Magnetic resonance imaging in juvenile idiopathic arthritis diagnosis and follow-up, beyond imagination
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Chapter 9

Pixel-by-pixel analysis of DCE-MRI curve shape patterns in knees of active and inactive juvenile idiopathic arthritis patients

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Submitted
Abstract

Objectives
To compare dynamic contrast-enhanced (DCE)-MRI parameters and the relative number of time intensity curve (TIC) shapes as derived from pixel-by-pixel DCE-MRI TIC-shape analysis between knees of clinically active and inactive juvenile idiopathic arthritis (JIA) patients.

Methods
This prospective observational study was approved by the institutional review board and written informed consent was obtained. DCE-MRI datasets of JIA patients were prospectively obtained. Patients were classified into two clinical groups: active disease ($n = 49$) and inactive disease ($n = 36$). Parametric maps, showing 7 different TIC shape types, were created per slice. Statistical measures of the relative number of different TIC shapes, maximal enhancement (ME), maximal initial slope (MIS), initial area under the curve (iAUC), time-to-peak (TTP), and enhancing volume (EV) of each voxel were calculated in a three-dimensional volume of interest of the synovial membrane.

Results
Imaging findings from 85 JIA patients were analyzed. Significantly higher numbers of TIC shape 4 ($P = 0.001$), median ME ($P = 0.004$), MIS ($P = 0.001$), iAUC ($P = 0.002$), and EV ($P = 0.013$) were observed in clinically active compared with inactive patients. TIC shape 5 was more present in the clinically inactive patients ($P = 0.018$). The intra-observer reliability was very good regarding all DCE-MRI parameters (ICC = 0.93-1.00)

Conclusions
The pixel-by-pixel DCE-MRI TIC-shape analysis method proved capable of differentiating clinically active from inactive JIA patients by the difference in the number of TIC shapes 4 and 5, as well as by the descriptive parameters ME, MIS, iAUC and EV. Therefore, it may serve as an objective, more quantitative outcome measure of imaging in clinical trials and future research.
Introduction

Juvenile idiopathic arthritis (JIA) is characterized by prolonged synovial inflammation that may lead to articular cartilage lesions and bone erosions, which are, together with inflammation, responsible for disability and reduced quality of life in JIA (1-4). Since more effective anti-rheumatic drugs are increasingly used in JIA, over the past decade, the key treatment goal is to obtain complete suppression of joint inflammation in order to prevent destructive changes (5, 6). To assess whether this goal has been reached in individual patients, as well as to compare the effects of different treatment schedules more sensitive, objective and accurate outcome measures are needed.

In JIA, synovitis is the most critical hallmark of disease activity. The inflamed synovial membrane is characterized by hypertrophy, increased numbers of inflammatory cells and neo-vascularization. Currently, contrast-enhanced magnetic resonance imaging (MRI) is considered to be the preferred imaging modality for the assessment of synovial hypertrophy (7, 8). Moreover, MRI is the most sensitive tool in the detection of erosive changes of cartilage and bone (9, 10). Despite its superiority in assessing disease activity and structural damage, MRI lacks quantitative analysis methods for the assessment of disease activity and for monitoring response to therapy. Consequently, the use of MRI as an outcome measure in both clinical practice and research is still under-utilized.

In both JIA and adult rheumatoid arthritis (RA), dynamic contrast-enhanced MRI (DCE-MRI) has been suggested as an accurate and objective outcome measure, since descriptive DCE-MRI parameters have been proven to correlate with clinical disease activity parameters and the degree of histological synovial inflammation (11-15). DCE-MRI is the time-dependent registration of changes in MRI signal during and after the injection of an intravenous contrast agent, resulting in time-intensity curves (TICs). The TIC shape represents characteristics of the tissue, such as vascularization, tissue perfusion, capillary permeability and interstitial space volume, and can be post-processed either by using semi-quantitative descriptive parameters or pharmacokinetic modeling.

To be valuable as an outcome measure in daily practice and clinical trials, a measure must be able to discriminate groups of interest. As the DCE-MRI pixel-by-pixel analysis method has been shown to be feasible in RA and valuable in distinguishing RA patients from healthy controls or non-RA patients (16, 17), we hypothesized that the same DCE-MRI analysis method could help to differentiate clinically active and inactive JIA patients based on the relative number of TIC shapes.
and semi-quantitative descriptive DCE-MRI parameters. Therefore, the aim of our study was to assess the discriminative value of the DCE-MRI pixel-by-pixel analysis method by comparing semi-quantitative descriptive DCE-MRI parameters and the relative number of TIC shapes as derived from DCE-MRI between knees of clinically active and clinically inactive JIA patients.

