28]. In vitro experiments at 11.7 Tesla demonstrated that CEST imaging can be used as a biomarker for cartilage GAG content (gagCEST) in bovine cartilage samples [29, 30]. However, GAG–OH protons resonate at frequency offsets ($\Delta\omega$) of only 1 and 1.5–2 ppm downfield from bulk water, and rate constants of chemical exchange (k) can be on the order of 1,000 s^{-1} [30]. At a magnetic field strength of 3.0 T, the $\Delta\omega$ of hydroxyl protons corresponds to a separation from bulk water of 128 Hz and 192–256 Hz in frequency units. As a consequence, radiofrequency power intended to selectively saturate –OH resonances simultaneously attenuates the bulk water signal (RF spillover), which impairs quantification of the CEST effect at 3.0 T. At higher fields, i.e., with increasing frequency differences, the RF spillover decreases, making ultra-highfield strengths, such as 7.0 T, ultimately favorable for CEST experiments.

After the introduction of the gagCEST approach, further studies have been performed with animals and humans to assess the feasibility of gagCEST imaging in vivo [31-33], and several imaging sequences for fast and reliable detection of gagCEST effects have been proposed [31, 34-36]. Most techniques are based on multiple image acquisition with pre-saturation at different offset frequencies ($\Delta\omega$). The remaining bulk water signal (MSat), normalised to a reference (MRef), is then plotted against the RF presaturation offset (z-spectrum).

Despite the requirements mentioned above, gagCEST imaging is a valuable tool for the non-invasive assessment of GAG content in vivo. A recent study demonstrated that gagCEST can

be used to reliably detect GAG in the knee cartilage of patients who had undergone cartilage repair surgery [37]. This study was conducted at 7.0 T with a 3D GRE-based measurement technique, and ^{23}Na MRI was used as a reference for GAG measurements. Moreover, the potential of gagCEST for GAG evaluation in intervertebral discs at 3.0 T has been demonstrated [38, 39]. Given the results from the latter studies, it seems possible that gagCEST can also be used to detect cartilage GAG content at 3 Tesla, which indicates the potential of this approach for use in the clinical routine. The main strength of gagCEST compared to other GAG-sensitive imaging techniques, such as dGEMRIC and sodium imaging, is the relatively short acquisition time, which covers the entire volume of a knee joint in approximately 10 min [37], and gagCEST does not require administration of contrast agent and can easily be implemented into a standard imaging protocol.

Metabolic Imaging of Muscles at 7 Tesla

Another MR method that has the potential to become increasingly important in clinical musculoskeletal MR at 7 Tesla is metabolic imaging or MR spectroscopy (MRS). MRS is a powerful noninvasive tool for the investigation of metabolite concentrations and studies of bioenergetics that could otherwise only be assessed by invasive muscle biopsies [40]. MRS provides information on a cellular level beyond the anatomical information assessed by standard imaging methods and aids in the understanding of various lesions [40-42], clinical diagnosis [42, 43], and treatment monitoring [44, 45].

The availability of fast and robust MRS methods at 7 Tesla will provide new opportunities for imaging a large clinical spectrum of musculoskeletal diseases, such as mitochondrial disorders [46, 47], glycolytic defects [48], systemic diseases affecting muscle metabolism [42], muscle injury [49], or diabetes [50, 51], for diagnostic use [42, 43], therapy monitoring [44, 45], and clinical research [42].

3. Conclusions

In conclusion, initial clinical studies demonstrate the potential of ultra-high-field MR at 7 Tesla, with the advantage of significantly improved sensitivity for other nuclei, such as ^{23}Na (sodium) and ^{31}P (phosphorus). This will provide new insights into physiology of healthy and diseased musculoskeletal tissues and the metabolism of muscle, and will, therefore, provide new in vivo clinical applications.

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