Crohn’s disease, advances in MRI
Ziech, M.L.W.

Citation for published version (APA):
Chapter 5

Dynamic Contrast-Enhanced MRI in patients with luminal Crohn’s disease

M.L.W. Ziech
C. Lavini
M.W.A. Caan
C.Y. Nio
P.C.F. Stokkers
S. Bipat
C.Y. Ponsioen
A.J. Nederveen
J. Stoker

Published in European Journal of Radiology.
Introduction

Grading of severity of disease activity is important in patients with Crohn’s disease to optimally determine the treatment strategy and response to treatment. Because clinical and laboratory parameters do not represent disease activity well, other methods are used such as ileocolonoscopy and MRI. A meta-analysis established that MRI was 91% accurate in detecting severe disease but only 62% in patients with mild disease or remission\(^1\). Efforts are therefore made to increase the accuracy of MRI in mild or inactive disease. Mild disease activity can be detected at colonoscopy as superficial ulcerations of the bowel wall. On standard MR enterography sequences their visibility is suboptimal\(^2\) and have a weak agreement when assessed by multiple observers\(^3\).

Gadolinium is an extracellular contrast agent that rapidly passes from the vasculature into the extracellular extravascular space, resulting in parenchymal enhancement. The increase in signal intensity of actively diseased bowel is caused by increased vascular permeability of inflammatory tissue, possibly with a positive correlation between mesenteric hypervascularity/vascular permeability and disease activity. This hypothesis is supported by findings by Brahme and Lindstrom\(^4\) who have shown that the degree of vascularity is closely related to the intensity of the inflammatory reaction in surgical specimens of Crohn’s disease. This finding is important as analysis of the time-dependent changes of signal intensity after administration of contrast medium by DCE-MRI reflects the status of tissue microcirculation and this may add valuable information about disease severity, such as the presence of mild ulcerative disease. Earlier studies on contrast enhancement of luminal Crohn’s disease have either determined enhancement ratios of pathological bowel wall versus normal bowel wall\(^5,6\) or subjectively determined the degree of enhancement (e.g. mild, moderate or marked enhancement)\(^7\).

Previous DCE-MRI studies have mainly focused on the presence of active versus inactive disease\(^8,11\) or used a reference standard based on clinical symptoms\(^6\). However, with these methods no differentiation is possible between the different disease activity stages necessary for management.

The purpose of this prospective study was to evaluate objective DCE-MRI parameters for the evaluation of disease severity in patients with luminal Crohn’s disease, with an emphasis on mild ulcerative disease.

Abstract

Objectives:

To prospectively assess DCE-MRI as compared to conventional sequences in patients with luminal Crohn’s disease.

Methods:

Patients with Crohn’s disease undergoing MRI and ileocolonoscopy within one month had DCE-MRI (3T) during intravenous contrast injection of gadobutrol, single shot fast spin echo sequence and 3D T1-weighted spoiled gradient echo sequence, a dynamic coronal 3D T1-weighted fast spoiled gradient were performed before and after gadobutrol. Maximum enhancement and initial slope of increase were calculated for four colon segments (ascending colon + coecum, transverse colon, descending colon + sigmoid, rectum) and (neo)terminal ileum. CRP, CDAI, per patient and per segment CDEIS and disease duration were determined.

Mean values of the (DCE-)MRI parameters in each segment from each patient were compared between four disease activity groups (normal mucosa, non-ulcerative lesions, mild ulcerative and severe ulcerative disease) with Mann-Whitney test with Bonferroni adjustment. Spearman correlation coefficients were calculated for continuous variables.

Results:

Thirty-three patients were included (mean age 37 years; 23 females, median CDEIS 4.4). Maximum enhancement and initial slope of increase correlated weakly with segmental CDEIS (\(r=0.485\) and \(r=0.206\)) and maximum enhancement per patient correlated moderately with CDEIS (\(r=0.551\)). Maximum enhancement was significantly higher in segments with mild (0.378) or severe (0.388) ulcerative disease compared to normal mucosa (0.304) (\(p<0.001\)). No ulcers were identified at conventional sequences. Maximum enhancement correlated with disease duration in diseased segments (\(r=0.492\)), not with CDAI and CRP.

