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MR imaging of ex-vivo mouse joints on a clinical 3T system with diagnostic SPION imaging using dUTE in an arthritis model.

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Introduction: Super paramagnetic iron oxide particles (SPION) accumulate in macrophages in the synovium of arthritic knees[1]. To monitor the time response of SPION accumulation in the synovium, a robust method to rapidly detect the presence of iron in the knee of mice is mandatory. We developed an MRI protocol based on a 3D difference Ultrashort Echo Time (dUTE) MR sequence for fast scanning of multiple mice knee specimen on a clinical 3T and present here its performance for SPION detection in an antigen induced arthritis (AIA) model in mice. This protocol is based on a 3D difference Ultrashort Echo Time (dUTE) MR sequence that has been described previously as a quantifiable positive contrast method for iron oxide detection in arthritic model in rat[2].

Methods: Arthritis was induced in mice using a standard AIA protocol in conformance with the institution ethical committee. At timepoints up to day 7 after SPION injection, mice were sacrificed to obtain multiple knee samples involving intra-articular (i.a.) injection of 6µg amino-PVA-SPION contrast agent[3] or intra-vascular (i.v.) 1mg amino-PVA-SPION (n=3-6 for each route, timepoint and dose). Arthritic and control samples consisted of ex vivo mouse knees arranged in holder with joints aligned forward. Scanning was carried out on a Siemens 3T Tim Trio clinical scanner with the knee coil using 3D difference Ultrashort Echo Time (dUTE) and 3D T1 gradient echo sequences, called 'VIBE' throughout. dUTE sequence parameters were: 3D isotropic matrix of 512 and 90mm FOV (field of view), giving a resolution of 180µm in all three directions, 50000 radial projections, ultrashort TE (echo time) of 0.07ms, TE2 2.46ms (for subtraction), TR (repetition time) 9.6ms and flip angle 10°, and the VIBE parameters: 3D isotropic resolution of 310µm, TR/TE 14.3/5.9ms and flip angle 12°. The whole examination for a single group of took around 20 minutes repeated for 7 signal averages with 42 knees at a time corresponding to an effective acquisition of <4 min for a single knee for both VIIBE and dUTE. A score for presence of iron was used to compare the different animal groups and MR sequences. For clarity, the results presented on the figures are from day 1 and day 7 with groups also assessed statistically including 4 hour and 4 days.

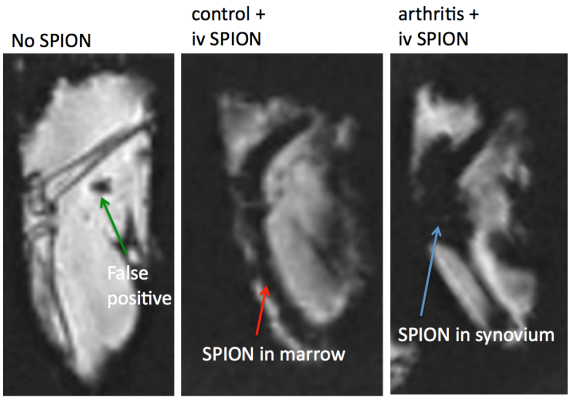

Figure 1: Sagittal slice of mice knee specimens imaged by a VIBE sequence in control (left), after an i.v. iron oxide (SPION) injection in normal (middle) and arthritic (right) mice. Accumulation of SPION in the synovium is only seen in arthritic knee whereas bone marrow uptake is present in both normal and arthritic knee.

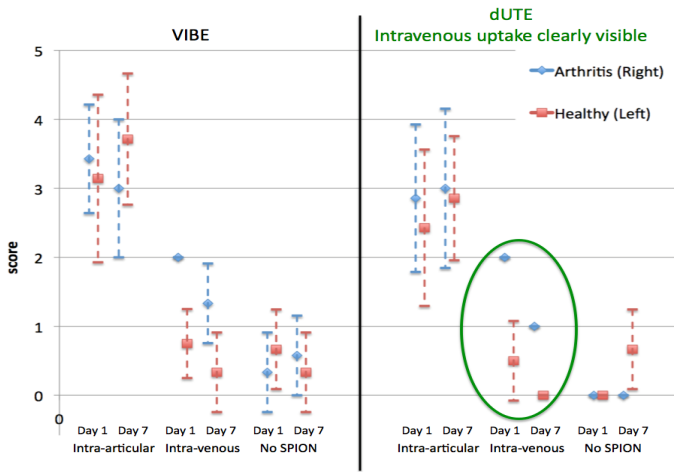

Figure 2 Comparison of SPION accumulation scoring (n=3-6 per group) at day 1 and 7 using both VIBE (left) and dUTE (right) sequences. Due to reduced "false positive" from artifacts dUTE outperformed VIBE for the quantification of SPION uptake. dUTE but not VIBE was able to demonstrate after i.v. iron injection an uptake of SPION in arthritic knee that decreased after 1 week.

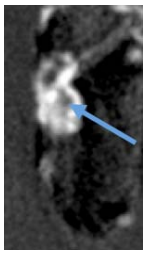

Figure 3. dUTE SPION signal on a sagittal image.

Results:
The spatial resolution achieved by our protocol was high enough to identify relevant anatomical landmarks of the mice knee as demonstrated in left image of Figure 1. The presence of SPION was easily detected by a strong signal loss in the bone marrow after i.v. injection (see middle image of Figure 1). Accumulation of iron in the synovium of arthritic knee was visible on both the VIBE and dUTE sequence (see right image of Figure 1 and Figure 3). However, dUTE sequence was more efficient than VIBE sequence to grade and quantify the amount of SPION. The graph in Figure 2 shows the scores for both AIA (right) knees and control (no arthritis/left) knees. With VIBE, SPION is clearly seen in addition to 'false positives' from other regions hypointense signals making scores less consistent. These areas of artifacts are avoided by the use of the dUTE positive iron contrast method. A Bonferroni ANOVA was carried out over all the cases (20 groups in all) with a significance set at 0.05. After i.v. injection of SPION, only dUTE was able to demonstrate a statistically significant uptake at day 1 and following decrease at day 7. After i.a. injection, both arthritic and control knees demonstrated an important SPION signal not evolving over time (no significant difference between knees and timepoints). VIBE showed non-significance comparing i.v. and no SPION, including comparison of control and AIA knees. For dUTE the arthritic knee after i.v showed significant difference from the control, from i.a. SPION and no SPION as illustrated with a difference showing evolution between day 1 and 7.

Discussion and Conclusions:
The diagnostic ability of dUTE acquisitions on a clinical scanner in mouse knee samples is illustrated. In agreement with previous publications, dUTE was the most efficient MR sequence to quantify small variation of SPION accumulation in the knee. Applying this protocol on 138 mice knee specimens demonstrated that the signal loss after i.a. injection of iron was not different between control and arthritic knee and that it did not evolve over a 7 day period. Signal saturation related to a too high dose of injected i.a. SPION may explain this paradoxical absence of signal clearance. On the other hand, one day after i.v. SPION injection, there was a significant change of signal intensity in the synovium of arthritic knee that was not present in control knee. This SPION signal decreased at day 7 but was still detectable in arthritic knees indicating that the SPION quantification could be efficient to monitor effect of treatment in this arthritic model in mice. Therefore, we demonstrated a robust and easily implementable protocol on a clinical MR system for fast assessment SPION uptake in knee specimens of arthritic mice with a strong potential for drug studies.

References:

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