Quantification of inhomogeneous iron oxide uptake in a model of AIA in rat.

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Introduction: This paper describes quantification in vivo in a clinically relevant model of unknown SPION uptake after intra venous injection in an antigen-induced arthritis (AIA) model in rat. In addition to the difficulties of quantifying SPION uptake with conventional signal loss images, the heterogeneous nature of both the components of the natural progression of the disease/treatment and the uptake of contrast agents has necessitated a semi-automated segmentation method. We use the dUTE positive contrast method for image acquisition and software developed for automatic segmentation to give pixel intensity histograms. Thus allowing quantification of both size and intensity characteristics of any chosen anatomy and its corresponding signal and contrast on an MR image. Following on from previously published concentration effects in phantom and single region measurements of mean signal intensity after i.a. injection (3) where the monotonic signal increase with concentration was shown for known values, we assess now by 3D semi-automated quantification an in vivo SPION signal and irregular uptake after i.v injection.

Methods: All particles described in this work are amino-PVA-SPIONs provided by EPFL (Lausanne) and University of Fribourg (7).

Animal handling and model: Female Lewis rats (Janvier, France), weighing 150-175g and aged two months at receipt, were used in this study. Ethical committee approval was obtained for the protocol and animals were kept in the institutions animal facility with free access to food and water. Rats (n=23) with antigen-induced arthritis in the right knee were given intravenous injection of 7mg iron oxide on day 5 after disease induction. Intra-venous (i.v.) injections gave a low, unknown, irregular uptake in multiple regions that requires 3D quantification.

Magnetic resonance imaging: 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. Quantifiable iron oxide particle detection by dUTE MRI (4) consisted of simultaneous acquisition and subtraction of two echo times 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°.

Image analysis: The analysis software allows segmentation of the two simultaneously acquired UTE and TE2 images and the positive contrast iron oxide image. Important features of the software include: semi-automatic segmentation (thresholding: a single pixel click fills a region using intensity threshold and a radius contraint), quantification of volume and signal intensity for both echoes and the difference image with the segmentation and export of signal intensity measurements for further analyses in statistical software. The semi-automatic threshold method selects regions of similar intensity around a user-defined point and this is repeated for the regions of iron in 3D. A histogram of pixel intensities and well as mean value and total volume are reported. Manual segmentation (n=16) was used as a gold standard for the validation of the analysis software.

Results

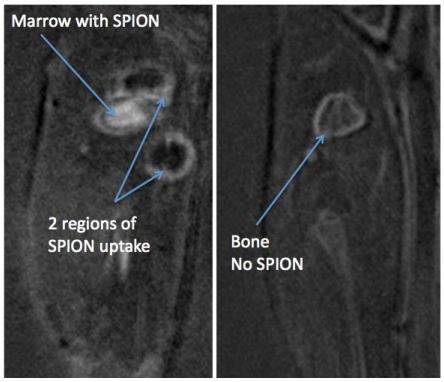

Figure 1. . Coronal slice from 3D dUTE of arthritic (left) and control knee (right) showing SPION uptake after i.v. injections of 7mg given 5 days before imaging in AIA rat showing two different parts of the synovium with iron uptake in the medial side of the knee. The right hand image shows only the cortical bone in a control knee.

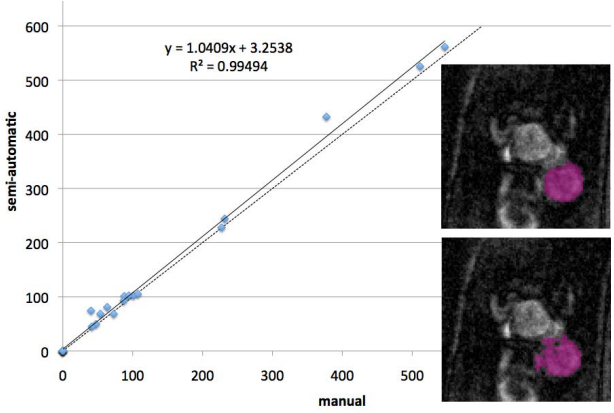

*Figure 2. Correlation between manual (top) and semi-automatic (bottom) segmentation in inhomogeneous regions of uptake (n=16). Both axes show pixel intensity*number of pixels. Dotted line: x=y, solid line: fit of data showing excellent agreement (p<0.0001).*

The automatic method was successful in all the cases and takes around 20 minutes per knee by comparison to the manual segmentation of 3 times the analysis time. Two repeated measurement using the automatic method gave a whole 3D integral difference of less than 10% compared to a variation of 200% over a normal group of 9 individuals.

Discussion and Conclusions:

3D quantification methods illustrate variation in number of pixels and intensity, but total 'iron quantification' integral gives a complete assessment of the irregular SPION uptake with easier and faster assessment using semi-automated segmentation. Figure 2 shows example images of the signal intensity and distribution variation after i.v. injection. Good agreement can be seen between the manual and automatic methods with manual taking about 3 times as long with around 50 images per 3D volume containing SPION signal. In addition on example images (Figure 2), the shape of the uptake can be more clearly represented on the automatic segmentation (unless it was actually done by selecting individual pixel – a method that would be prohibitively time consuming). We therefore introduced a fast and robust method to quantify SPION uptake in arthritic knee. Work-in progress includes comparison with iron estimation from histology as well as assessment of treatment effects in the arthritis.

References

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