Conclusions:

DCE-MRI can be used as a method for detecting Crohn’s disease ulcerative lesions.
Ethical permission was obtained by the hospitals medical ethics committee and written informed consent was obtained from all patients.

Forty consecutive patients with known Crohn’s disease who were scheduled for ileocolonoscopy and MR enterography within one month for assessment of disease activity were prospectively included from February 2009 to November 2010. Exclusion criteria were age <18 years and contraindications for undergoing MR imaging (such as pacemakers, metallic implants etc).

**Materials and methods**

Patients fasted four hours before the exam and drank 1600 ml of Mannitol (2.5%) (Baxter, Utrecht, the Netherlands) one hour before the scan. Images were acquired with patients in supine position using a 3-T MR imaging unit (Intera, Philips Healthcare, Best, the Netherlands) with a 16-channel torso phased array body coil. The protocol consisted of axial and coronal single shot fast spin echo (SSFSE) sequences followed by a coronal fat-saturated SSFSE sequence and coronal 3D T1-weighted spoiled gradient echo sequence (SPGE) (table 1). A dynamic coronal 3D T1-weighted fast spoiled gradient echo (FFE) sequence (DCE-MRI sequence) was performed, consisting of 450 consecutive scans with a temporal resolution of 0.82 seconds with a spatial resolution of 2.78x2.78x2.5mm (FOV: 400x400x 35mm) for a total duration of 6 minutes and 11 seconds. The sequence was performed in free-breathing; patients were instructed to breathe regular in a slow frequency. The 3D DCE-MRI sequence was configured with a Cartesian acquisition mode in k-space, the profile order was set to low-high, a radial turbo direction was used, and in the z-direction the resolution was doubled during reconstruction. The temporal resolution was chosen as high as possible, since we wanted to correct retrospectively for respiratory motion. Therefore, we used interpolation in the z-direction together with a radial readout method. The dynamic volume was placed on the location of visibly inflamed bowel (on SSFSE images) or when absent the terminal ileum. When multiple segments were inflamed, the sequence was angulated so all visible inflamed segments were in the FOV. Colonoscopy results were not taken into account when placing the DCE-MRI slice. Twenty milligram butylscopolaminebromide (Buscopan, Boehringer, Ingelheim, Germany) was given immediately before the DCE-MRI sequence and before the post-contrast 3D T1-weighted spoiled gradient echo sequences. Ten seconds after the start of the dynamic sequence 0.1 ml/kg bodyweight of gadobutrol (Gadovist 1.0 mmol/ml, Bayer Schering Pharma, Berlin, Germany) was injected through a 20 GA intravenous catheter in the antecubital vein by bolus injection (5 ml/s) using an automated injection pump (Mallinckrodt Optistar, Liebel-Flarsheim, Cincinnati, Ohio, USA). Injection of contrast medium was immediately followed by a bolus of 15 or 20 ml saline (5 ml/s), depending on the length of the contrast injection tube. After completion of the dynamic sequence a coronal 3D T1-weighted SPGE (scan parameters identical to pre-contrast 3D T1-weighted SPGE) and an axial 3D T1-weighted SPGE with fat saturation were acquired.