Materials and Methods

Patients
This study was approved by the institutional review board. Written informed consent was obtained from the parents of each child. No conflicts of interest were noted. Patients visited one of the outpatient clinics of three tertiary pediatric rheumatology centers. At time of presentation, all patients had clinical and laboratory assessments, followed by MRI. Inclusion criteria were clinical active arthritis (active disease; newly diagnosed JIA or relapsing/unremitting disease), or follow-up of JIA patients with clinical inactive disease who had a history of clinically evident arthritis in at least one knee (inactive disease). All clinically active patients fulfilled the international league of associations for rheumatology (ILAR) criteria for JIA, defined as an arthritis of unknown etiology that begins before the age of 16 and persists for at least 6 weeks (18). JIA patients with clinically inactive disease met the preliminary criteria for inactive disease in JIA as described by Wallace et al. (19). For ILAR classification, all newly diagnosed JIA patients were clinically evaluated and reclassified if necessary after a period of 6 months (18). Exclusion criteria were: a history of intra-articular corticosteroid injection within the last six months, the need for anesthesia during the MRI examination, and general contraindications for MRI.

Clinical assessment
Physical examination was performed by the same experienced pediatric rheumatologists during the research period. Clinical assessment included a 67-joint count defining the presence of swelling, pain on motion/tenderness and limited range of motion. A physician’s global assessment of overall disease activity, a patient’s global assessment of overall well-being and an assessment of patient’s pain were all measured on a 100 mm visual analogue scale. Functional ability was evaluated by the Dutch version of the childhood health assessment questionnaire (CHAQ) (20, 21). Laboratory tests included the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) level.


**MRI protocol**

In order to optimize feasibility, the MR images were obtained using an open-bore 1.0-T magnet (Panorama HFO, Philips Medical Systems, Best, the Netherlands) (22). No sedation was used. DCE-MR images were acquired by using an axial three-dimensional T1-weighted gradient-echo dynamic sequence that resulted in 24 consecutive images of 18 sections with a temporal resolution of 15.7 seconds (TR 8.1 ms; TE 6.9 ms; slice thickness 4 mm; field of view 180 × 180 mm; matrix 256 × 256).

The children were placed in the supine position with the knee joint centrally in the magnetic field in a dedicated knee coil. MRI of the clinical most involved knee was performed. With respect to the JIA patients in clinical remission, the former most affected joint was scanned. If there were no differences in clinical activity between knees, the right knee was considered to be the target joint. A 22-gauge needle infusion line was inserted in the antecubital vein. Forty-five seconds after the initiation of the DCE-MRI sequence, a bolus of a contrast agent (0.1 mmol per kilogram of body weight, gadobutrol, Bayer healthcare, Berlin, Germany) followed by a 15 ml saline chase was delivered at an injection rate of 3 ml/sec by using an automatic injection device (Medrad, Warrendale, PA, USA).

**DCE-MRI analysis**

DCE-MR images were processed by using an in-house developed software program (Dynamo) running on Matlab (Mathworks, Natick, Mass, USA) (23, 24). The program analyzes the time-dependent signal intensity changes of every voxel in an imaged volume. Every voxel with its TIC was classified into one of seven predefined TIC shape categories (non-enhancing (1), slow enhancing (2), fast enhancing followed by either a plateau phase (3), washout phase (4) or gradual increase (5), arterial patterns (6) and undefined (7)), which is associated with a color (Figure 1). This resulted in a color-coded shape map (Figure 1) or when analyzing contiguous sections in three-dimensional parametric TIC shape volumes (24). Similarly, the program calculates the median maximal enhancement (ME; maximal enhancement of all voxels with TIC shape type 2–7 enhancement), median time to peak (TTP; time between the start of enhancement and maximal signal intensity), median maximal initial slope (MIS; maximal slope of increase of all TIC shape type 2–7 enhancing voxels), median initial area-under-the-curve (iAUC, calculated for 90 seconds time interval after contrast injection), and the enhancing volume (EV, total volume in milliliters of all enhancing voxels i.e. with TIC shape type 2–7) for each voxel in the imaged volume.
Figure 1. TIC shape categories resulting in a parametric color-coded TIC shape map. Type 1, no enhancement; type 2, slow enhancement; type 3, fast enhancement followed by a 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, enhancing but unclassified (not shown)).

