The Effect of Charge on the Uptake Kinetics and Distribution of Gadolinium Chelates in dGEMRIC Cartilage MRI

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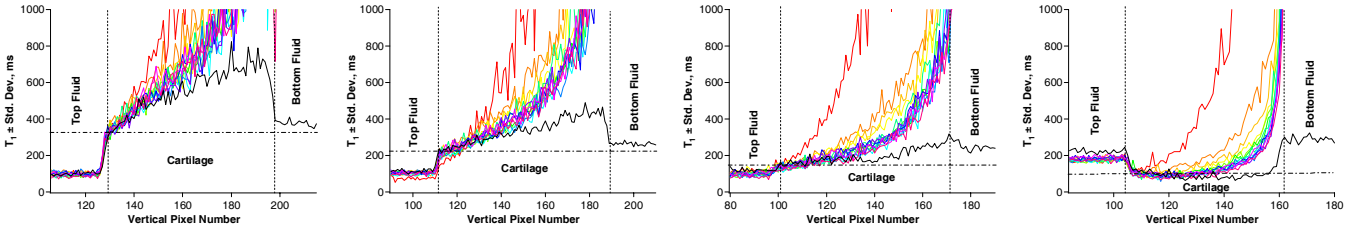
Introduction:

Proteoglycans (PG's) are cartilage macromolecules which contain numerous side chains bearing sulfate and carboxyl groups that are negatively charged at physiological pH. Repulsion between these tissue-fixed charges imparts resilience to cartilage under joint loading. In the early stages of osteoarthritis, PG loss results in cartilage softening and progressive failure in joint function. dGEMRIC[1] is a contrast-enhanced T_1-weighted MRI technique which has been used to monitor PG loss non-invasively in vivo. In dGEMRIC, the anionic contrast agent $GdDTPA^{2-}$ is injected either intravenously or directly into the joint fluid and allowed to equilibrate with cartilage, ultimately achieving a tissue concentration inversely proportional to local fixed negative charge, and thus PG, concentration. Unfortunately, diffusion of $GdDTPA^{2-}$ into cartilage is slow, so that a delay of at least 2h is typically required between injection and post-Gd MRI[2]. This delay not only limits patient throughout but also precludes measuring cartilage and fluid T_1's both before and after equilibration in a single MRI session, which would be highly desirable for accurate quantitation. We hypothesized that alternative Gd chelates, bearing a charge of -1 or a positive charge, could equilibrate more rapidly into cartilage than $GdDTPA^{2-}$ while still permitting the visualization and estimation of PG concentration by T_1-weighted MRI. We tested this hypothesis by observing the diffusion of Gd chelates of charge -2, -1, 0 and +1 into plugs of bovine nasal septum cartilage (BNC), a spatially-uniform, reproducible model for articular cartilage, via repeated acquisition of T_1 maps during equilibration in the scanner.

Methods: Cartilage samples were obtained from adjacent regions of a nasal septum harvested from a 1 year old calf. In each experiment, four plugs of diameter 7.75mm (ca. 0.18g) were excised using a corneal trephine. Each plug was inserted into a glass NMR tube with inner diameter 8.0mm filled with DPBS buffer, then the plug was pushed down to the field center height. Each plug made a close sliding fit with its tube, preventing direct liquid contact with the edges of the plug. 2 mM contrast agent solutions were prepared in DPBS by diluting stock solutions of $GdDTPA^{2-}$ (Magnevist, Berlex Imaging), $GdDOTA^{-}$ (Dotarem, Guerbet) and GdDTPA-BMA (neutral; Omniscan, Amersham). The novel cationic contrast agent $GdDO2A^{+}$ (GdDOTA-bis-amide) was prepared by Macrocyclics, Inc. (Dallas, TX) as the chloride salt and was dissolved directly in DPBS to give a 2mM solution. The pH of all four solutions was adjusted to 7.4± 0.1. Just prior to MRI, the liquid above each plug was replaced by 4 ml of one of these four solutions. The four tubes were then placed in a homebuilt sample holder, which was inserted into a Bruker DMX400 NMR spectrometer equipped with 3-axis shielded gradients and a 30mm ^{1}H birdcage coil. Probe temperature was regulated at 37.0±0.1°C using the spectrometer's variable temperature controller. Based on an initial axial pilot scan, a single, 0.5mm thick slice, parallel to the B_0 axis, was selected through the center of each plug so as to visualize the cartilage as well as the fluid lying above and below. Other MRI parameters included FOV 1.5×1.5cm (V×H), MTX 256×128, SW=50 kHz, TE =12.8 ms and NEX=2. T_1 maps were generated using a spin-echo sequence with TR varying between 1.6s and 0.09s in 12 steps. T_1 maps were acquired repeatedly during gadolinium equilibration in order to compare the rates of diffusion of each chelate into cartilage. For each slice in each scan, an 11 pixel-wide band was defined perpendicular to a flat region of the plug and pixels in each row were averaged and subjected to a 3-parameter fit versus TR to give a plot of T_1 versus vertical position.

Results and Discussion:

Below, T_1 profiles are shown in temporal order from red (1.5 h post-Gd) to violet (18 h) and black (14 days). Since PG concentration in BNC is assumed to be independent of depth, complete equilibration would be indicated by constant T_1 within the cartilage and equal T_1 in the fluid above and below. We observed the least and most complete equilibration at any given time with $GdDTPA^{2-}$ and $GdDO2A^{+}$, respectively. Moreover, GdDO2A gave cartilage-fluid T_1 contrast at least as pronounced as GdDOTA-, suggesting that the new, cationic chelate may be well-suited for fast dGEMRIC measurements.



GdDTPA (Charge -2) **GdDOTA (Charge -1)** **GdDTPA-BMA (Charge 0)** **GdDO2A (Charge +1)**

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References: 1. Bashir A et al, Magn Reson Med 36:665-73 (1996); 2. Burstein D et al, Magn Reson Med 45:36-41 (2001)