Table 1. Scan parameters at 3T

<table>
<thead>
<tr>
<th>Sequences</th>
<th>SSFSE</th>
<th>SSFSE</th>
<th>3D T1-w SPGE</th>
<th>DCE-sequence</th>
<th>3D T1-w SPGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direction</td>
<td>Axial and coronal</td>
<td>Coronal</td>
<td>Coronal</td>
<td>Coronal</td>
<td>Axial</td>
</tr>
<tr>
<td>Fat saturation</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>TR (ms)</td>
<td>516-758</td>
<td>1370-1450</td>
<td>1.87-2.19</td>
<td>2.9</td>
<td>1.87-2.19</td>
</tr>
<tr>
<td>TE (ms)</td>
<td>65-118</td>
<td>70</td>
<td>1.0</td>
<td>1.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Flip angle</td>
<td>90</td>
<td>70</td>
<td>10</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Slice thickness/gap (mm)</td>
<td>4/1</td>
<td>7/1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Slices</td>
<td>40</td>
<td>45</td>
<td>100</td>
<td>450</td>
<td>180</td>
</tr>
<tr>
<td>FOV (mm)</td>
<td>400x400</td>
<td>375x300</td>
<td>400x400x200</td>
<td>400x400x35</td>
<td>400x400x140</td>
</tr>
<tr>
<td>Matrix</td>
<td>256*256</td>
<td>288*288</td>
<td>192<em>192</em>100</td>
<td>144<em>144</em>14</td>
<td>208<em>208</em>70</td>
</tr>
<tr>
<td>SENSE factor</td>
<td>2.5</td>
<td>2</td>
<td>1.5</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

**Gating and registration**

To reduce motion effects in the data, a gating and registration procedure was applied (see appendix I).
Region of interest (ROI)
The small bowel and the colon were divided into five segments: terminal ileum, cecum and ascending colon, transverse colon, and descending colon and sigmoid in concordance with the CDEIS, so there could be a direct segment comparison between MRI and CDEIS. ROIs were drawn with ITK-SNAP on the DCE-sequence by a research fellow on all available slices where the segment was visible. The ROI included the whole available segment (bowel wall and intraluminal contrast). The rectum was not in the FOV in all patients.

Analysis of DCE-MRI
We analyzed the DCE-MRI data in a semi-quantitative fashion. The first 300 DCE volumes (= 246 seconds) were used for analysis, since peristalsis resumed after this period. In each ROI we calculated the relative maximum enhancement, the initial slope of increase (figure 1) and the shape of the TIC on a pixel-by-pixel basis. Seven different curve shapes (six defined and one undefined shape), automatically classified according to the scheme described by Lavini et al., were each assigned a unique colour (figure 2). The pixel-by-pixel TIC classification was then rendered in a colour-coded map, providing a high resolution description of the curve shapes in the whole area of interest. We calculated the total number of pixels classified for each of the seven curve shapes, and the relative occurrence of each of these (number of pixels per shape/total number of pixels in the ROI). Average values of other semi-quantitative parameters (maximum enhancement, initial slope of increase) were then calculated across the ROI. These calculations were performed with home-written software.

Subjective image analysis
Per segment the following features were assessed in consensus by two experienced abdominal radiologists with respectively 17 years (450 MRI small bowel) and 16 years, (1070 MR small bowel) experience. Quality of distension and visibility of the bowel wall was assessed in three categories (insufficient, sufficient, optimal). Wall thickness was measured on the SSFSE sequence using callipers. Mural signal intensity on SSFSE images was first subjectively assessed compared to cerebral spinal fluid (CSF) signal intensity as no, mild, moderate, or severe high signal intensity (severe high signal intensity when the bowel wall have a signal intensity similar as CSF). Although increased signal intensity of oedematous bowel wall never increases to the signal intensity of CSF, this is the best parameter to compare because of its high water content. The signal intensity was then measured with a ROI in the bowel wall and a ROI in the CSF; the signal intensity ratio was calculated (mural T2 signal intensity/CSF signal intensity x100%). A stratified pattern on SSFSE images is thought to be present in inflamed bowel wall with also a fibrous component. The presence of a stratification pattern was scored as layered yes or no.

The bowel wall enhancement was first subjectively assessed as no, mild, moderate or severe pathological enhancement compared to a 3D T1-weighted spoiled gradient echo pre-contrast sequence. Then, a ROI was drawn in the most severely enhanced part of the segment and on the same site on the pre-contrast series. The enhancement ratio was calculated (signal intensity post-contrast/pre-contrast x100%). The enhancement pattern was subjectively assessed as layered yes or no.

