



UvA-DARE (Digital Academic Repository)

Clinical and molecular classification of very early arthritis patients

van de Sande, M.G.H.

Publication date
2012

[Link to publication](#)

Citation for published version (APA):

van de Sande, M. G. H. (2012). *Clinical and molecular classification of very early arthritis patients*.

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

¹ Department of Radiology, Academic Medical Center/University of Amsterdam, Amsterdam, the Netherlands

² Division of Clinical Immunology and Rheumatology, Department of Internal Medicine, Academic Medical Center/University of Amsterdam, Amsterdam, the Netherlands

Radiology. 2009 Oct;253(1):234-40

nine

RHEUMATOID SYNOVIAL INFLAMMATION: PIXEL-BY-PIXEL
DYNAMIC CONTRAST ENHANCED MR IMAGING TIME-INTENSITY
CURVE SHAPE ANALYSIS: A FEASIBILITY STUDY

Christiaan van der Leij MD¹, Marleen GH van de Sande MD²,
Cristina Lavini PhD¹, Paul P Tak, MD PhD², Mario Maas, MD PhD¹

ABSTRACT

Purpose: To analyze the distribution of different shapes of time-intensity curves (TIC) in synovial tissue of patients with rheumatoid arthritis (RA) and to compare relative numbers of TIC-shapes between RA patients and healthy controls.

Materials and Methods: This prospective study was approved by the Institutional Review Board; patients and healthy controls gave written informed consent. A dynamic contrast-enhanced MRI (DCE-MRI) of the knee joint of five early RA patients and 5 healthy controls was performed (1.5 T, GRE, TR/TE/flip 8.1/3.5/30, 20*20 slices, temporal resolution 21s). Parametric maps showing 7 different TIC-shape types were created. Spatial information of the synovial TIC-shape distribution pattern and relative number of TIC-shapes were calculated in a 3 dimensional ROI. Relative TIC-shape numbers were compared using the non-parametric Mann-Whitney-U test.

Results: Synovial enhancement of RA patients consisted of type 2 TIC-shapes (slow enhancing) with heterogeneous zones of type 3, 4 and 5 TIC-shapes (fast enhancing followed by plateau phase (3), early washout phase (4), slow increase (5)) compared to almost only type 2 TIC-shapes in healthy controls. The heterogeneous zones were seen in the lateral and medial knee compartments and around the cruciate ligaments. A significantly higher relative number of type 4 TIC-shapes was observed in the RA patient group (16.5% vs 6.9% $P=0.008$).

Conclusion: The pixel-by-pixel DCE-MRI TIC shape analysis may be able to distinguish RA patients from healthy controls based on the relative number of type 4 TIC-shapes. This study provides the rationale for future research evaluating the utility of this approach in clinical practice.

INTRODUCTION

Magnetic resonance imaging (MRI) is increasingly used in the evaluation and follow up of rheumatoid arthritis (RA) patients. It allows the detailed evaluation of effusions and involved soft tissues like (inflamed) synovium, tendons and tendon sheets. Furthermore, using MRI, erosions are detected earlier and with a higher sensitivity compared to plain x-rays.[1; 2] To visualize (inflamed) synovial tissue on MR images, the use of intravenous contrast agent (Gd-DTPA) is recommended.[3] It increases the synovial signal intensity on T1 weighted acquisitions and synovial conspicuity from surrounding tissues and joint effusions.

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is the time-dependent registration of changes in MR-signal intensity during, and after the intravenous injection of a contrast agent. Results are rendered as time-intensity curve (TIC) that can be post-processed either using descriptive parameters (e.g. rate of (early) enhancement (R(E)E), maximal enhancement (ME)) or pharmacokinetic modeling (e.g. Tofts model[4]). In RA, descriptive DCE-MRI parameters have been shown to correlate with clinical disease activity parameters like ESR and CRP,[5-7] histologic signs of inflammation [6; 8; 9] and vascularity scores.[6; 8; 10]. Therefore, these DCE-MRI parameters have been suggested as objective markers of synovial inflammation.

