Development and clinical applications of the time intensity curve shape analysis in dynamic contrast enhanced MRI: a pixel-by-pixel approach
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CHAPTER 5

Rheumatoid synovial inflammation: pixel-by-pixel dynamic contrast enhanced MR imaging time-intensity curve shape analysis: a feasibility study.

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ABSTRACT

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

**Materials and Methods:** This prospective study was approved by the institutional review board; patients and control subjects gave written informed consent. Dynamic contrast magnetic resonance (MR) imaging of the knee joint in five patients with early RA and in five control subjects was performed. Parametric maps showing seven TIC shape types were created. Spatial information of the synovial TIC shape distribution pattern and relative number of TIC shapes were calculated on a three-dimensional region of interest. Relative TIC shape numbers were compared by using a nonparametric Mann-Whitney U test.

**Results:** Synovial enhancement in patients with RA consisted of type 2 TIC shapes (slow enhancement) with heterogeneous zones of types 3 (fast enhancement followed by plateau phase), 4 (fast enhancement followed by early washout phase), and 5 (fast enhancement followed by slow enhancement increase) TIC shapes, compared with almost only type 2 TIC shapes in control subjects. 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 patient group compared with the control group (16.5% vs. 6.9%, P = .008).

**Conclusion:** The pixel-by-pixel dynamic contrast enhanced MR imaging TIC shape analysis may help distinguish patients with RA from control subjects on the basis of the relative number of type 4 TIC shapes. This study provides the rationale for future research to evaluate the utility of this approach in clinical practice.
Magnetic resonance (MR) imaging has been increasingly used in the evaluation and follow-up of patients with rheumatoid arthritis (RA). It allows detailed evaluation of effusions and involved soft tissues, such as inflamed synovium, tendons, and tendon sheets. Furthermore, by using MR imaging, erosions are detected earlier and with a higher sensitivity than with conventional radiography (1,2). To visualize inflamed synovial tissue on MR images, the use of intravenous contrast agent (gadopentetate dimeglumine) 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 MR imaging is the time-dependent registration of changes in MR signal intensity during and after intravenous injection of a contrast agent. Results are rendered as time intensity curves (TICs) that can be postprocessed either by using descriptive parameters (e.g., rate of early enhancement, maximal enhancement) or pharmacokinetic modelling (e.g., Tofts’ model [4]). In RA, descriptive dynamic contrast enhanced MR imaging parameters have been shown to correlate with clinical disease activity parameters like erythrocyte sedimentation rate and C-reactive protein level (5–7), histologic signs of inflammation (6,8,9), and vascularity scores (6,8,10). Therefore, these dynamic contrast enhanced MR imaging parameters have been suggested as objective markers of synovial inflammation. Both postprocessing methods have some disadvantages. Descriptive parameters are directly derived from the measured signal intensity, which makes them sensitive to variations in acquisition protocols and dependent on other factors such as imager type and coil used (11). Therefore, data cannot be directly compared between different MR imaging settings, which limits their use in research and clinical settings. Pharmacokinetic parameters represent absolute physiologic values (e.g., permeability) and are, therefore, relatively insensitive to variable MR imager settings (4,12). However, outcomes depend on the model used. Moreover, additional MR imaging sequences other than the clinically relevant dynamic contrast enhanced MR imaging acquisition are required, which prolongs the acquisition time. In addition, because of the greater complexity of pharmacokinetic modelling compared with 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 dynamic contrast enhanced MR imaging (post-processing) techniques, a new dynamic contrast-enhanced MR imaging analysis
and imaging method was developed by using a three-dimensional pixel-by-pixel method to help visualize differently shaped TICs within a volume of interest (13). The purpose of this study was to analyze the distribution of different shapes of TICs in synovial tissue of patients with RA and to compare relative numbers of TIC shapes between patients with RA and healthy control subjects.

MATERIALS AND METHODS

Patients
This prospective study was approved by the institutional review board; patients and healthy control subjects gave written informed consent. No conflicts of interest were noted. Five consecutive patients who fulfilled the 1987 American College of Rheumatology classification criteria for RA (14) at the time of inclusion and who had 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 active arthritis, based on clinical findings, of at least a knee, wrist, or ankle joint, with disease duration of less than 1 year. Patients were excluded if they were taking or had previously taken disease-modifying antirheumatic drugs or corticosteroids. Five healthy control subjects were asked to voluntarily enrol 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 control subjects were excluded if there were contraindications for contrast enhanced MR imaging (claustrophobia, metal implants, or elevated serum creatinine level). No patients were excluded because of clinical or technical reasons. In both the patient and the healthy control subject groups, 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 years) for the total group, 47 years (range, 26–70 years) for the male group, and 31 years (range, 22–52 years) for the female group.