The presence of ulcerations on any of the sequences was evaluated.

On a per patient basis, the presence of the comb sign (increased mesenteric vascularity), creeping fat (fibrofatty proliferation around the bowel wall), infiltrate, fistula, abscess and stenosis (lumen reduction of >50%) were assessed. The diameter of the largest intra-abdominal lymph node was measured (short axis) and subjective enhancement (pathological enhancement yes/no) was assessed. The lymph node enhancement ratio was calculated (signal intensity post-contrast/pre-contrast x100%).

Reference standards
All patients underwent the hospital’s standard preparation for ileocolonoscopy. Patients ingested either 4L of polyethylene glycol electrolyte solution (KleanPrep; Norgine, Amsterdam, The Netherlands) or 2 L Moviprep (Norgine, Amsterdam, the Netherlands) combined with two L tap water for bowel cleansing on the evening before and/or the day of the endoscopy. The ileocolonoscopy was performed with a standard colonoscope (Olympus CF-Q160AL or CF-Q180AL, Olympus Medical Systems Europe, Hamburg, Germany) by either a gastroenterologist or a senior resident in gastroenterology under direct supervision of a gastroenterologist. The performing endoscopist was aware of the patient history, but blinded for the MRI results.

The CDEIS was determined by one of two gastroenterologists experienced in endoscopy in inflammatory bowel disease (during the ileocolonoscopy or on DVD). CDEIS includes several parameters: superficial ulcerations, deep ulcerations and the relative length of bowel affected by these ulcerations or disease activity in general (this also could be oedema or erythema). These parameters were used to assess disease severity in four categories: normal mucosa, non-ulcerative lesions, superficial ulcerations (mild ulcerative disease), deep ulcerations (severe ulcerative disease). These different severities were compared to (DCE-) MRI parameters. A segmental CDEIS was calculated using only the scores of that segment. Scoring a segmental CDEIS was performed to enable more accurate matching between MRI and
endoscopy per segment. All segments that could be evaluated with ileocolonoscopy were included in the analysis. In patients where the terminal ileum could not be intubated, only the colonic segments were evaluated.

The CDAI and CRP were assessed in all patients as secondary reference standards.\textsuperscript{17}

Statistical analysis
Normality of all data was tested by using normal plots. For data not normally distributed, medians with interquartile ranges were determined for descriptive values. Spearman correlation coefficients were calculated for continuous variables. Correlation coefficient values were interpreted as follows: 0.0 not correlated; 0.2 weakly correlated; 0.5 moderately correlated; 0.8 strongly correlated; 1.0 perfectly correlated. For comparisons between groups the Mann-Whitney test with Bonferroni adjustment for multiple testing was used. Association between ordinal subjective parameters and CDEIS were assessed by the Chi-2 intraclass correlation. For comparison of non ulcerative lesions we excluded the segments that contained superficial or deep ulcerations as well, as they are not separately scored in the CDEIS. When comparing disease duration, with DCE-data only the segment with the highest maximum enhancement and initial slope of increase was used. To minimize clustering effect we used non parametric testing and give median values.

Statistical analysis was performed by using software PASW statistics 18 (Chicago, IL, USA). A p-value < 0.05 was considered statistical significant, p<0.008 for multiple testing between the four groups.

Results
Forty patients were initially included in our study. Seven patients had to be excluded because of an incomplete reference standard (three patients), technical failure of dynamic sequence/MRI (two patients) and negative for Crohn’s disease (two patients, diagnosis was changed to negative for IBD and ulcerative colitis based on colonoscopy and pathology results). Thus, 33 patients (mean age 37 years, range 19-72; 23 females) with histologically proven Crohn’s disease were evaluated. No vasodilating drugs were used by these patients. Twenty-five patients (76%) were on Crohn’s disease maintenance therapy. Two patients used methotrexate (6%), three 5-ASA (9%), 13 purine-antagonists (39%), six steroids (18%) and 10 anti-Tumour Necrosis Factor (30%). Sixteen patients (49%) previously underwent an ileocecal resection. Twenty segments (12%) were of insufficient quality due to suboptimal distension and/or suboptimal contrast between lumen and bowel wall) to be used for grading. In total 144 (89%) segments could be evaluated. It was always possible to include all visible inflamed bowel segments in the DCE-ROI. All data except initial slope of increase, enhancement ratio and T2 signal intensity ratio were not normally distributed.

