Modified Magnetic Resonance Spectroscopy Diagnosis of Painful and Non-Painful Lumbar Intervertebral Discs

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Introduction:

While significant effort has been directed toward improving treatments for discogenic back pain, relatively little has been done to improve the diagnosis of painful discs. MRI is sensitive to changes in disc and endplate hydration and structural morphology, but not specific for differentiating between painful and non-painful degenerative discs. Provocative discography (PD) is often performed to localize painful discs, but has significant limitations including invasiveness, pain, risks of disc damage, subjectivity, lack of standardization of technique. A non-invasive radiographic technique to accurately differentiate between discs that are painful and non-painful may offer significant guidance in directing treatments and developing an evidence-based approach to the care of patients with lumbar degenerative disc disease (DDD).

Previously reported lab experiments used 11T HR-MAS Spectroscopy to compare chemical signatures of different types of *ex vivo* disc nuclei removed at surgery.[1] These studies demonstrated that certain chemicals in disc nuclei, e.g. lactic acid (LA) and proteoglycan (PG), may provide spectroscopically quantifiable metabolic markers for discogenic back pain. This is consistent with other studies that suggest DDD pain is associated with poor disc nutrition, anaerobic metabolism, lactic acid production (e.g. rising acidity), extracellular matrix degradation (e.g. reducing proteoglycan), and increased enervation in the painful disc nuclei. In many clinical contexts, ischemia and lowered pH cause pain, likely by provoking acid-sensing ion channels in nociceptor sensory neurons.

The goal of this study is to develop a reliable approach for acquiring MRS signatures of the chemical composition of the intervertebral disc, and to correlate these MRS signatures with the clinical presentation of the patient and other standard diagnostic measures such as PD. We also hoped to assess whether MRS might provide a non-invasive alternative for diagnosing painful DDD.

Methods:

Clinical Study Population: This study included 65 discs from 36 total subjects. Thirty-eight discs were from 17 patients with a clinical diagnosis of chronic, severe low back pain (LBP group), and 27 discs were from 19 asymptomatic volunteers (ASY Group). 25 discs in 12 of the LBP patients also received PD (PD Group). All 65 discs were evaluated for single voxel magnetic resonance spectroscopy (SV-MRS) pulse sequence, data acquisition, and signal processing parameter development of a new DDD-MRS approach. 52 discs from 31 subjects were used as controls for developing and assessing the diagnostic application of the DDD-MRS approach. Thirteen discography positive (PD+) discs from the PD Group were used as positive control (PC) discs, and 12 discography negative (PD-) discs from the PD Group plus all the ASY discs were used as negative control (NC) discs.

Study Design: Standard lumbar MRI was performed on all subjects. PD performed within the PD Group was conducted by discographers per their discretionary techniques. All PD+ criteria included: >=6 pain intensity score concordant to typical back pain on PD; <=50psi above opening pressure (where measured); and a negative control disc (except one). All PD- discs had <6 pain intensity scores per PD. Pain questionnaires, including ODI and VAS, were completed by all subjects. DDD-MRS that includes a custom developed pulse sequence and signal processing algorithm, was performed on regions of interest within nuclei of all discs included in the study. A 3.0T GE Signa MRI system and 8-channel local spine detector coil were used with the DDD-MRS. Information along spectral regions of the acquired DDD-MRS signals and associated with various chemicals of interest were evaluated against control diagnoses across the PC and NC groups. Multi-variate regression analyses were performed to fit the dicotomous response (PC vs NC) to the continuous spectral measures and develop a DDD-MRS diagnostic algorithm for positive (MRS+) and negative (MRS-) pain diagnoses. Receiver operator characteristic (ROC) curves were generated, and area under the curve (AUC) was calculated to assess the accuracy of the developed test. Five-fold cross-validation was performed to assess the generalizability of the predictive relationship.

DDD-MRS diagnostic outcomes for each disc were based on a single number calculated via the developed algorithm based upon four weighted factors derived from regions of the acquired MRS signals and associated with three chemicals -- PG, LA, and alanine (AL) (and with overlapping lipid contribution). Positive numerical results were assigned MRS+, and negative results were assigned MRS-. These DDD-MRS results were compared against all PC and NC diagnoses, PD results alone, and portion of the NC group represented by the ASY group alone. Sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values were also calculated per control comparisons.

Results:

DDD-MRS data demonstrated a strong correlation with the clinical diagnoses (R^2=.89, p<.00001), with AUC of .99 and cross-validation resulting in only deminimus variance in the R^2. DDD-MRS correctly matched 50/52 (96.2%) of all PC & NC diagnoses across the PD and ASY groups. Of the 13 MRS+ discs, 12 discs were from the PC group (PPV = 92%). Of the 40 discs that were MRS-, 39 were from the NC group (NPV = 97%). DDD-MRS sensitivity was 92% and specificity was 97%. Mean DDD-MRS algorithm results for the PC and NC groups were .97±.77 and -1.40±.65 (R2=.89, p<.00001, Figure 1). DDD-MRS results matched PD results in 23/25 (92.0%) discs of the PD Group: 12/13 (96.2%) PD+ and 11/12 (91.7%) PD-. Mean DDD-MRS algorithm results for PD+ and PD- groups were .97±.77 and -1.39±0.72 (p<.00001). DDD-MRS results correlated with PD pain intensity scores (R^2=.73). DDD-MRS results matched all 27/27 (100%) NC results represented by the ASY group. The mean DDD-MRS algorithm results for the ASY group were -1.4±.63, which differed significantly vs. PD+ but non-significant vs. PD- results (Figure 1; p<.0001; p=0.46).

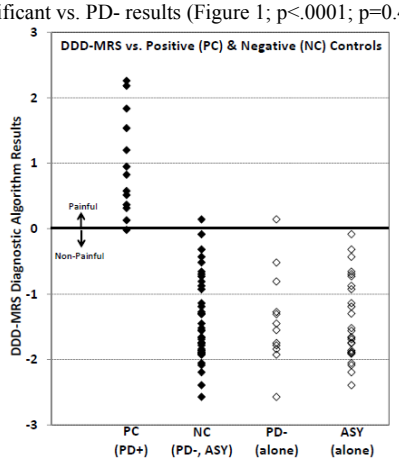

Figure 1: DDD-MRS results in PC(PD+), NC(PD-,ASY), PD-, ASY groups.

Discussion:

The differentiation of painful and non-painful lumbar degenerative discs is an important goal in the accurate assessment of pain generators, and in guiding clinical management of patients with lumbar degenerative disc disease. The novel application of Magnetic Resonance Spectroscopy developed and evaluated under this study proposes a non-invasive, objective, and quantifiable measure of the chemical composition of the lumbar intervertebral disc. The MRS diagnostic algorithm developed and used in this study demonstrates a high degree of sensitivity in identifying patients with a clinical assessment of lumbar discogenic pain and a positive discogram, and a high degree of specificity in identifying levels that are not painful, without any false positive results observed in asymptomatics. While this study is encouraging, the diagnostic approach was developed and applied retrospectively across the study population. Cross validation suggests this may be applicable across a general population however, further evaluation in more subjects, and in prospective studies, is warranted to confirm these findings.

References: [1]Keshari et al., SPINE 2008