Advanced MRI in inflammatory arthritis

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Chapter 1

General introduction

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In inflammatory joint disease (arthritis) the synovial lining of the joint becomes inflamed, a process called synovitis. In some inflammatory joint diseases the inflamed synovium can destruct the joint cartilage and erode into the underlying bone (called erosions). Another process that often accompanies the inflammation of a joint is an inflammatory reaction of the joint ligament attachments (enthesitis).
There are several types of inflammatory joint diseases. Distinction between these types is primarily based on clinical presentation (e.g. distribution of arthritis, comorbidities) and laboratory tests. Rheumatoid arthritis (RA) and spondyloarthritis (SpA) are the most common forms. As both types of inflammatory joint diseases can cause joint destruction when not treated appropriately or when treatment is delayed, an early diagnosis is essential.

RA vs. SpA

In RA the synovium is the primary site of inflammation, whereas in SpA it is hypothesized that the inflammation starts in the enthesis.[1] This hypothesis was based on an observational study of 10 RA and 10 SpA patients. After this publication, the higher prevalence of enthesitis in SPA was confirmed in several studies,[2–5] however, other studies did not find more enthesitis in SpA patients compared to other inflammatory joint diseases.[6–9] Therefore, controversy still exists about the validity of this hypothesis.

Imaging in inflammatory joint diseases

Magnetic resonance imaging (MRI) is being increasingly used to study the inflamed joints. MRI allows for the easy differentiation and delineation of joint structures (e.g. bone, cartilage, ligaments), joint fluid accumulation and evaluation of the surrounding soft tissues. Besides, it is a superior technique compared to conventional radiography to (early) visualize joint destruction and erosive disease that may accompany joint arthritis.[10,11] After contrast injection, it reliably visualizes the synovial tissue, and is therefore the imaging technique of choice in the evaluation of synovitis.[12]

Dynamic Contrast material Enhanced (DCE-)MRI

DCE-MRI is an advanced imaging method. During and after contrast injection, sequential MRI-scans are made of a volume (e.g. joint). Each following scan shows the

following stage of contrast enhancement of structures within this volume. As this contrast enhancement results in change of signal intensity within the imaged volume, time-intensity curves (TIC) are the result when signal intensity is plotted against time. The TICs can be post-processed using different approaches.

The easiest and most straightforward approach is a **qualitative analysis**. In this method, parameters, such as the (early) enhancement rate/initial rate of enhancement (E(E)R/IRE) and the maximum enhancement (ME) are derived directly from the TIC. This makes it very simple and fast and this method is available in many post-processing software packages. However, outcomes are very sensitive to variations in acquisition protocols and depend strongly on used scanner and coil type.[13]

A second post-processing method entails the use of a **pharmacokinetic model (PKM)** that describes the physics of contrast behavior in an imaged volume. Tofts et al. introduced one of the earliest and mostly used models,[14] a modification of the Kety and Schmidt model[15] for a Gd-based, non-freely diffusible contrast agent. In this model, the arterial enhancement curve (the Arterial Input Function, AIF) and the absolute contrast concentration are used to calculate the parameters K^{trans} (the volume transfer constant between the plasma and extracellular extravascular space (EES) volume, v_e (the fractional volume of the EES), K_{ep} (the transfer constant between the EES and plasma) and v_p (Plasma volume). This approach provides absolute values that are supposed to be reproducible and can be compared even if they are obtained using different scanner settings.[14,16] However, extra MRI acquisitions are needed besides the DCE-MRI scan to calculate the absolute T1 values at baseline, a process needed to calculate the absolute contrast concentration of each following phase. The extra sequence needed for the T1 mapping results in longer acquisition times. Furthermore, Tofts' model relies on non-linear fitting of the data, something that leads to large uncertainties especially if the data are noisy. Moreover, Tofts' model requires the temporal resolution of the dynamic scan to be high in order to determine the AIF accurately. The latter needs to be either selected by hand, or with an automatic algorithm. Flow artefacts also affect the intensity of the AIF, which can result in inaccurate PKM parameters. Summing up, although quantitative, PKM is a complicated, non-robust and computationally demanding post-processing method that can hardly be implemented in the daily clinical radiological practice.