The median time between colonoscopy and MRI was 8 days (IQR 6-16). MRI and colonoscopy was not performed one the same day. Median CDEIS was 4.4 (IQR 1.6-6.9). Median segmental CDEIS was 0 (IQR 4.5). Median CDAI was 141 (IQR 81-226). Median CRP was 6 (IQR 1-22), median disease duration 10 years (6-14).

Analysis of conventional MRI data
Per segment data
Wall thickness was weakly correlated with segmental CDEIS (r=0.418, p<0.001) (table 2, figure 3). The subjective assessment of T2 signal intensity was significantly associated with segmental CDEIS (p<0.001), but the T2 signal intensity ratio was not correlated. Patients with a layered pattern on SSFSE images had a higher segmental CDEIS (median 4 versus 0, p=0.014) (table 3).

Table 2: Correlations between conventional MRI images and reference parameters (CDEIS). NS=not significant. Categorical variables with linear by linear association, continuous variables with spearman correlation.

<table>
<thead>
<tr>
<th>Total number of segments analysed</th>
<th>Correlation/Association segmental CDEIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wall thickness\textsuperscript{a}</td>
<td>137</td>
</tr>
<tr>
<td>Mural signal intensity SSFSE subjective\textsuperscript{a}</td>
<td>134</td>
</tr>
<tr>
<td>Mural signal intensity SSFSE ratio\textsuperscript{a}</td>
<td>134</td>
</tr>
<tr>
<td>Subjective bowel wall enhancement\textsuperscript{a}</td>
<td>134</td>
</tr>
<tr>
<td>Enhancement ratio\textsuperscript{a}</td>
<td>123</td>
</tr>
<tr>
<td>Maximum enhancement\textsuperscript{b}</td>
<td>99</td>
</tr>
<tr>
<td>Initial slope of increase\textsuperscript{b}</td>
<td>99</td>
</tr>
</tbody>
</table>

\textsuperscript{a}based on segments were CDEIS and MRI parameter was available. \textsuperscript{b}based on segments that were included in DCE volume.
Table 3. Median values with interquartile ranges for CDEIS, CDEIS per segment. NS = not significant.

<table>
<thead>
<tr>
<th>MRI feature</th>
<th>Present</th>
<th>Absent</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDEIS Comb sign</td>
<td>4.8 (4.2-9.0)</td>
<td>1.7 (0.0-5.3)</td>
<td>0.012</td>
</tr>
<tr>
<td>Creeping fat</td>
<td>6.1 (4.2-11.1)</td>
<td>4.0 (1.4-5.8)</td>
<td>0.123</td>
</tr>
<tr>
<td>Enhancing lymph nodes</td>
<td>5.2 (3.6-10.0)</td>
<td>1.6 (0.0-4.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Fistula</td>
<td>4.3 (3.0-4.3)</td>
<td>4.4 (1.6-7.4)</td>
<td>0.970</td>
</tr>
<tr>
<td>Infiltrate</td>
<td>4.6 (3.4-7.1)</td>
<td>4.2 (1.6-7.4)</td>
<td>0.454</td>
</tr>
<tr>
<td>Abscess</td>
<td>5.6 (5.6-5.6)</td>
<td>4.3 (1.6-7.2)</td>
<td>0.528</td>
</tr>
<tr>
<td>CDEIS per segment SSFSE stratification</td>
<td>24 (0-26)</td>
<td>0 (0-4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Stratified enhancement pattern</td>
<td>1 (0-24)</td>
<td>0 (0-6)</td>
<td>0.114</td>
</tr>
</tbody>
</table>

Subjective enhancement was significantly associated with segmental CDEIS (p < 0.001). The enhancement ratio was not correlated with segmental CDEIS. Patients with layered enhancement (12 patients) did not have a significantly higher segmental CDEIS (median 0 versus 1, p = 0.093). No ulcerations could be detected on the conventional sequences. Between the four disease severity groups T2 SI ratio and T1 enhancement ratio did not differ (table 4 and figure 4).