As no synovium was expected distal to the proximal tibial epiphysis, the proximal tibial epiphysis 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 16, so this volume was analyzed in every patient. Regions of interest (ROIs) were manually delineated on the selected image sections in every patient on T1-weighted images. The ROI was drawn to exclude enhancing skin, large vessels, muscle tissue, and the epiphyseal plate. Only the enhancing synovial tissue within the ROI is analyzed, as the non-enhancing tissue within the ROIs is ignored by the analysis method. To maintain consistency of the results, the selection of the image sections and ROI delineation was performed by a radiology trainee (RH, 5 years of experience in musculoskeletal radiology), supervised by a musculoskeletal radiologist (MM, 18 years of experience in musculoskeletal radiology and experienced with the DCE-MRI technique (16, 17).

**TIC shape analysis**

To correct for different sizes of knees, 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. For statistical analysis, only type TIC shape type 2, 3, 4, and 5 were of interest (TIC shape types 1, 6 and 7 reflecting “no enhancement”, “arterial pattern”, and “undefined pattern”, respectively). The other enhancing TIC shape types (types 6 and 7) were used only for the calculation of the relative number per TIC shape type. To analyze the intra-reader reliability of the TIC shape analysis method, the ROI delineation process and postprocessing were performed a second time in the first 10 consecutive JIA patients within an interval of at least six months by the same reader.
Statistics
Descriptive statistics were reported in terms of percentages, means, medians, ranges, inter-quartile ranges and standard deviations. The student’s t-test, Fisher exact test, and Mann-Whitney U test were used to analyze differences between groups. All tests assumed a two-tailed probability and a $P$ value of less than 0.05 indicated a significant difference. The single measure intraclass correlation coefficient (ICC) was used to analyze reliability, and was classified as follows: ICC $<0.40 = \text{poor}$, $\geq 0.40–0.60 = \text{moderate}$, $>0.60-0.80 = \text{substantial}$, and $>0.80 = \text{good}$ reliability. All data were analyzed by using SPSS version 19.0 (IBM SPSS, Chicago, ILL, USA).

Results
Patients
In this prospective study, MRI data sets of 100 patients were collected between May 2011 and October 2012. Fifteen (15.0%) patients were excluded: 7 patients were excluded due to movement artifacts, and 8 patients, who initially had suspected JIA, were later reclassified because of a non-rheumatological ailment. Therefore, findings from 85 JIA patients (64.7% female patients) with a mean age of 13.6 years (SD 2.5) were analyzed. The frequency of JIA subtypes was as follows: 28 (32.9%) persistent oligoarthritis, 12 (14.1%) extended oligoarthritis, 27 (31.8%) polyarthritis, 3 (3.5%) psoriatic arthritis, 12 (14.1%) enthesitis-related arthritis, and 3 (3.5%) undifferentiated JIA. Of these patients, 31 (36.5%) received no medication, 15 (17.6%) patients NSAIDs only, 27 (31.8%) patients received additional synthetic DMARDs, whereas 12 (14.1%) patients were treated with biological DMARDs including tumor necrosis factor-α inhibitors (all in combination with methotrexate).

Of these 85 JIA patients, 49 (57.6%) had clinical active disease (26 newly diagnosed JIA, 23 relapsing/unremitting disease), and 36 (42.4%) had clinical inactive disease. An extensive overview of the clinical characteristics and differences between the studied groups is presented in Table 1. Concerning the clinically active JIA patients, no significant differences were observed between the newly diagnosed JIA patients and the JIA patients with relapsing/unremitting disease in age, gender, physician’s global assessment of overall disease activity, C-HAQ scores, number of active joints, number of joints with limited range of motion, and laboratory measures of inflammation (ESR and CRP). Obviously, differences were found concerning the disease duration at inclusion (0.2 vs. 5.6 years, $P < 0.001$), and also regarding the patient’s global assessment of overall well being (54 vs. 26, $P = 0.004$), and the self-assessment of patient’s pain (64 vs. 40, $P = 0.002$, respectively).
Table 1. Patient characteristics of 85 JIA patients

