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

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Summary

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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.
Particles

All particles described in this work are amino-PVA-SPIONs provided by EPFL/Uni Fribourg with or without coupled fluorophore dye. The superparamagnetic iron oxide nanoparticles were manufactured by an aqueous co-precipitation method. (Chastellain M, Petri A, Hofmann H. J Colloid Interface Sci 2004;278(2):353-360). The colloidal particles were further coated with a mixture of poly(vinyl alcohol) (PVA) and vinyl alcohol/vinyl amine copolymer. Surface derivatization of polymer-coated particles with a dye in a magnetic bed reactor. (Steitz B, Salaklang J, Finka A, O’Neil C, Hofmann H, Petri-Fink A. Bioconjug Chem 2007;18(5):1684-1690).
Methods

15 female Lewis rats (2 months old) were scanned immediately after intra-articular injection in the knee of iron oxide nanoparticles.

Amino-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.

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.
Methods

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 (ultrashort TE, 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°
**dUTE** gives high-resolution 3D anatomical images with suppressed background, reduced artifacts and high iron contrast, and allows automatic quantification of iron oxide.
Methods

Non-normalised signal intensity of synovial iron region is measured in a region of interest as a function of concentration ($\mu$g/ml) of solution injected intra-articular into the knee joint of healthy rats.

Signal intensity on MRI is measured immediately after injection of 50$\mu$l of amino-PVA-SPION in PBS.
Images

In-vivo results at 50µg/ml concentration. Iron oxide volume 50µL injected.

UTE, TE(2), dUTE, dUTE fusion on anatomy and sagittal for localization.

Region of synovial iron is clearly delineated. Several example slices are given throughout the knee.

Red is low iron signal, through yellow to white for high iron concentration.

Last image row shows also the contralateral knee without injection.
**Images: In-vivo results**

**Synovial iron**

**VIBE, dUTE, UTE and TE2 images of a control**

and at 50µL volume i.a. injection 12.5µg/ml, 50µg/ml and 200µg/ml
**Images: In-vivo results**

**Synovial iron**

**VIBE, dUTE, UTE and TE2 images of a control**

and at 50\(\mu\)L volume i.a. injection

12.5\(\mu\)g/ml, 50\(\mu\)g/ml and 200\(\mu\)g/ml
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 comparing sensitivity and ambiguity at different concentrations showing monotonic concentration dynamic of dUTE.
In vivo quantification

In-vivo results showing synovial iron signal in green emphasizing both the sensitivity to concentration from the slope and the contrast due to the separation of the iron data from the red/blue muscle/bone data. Error bars 95%.

dUTE and VIBE

Each plot shows the effect of injected concentration on the signal intensity in the region of uptake (green) as well as the signal for muscle (red) and bone (blue).
In vivo quantification

*In-vivo results showing synovial iron signal in green emphasizing both the sensitivity to concentration from the slope and the contrast due to the separation of the iron data from the red/blue muscle/bone data. Error bars 95%.*

Top row, dUTE and VIBE,

Bottom row, the individual echoes for creating dUTE (UTE and TE2).

Each plot shows the effect of injected concentration on the signal intensity in the region of uptake (green) as well as the signal for muscle (red) and bone (blue).
Contrast-to-noise (difference between synovial iron and other tissue, normalised by noise background signal for the appropriate sequence)

High and positive at all concentrations for dUTE compared to VIBE.

Values are mean of 3 animals per group with 95% error bars.
Heterogeneous signal \textit{in vivo} quantification

Quantification of whole heterogeneous volume: pixel intensity and frequency, and integral for each concentration.

\textit{Illustrates variation in number of pixels and intensity, but total ‘iron quantification’ integral is linear with concentration. Good correlation.}
Heterogeneous signal In vivo quantification

Quantification of whole heterogeneous volume: pixel intensity and frequency, and integral for each concentration.

Illustrates variation in number of pixels and intensity, but total ‘iron quantification’ integral is linear with concentration. Separation.
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,

Limited susceptibility artifacts and high contrast, open possibilities for quantification of other heterogeneous regions of iron uptake in more complex models.
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- Thank you
- Questions?
References