It is known that both post-processing methods have some disadvantages. Descriptive parameters are directly derived from the measured signal intensity, which make them sensitive to variations in acquisition protocols and dependent on other factors, such as scanner type and used coil.[11] Therefore, data cannot be directly compared between different MRI settings, which limits their use in research and clinical settings. Pharmacokinetic parameters represent absolute physiological values (e.g. permeability) and are, therefore, relatively insensitive to variable MR scanner settings.[4; 12] However, outcomes depend on the model used. Moreover, additional MRI sequences other than the clinically relevant DCE-MRI scan are required which prolongs the acquisition time. In addition, because of their greater complexity compared to the relatively simple descriptive post-processing method, these are more computationally demanding and more prone to errors.[13]

To overcome the aforementioned disadvantages of the different DCE-MRI (post-processing) techniques, a new DCE-MRI analysis and imaging method was developed, using a 3D pixel by pixel method to visualize differently shaped TICs within a volume of interest. [13]

The purpose of this study was to analyze the distribution of different shapes of time-intensity curves in synovial tissue of patients with RA and to compare relative numbers of TIC-shapes between RA patients and healthy controls.

MATERIAL AND METHODS

Patients

This prospective study was approved by the Institutional Review Board; patients and healthy controls gave written informed consent. This study was financially supported by the non-profit Dutch Arthritis Association; no conflicts of interest were noted.

Five consecutive patients that fulfilled the 1987 ACR classification criteria for RA [14] at the time of inclusion with an active arthritis of a knee joint were selected from an early arthritis

cohort between February and November 2004. The inclusion criteria of this early arthritis cohort consisted of an active arthritis, based on clinical findings, of at least a knee, wrist or ankle joint with a disease duration of less than one year. Patients were excluded if they were taking or had previously taken disease-modifying antirheumatic drugs or corticosteroids. Five healthy controls were asked to voluntarily enroll in this study between January and April 2008. Exclusion criteria consisted of having knee complaints, knee trauma or knee surgery in the medical history. Both patients and healthy controls were excluded if there were contraindications for (contrast-enhanced) MRI (claustrophobia, metal implants, elevated serum creatinine). No patients were excluded due to clinical or technical reasons.

In both the patients and the healthy control group, an equal number of men and women was analyzed. Age and weight were also comparable between the two groups (table 1). The mean age was 39 years (range 22-70) for the total group, 47 (26-70) for the male group and 31 (22-52) for the female group.

MRI acquisition

Images were acquired on a 1.5 T MRI-scanner (GE Signa Horizon Echospeed, LX9.0, General Electric Medical Systems, Milwaukee) using a 3D T1-weighted gradient echo dynamic sequence that consisted of 20 consecutive images of 20 slices with a temporal resolution of 22 seconds (TR/TE/flip 8.1/3.5/30, slice thickness 4 mm, FOV 18 cm, 256*256 matrix, axial orientation). The total imaging time was 7 minutes and 19 seconds.

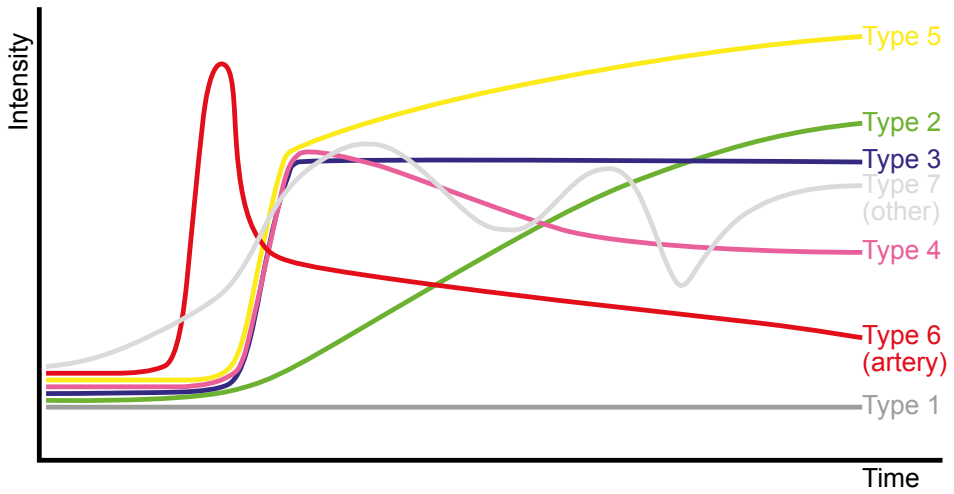
Patients and healthy controls were placed supine with the knee joint centrally in the magnetic field in a dedicated extremity coil (Quadrature Detection). The inflamed knee of the RA patients and an arbitrarily chosen knee of the healthy controls were imaged. A 20 gauge

Table 1. Patient characteristics, descriptive and time-intensity curve (TIC)-shape parameters.