A third, more recently developed post-processing method is the **TIC-shape analysis**, which uses a technique that lies in between the two other techniques. It evaluates the form of the TIC in each voxel in an imaged volume and classifies these voxels into a category of 7 different enhancement-types ((TIC)-shape types).[17] These categories are: no enhancement (type 1), slow gradual enhancement (type 2), fast enhancement followed by a plateau phase (type 3), fast enhancement followed by washout (type 4), fast enhancement followed by a slower rate of enhancement (type 5), an arterial enhancement curve (type 6) and a category of unclassifiable enhancement curves

(type 7) (Image 1.1 (see under)). This method is thought to be robust, reproducible and sensitive, while not requiring heavy computations and additional MRI acquisitions.

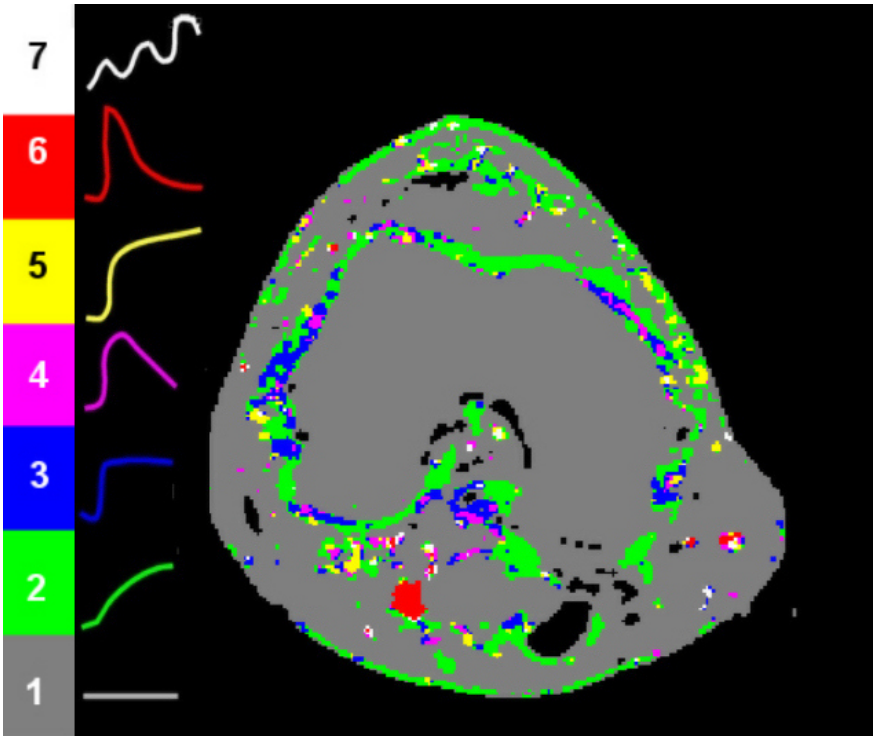

Image 1.1 A cross sectional image from a DCE-MRI scan of a knee joint, post-processed using TIC-shape analysis. The distribution of the various TIC-shapes (legend left side) across the joint is easily visualized.

DCE-MRI in inflammatory joint diseases

In RA patients, IRE/(E)ER have been correlated to acute phase reactants (CRP and ESR),[18–20] histologic signs of inflammation,[19,21,22] and vascularity scores[21–23] and is associated with erosive disease[24] in the shoulder. A higher ER has also been shown to be predictive for the development of erosions in wrist joints[25] and after treatment a decrease of (E)ER/IRE has been observed.[25–29] Pharmacokinetic modeling is less studied in inflammatory joint disease. It has been evaluated in the differentiation of OA vs RA[30] and in the evaluation of treatment in RA patients,[31,32] however there is little consistency in the model used.

Heterogeneity of inflammation

Many studies have used a single slice approach or manually selected one or a few region(s) of interest (ROI). In this way only a small part of the synovial tissue is

evaluated. It has been shown that inflammation in arthritis patients is not homogeneously distributed across the joint, both histologically[33,34] and on DCE-MRI.[20,23,35,36] This means that, when only a small part of the synovium is analyzed, the obtained measurements may over- or underestimate the degree of disease activity. Therefore, it is conceivable that a DCE-MRI analysis of a larger volume of the synovium/synovitis may provide a more precise estimation of local disease activity. Besides, it even may be helpful in the determination of the form of the disease.

