MR DIFFUSION MEASUREMENTS ARE SENSITIVE IN DETECTING THE EFFECT OF AGE AND LOADING ON THE RESPONSE OF INTERVERTEBRAL DISCS

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Introduction: Intervertebral disc disease has been significantly linked to low back pain, a major health problem in the US. The progression of this disease is associated with marked degradation in the composition, structural and material properties of the disc's tissues leading to significant loss in its static, dynamic and visco-elastic mechanical response. Diffusion weighted MR measurements yielding apparent diffusion coefficients (ADC) of water within the disc, were recently shown to be useful in detecting changes in disc physiology and in its structure both *in vivo* and *in vitro*. In view of the critical role of the interaction between water molecules and the macro-molecules of the disc in determining its poro-elastic mechanical behavior, the ability to noninvasively interrogate this interaction could provide direct information on the disc's mechanical function. The aim of this MR study was to contrast the ability of diffusion and T2 weighted protocols to detect the affect of age and mechanical loading on the disc's anatomy.

Methods: L2-L3 discs, obtained from human donors aged 39 and 72 years old, were exposed to compressive load of 200N for period of three hours and then mounted within a custom imaging chamber (Fig 1). At the center for Basic MR Research, BIDMC, the chamber was located in the horizontal bore magnet (BioSpec 4.7T, Bruker BioSpin Inc., MA) with the disc's main anatomical axes aligned with the Z, X and Y axes of the MR device. A 72mm coil (Bruker BioSpin Inc.), was used to obtain a single axial slice at the center of the disc (FOV60mm, 128*128 matrix, 2mm slice thickness). Each disc was imaged ***un-loaded*** using the following protocols: *T2Map*: CPMG sequence with slice selective excitation and refocusing pulsesand phase encode rewinders (32 echoes, TR/TE=5000/7..247ms in 7ms spacing, 1 signal average per encoding step) and *Diffusion imaging*: diffusion sensitization gradients applied along three orthogonal directions, [(1,0,0), (0,1,0), (0,0,1) gradient configuration]. The b-factor was calculated through the relation $[b=3(\gamma\delta g)^2\text{-}(\Delta\text{-}\delta/3)]$[1] with Δ and δ fixed at 14 and 8 ms. *g:* was varied to change the b-factor from 100 to1000 mm^2/s. Pulse sequence parameters included an echo time of 28 ms, and repetition 500 ms. Once measurements were completed, the chamber was retrieved, the disc loaded in compression (800N), the chamber re-registered within the MR coil and the two MR protocols repeated a second time.

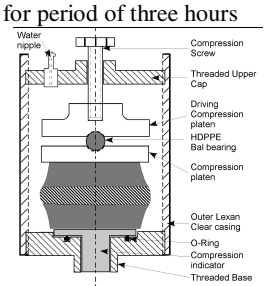

Fig 1. A diagram of the MR imaging chamber

Data analysis: T2Map and diffusion data were analyzed in Matlab (R14, Mathworks, MA). The annulus and nucleus regions were segmented from the axial images and each region bisected to yield 4 ROI quadrants. For each MR measurement, a MANOVA repeated measure model (JMP 5.1, SAS, NC) was used to test for change in the mean and standard deviation for the following parameters; loading (unload vs. loaded), age (39 vs. 72), region (nucleus vs. annulus) and spatial location (anterior vs. posterior and lateral vs. medial) as main effects. Age*Loading, Age*Region, Loading*region; were set as cross terms to determine interactions. Significance between individual parameters was tested using Tuckey HSD test.