	Healthy controls	Patients	P-value
Patient characteristics			
Female/Male	2/3	3/2	0.99
Age	37.0 (20.3-53.7)	41.2 (15.1-67.3)	0.99
Weight	75.6 (45.4-105.8)	85.2 (57.4-113.0)	.548
Left/Right knee	3/2	3/2	0.99
Enhancing volume and descriptive parameters			
EV	19.3 (2.1-36.4)	53.0 (12.1-93.9)	.151
MME	0.58 (0.44-0.73)	1.10 (0.51-1.68)	.056
MIS	10.6 (8.8-12.5)	14.9 (9.4-20.4)	.222
Relative number of TIC shapes			
Type 2	74.2% (61.5-86.9)	61.1% (51.0-71.3)	.056
Type 3	2.8%(1.0-4.6)	6.6% (1.1-12.1)	.056
Type 4	6.9% (3.5-10.2)	16.5% (8.6-24.4)	.008
Type 5	8.4% (2.7-13.9)	7.4% (4.3-10.4)	0.99

Means and 95% confidence intervals shown for illustrative purposes (EV= enhancing volume in ml, MME=mean maximal enhancement, MIS=mean initial slope)

needle infusion line was inserted in the right antecubital vein. Sixty seconds after the initiation of the dynamic protocol, a bolus of a Gd-DTPA contrast agent (Magnevist, Schering® Berlin, 0.1 mg/kg) followed by a 15 ml saline chase was delivered at an injection rate of 5 ml/s using an automatic injection device (MEDRAD® Spectris MR Injector).



NINE

Figure 1. 7 Different time-intensity curve (TIC)-shape types. Type 1: no enhancement, type 2: slow enhancing, type 3: fast enhancing followed by plateau phase, type 4: fast enhancing followed by washout phase, type 5: fast enhancing followed by gradual increase, type 6: artery, type 7: other.

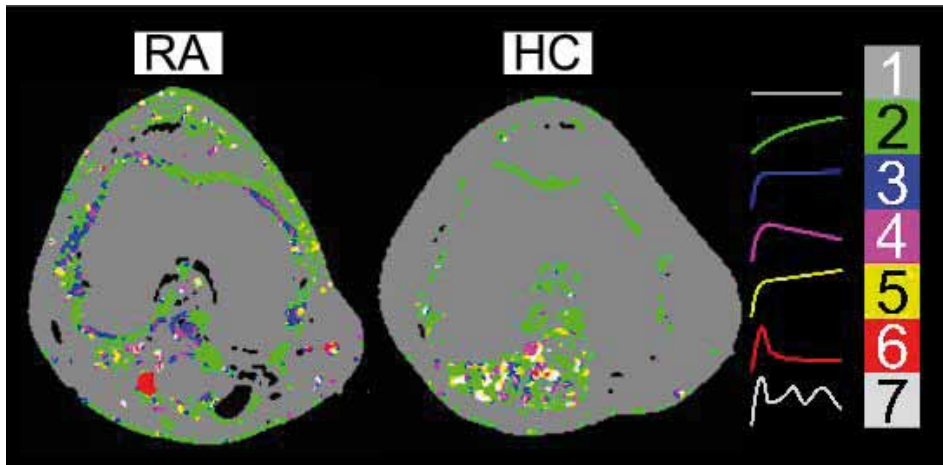


Figure 2. Parametric TIC-shape map of one rheumatoid arthritis (RA) patient (left) and one healthy control (HC) (right) with legend of TIC-shapes. The synovial layer of the patient is markedly thickened compared to the HC, and shows enhancement heterogeneity lateral, medial and intercondylar.

