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Evaluating automated dynamic contrast enhanced wrist 3 T MRI in healthy volunteers: One-year longitudinal observational study

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ABSTRACT

Rational and Objective: Dynamic contrast enhanced (DCE)-MRI has great potential to provide quantitative measure of inflammatory activity in rheumatoid arthritis. There is no current benchmark to establish the stability of signal in the joints of healthy subjects when imaged with DCE-MRI longitudinally, which is crucial so as to differentiate changes induced by treatment from the inherent variability of perfusion measures. The objective of this study was to test a pixel-by-pixel parametric map based approach for analysis of DCE-MRI (Dynamika) and to investigate the variability in signal characteristics over time in healthy controls using longitudinally acquired images.

Materials and Methods: 10 healthy volunteers enrolled, dominant wrists were imaged with contrast enhanced 3T MRI at baseline, week 12, 24 and 52 and scored with RAMRIS, DCE-MRI was analysed using a novel quantification parametric map based approach. Radiographs were obtained at baseline and week 52 and scored using modified Sharp van der Heidje method. RAMRIS scores and dynamic MRI measures were correlated.

Results: No erosions were seen on radiographs, whereas MRI showed erosion-like changes, low grade bone marrow oedema and low-moderate synovial enhancement. The DCE-MRI parameters were stable (baseline scores, variability) (mean ± st.dev); in whole wrist analysis, ME_{mean} (1.3 ± 0.07, −0.08 ± 0.1 at week 24) and IRE_{mean} (0.008 ± 0.004, −0.002 ± 0.005 at week 12 and 24). In the *rough* wrist ROI, ME_{mean} (1.2 ± 0.07, 0.04 ± 0.02 at week 52) and IRE_{mean} (0.001 ± 0.0008, 0.0006 ± 0.0009 at week 52) and *precise* wrist ROI, ME_{mean} (1.2 ± 0.09, 0.04 ± 0.04 at week 52) and IRE_{mean} (0.001 ± 0.0008, 0.0008 ± 0.001 at week 24 and 52). The Dynamic parameters obtained using fully automated analysis demonstrated strong, statistically significant correlations with RAMRIS synovitis scores.

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Conclusion: The study demonstrated that contrast enhancement does occur in healthy volunteers but the inherent variability of perfusion measures obtained with quantitative DCE-MRI method is low and stable, suggesting its suitability for longitudinal studies of inflammatory arthritis. These results also provide important information regarding potential cut-off levels for imaging remission goals in patients with RA using both RAMRIS and DCE-MRI extracted parametric parameters.

1. Introduction

Evaluation of disease activity in rheumatoid arthritis (RA) is based on a combination of clinical, laboratory and imaging data, of which imaging reveals information about joint destruction and soft tissue changes over time. Treatment of RA patients has been improved with introduction of biologic agents, which target specific cytokines or cells involved in the disease [1,2]. Nonetheless, most patients achieve only partial therapeutic responses and many do not respond at all. Thus new drugs are needed. In order to expedite early phase assessment of efficacy for inflammation reduction and disease modification, there is a high demand for optimisation of imaging techniques, image reading and quantification of follow-up of patients.

Dynamic contrast enhancement (DCE)-MRI is an imaging technique where MR images are acquired sequentially over the same slices over time following an injection of Gadolinium contrast agent [3]. It is considered a valuable modality for quantitative reproducible assessment of the inflamed synovium in patients with RA [4]. DCE-MRI provides important information about the time dependent tissue contrast uptake, allowing to quantify regional activity and changes in synovitis [4–9] and bone marrow oedema (BME) [10], which have shown high predictive value in future disease progression [11,12].

Rheumatoid Arthritis MRI Scoring System (OMERACT-RAMRIS) [13], is the current widely used method for quantifying MRI synovitis. It uses, a scale from 0 to 3 for selected joints based on an atlas, grading synovitis from none to mild, moderate and severe (worst imaginable). It requires a highly skilled observer and produces rigid scores, which only allows capturing changes in volume of 30% magnitude.

We know from studies using ultrasound Doppler for quantification of synovitis in the MCP and wrist joints of patients with RA receiving structure modifying treatments, that it is crucial to measure even slightest variations in patient's condition through quantifying changes in synovial perfusion/inflammation, which seems to carry prognostic value [14–16]. Such changes should be measured in reproducible and objective manner, preferably on a continuous scale.