MR Imaging Acquisition
Images were acquired with a 1.5-T MR imager (GE Signa Horizon Echospeed, LX9.0; GE Medical Systems, Milwaukee, Wis) by using a three-dimensional T1-weighted gradient-echo dynamic sequence that resulted in 20 consecutive images of 20 sections with a temporal resolution of 22 seconds (repetition time, 8.1 msec; echo time, 3.5 msec; flip angle, 30°; section thickness, 4 mm; field of view, 18 cm;
256 × 256 matrix; axial orientation). The total imaging time was 7 minutes 19 seconds.

**Figure 1:** Graph of seven TIC shape types. Type 1 shows no enhancement; type 2, slow enhancement; type 3, fast enhancement followed by plateau phase; type 4, fast enhancement followed by washout phase; type 5, fast enhancement followed by gradual enhancement increase; type 6, arterial enhancement; type 7, unclassified enhancement (other).

**Figure 2:** Parametric TIC shape map of one patient with RA and one healthy control subject (HC), with legend of TIC shapes. The synovial layer of the patient is markedly thickened compared with that of the control subject and shows enhancement heterogeneity in lateral compartment, medial compartment, and intercondylar region.

Patients and healthy control subjects were placed in the supine position with the knee joint centrally in the magnetic field in a dedicated extremity coil (quadrature coil).
The inflamed knee of the patients with RA and an arbitrarily chosen knee of the healthy control subjects were imaged. A 20-gauge needle infusion line was inserted in the right antecubital vein. Sixty seconds after the initiation of the dynamic protocol, a bolus of a contrast agent (0.1 mg per kilogram of body weight, gadopentetate dimeglumine, Magnevist; Schering, Berlin, Germany) followed by a 15-mL saline chase was delivered at an injection rate of 5 mL/sec by using an automatic injection device (Spectris; Medrad, Warrendale, Pa).

<table>
<thead>
<tr>
<th>Healthy Controls</th>
<th>Patients</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male (n)</td>
<td>2/3</td>
<td>3/2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.0 (20.3-53.7)</td>
<td>41.2 (15.1-67.3)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.6 (45.4-105.8)</td>
<td>85.2 (57.4-113.0)</td>
</tr>
<tr>
<td>Right to left knee ratio</td>
<td>3/2</td>
<td>3/2</td>
</tr>
</tbody>
</table>

**Enhancing volume and descriptive parameters**

<table>
<thead>
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<th></th>
<th>Healthy Controls</th>
<th>Patients</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhancing Volume (mL)</td>
<td>19.3 (2.1-36.4)</td>
<td>53.0 (12.1-93.9)</td>
<td>.151</td>
</tr>
<tr>
<td>Mean Maximum Enhancement</td>
<td>0.58 (0.44-0.73)</td>
<td>1.10 (0.51-1.68)</td>
<td>.056</td>
</tr>
<tr>
<td>Mean Initial Slope</td>
<td>10.6 (8.8-12.5)</td>
<td>14.9 (9.4-20.4)</td>
<td>.222</td>
</tr>
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</table>

**Relative number of TIC-shapes (%)**

<table>
<thead>
<tr>
<th>Type</th>
<th>Healthy Controls</th>
<th>Patients</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>74.2 (61.5-86.9)</td>
<td>61.1% (51.0-71.3)</td>
<td>.056</td>
</tr>
<tr>
<td>3</td>
<td>2.8 (1.0-4.6)</td>
<td>6.6% (1.1-12.1)</td>
<td>.056</td>
</tr>
<tr>
<td>4</td>
<td>6.9 (3.5-10.2)</td>
<td>16.5% (8.6-24.4)</td>
<td>.008</td>
</tr>
<tr>
<td>5</td>
<td>8.4 (2.7-13.9)</td>
<td>7.4 (4.3-10.4)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

**Table 1.** Patient characteristics and Dynamic Contrast enhanced MR imaging Parameters

**MR Imaging Data Analysis**

Images were transferred to a standard personal computer workstation and were processed by using a program developed in-house with software (Matlab; Mathworks, Natick, Mass). This program analyzes the time dependent signal intensity changes of every voxel in an imaged volume. Every voxel with its TIC is classified into one of seven predefined TIC shape categories, which is associated with a color (Fig 1). This results in a color coded shape map for each image section (Fig 2) and three-dimensional parametric TIC shape volumes when analyzing contiguous sections (13).

