Concentration dynamic response assessment for intra-articular injected iron-oxide nanoparticles.

Lindsey A Crowe[1], Frank Tobalem[1], Wolfgang Wirth[2], Azza Gramoun[1], Benedicte M A Delattre[1], Kerstin Grosdemange[1], Jatuporn Salaklang[3], Anthony Redjem[3], Alke Petri-Fink[3], Felix Eckstein[2], Heinrich Hofmann[4], and Jean-Paul Vallée[1]

[1]Faculty of Medicine/Department of Radiology, University of Geneva, Geneva, Switzerland, [2]Institute of Anatomy & Musculoskeletal Research, Paracelsus Medical University, Salzburg, Austria, [3]Adolphe Merkle Institute, University of Fribourg, Fribourg, Switzerland, [4]Powder Technology Laboratory, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

Introduction

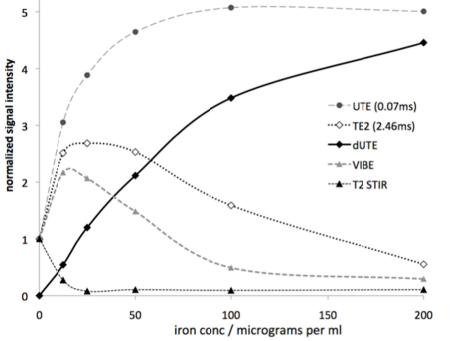
Nanoparticle technology, including superparamagnetic iron oxide nanoparticles (SPIONs), is of emerging importance for monitoring onset, progression and treatment of inflammatory diseases such as arthritis and drives development of imaging techniques. Studies require sensitive imaging protocols for the detection and quantification of particles over a range of concentrations. Intra-articular injections of iron were compared to a concentration phantom using a difference-Ultrashort Echo Time sequence.

Methods

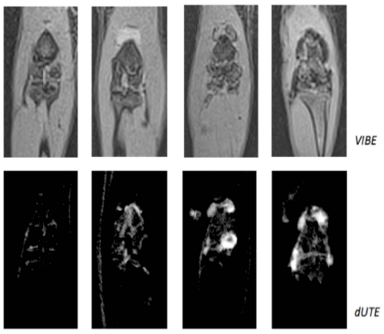
15 female Lewis rats (2 months old) were scanned immediately after intra-articular injection in the knee of iron oxide nanoparticles (A-PVA-SPION, 5 concentrations in 50µl of physiological NaCl ranging from 12.5 to 200µg/ml). Scanning used a Siemens Magnetom Trio 3T clinical scanner and the manufacturers 4cm loop coil. The protocol included 3D T1 gradient echo (VIBE), with parameters TR/TE 14.3/5.9ms, flip angle 12°, fat suppression, isotropic resolution 0.31mm, and FOV 100mm. dUTE consisted of the acquisition and subtraction of two echo times (ultrashortTE, and short TE2) leading to positive contrast from short T2* species and reduced signal elsewhere. Parameters were 3D isotropic resolution of 0.18mm, an 80mm FOV, 50000 radial projections, UTE/TE2 0.07ms/2.46ms (for in-phase fat/water image), TR 9.6 ms and flip angle 10°.

A phantom was constructed with the same solutions as those injected, plus water. Numerical analysis was carried out using ANOVA with post-hoc Bonferroni (PASWStatistics 18.0) and a $p < 0.05$ was considered significant. Ethical committee approval was obtained for the complete protocol and animals were kept in the institutions animal facility with free access to food and water.