Reproducibility of DCE-MRI in inflammatory joint diseases

As TIC-shape analysis is relatively easy, fast and cost-effective, we expect this post-processing technique to be ideal to study synovial inflammation. The reliability of this technique in arthritis patients, however, is unclear. Moreover, data concerning reproducibility of DCE-MRI analysis combined with any of the post-processing methods is scarce. The test-retest reproducibility has only been evaluated by 2 studies, both within one scanner. Østergaard et al. calculated an inter-MRI variation of 15% (evaluating the whole synovium on one slice) and of 27% (evaluating 4 points of interest) in the qualitative parameter REE/IRE in 6 patients within 3 days.[23] Hodgson et al measured the repeatability of PKM parameters in 8 arthritis patients within 14 days, also within one scanner. The test-retest root mean square coefficient of variation (RMS-CoV) of the parameter K^{trans} in this study was 27%, of the parameter Ve it was 16% and 78% in the parameter plasma volume (v_p).[31] There is more data on the inter-observer variation, all in studies using a qualitative post-processing method. Intraclass correlation coefficients (ICC) observed were very high (0.91-1.00) for the parameter IRE/(E)ER and the parameter ME (0.93-1.00)[20,25,36–38] making the inter-observer variability very low.
There is no data on the reproducibility of DCE-MRI between different scanners in arthritis patients and no direct comparison between different post-processing methods in the same patients. This is essential information in the scope of multicenter or multi-scanner research or patient care.

Clinical relevance

In early arthritis it is not always possible to distinguish the different forms of inflammatory joint diseases based on clinical presentation and laboratory findings. Besides, predicting the course of disease, for example whether the patient will develop erosions, is (often) not possible. Investigating the use of DCE-MRI as a biomarker that might be helpful in the early differentiation of inflammatory joint diseases and might predict disease outcome could therefore be very helpful. Besides, having a reliable, non-invasive marker of disease activity could be of pivotal value in the early evaluation of sometimes very costly treatment regiments.

Aims of this thesis

1. To evaluate whether DCE-MRI combined with the TIC-shape analysis is a viable method that can be used to evaluate joint inflammation in the earliest phases of arthritis.
2. To assess the robustness and reproducibility of the TIC-shape analysis, and to compare it with other existing post-processing methods.
3. To assess whether advanced imaging can provide insight in the pathophysiology of the 2 most common forms of arthritis: RA and SpA.
4. To assess whether DCE-MRI in combination with the TIC-shape analysis, PKM or both could be helpful in the differentiation between various inflammatory joint diseases arthritis types in the earliest phases of disease and predicting outcome.

Outline of this thesis

To evaluate if the TIC-shape analysis is a valid and useful method to evaluate and quantify synovial inflammation, in **chapter 2** we compare DCE-TIC-shape analysis parameter outcomes between healthy and inflamed synovial tissue.

To assess the robustness of TIC-shape analysis compared to qualitative analysis and PKM, in **chapter 3** we test the reproducibility of the three post-processing methods between imaging sessions on the same scanner and between different scanners, different magnetic fields and scanner settings in a cohort of early arthritis patients.

In **chapter 4** we compare PKM and TIC-shape analysis outcomes to each other and both outcomes to several selected clinical parameters to assess the relationships between both post-processing techniques and to evaluate which technique best reflects the disease activity.

Both in RA and SpA synovitis is an important feature of disease. MRI is known to reflect tissue characteristics of inflammation. Studying synovial inflammation by MRI between different inflammatory diseases and in different time points of the disease course might increase our insight in the pathogenesis of SpA and RA. Furthermore it might help in the differential diagnosis in patients presenting with arthritis.

In **chapter 5** we compare the presence of synovitis and enthesitis in early arthritis patients with SpA and RA to assess which compartment of the joint is affected in the early phases of arthritis.

As elevated serum levels of RA specific autoantibodies precede the onset of arthritis in RA it is possible to study characteristics of the synovium in the pre-clinical phase of

disease, before the onset of arthritis. In **chapter 6** we evaluate whether DCE-MRI combined with TIC-shape analysis or histology will already show signs of synovial inflammation in individuals with elevated RA specific autoantibodies but without arthritis.

To evaluate whether TIC-shape analysis is helpful in the diagnostic differentiation in early arthritis patients, in **chapter 7**, we apply this method to a cohort of early arthritis patients and compare TIC shape expression between the diagnostic patient subgroups.

Angiogenesis is one of the hallmarks of synovial inflammation. PKM is believed to provide quantitative parameters that reflect microcirculation and hereby synovial inflammation. In **chapter 8** we investigate the PKM parameters in patients with early arthritis and validate these parameters by assessing their correlation with the number of synovial endothelial cells (ECs).

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