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

We compared the maximum number of sections in every joint to make sure the largest possible volume of synovium was analyzed. We also compared the same number of sections in every patient and healthy control subject. 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 sections in every participant. This was done on the maximal enhancement maps, because of the increased conspicuity of synovial tissue on these images. The ROI was drawn to exclude enhancing skin and muscle tissue. The nonenhancing tissue (eg, 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 sections and ROI delineation was performed by one investigator (C.v.d.L., with 1 year of experience in musculoskeletal dynamic contrast enhanced MR imaging) who was supervised by a radiologist (M.M., with 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 subject groups on all parametric TIC shape maps. The thickness was semi-quantitatively scored (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 of 1) or absent (score of 0) in the lateral compartment, medial compartment, suprapatellar bursa, intercondylar region, and patellofemoral region.

*Semiautomatic analysis.* To correct for different sizes of knee joints, we used the relative number of enhancing voxels per TIC shape type. This was defined as the
absolute number of voxels of a TIC shape type divided by the absolute numbers of TIC shape types 2–7 added together and multiplied by 100%. For statistical analysis, only type 2, 3, 4, and 5 TIC shapes were of interest. The other enhancing TIC shape types (types 6 and 7) were used only for the calculation of the relative number per TIC shape type.

The other parameters used were mean maximum enhancement (defined as the maximal enhancement of all voxels with TIC shape type 2–7 enhancement divided by the number of voxels), mean initial slope (defined as the maximal slope of interest of all TIC shape type 2–7 enhancing voxels divided by the number of voxels), and the enhancing volume (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 milliliters).

After 3 months, the ROI delineation process and postprocessing were performed a second time in all subjects in random order by the same investigator (C.v.d.L.), who was blinded to results, to test for intra-observer reliability.

![Graphs of relative number of type 2–5 TIC shapes in healthy control subjects and patients. Relative number of type 4 TIC shapes differed significantly between the two groups (P=.008).](image)

**Figure 3:** Graphs of relative number of type 2–5 TIC shapes in healthy control subjects and patients. Relative number of type 4 TIC shapes differed significantly between the two groups (P=.008).

**Statistical Analysis**

Standard software (SPSS, version 12; SPSS, Chicago, Ill) was used for statistical analysis. The Fisher exact test was used to test for differences in sex and knee side between the patients and healthy control subjects. Because we assumed the relative number of TIC shapes to be continuous data, which can vary between 0 and 1, we used a nonparametric Mann-Whitney U test. A Mann-Whitney U test was also used to test for differences in age and weight, ROI size, descriptive dynamic contrast enhanced MR imaging parameters, and enhancing volume. Intraclass correlation coefficients were calculated to determine intra-observer reliability (15).
A P value less than .05 was considered to indicate a statistically significant difference.

RESULTS

Synovial Thickness
On the parametric TIC shape maps (Fig 2), the enhancing synovial layer scores were as follows: Three patients showed large enhancing volume (score of 2), and one patient showed medium enhancing volume (score of 1). One patient showed minimal enhancing volume (score of 0). Two healthy control subjects showed medium enhancing volume (score of 1), and three showed minimal enhancing volume (score of 0).

Synovial Enhancement Pattern
The synovial tissue of the healthy control subjects 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 patients with RA 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 four patients and in two healthy control subjects, in the medial compartment in five patients and in none of the healthy control subjects, in the suprapatellar bursa in two patients and in none of the healthy control subjects, in the intercondylar region in four patients and in two healthy control subjects, and in the patellofemoral region in two patients and in none of the healthy control subjects.

Semiautomatic Analysis
A significantly higher relative number of type 4 TIC shapes was observed in patients compared with healthy control subjects (6.9% vs 16.5%, P = .008) (Table, Fig 3). The relative number of the type 2, 3, and 5 TIC shapes did not significantly differ between the two groups.