MRI-data analysis

Images were transferred to a standard pc workstation and processed using a program developed in house on Matlab (Matlab®, The Mathworks™, Natick, Mass.). This program analyzes the time-dependent signal intensity changes (TIC) of every voxel in an imaged volume. Every voxel with its TIC is classified into one of 7 predefined TIC shape categories which is associated to a unique color (figure 1). This results in a color-coded shape map for each image slice (figure 2) and 3d parametric TIC-shape volumes when analyzing contiguous slices.[13]

In a similar way, the image analysis program calculates the ME (defined as the difference between maximal signal intensity and baseline, divided by signal baseline), time to peak (TTP, defined as the time between the start of enhancement and maximal signal intensity) and maximal slope of increase (MSI, defined as the largest positive signal difference between two successive scans) for each voxel in the imaged volume. The total number of generated maps for every subject was 80 (4 parameters, 20 image slices).

We compared the maximum number of slices in every joint, to make sure the largest possible volume of synovium was analyzed. We also compared the same number of slices in every patient and healthy control. No synovium was expected distal to the tibial plateau, so this was chosen as the most distal border. While the joint coverage differed slightly between the individual knee joints, the maximal number of contiguous images was 12, so this volume was analyzed in every individual.

Regions of interest (ROIs) were manually delineated on the 12 selected image slices in every subject. This was done on the ME maps, because of the increased conspicuity of synovial tissue on these images. The ROI was drawn to exclude enhancing skin and muscle tissue. The non-enhancing tissue (e.g. bone and cartilage) within the ROIs is ignored by the analysis software, which leaves the enhancing synovial tissue and vascular structures within the ROI for analysis.

The selection of the image slices and ROI delineation was performed by one investigator (CvdL, 1 year experience in DCE-MR musculoskeletal imaging), supervised by a radiologist (MM, 15 years of experience in musculoskeletal radiology) to maintain consistency of the results.

TIC shape analysis

Visual analysis of color coded TIC-shape maps

The synovium was analyzed visually and semi-automatically. The thickness and TIC-shape enhancement pattern of synovial tissue were compared between the patient and healthy control group on all parametric TIC-shape maps. The thickness was semi-quantitatively scored 0-2 (0: no or minimal enhancing volume, 1: medium enhancing volume, 2: large enhancing volume). The distribution of the different TIC-shapes throughout the synovium was described. The occurrence of (zones with) type 3, 4 and 5 TIC-shapes (instead of type 2) was visually scored as present (score 1) or absent (score 0) in the lateral compartment, medial compartment, suprapatellar bursa, intercondylar and patellofemoral region.

Semi-automatic analysis

To correct for different sizes of knee joints, we used the relative number of enhancing voxels per TIC-shape type. This is defined as the absolute number of voxels of a TIC-shape type divided by the absolute numbers of TIC-shape type 2-7 together times 100%. For statistical analysis,

only type 2, 3, 4 and 5 TIC-shapes were of interest. The other enhancing TIC-shape types (6 and 7) were used only for the calculation of the relative number per TIC-shape type.

The other parameters used were the mean maximal enhancement (MME), defined as the ME of all voxels with TIC-shape type 2-7 enhancement divided by the number of voxels, the mean initial slope (MIS), defined as the MSI of all TIC-shape type 2-7 enhancing voxels divided by the number of voxels, and the enhancing volume (EV), defined as the total number of all TIC-shape type 2-7 enhancing voxels within the volume of interest multiplied by the voxel volume in cc.

After three months, the ROI delineation process and post-processing were performed a second time by the same investigator (CvdL) on all subjects, blinded and in random order, to test for intra-observer reliability.

Statistical Analysis

Standard statistical software (SPSS version 12, SPSS Inc., Chicago, IL.) was used for the statistical analysis. The Fisher exact test was used to test for differences in gender and knee side between the patient group and healthy controls. As we assumed the relative number of TIC-shapes to be continuous data which can vary between 0 and 1, we used the non-parametric Mann-Whitney-U test. The Mann-Whitney-U test was also used to test for differences in age and weight, ROI size, descriptive DCE-MRI parameters and EV. Intraclass correlation coefficients (ICC) were calculated to determine the intra-observer reliability (15). Statistical significance was defined as $P < 0.05$.

RESULTS

TIC shape analysis

Synovial thickness

On the parametric TIC-shape maps (figure 2), the enhancing synovial layer scores were as follows: Three patients showed large enhancing volume (score 2), and one patient medium enhancing volume (score 1). One patient showed minimal enhancing volume (score 0). Two healthy controls showed a medium enhancing volume (score 1), and three showed minimal enhancing volume (score 0).

