FAST FIELD-CYCLING NMR OF CARTILAGE: A WAY TOWARD MOLECULAR IMAGING

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a. Purpose

A previous pilot study (presented at OARSI 2012) showed that Fast Field-Cycling NMR (FFC NMR) can be used to characterise the dispersion curves of cartilage in the region 0.4 to 3 MHz proton Larmor frequency. One feature of these dispersion curves, quadrupolar peaks, arise from relatively well known interactions between water protons and the ^{14}N nuclei of certain immobilised proteins. We have also previously shown that osteoarthritic cartilage gives rise to smaller quadrupolar peaks than cartilage from healthy volunteers. However, the exact protein responsible for the quadrupolar peaks observed in cartilage samples is uncertain. This present work aims to determine the protein responsible for the quadrupolar peaks observed in cartilage and how these signals correlate with disease progression.

b. Methods

Cartilage samples from femoral heads and knee joints were obtained after consenting patients undergoing joint replacement surgery or above-knee amputation at NHS Grampian Hospitals. All work with human tissue was approved by the North of Scotland research ethic committee. First, a pilot study was conducted on a commercial FFC NMR scanner (Stelar s.r.l, Mede, Italy). We used a pulse sequence with a short acquisition time (< 1 ms), and included 7 patients undergoing arthroplasty for osteoarthritis (OA) and 5 patients undergoing hemiarthroplasty for hip fracture. The hip fracture group had no clinical or radiological evidence of OA prior to the fracture being sustained and there was no macroscopic evidence of cartilage degeneration seen intra-operatively on femoral head inspection. In a second, larger study, we examined the cartilage from 50 patients with evidence of OA changes and 50 without using both long (~20 ms) and short acquisition times.

We also measured the quadrupolar signals from a variety of samples using both long and short acquisition times including: normal and osteoarthritic human cartilage; collagen preparations using distilled water and a commercially available porcine collagen sponge (Collatamp; Tribute pharamaceutical); glycosaminoglycan extracts from human cartilage (both liquid and lyophilised); and human cartilage which had been extracted of its glycosaminoglycan (GAG) content with 4M guanidinium chloride.

c. Results

Variations of the quadrupolar signals were visible between short (< 1ms) and long (CPMG echo trains, 20 ms) acquisitions. Long acquisitions did not show any contrast between normal and diseased cartilage whereas significant differences in quadrupolar peak amplitude were observed using short acquisition time sequences (3.6 s^{-1} vs 2.2 s^{-1}, $p < 0.01$). We observed no quadrupolar peaks in glycosaminoglycan extracts from cartilage, whether liquid or lyophilised.

Preparations containing 50%w/w collagen showed quadrupolar peaks indicating that collagen may be the source of this signal in cartilage. However, the quadrupolar peaks observed using short acquisition times were only seen in cartilage which had not been extracted of its GAG content. This suggests that the quadrupolar peaks observed in cartilage are likely to be linked to the macromolecular collagen fibril network and are reduced with decreasing matrix integrity. Interestingly, the short-lived component of the FFC-NMR signal was not evident in GAG-extracted cartilage cores from healthy or diseased cartilage. However, the long-lived signal was unaffected and was not found to be correlated with OA changes.

d. Conclusions

GAG extracts of cartilage samples and analysis of collagen preparations have shown that GAGs are not likely to be the proteins responsible for quadrupolar peaks. The amide linkages on the backbone of collagen are therefore indicated as the source of quadrupolar peaks but the organisation of the macromolecular collagen network within the cartilage matrix also seems to play an important role in the interaction between collagen proteins and water protons.

When this matrix is disturbed, such as after GAG-extraction, the amplitude of quadrupolar peaks are significantly diminished and there is a loss of the short-lived FFC NMR signal. Therefore it is likely that the quadrupolar signals of cartilage report on the macromolecular organisation of the collagen network within the cartilage. We are thus preparing methods to image this signal *in vivo* using FFC MRI and zero echo time acquisition techniques. We hope applications of this technique will allow new ways to non-invasively detect and stage osteoarthritic cartilage before morphological structural changes occur, as are appreciated with conventional MRI techniques.