Results: in the *unloaded condition*, the 39 year old disc exhibited clear delineation between the annulus and nucleus for both imaging protocols (**Fig 2.A**). Compared to the annulus, the nucleus exhibited significant increase in T2 relaxation (T2map) and diffusion levels (ADC), a mean±S.D of ((106.9±24.7 vs. 71.4±126.0)ms, P<0.01) and (12.9±1.8 vs. 9.8±2.9).$10^{-4}mm^2.s^{-1}$, respectively, P<0.001)). Though the annulus exhibited marked anisotropy (Z=10.2> X=9.9 >Y=9.4).$10^{-4}mm^2.s^{-1}$, no such differences were observed within the nucleus. By comparison, the 72 year old disc demonstrated marked loss in tissue definition (**Fig 2.b**). Compared to the nucleus, the annulus exhibited significant increase in T2 measures (71.0±125.8 vs. 106.9±14.1ms, p<0.01) but little difference in mean diffusion values (9.7±2.4 vs. 9.9±3.1).$10^{-4}mm^2.s^{-1}$, p>0.05). Compared to the younger disc, the degree of anisotropy within the annulus was markedly reduced.

Under compressive load, the 39 year old disc exhibited significantly increased diffusion at the nucleus ((10.3 ± 2.7 vs.12.9 ± 1.8)$10^{-4}mm^2.s^{-1}$, p<0.01). In the annulus, mean diffusion underwent a significant decrease ((8.1 ± 2.7 vs. 8.9 ± 1.8).$10^{-4}mm^2.s^{-1}$, p<0.01) whilst the measurement variance was significantly increased across the tissue (15%, p<0.05). For both mean and variability, the nucleus and annulus exhibited axes dependent response, the changes being significant for Z and X axes (p<0.05). T2 measures, though exhibiting a significant decrease in variance within the annulus (58.2 ± 94.7ms vs. 95.3 ± 126ms, p<0.05), demonstrated little change either in mean, for both anatomical regions or in variance within the nucleus. By comparison, the 72 year old disc showed little change in either mean or variance for either annuls or nucleus for T2 measures. By contrast, diffusion in the nucleus was significantly reduced ((8.9±2.4 vs. 9.9±3.1).$10^{-4}mm^2.s^{-1}$, p<0.05) whilst little difference occurred within the annulus. Both regions demonstrated uniform change irrespective of the axis of measurement.

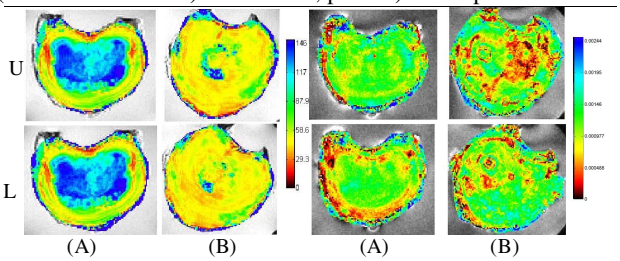

Fig. 2. T2Map and diffusion weighted (trace values [($\sum D_{x..z}$)/3]) MR images of 39 (A) vs. 72 years (B) old discs under Unloaded vs. Loaded.

Discussion: This study demonstrated that while both protocols can delineate the anatomy of the discs and highlight changes in the anatomy with age, diffusion measurements demonstrated increased sensitivity in detecting the differences in the mechanical response of the disc, independent of age. The diffusion measurement, in agreement with clinical studies [2], demonstrated both discs to respond very differently to the applied strain. In the older disc, the loss of tissue definition, increased variability at the nucleus, and conversely, decreased variability within the annuls, suggests a loss of demarcation between the tissues. The relative uniformity of the change in diffusion values, in response to the applied displacement and the reduction in diffusion anisotropy, suggested the older disc to have become, in effect, more "cartilaginous", one of the hall marks of disc degeneration. By comparison, the tissues in the younger disc retained clear differences in their response to the applied load. Both the increase in diffusion in the nucleus, independent of the axis of measurement, and the axis dependent reduction in the mean diffusion within the annulus, indicated that both regions were functional. These changes are in agreement with the expected effects of the highly structured annulus tissue vs. the highly hydrated nucleus on the diffusion of water within these tissues. Our current effort is aimed at elucidating the effects of age and degenerative level on the change in spatial diffusion patterns as a function of vertebral level and loading mode.

References: [1] Stejskal E.O, J.Chem. Phys., **43**(3), 1965. p.579–603; [2] Kerttula, L. Acta Radiologica, 2001. **42**(6): p.585-591;