Synovial enhancement pattern

The synovial tissue of the healthy controls consisted predominantly of type 2 TIC-shapes with sporadic small zones of the type 3, 4 and 5 TIC-shapes, while the synovial tissue of the RA patients consisted mainly of type 2 TIC-shapes with multiple zones of type 3, 4 and 5 TIC-shapes. This was also seen in the patient with minimal enhancing synovial volume.

Zones with heterogeneous enhancement (type 3, 4 and 5 TIC-shapes) were seen in the lateral compartment in 4 patients and two healthy controls, in the medial compartment in 5 patients and none of the healthy controls, in the suprapatellar bursa in two patients and none of the healthy controls, intercondylar in 4 patients and 2 healthy controls and patellofemoral in 2 patients and none of the healthy controls.

Semi-automatic analysis

A significantly higher relative number of type 4 TIC-shapes was observed in the patient group compared to the healthy controls (6.9% vs 16.5%, $P = 0.008$) (Table 1, figure 3). The relative number of the types 2, 3 and 5 TIC-shapes did not significantly differ between the two groups.

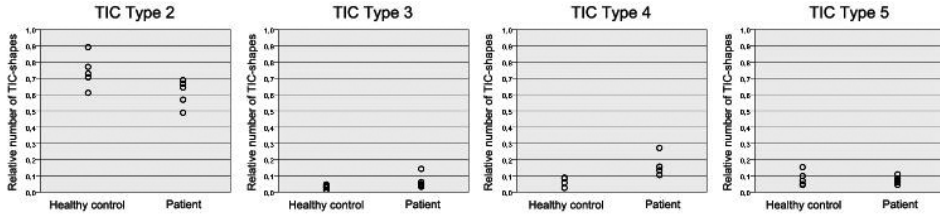


Figure 3. Relative number of type 2-5 TIC-shapes. The healthy control group is displayed left. The relative number of type 4 TIC-shapes (third on the row) differed significantly ($P=0.008$).

No significant differences were observed in the descriptive parameters MME and MIS, and the EV (figure 4). Also ROI size did not significantly differ (mean volume of interest (12 ROI's) in the patient group: 281 ml (range 207-392), healthy controls: 229 ml (177-260), $P=0.548$).

The intraobserver reliability in the total group was very high for the TIC-shape parameters (type 2: ICC 1.00 (95% CI 0.97-1.00, $P<0.001$), type 3: 1.00 (0.98-1.00, $P<0.001$) type 4: 1.00 (0.98-1.00, $P<0.001$) type 5: 0.99 (0.96-1.00, $P<0.001$), the descriptive parameters (MME: 1.00 (1.00-1.00, $P<0.001$) MIS: 0.99 (0.97-1.00, $P<0.001$), EV (0.99 (0.96-1.00, $P<0.001$)) and ROI size (0.95 (0.79-0.99, $P<0.001$)).

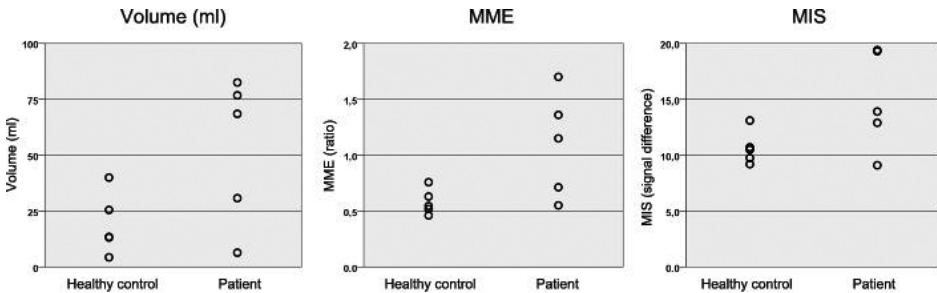


Figure 4. Enhancing volume (EV) in ml, mean maximal enhancement (MME) and maximum initial slope (MIS). The healthy control group is displayed left.

DISCUSSION

The purpose of our study was to investigate if TIC-shape analysis may assist in detecting synovial inflammation. These preliminary results suggest that, using TIC-shape analysis, it may be possible to demonstrate a significant difference between early RA patients and healthy controls, and that this approach allows the evaluation of enhancement heterogeneity. Our results also suggest that synovial thickness within early RA patients is generally increased compared to healthy controls, and enhancement heterogeneity differs from healthy controls. Enhancement heterogeneity, however, not only occurs within the synovium of RA patients, but, to a lesser degree, also in healthy controls.