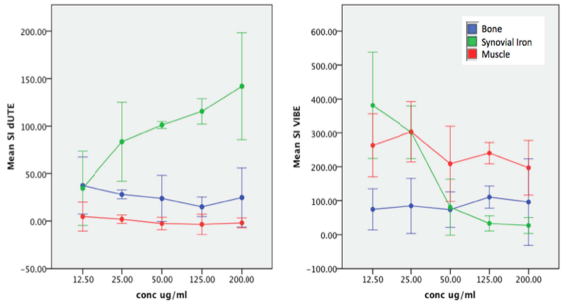
Results



***A:** Phantom results. Comparison of signal intensity versus concentration of iron oxide in sample tubes, normalized to the signal at concentration 0 (water). Proposed dUTE method and conventional signal loss sequences at different concentrations, showing monotonic concentration dynamic of dUTE.*



***B:** In-vivo results. Synovial iron on VIBE, dUTE images of a control and at 50µL volume i.v. injection of 12.5µg/ml, 50µg/ml and 200µg/ml*



***C:** Signal intensity showing contrast of synovial iron (green line) and other tissue. Contrast between synovial iron and other tissues is high and positive at all concentrations for the dUTE sequence compared to VIBE. Mean of the 3 animals per group with 95% error bars.*

***Figure 1A-C** Regions drawn on phantom and synovium.*

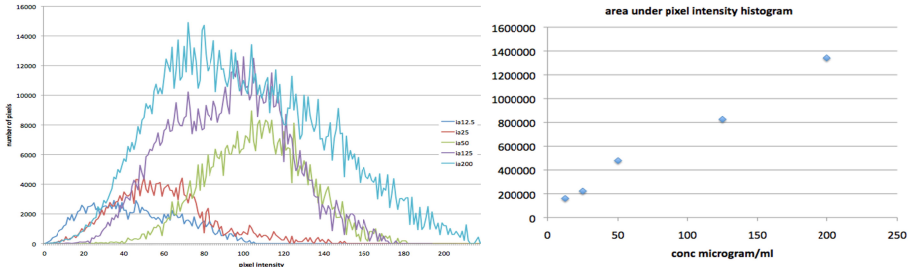


***Figure 2** Quantification of whole of heterogeneous volume- pixel intensity and frequency and integral for each concentration*

Conventional signal loss measurements of tissues containing iron oxide nanoparticles saturate at medium concentrations and show a peaked non-proportional intensity to concentration profile due to the competing effects of T1 and T2 relaxation unlike the monotonic dUTE response (Figure 1A). Figure 1 B shows both the signal increase with concentration in dUTE and the contrast for iron at all concentrations. Figure 1C illustrates that despite the good concentration effect at low concentrations with VIBE, the signal soon saturates to the level of noise/bone and there are intermediate concentrations when the iron signal crosses the muscle signal.

Only for dUTE is there significant difference between signal for synovial iron, bone and muscle ($p<0.013$). TE2 shows no significant difference between iron and bone, whereas the difference between synovial iron and muscle was significant ($p<0.04$). Both volume and intensity can be quantified for full assessment of heterogeneous regions of signal (Figure 2).

Discussion and Conclusions

An important factor gained by the dUTE sequence is the distinction of synovial iron signal intensity from tissues (muscle, bone) and noise, unlike any of the classical sequences compared, or the simple single echo of the UTE acquisition. The dUTE sequence (difference-Ultrashort Echo Time) gives positive, unambiguous signal characteristics and monotonic increasing concentration response (linear for physiologically relevant concentrations) over a wide range in a phantom and a rat model, with limited susceptibility artifacts and high contrast to all other tissues, opening possibilities for quantification.

References

Butoescu N, Jordan O, Petri-Fink A, Hofmann H, Doelker E. J Microencapsul 2008;25(5):339-350.
Beckmann N, Falk R, Zurbrugg S, Dawson J, Engelhardt P. Magn Reson Med 2003;49(6):1047-1055.
Nielles-Vallespin S, Weber MA, Bock M, Bongers A, Speier P, Combs SE, Wohrle J, Lehmann-Horn F, Essig M, Schad LR. Magn Reson Med 2007;57(1):74-81.
Crowe LA, Ris F, Nielles-Vallespin S, Speier P, Masson S, Armanet M, Morel P, Toso C, Bosco D, Berney T, Vallee JP. Am J Transplant 2011;11(6):1158-1168.