A novel computer-aided system, Dynamika, was recently introduced into clinical research; its quantitative approach is based on application of a pixel-by-pixel parametric map based analysis method [17], which allows for continuous assessment of synovial changes and due to automation of the 'reading' and computer guidance in image analysis, does not require an observer to undergo extensive training. The automation of reading allows for high reproducibility of the results and eliminates inter-reader variability.

This new method has been validated in a high number of patients and correlated with RAMRIS [12], showing that automated procedure is not only faster but more sensitive to change on therapeutic intervention.

However, to date, it was assumed that any changes seen in MRI and DCE-MRI images can be solely attributed to the treatment effect, whereas it is known that MRI and DCE-MRI have inherited variability due to various factors, such as image quality reduction due to patient movement artefacts, hardware instability or variability in patient condition etc. Therefore, any quantitative parameters extracted from DCE-MRI should be adjusted to these factors.

There are very few studies validating longitudinal changes in imaging measures in a healthy population [18]. Previously, RAMRIS has been used to analyse healthy volunteers [18]. However, the RAMRIS score is too rigid to reliably address subtle changes in flow and thus synovitis.

This study supports the use of a novel more sensitive approach for analysis of DCE-MRI and aims to benchmark the 'normal' level of enhancement as seen in DCE-MRI acquired from healthy controls. The focus of this study is to validate the background change occurring over time as imaged with DCE-MRI to allow a reader to make a judgement on what changes can be truly attributable to the treatment effect.

To our knowledge this is the first longitudinal study to explore 3T MRI DCE-MRI change in healthy volunteers using fully-automated and objective analysis method. This validation is crucial if this imaging technique or analysis methods are to be incorporated in RA drug trial design or research studies focusing on early disease detection or treatment effect assessment.

2. Methods

2.1. Patients

10 healthy volunteers were enrolled: 3♂ and 7♀, age range: 24–40 years, BMI 19–29.9 kg/m^2. Dominant hands were imaged on 3T (Philips Intera) MRI at baseline, week 12, 24 and 52. MRI safety checks, blood test for estimated glomerular filtration rate (required eGFR > 60 ml/min), urine βHCG pregnancy and hand examination to exclude the presence of pain or swelling were performed at each visit. Subjects with history of arthropathy or MRI safety issues were excluded.

In total 28 MRI scans were performed; 9 subjects completed baseline, 7 subjects completed week 12, 24 visits and 2 subjects dropped out at week 52 due to pregnancy and a surgery. Wrist imaging was performed using a dedicated SENSE wrist coil, in a purpose built subject 'bridge' positioning device [19,20] to allow for similar and comfortable wrist positioning in a longitudinal fashion.The following imaging parameters, abbreviated as Time to Echo (TE), Time of Repetition (TR), Flip Angle (FA), Field of View (FOV)

- T2w TSE: TR/TE/FA: 9000 ms/55 ms/90°, FOV: 120 mm × 97 mm × 82 mm, Acquisition matrix: 208 × 168, slices: 140 (thickness: −0.58 mm, order: interleaved), reconstructed voxel was 0.54 mm × 0.54 mm × 1.16 mm, Time: 7 min 48.2 s.
- Pre- and post-contrast T1wFFE: TR/TE/FA:11 ms/2.3 ms/20°, FOV: 120 mm × 98 mm × 82 mm, Acquisition matrix: 240 × 196, 164 temporal slices acquired in 3D mode, voxel size 0.5 mm × 0.5 mm × 0.5 mm, Time: 5 min 55.4 s.
- DCE-MRI: Orientation/position: Prone/head first, TR/TE/FA: 3.8 ms/2.1 ms/20°, FOV: 120 mm × 95 mm × 80 mm, Acquisition matrix: 96 × 75, 127 temporal slices, 40 dynamic frames in 3D scan mode, voxel size: 1.25 mm × 1.25 mm × 0.63 mm, dynamic time: 10.3 s, time: 6 min 52.8 s. 40 s delay from the start of image acquisition to contrast injection of Gadolinum-DTPA, 0.2 ml/kg.