The relative number of type 4 TIC-shapes differed significantly between the patient group and healthy controls. In general, time-intensity curves reflect the uptake of contrast agent in tissue, representing tissue physiology. The type 4 TIC-shape consists of a rapid enhancement phase followed by an early washout. The rate of initial enhancement has been correlated to histological vascularity scores, meaning that a higher initial rate reflects increased tissue vascularisation.[6; 8; 10] The early washout phase is most likely explained by the backflux of contrast agent due to the increased vascular permeability. Both increased tissue vascularisation and permeability are characteristics of inflamed synovial tissue. This explains why especially type 4 TIC-shape shows a clear difference between healthy controls and RA patients with an inflamed knee joint. Another, perhaps additional, explanation for the early washout phase could be the passive diffusion of contrast agent into effusion fluid. However, first signs of contrast agent diffusion into joint effusions have been described 6-8 minutes after intravenous contrast agent injection.[16] Therefore, it appears unlikely that this would be an important contributing factor considering the scan length of 7 minutes and 19 seconds.

The association of TIC-shapes and disease is quite new in arthritis research, but has proven its value in the differentiation of malignant tumors from benign tumors. In breast lesions, for example, a sensitivity and specificity has been reported of 91% and 83%, respectively, in relating malignancy to differently shaped TICs.[17] In this study, TIC-shapes with initial rapid enhancement followed by a plateau phase or washout (i.e. in our analysis type 3 and 4) were associated with malignancy. In synovial sarcomas, Rijswijk et al. reviewed DCE-MRI enhancement of 10 synovial sarcomas and reported a type 4 TIC-shape in 5, a type 5 in 3, a type 3 in 1 and a type 2 enhancement in only one patient.[18] As the inflammatory process of RA shares some features with malignant lesions such as enhanced vascularisation, increased vessel permeability and invasive growth of the synovial tissue into bone and cartilage, we believed that this method might be of use in the diagnostic and/or prognostic classification of arthritis patients as well. Demonstrating differences between inflamed and non-inflamed joints is a first step in evaluating the potential of this approach.

Our study shows that this approach is able to visualize enhancement heterogeneity within the synovium of patients with RA. This synovial heterogeneity consisted of zones with initial fast enhancing TIC-shape types (type 3-5) that were seen in the lateral and medial compartments and intercondylar. Heterogeneity of enhancement within synovial tissue of rheumatoid arthritis patients has been described in previous publications using DCE-MRI, and locations described are consistent with our results.[6; 7; 16; 19; 20] These results are consistent with previous observations showing heterogeneity on the cellular and molecular level. [21; 22]

In most studies focusing on the analysis of synovium using DCE-MRI, small ROIs were analyzed on a limited number of slices. This can be disadvantageous as small volume analysis of heterogeneous tissue may result in the under- or overestimation of inflammatory activity. Besides, enhancement data within the ROI are usually averaged to one parameter or TIC. Spatial information regarding the heterogeneous enhancement within the ROI is lost and small focal areas of inflammation in larger ROIs might be averaged out. As our technique provides analysis of the entire synovium, a better estimation of actual disease activity compared to small volume analysis is expected.

Another feature of this pixel by pixel based whole synovium analysis is the possibility to allocate zones with specific types of TIC-shapes. It can be hypothesized that the appearance of

TIC-shape types that show a high initial slope (i.e. type 3, 4 and 5) represent a more aggressive inflammation, which may precede nearby erosion formation. Hermann et al. [23] described a higher rate of enhancement in patients with erosive RA compared to non-erosive disease of the shoulder, and Huang et al. [24] found higher enhancement rates predictive for development of erosions in the wrists. Spatial information about the location of the erosions and synovial enhancement heterogeneity was, however, not obtained. The technique used in our study is able to visualize enhancement distribution throughout the synovial volume. Comparing the location of zones with fast enhancing TIC-shapes with the location of erosion formation in longitudinal prospective studies might reveal a prognostic feature of pixel-by-pixel TIC-shape analysis.