<table>
<thead>
<tr>
<th></th>
<th>Active disease</th>
<th>Inactive disease</th>
<th>P value&lt;br&gt;</th>
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<tr>
<td></td>
<td>n = 49 (57.6%)</td>
<td>n = 36 (42.4%)</td>
<td></td>
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<tr>
<td>No. (%) of female patients</td>
<td>31 (63.3)</td>
<td>24 (66.7)</td>
<td>0.820&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age at study visit, mean years (SD)</td>
<td>13.2 (2.7)</td>
<td>14.2 (2.0)</td>
<td>0.046&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Disease duration at study visit, years</td>
<td>0.4 (0.1 – 5.8)</td>
<td>6.6 (3.6 – 8.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inactive disease duration at study visit, years</td>
<td>-</td>
<td>0.9 (0.7 – 1.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Physician’s global assessment of overall disease activity&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22 (14 – 44)</td>
<td>0 (0 – 0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient's global assessment of overall well-being&lt;sup&gt;c&lt;/sup&gt;</td>
<td>47 (10 – 63)</td>
<td>1 (0 – 25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient's pain assessment&lt;sup&gt;e&lt;/sup&gt;</td>
<td>52 (31 – 72)</td>
<td>3 (0 – 32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-HAQ score&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.875 (0.250 – 1.625)</td>
<td>0.125 (0.000 – 0.875)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of active joints</td>
<td>2 (1 – 5)</td>
<td>0 (0 – 0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of joints with limited range of motion</td>
<td>1 (0 – 4)</td>
<td>0 (0 – 0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm/hour</td>
<td>5 (4 – 9)</td>
<td>4 (2 – 7)</td>
<td>0.044</td>
</tr>
<tr>
<td>C-reactive protein level, mg/l</td>
<td>0.6 (0.0 – 2.0)</td>
<td>0.4 (0.0 – 1.1)</td>
<td>0.274</td>
</tr>
</tbody>
</table>

<sup>a</sup> Except where otherwise indicated, values are median (inter-quartile range)
<sup>b</sup> P values indicate differences between groups. Except where otherwise indicated, the Mann-Whitney U test was used.
<sup>c</sup> Fisher’s exact test
<sup>d</sup> Student’s t-test
<sup>e</sup> Measured on a 0-100 mm visual analogue scale (0 = best, 100 = worst)
<sup>f</sup> Units; 0 = best, 3 = worst

TIC shape analysis

As shown in Figure 2, a significantly higher relative number of TIC shape 4 was observed in the clinically active group compared with the inactive JIA patients (7.6% vs. 5.2%, P = 0.001). In contrast to the higher relative number of TIC shape 5 in the clinically inactive versus active patients (16.1% vs. 14.0%, P = 0.018). An example of TIC shape maps of a patient with active disease and inactive disease is depicted in Figure 3.

Descriptive DCE-MRI parameters

A significant difference between active and inactive JIA patients was observed with respect to the ME, MIS, iAUC and EV as shown in Figure 4 (0.51 vs. 0.47, P = 0.004; 16.0 vs. 14.0, P = 0.001; 47.8 vs. 38.2, P = 0.002; 99.1 vs. 80.5, P = 0.013, respectively). Figure 5 shows an example of parametric ME maps of a patient with active disease and inactive disease.

As illustrated in Figures 2 and 4, no significant differences were observed in the relative number of TIC shapes and the descriptive DCE-MRI parameters between patients with newly diagnosed JIA (blue dots) and patients with relapsing/unremitting disease (red dots).
Figure 2. Scatter dot plots (including medians and inter-quartile ranges) of relative number of TIC shapes 2, 3, 4 and 5 in 49 clinically active (blue dots newly diagnosed JIA, red dots relapsing / unremitting disease), and 36 clinically inactive JIA patients. *P* values indicate differences between groups (Mann-Whitney *U* test).

Figure 3. Example of parametric TIC shape maps of a 17 years old girl with active disease (left) and a 14 years old girl with inactive disease (right). The synovial membrane of the clinically active JIA patient is obviously thickened and shows a more heterogeneous TIC shape pattern (clearly more TIC shapes 4) compared with the inactive patient.
Figure 4. Scatter dot plots (including medians and inter-quartile ranges) of semi-quantitative descriptive DCE-MRI parameters including the (a) median maximal enhancement (ME), (b) maximal initial slope (MIS), (c) initial area under the curve (iAUC), and (d) enhancing volume (EV) in milliliters in 49 clinically active (blue dots newly diagnosed JIA, red dots relapsing / unremitting disease), and 36 clinically inactive JIA patients. P values indicate differences between groups (Mann-Whitney U test).

Figure 5. Example of parametric median maximal enhancement (ME) maps of a 17 years old girl with active disease (left) and a 14 years old girl with inactive disease. The synovial membrane of the clinically active JIA patient shows markedly increased maximal enhancement values compared with the inactive JIA patient.
**Intra-observer reliability of DCE-MRI TIC-shape analysis method**

The intra-observer reliability was good for all TIC shape parameters (ICC 0.93-1.00). For the TIC shape parameters intra-observer variability was as follows: type 2 ICC 0.99 (95%CI 0.97-1.00), type 3 ICC 0.99 (95%CI 0.99-1.00), type 4 ICC 0.93 (95%CI 0.72-0.98), and type 5 ICC 1.00 (95%CI 1.00-1.00). Concerning intra-observer reliability of the descriptive DCE-MRI parameters ICC's were as follows: ME, ICC 0.99 (95%CI 0.96-1.00); MIS, ICC 1.00 (95%CI 1.00-1.00); TTP, ICC 0.97 (95%CI 0.87-0.99); iAUC, ICC 1.00 (95%CI 0.99-1.00); and EV, ICC 0.98 (95%CI 0.92-1.00).