Table 4. MRI parameters for the different disease severity groups assessed at ileocolonoscopy. NS = not significant. Values are means with IQR.

<table>
<thead>
<tr>
<th></th>
<th>Normal mucosa N=112</th>
<th>Non ulcerative lesions N=12</th>
<th>Mild ulcerative disease N=22</th>
<th>Severe ulcerative disease N=11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wall thickness (mm)</td>
<td>2 (2-3)</td>
<td>3 (2-3)</td>
<td>6.5 (2-8)</td>
<td>5.4 (2-9)</td>
</tr>
<tr>
<td>Mural signal intensity SSFSE ratio</td>
<td>33 (24-43)</td>
<td>36 (27-40)</td>
<td>38 (31-46)</td>
<td>32 (22-38)</td>
</tr>
<tr>
<td>Enhancement ratio</td>
<td>148 (120-175)</td>
<td>163 (130-192)</td>
<td>164 (110-230)</td>
<td>144 (91-193)</td>
</tr>
<tr>
<td>Maximum enhancement</td>
<td>0.304 (0.279-0.352)</td>
<td>0.338 (0.295-0.338)</td>
<td>0.378 (0.323-0.504)</td>
<td>0.388 (0.339-0.500)</td>
</tr>
<tr>
<td>Initial slope of increase</td>
<td>27.7 (22.5-33.8)</td>
<td>25.0 (20.4-33.3)</td>
<td>31.7 (24.1-36.7)</td>
<td>39.5 (27.1-46.0)</td>
</tr>
</tbody>
</table>

*normal mucosa versus mild disease group

Per patient data

The comb sign was present in 15 patients (46%), creeping fat in 10 patients (30%) and enhancing lymph nodes in 21 patients (64%). Six patients had an infiltrate (18%), 21 a stenosis (64%), two an intra-abdominal fistula (6%) and one an abscess (3%). In patients with a comb sign, with a stenosis or where enhancing lymph nodes were present, CDEIS was significantly higher (p = 0.012, p = 0.004 and p = 0.003, respectively) (table 3). No differences in CDEIS were found between patients with/without the presence of creeping fat, fistulas, infiltrate or abscess. Short axis diameter of the largest lymph node did not correlate with CDEIS and CDAI, but with CRP (r = 0.533, p = 0.002). Pathological lymph node enhancement ratio did not correlate with CDEIS, CDAI and CRP.
Analysis of DCE-MRI

Per segment data
Median maximum enhancement was 0.337 (range 0.223 – 0.875). Median initial slope of increase was 27.5 (range 8.4-57.1). Maximum enhancement correlated weakly with segmental CDEIS (r=0.485, p<0.001) (figure 3), initial slope of increase correlated weakly with segmental CDEIS (r=0.206, p=0.041). Maximum enhancement differed significantly between the four severity groups (p<0.001); maximum enhancement was significantly higher in the mild ulcerative disease and severe ulcerative disease groups compared to the normal mucosa group (both p<0.001) (table 4 and figure 4). In addition, wall thickness was larger in the mild ulcerative disease group than the normal mucosa group (p<0.001) (figure 4). Initial slope of increase did not differ significantly between groups, but there was a trend towards an increase in initial slope of increase when disease severity was higher (figure 4). In diseased segments (CDEIS>0) disease duration correlated with maximum enhancement (r=0.492, p=0.002). No correlations were found between TIC curve types and segmental CDEIS. Relative pixel counts were not significantly different in segments with or without ulcerations.