Our study is limited by the small numbers of patients and healthy controls included. However, as we did observe a significant difference in type 4 TIC-shape, we believe TIC-shape analysis may be able to distinguish inflamed from non-inflamed joints and our present study provides the rationale to test this in larger cohorts of patients. Another limitation of this study is the lack of data about the reproducibility of this technique within patients scanned at two different time points within one scanner and between different scanners. Assessing the reproducibility fell beyond the scope of our pilot study, but before applying DCE-MRI TIC-shape measurements to larger patient groups, this issue needs to be addressed. The TIC classification scheme we used in this work produces results that can be dependent on the signal-to-noise ratio (SNR) of the images. Therefore we used thresholds to exclude pixels with excessive low SNR.[13] The choice of the thresholds for this study was based on experimental observations; the thresholds needed to be low enough to include all of the synovium in the classification, while preventing misclassification (type 7 as in [13]). As the same threshold was applied to all patients and healthy controls, we can expect that possible misclassifications would have affected all scans in the same degree. Therefore, we believe the SNR threshold settings have not influenced the outcomes presented here.

In summary, these preliminary results suggest that, using TIC-shape analysis, it may be possible to demonstrate a significant difference between early RA patients and healthy controls, and that this approach allows the evaluation of enhancement heterogeneity.

Advances in Knowledge:

- » Pixel-by-pixel time-intensity curve (TIC) shape analysis can differentiate rheumatoid arthritis (RA) patients and healthy controls based on the relative number of “aggressive” (i.e. type 4) TIC shapes.
- » Pixel-by-pixel TIC-shape analysis visualizes synovial enhancement heterogeneity.

Implications for patient care:

This study provides the rationale for future research evaluating the utility of this approach in clinical practice as it might become a biomarker that is useful in further diagnostic classification or and in determining prognosis.