**Discussion**

In this study we compared semi-quantitative descriptive DCE-MRI parameters and the relative number of DCE-MRI TIC shapes between knees of clinically active and inactive JIA patients. The pixel-by-pixel DCE-MRI TIC-shape analysis was able to differentiate clinically active from inactive JIA patients using the relative number of TIC shapes 4 and 5 and descriptive parameters ME, MIS, iAUC and EV.

MRI is the most sensitive imaging modality for the evaluation of synovitis, providing the most critical hallmark of disease activity in JIA (8). However, MRI is still underutilized in both daily practice and clinical trials owing to the lack of quantitative analysis methods. Several scoring methods have been proposed in JIA (25, 26), but these can not be used to quantify the heterogeneous disease activity of the synovial membrane. With DCE imaging, the outcome of statistical measures derived from the TIC-shape analysis could differentiate clinically active from inactive arthritis in JIA. A significantly higher relative number of TIC shapes 4 were observed in the clinically active group, in line with studies in RA patients (16, 17). Although we observed a significant difference between groups regarding the relative number of TIC shapes 4, there is considerable overlap in the relative number of TIC shapes between clinically active and inactive JIA patients. The discriminative value of TIC type 4 in JIA is, therefore, uncertain and should be evaluated in prospective follow-up studies. Furthermore the possibility to combine the TIC shape with the other semi-quantitative measures (ME, etc) to provide a multi-feature analysis should be further investigated.
In the current study, we used a pixel-by-pixel DCE-MRI TIC-shape analysis method that was developed based on a three-dimensional pixel-by-pixel classification. This helps to visualize differently shaped TICs within a volume of interest (24). Compared to the semi-quantitative descriptive or pharmacokinetic modeling analysis methods, this pixel-by-pixel technique is less computationally demanding and more reliable, because it does not make use of model assumptions or non-linear fitting.

In JIA, DCE-MRI has been used to examine synovitis (14, 27). For the first time, we assessed the TIC shape of every pixel in the whole synovial volume in JIA. The pixel-by-pixel analysis method allows direct visualization of the heterogeneously distributed disease, which avoids under- or overestimation of the level of inflammation. The TIC shape of every pixel is determined by physiological tissue characteristics, such as vascularization, vessel perfusion, vessel permeability and interstitial space volume (28, 29). Joint inflammation, and the accompanying neo-vascularization, can therefore affect these tissue characteristics. TIC shapes 3, 4 and 5 are characterized by fast initial enhancement, while only TIC shape 4 is typified by fast enhancement followed by a quick washout phase. Vessel permeability and interstitial space volume are both known to be of significance during this washout phase (30). This could explain the observed differences between clinically active and inactive JIA patients.

Concerning the semi-quantitative descriptive DCE-MRI parameters, significant differences were observed between the studied groups. The semi-quantitative descriptive parameters are directly obtained from the measured signal intensity, rendering them susceptible to variations in imaging protocols and to technical factors such as scanner type and coil type (31). Therefore, the interpretation of descriptive parameters – in contrast to the TIC shape analysis method – is difficult, making research site comparison based solitary on semi-quantitative descriptive DCE-MRI parameters complicated.

In the current study, the pixel-by-pixel DCE-MRI TIC-shape analysis method was shown to be a reliable method as the intra-observer reliability concerning the analysis method was good regarding all parameters. The ICC's ranged from ICC 0.93 up to ICC 1.00. These values are comparable to reliability scores described previously (16).

We observed a significant higher relative number of TIC shape 5 in the clinically inactive JIA group. Whether this observation can be interpreted as a normal expression of the growing knee or as residual activity after an evident arthritis, is unclear. Thus, our study was in fact limited by the lack of healthy controls.
In conclusion, the pixel-by-pixel DCE-MRI TIC-shape analysis method was able to differentiate groups of clinically active and inactive JIA patients with respect to the relative number of TIC shapes 4 and 5 and descriptive parameters ME, MIS, iAUC and EV. Our results support the use of the pixel-by-pixel DCE-MRI technique as an objective and quantitative outcome measure in clinical trials and future research. The considerable overlap observed between the studied groups suggests the need for a multi-feature analysis, which might be able to discriminate patient groups more accurately, and prospective follow-up studies are warranted for the evaluation of the discriminative value of these features in JIA.
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