A Novel pH-Dependent Magnetic Resonance Imaging (MRI) Method for the Non-Invasive Detection of Discogenic Pain

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Disclosures:


\textbf{Introduction}: Intervertebral disc (IVD) degeneration is often associated with back pain. However, although degenerate discs can be identified using MRI, they do not always cause pain. Therefore, if a patient with lower back pain has several degenerate discs, further examination is required. Standard procedures include discography, which is a painful, invasive procedure that uses intradiscal injections to apply pressure to the suspected discs and reproduce the patient’s discogenic pain. Apart from being painful, this procedure entails severe effects on the examined discs including accelerated disc degeneration, disc herniation, loss of disc height, and damage to the adjacent endplates. In addition, the diagnosis is subjective to variations of the placement of the needle, pressure exerted, and anesthesia. Therefore, an MRI method for non-invasive detection of painful degenerative discs is highly desirable. Such a method will spare patients from the pain and prevent the adverse effects that are currently linked to discography. Attempts have been made to find a correlation between discogenic pain and a specific biomarker that can be visualized using MRI. They relied either on structural changes in the disc and its surrounding tissues, or on changes in proteoglycan (PG) and lactate within the disc. Yet, these methods were either tested on a relatively small number of patients only or are challenging to use on clinical imaging systems. It has been postulated that the acidic environment in the disc is a major player in discogenic pain. Therefore, it was hypothesized that pain-causing discs could be diagnosed by detecting low pH levels noninvasively using MRI. Several studies have attempted to evaluate pH using MR spectroscopy (MRS) or CEST as a measure for detecting low back pain. However, in vivo MRS is challenging because of low SNR, physiological motion, and bone susceptibility induced line broadening, making the assessment of lactate imprecise. A recent study found a non-linear dependence of the CEST effect of GAG on pH in IVD specimens. However, the study was performed ex vivo at 7.0T and the effectiveness of the method on clinical MR systems (1.5 or 3.0T) has not been shown. Hence, at present, there is no reliable and accurate non-invasive diagnostic test to effectively detect discogenic pain. We hypothesized that the ratio of R1p dispersion and -OH (hydroxyl proton) chemical exchange saturation transfer (RROCS) is correlative to pH levels in IVDs and can accurately detect painful degenerative discs.

\textbf{Methods}: We tested the hypothesis using numerical simulations, glycosaminoglycans (GAG) phantoms, porcine spine explants and human patients suffering from low back pain. To quantify the exchange rate of GAG phantoms under different pH levels, GAG phantoms with concentration of 150mM were prepared from chondroitin sulphate A (Aldrich-Sigma) in PBS and their pH levels were titrated to 7.04, 6.68, 6.40, and 6.00. To verify the dependence of CEST and R1p dispersion on GAG concentration and pH at 3.0T, samples of GAGs with concentrations of 50, 100, 150 and 200mM were prepared and their pH levels were titrated to values around 7.2, 7.0, 6.7, 6.3 and 6.0 respectively. Next, 0.05mL Na-Lactate (Sigma Aldrich) with different concentrations was injected into the nucleus pulposus of porcine lumbar discs, ex vivo. Actual tissue pH level was then measured using a custom-made tissue pH probe (Warner Instruments) by inserting the electrode into the center of the disc. Finally, four male (ages 42.8±18.3) and two female (ages 55.5±2.1) subjects with chronic low back pain (> 6 months) due to moderate degenerative disc disease at any lumbar level from L1 to S1 that were scheduled for provocative discography, were recruited from the Cedars-Sinai Medical Center. Recruiting criteria included: unresponsiveness to conservative therapy for at least 3 months (including physical therapy), low back pain of at least 40 mm on a 100 mm Visual Analog Scale with either leg pain less than back pain or nonradicular of origin, lumbar disc pathology having a modified Pfirrmann score of 3, 4, 5 or 6, with a herniation of no greater than 6 mm and no neurological compression, and pain/pathology not originated from facet joints or stenosis. The patients were scanned in a 3T MR scanner (Siemens) 1-4 (average = 1.9) weeks before scheduled discography to avoid compounding effects of potential disc damage caused by the procedure. A total of 23 disc levels were studied. Cedars Sinai Institutional Review Board approved the study and informed consent was obtained from all volunteers. 1-4 (average = 1.9) weeks before scheduled discography to avoid compounding effects of potential disc damage caused by the procedure. Phantoms were first scanned using a 9.4 T Bruker Biospec Imager (Bruker Biospin), using a volume transmit and receive RF coil.
Image readout was single-slice Rapid Acquisition with Refocused Echoes (RARE) sequence with spin-lock preparation. Next phantoms, porcine spine, and human imaging were performed on a 3.0 T clinical scanner (Magnetom Verio, Siemens Medical Solutions, Erlangen, Germany). RF was transmitted using body coil, supporting a maximum RF duration of 100ms. Imaging of phantoms in the axial plane was conducted using CEST and spin-lock TSE, with a 24-elements spine coil and a body matrix coil. Shimming was done manually, and remained unchanged throughout CEST and water saturation shift referencing (WASSR) acquisition. CEST-preparation was achieved by using a train of Gaussian pulses and a 50% duty cycle. To correct for B0 field inhomogeneity, WASSR method was employed to determine water pool resonance frequency by using the same CEST pulse sequence but with decreased saturation amplitude and duration. Spoiler gradients were inserted after the CEST/WASSR preparation to spoil any residual transverse magnetization. Acquisition included CEST images, one image without saturation (S0), and WASSR images. Three IVDs of the porcine spine were individually scanned with 2D axial slice. Each IVD was manually shimmed. Following localizer and standard T1/T2-weighted TSE acquisitions, on each patient a 2D sagittal slice cutting through the center of IVDs was used for CEST and spin-lock imaging.

**Results:** Our phantom results showed that while both CEST and R1ρ dispersion were dependent on pH, R1ρ dispersion was more sensitive to changes in pH levels. The pig disc imaging showed that a lower pH was correlated with higher RROC. These RROC values differed from that of GAG phantoms because they had different MR parameters such as T1 and T2. Nevertheless a similar pH dependence trend was observed. In the patient study the average normalized RROC values of discs with positive and negative discography outcome were 3.3±2.6 and 1.1±0.2, respectively (mean ± SE), and significant difference was identified between them by paired t-test (p=0.013). ROC analysis revealed that this approach had high prediction power for discs with positive discography with an area under the curve (AUC) of 1.00 (Figure 1).

**Discussion:** In conclusion, in this study a novel pH level dependent imaging technique was proposed and verified by numerical simulations, studies on GAG phantoms, and porcine spines. A patient study showed significantly higher RROC values in IVDs with positive discography, indicating those discs have lower pH levels.

**Significance:** We propose a pH-dependent MRI method that has the potential to detect painful degenerate discs without the need for provocative discography, which could revolutionize current practice in spine surgery. Further studies with higher number of patients are required to further validate and establish this method.

**Acknowledgments:**
References:
Figure 1: Result of a typical patient suffering from low back pain. In this subject 2 positive and 2 negative discs were identified by discography (a). B0 off-resonance map as calculated by WASSR showed good shimming (|B0|<0.1ppm) was achieved in NP regions in the discs (b). Both RROC and normalized RROC had a clear threshold between positive and negative discs (g-h).