Per patient data
Median maximum enhancement was 0.334 (range 0.28-0.45). Median initial slope of increase was 29.6 (range 8.7-42.5). Maximum enhancement was moderately correlated with total CDEIS (r=0.551, p=0.001), but not with CDAI and CRP. Initial slope of increase correlated not with any of the per patient indices.

Discussion
Our results suggest that DCE-MRI can be used for grading Crohn's disease activity. Maximum enhancement was significantly higher in the mild ulcerative and severe ulcerative disease groups compared to the normal mucosa group indicating a higher perfusion in inflamed segments. In addition, a moderate correlation was found between maximum enhancement and CDEIS, both on a per patient and on a per segment basis signifying that maximum enhancement can be used to assess disease activity in Crohn's disease patients.

Our study had several strengths: we compared the CDEIS per segment with DCE-MRI data which is more comparable than per patient indices. In addition, our study comprises the whole disease activity spectrum, with emphasis on mild ulcerative disease activity (superficial ulcerations) (figure 5), in contrast to other studies that only compare the presence or absence of disease. We used a pixel by pixel analysis within the ROI to calculate the DCE-MRI parameters for every individual pixel within the ROI instead of one maximum enhancement and initial slope of increase for the whole ROI. This way variation in DCE-MRI parameters can be seen across the whole ROI instead of one specific point per segment.

An advantage of 3T MRI compared to lower field strengths is the relatively higher temporal resolution that can be achieved with higher field strength, which gives a curve based on more time points. In our study the temporal resolution was 0.82 seconds. Most other DCE-MRI studies have a relative lower temporal resolution of 3-12 seconds or even larger than 15 seconds. A high temporal resolution enables a detailed analysis of the contrast uptake. In addition, free breathing motion artefacts were minimal during our short dynamic scan time.

Several studies found a higher maximum enhancement in patients with active Crohn's disease, although no correlation was found with a pathology-based reference standard. We found a moderate correlation with segmental CDEIS and a higher maximum enhancement in patients with mild ulcerative and severe ulcerative disease (figure 6), corresponding with the hypothesis that diseased segments have a larger contrast uptake. The ulcerations detected at ileocolonoscopy could not be seen on the conventional series, but were detected with DCE-MRI, which is a relevant finding given the present limitations in correctly identifying mild ulcerative disease. Low sensitivity for detecting ulcerations can be due to low spatial resolution. Although median maximum enhancement was higher in segments with non ulcerative lesions as compared to normal mucosa, this was not a significant difference. Conceivably further improvements in DCE MRI protocols can in the future expand this technique.

In comparing the four disease activity groups, there was no significance difference between groups although we observed a trend that initial slope of increase was higher in segments with worse disease severity (figure 3). Also, segmental CDEIS was weakly correlated with initial slope of increase. In this case we might speculate that an increased permeability might be responsible for this.

We found a positive correlation of maximum enhancement with disease duration in diseased segments. This was earlier demonstrated in another study. Our hypothesis is that during longstanding disease and multiple exacerbations the extravascular space of the bowel increases which gives rise to increased enhancement. Another possibility could be that the vascular space is increased due to neo-angiogenesis. Our data do not support the hypothesis
that patients with longstanding disease have increased permeability as initial slope of increase was not increased in those patients with longstanding disease. An increased permeability results in easier and faster extravasation of the contrast agent into the extravascular space, resulting in a quicker signal enhancement. Further studies need to be performed on the relation between contrast enhancement, acute and chronic inflammation as both disease duration and active current inflammation seem to play a part.

For the conventional MRI parameters correlations were found for wall thickness, contraction and active current inflammation seem to play a part. The relation between contrast enhancement, acute and chronic inflammation as both disease duration and active current inflammation seem to play a part.