No significant differences were observed in the descriptive parameters mean maximal enhancement and mean initial slope and enhancing volume (Fig 4). ROI size did not significantly differ (mean volume of interest of 12 ROIs) between the patient group (281 mL; range, 207–392 mL) and the healthy control subject group (229 mL; range, 177–260 mL) (P = .548).
The intraobserver reliability in the total group was high for the TIC shape parameters (type 2: intraclass correlation coefficient [ICC], 1.00 [95% confidence interval: 0.97, 1.00]; P = .001; type 3: ICC, 1.00 [95% confidence interval: 0.98, 1.00]; P = .001; type 4: ICC, 1.00 [95% confidence interval: 0.98, 1.00]; P = .001; type 5: ICC, 0.99 [95% confidence interval: 0.96, 1.00]; P = .001), the descriptive parameters (mean maximum enhancement: ICC, 1.00 [95% confidence interval: 1.00, 1.00]; P = .001; mean initial slope: ICC, 0.99 [95% confidence interval: 0.97, 1.00]; P = .001), enhancing volume (ICC, 0.99 [95% confidence interval: 0.96, 1.00]; P = .001), and ROI size (ICC, 0.95 [95% confidence interval: 0.79, 0.99]; P = .001).

**Figure 4**: Graphs of enhancing volume in milliliters, mean maximal enhancement (MME), and maximal initial slope (MIS) in healthy control subjects and patients.

**DISCUSSION**

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

The relative number of type 4 TIC shapes differed significantly between patients and healthy control subjects. In general, TICs reflect the uptake of contrast agent in tissue, which represents 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 histologic vascularity scores, which means that a higher initial rate reflects increased tissue vascularisation (6,8,10). The early washout phase is most likely explained by the back flux of contrast agent due to increased vascular permeability. Both increased tissue vascularisation and permeability are characteristics of inflamed synovial tissue.

This explains why type 4 TIC shape especially showed a clear difference between healthy control subjects and patients with RA 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, when the imaging length of 7 minutes 19 seconds is considered.

The association of TIC shapes and disease is quite new in arthritis research but has proved its value in the differentiation of malignant from benign tumors. In breast lesions, for example, a sensitivity and specificity of 91% and 83%, respectively, has been reported in relating malignancy to differently shaped TICs (17). In this study, TIC shapes with initial rapid enhancement followed by a plateau phase or washout (ie, types 3 and 4) were associated with malignancy. For synovial sarcomas, van Rijswijk et al (18) reviewed dynamic contrast enhanced MR imaging enhancement of 10 synovial sarcomas and reported a type 4 TIC shape in five patients, a type 5 shape in three patients, a type 3 shape in one patient, and a type 2 shape in one patient. Because the inflammatory process of RA shares some features with malignant lesions, such as enhanced vascularization, 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 patients with arthritis as well. Demonstrating differences between inflamed and non-inflamed joints is a first step in evaluating the potential of this approach.

Our study results show that this approach helps visualize enhancement heterogeneity within the synovium of patients with RA. This synovial heterogeneity consisted of zones with initial fast enhancing TIC shape types (types 3–5) that were seen in the lateral and medial compartments and the intercondylar region. Heterogeneity of enhancement within synovial tissue of patients with RA by using dynamic contrast enhanced MR imaging has been described in previous studies,
and locations described were consistent with our results (6,7,16,19,20). These results were consistent with previous observations that showed heterogeneity on the cellular and molecular level (21,22).

In most studies on the analysis of synovium by using dynamic contrast enhanced MR imaging, small ROIs were analyzed on a limited number of sections. This can be disadvantageous because 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. Because our technique provides analysis of the entire synovium, a better estimation of actual disease activity compared with 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 (ie, types 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 than in those with nonerosive 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 helps 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 was limited by the small numbers of patients and healthy control subjects included. However, because we observed a significant difference in type 4 TIC shape between patients and control subjects, we believe TIC shape analysis may help distinguish inflamed from noninflamed joints, and our present study provides the rationale to test this in larger cohorts of patients. Another limitation of this study was the lack of data about the reproducibility of this technique within patients imaged at two different time points within one imager and imaged with
different imagers. Assessing the reproducibility fell beyond the scope of our pilot study, but before applying dynamic contrast enhanced MR imaging TIC shape measurements to larger patient groups, this issue needs to be addressed. The TIC classification scheme we used in this study produces results that can be dependent on the signal-to-noise ratio of the images. Therefore, we used thresholds to exclude pixels with excessively low signal-to-noise ratio (13). The choice of the thresholds for this study was on the basis of 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 Lavini et al [13]). Because the same threshold was applied to all patients and healthy control subjects, we can expect that possible misclassifications would have affected all acquisitions in the same degree. Therefore, we believe the signal-to-noise ratio threshold settings have not influenced the outcomes presented here.

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

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REFERENCES