Funding: Dutch Arthritis Association; Grant Number: 07-1-101

REFERENCES

1. Østergaard M, Hansen M, Stoltenberg M, Jensen KE, Szkudlarek M, Pedersen-Zbinden B, et al. New radiographic bone erosions in the wrists of patients with rheumatoid arthritis are detectable with magnetic resonance imaging a median of two years earlier. *Arthritis Rheum.* 2003 Aug ;48(8):2128-31.
2. Døhn UM, Ejbjerg BJ, Hasselquist M, Narvestad E, Møller J, Thomsen HS, et al. Detection of bone erosions in rheumatoid arthritis wrist joints with magnetic resonance imaging, computed tomography and radiography. *Arthritis Res. Ther.* 2008 ;10(1):R25.
3. Kursunoglu-Brahme S, Riccio T, Weisman MH, Resnick D, Zvaifler N, Sanders ME, et al. Rheumatoid knee: role of gadopentetate-enhanced MR imaging. *Radiology.* 1990 Sep ;176(3):831-5.
4. Tofts P, Brix G, Buckley D, Evelhoch J, Henderson E, Knopp M, et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusible tracer: standardized quantities and symbols. *J. Magn Reson. Imaging.* 1999 ;10(3):223-232.
5. Cimmino M, Innocenti S, Livrone F, Magnaguagno F, Silvestri E, Garlaschi G. Dynamic gadolinium-enhanced magnetic resonance imaging of the wrist in patients with rheumatoid arthritis can discriminate active from inactive disease. *Arthritis Rheum.* 2003 May ;48(5):1207-1213.
6. Østergaard M, Stoltenberg M, Lovgreen-Nielsen P, Volck B, Sonne-Holm S, Lorenzen I. Quantification of synovitis by MRI: correlation between dynamic and static gadolinium-enhanced magnetic resonance imaging and microscopic and macroscopic signs of synovial inflammation. *Magn Reson. Imaging.* 1998 ;16(7):743-754.
7. Palosaari K, Vuotila J, Takalo R, Jartti A, Niemela R, Haapea M, et al. Contrast-enhanced dynamic and static MRI correlates with quantitative ⁹⁹Tcm-labelled nanocolloid scintigraphy. Study of early rheumatoid arthritis patients. *Rheumatology.(Oxford).* 2004 Nov ;43(11):1364-1373.
8. Tamai K, Yamato M, Yamaguchi T, Ohno W. Dynamic magnetic resonance imaging for the evaluation of synovitis in patients with rheumatoid arthritis. *Arthritis Rheum.* 1994 ;37(8):1151-1157.
9. Gaffney K, Cookson J, Blake D, Coumbe A, Blades S. Quantification of rheumatoid synovitis by magnetic resonance imaging. *Arthritis Rheum.* 1995 Nov ;38(11):1610-1617.
10. Gaffney K, Cookson J, Blades S, Coumbe A, Blake D. Quantitative assessment of the rheumatoid synovial microvascular bed by gadolinium-DTPA enhanced magnetic resonance imaging. *Ann. Rheum. Dis.* 1998 Mar ;57(3):152-157.
11. Hodgson RJ, O'Connor P, Moots R. MRI of rheumatoid arthritis image quantitation for the assessment of disease activity, progression and response to therapy. *Rheumatology.* 2008 Jan 1;47(1):13-21.
12. Jackson A. Analysis of dynamic contrast enhanced MRI. *Br J Radiol.* 2004 ;77 Spec No 2S154-66.
13. Lavini C, de Jonge M, van de Sande M, Tak P, Nederveen A, Maas M. Pixel-by-pixel analysis of DCE MRI curve patterns and an illustration of its application to the imaging of the musculoskeletal system. *Magn Reson. Imaging.* 2007 Jun ;25(5):604-612.
14. Arnett F, Edworthy S, Bloch D, McShane D, Fries J, Cooper N, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 1988 Mar ;31(3):315-324.
15. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull.* 1979 Mar ;86(2):420-8.
16. Yamato M, Tamai K, Yamaguchi T, Ohno W. MRI of the knee in rheumatoid arthritis: Gd-DTPA perfusion dynamics. *J. Comput. Assist. Tomogr.* 1993 ;17(5):781-785.
17. Kuhl C, Mielcarek P, Klaschik S, Leutner C, Wardelmann E, Gieseke J, et al. Dynamic breast MR imaging: are signal intensity time course data useful for differential diagnosis of enhancing lesions? *Radiology.* 1999 Apr ;211(1):101-110.
18. van Rijswijk C, Hogendoorn P, Taminiau A, Bloem J. Synovial sarcoma: dynamic contrast-enhanced MR imaging features. *Skeletal Radiol.* 2001 Jan ;30(1):25-30.
19. Rhodes LA, Tan AL, Tanner SF, Radjenovic A, Hensor EMA, Reece R, et al. Regional variation and differential response to therapy for knee synovitis adjacent to the cartilage-pannus junction and suprapatellar pouch in inflammatory arthritis: Implications for pathogenesis and treatment. *Arthritis Rheum.* 2004 ;50(8):2428-2432.
20. Østergaard M, Stoltenberg M, Henriksen O, Lorenzen I. Quantitative assessment of synovial inflammation by dynamic gadolinium-enhanced magnetic resonance imaging. A study of the effect of intra-articular methylprednisolone on the rate of early synovial enhancement. *Rheumatology.* 1996 Jan 1;35(1):50-59.

21. Tak PP, Smeets TJ, Daha MR, Kluin PM, Meijers KA, Brand R, et al. Analysis of the synovial cell infiltrate in early rheumatoid synovial tissue in relation to local disease activity. *Arthritis Rheum.* 1997 Feb;40(2):217-25.
22. Kasperkovitz PV, Timmer TCG, Smeets TJ, Verbeet NL, Tak PP, van Baarsen LGM, et al. Fibroblast-like synoviocytes derived from patients with rheumatoid arthritis show the imprint of synovial tissue heterogeneity: evidence of a link between an increased myofibroblast-like phenotype and high-inflammation synovitis. *Arthritis Rheum.* 2005 Feb;52(2):430-41.
23. Hermann K, Backhaus M, Schneider U, Labs K, Loreck D, Zuhlsdorf S, et al. Rheumatoid arthritis of the shoulder joint: comparison of conventional radiography, ultrasound, and dynamic contrast-enhanced magnetic resonance imaging. *Arthritis Rheum.* 2003 Dec;48(12):3338-3349.
24. Huang J, Stewart N, Crabbe J, Robinson E, McLean L, Yeoman S, et al. A 1-year follow-up study of dynamic magnetic resonance imaging in early rheumatoid arthritis reveals synovitis to be increased in shared epitope-positive patients and predictive of erosions at 1 year. *Rheumatology.(Oxford).* 2000 Apr;39(4):407-416.