An increased permeability increases not linearly but increased disease activity. An explanation could be that this might be due to a fibrous component within the bowel wall after previous inflammation that limits thickening of the bowel wall. This could also be the explanation for the fact that in our cohort wall thickness was smaller (though not significant) in segments with severe disease activity. Only the subjective assessment of mural T2 signal intensity and enhancement was significantly associated with segmental CDEIS. ROI based measurements did not correlate, thus no advantage was shown for the use of ROI based measurements over the subjective assessment by the radiologist when evaluating conventional MRI sequences. In addition, ROI based measurements have a known poor interobserver agreement, which can lead to poor reproducible results.

Our study had some limitations. No optimal reference standard is available in Crohn’s disease. We chose to adopt CDEIS, which is a colonoscopy based scoring system that grades disease activity. Only intraluminal lesions can be assessed with colonoscopy. Other possible reference standards have different disadvantages: biopsies do not cover the whole segment and surgical resection specimens are more difficult to obtain as most patients receive medical treatment first and often concern more refractory, fibrotic disease. Nevertheless, in the absence of more reliable reference standards colonoscopy is the most favourable.

Another limitation that arose from the study protocol is the delayed timing of the conventional post contrast sequences. The duration of the DCE-MRI sequence was six minutes, the 3D T1-weighted spoiled gradient echo sequence was performed thereafter. Because of this delay in one patient the sequence could not be evaluated as already renal outwash was seen, indicating a too late evaluation of bowel enhancement at the conventional T1-w sequences.

To perform the DCE-sequence with a high temporal resolution (0.82s) was at the expense of spatial resolution. However, in our opinion, the spatial resolution of 2.78x2.78x2.5mm was sufficient for a ROI-based analysis. In addition, our free-breathing abdominal data required non-rigid registration of the dynamic volumes. We empirically observed a residual misalignment of 1 to 2 voxels which we considered sufficiently low to justify an ROI-analysis. A purely voxel-based approach requires more research on accurate registration of DCE-MRI data.

Because of technical limitations, the FOV of the DCE volume was limited to 400x400x35mm. When placing the ROI our aim was to include all segments as a whole, but the rectum could not be included in the FOV in all patients, because of its posterior position. In addition, in some segments, parts were outside the FOV, so could not be included in the DCE-analysis.

When performing a per segment analysis (with multiple segments per patient), a clustering effect could create a bias and this effect can be adjusted if results are presented as either proportion (for binomial data) or means (for normal distributed data). We collected continuous data, but these were not normally distributed and therefore we used nonparametric testing, resulting in median values instead of means.

We did not perform a quantitative DCE-MRI analysis, as had been done in other studies. A quantitative analysis requires an adequate model, which is very much dependent on several unknown or chosen parameters such as the arterial input function, T1 of blood and bowel tissue. In further research, we aim to accurately determine these parameters.

Conclusions
DCE-MRI can be used as a method for detecting Crohn’s disease lesions, including mild ulcerative disease (superficial ulcerations), that are often missed on conventional MRI sequences.

Role of the Funding Source
A research grant was given by Nuts Ohra foundation. Nuts Ohra foundation was not involved in designing or conducting the study, did not have data access and was not involved in data analysis or preparation of the manuscript.

Appendix 1: GATING AND REGISTRATION
We performed retrospective gating on one phase out of the respiratory cycle on the DCE-MRI sequence to remove the discontinuities between tissue layers that are present in bowel data sets due to breathing. We computed the L2-norm (or Sum of Squared Differences) of all dynamics to the center dynamic, which shows oscillatory behaviour, and selected local minima...
based on the Gaussian-weighted second-order derivative. This subset of our data was then non-rigidly registered. The dynamic with the lowest accumulative L2-norm with respect to all dynamics within the subset was chosen as reference. We then adopted a Discrete Cosine Transformation model\(^1\) with two subsequent cut-off bases of 50 and 25 mm to allow for global and local convergence. Figure 7 illustrates the followed procedure within one time slice of a single subject. On average, one out of five volumes was selected, resulting in an effective time resolution of 4 seconds.

References


