Magnetic resonance imaging in Crohn's disease
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Mapping of T1-values and Gadolinium-concentrations in MRI as indicator of disease activity in luminal Crohn’s disease: a feasibility study

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Submitted
ABSTRACT

**Purpose:** To determine the feasibility of T1-mapping and calculation of Gadolinium-values in luminal Crohn’s Disease (CD).

**Materials & Methods:** Nine patients with active CD were included. For each patient disease activity was determined, based on endoscopic and histopathological results. The Crohn’s Disease Endoscopic Index of Severity (CDEIS), the Harvey-Bradshaw index (HBI) and C-reactive protein (CRP) were also determined as reference standards. T1-measurements were performed before and after intravenous administration of Gadodiamide in 14 slices in a single breath-hold using the Look-Locker (LL) sequence in combination with a segmented 3D Turbo Field Echo sequence. A Region of Interest (ROI) was drawn around inflamed bowel loops and the mean Gadolinium-concentration within the ROI was calculated. Gadolinium-concentrations were compared between patients with mild and marked disease, as determined by the reference standards.

**Results:** Mean Gadolinium-concentrations were higher in bowel loops of patients with more active disease, as defined by endoscopic and histopathological examination, CRP and HBI.

**Conclusion:** By using a breath-hold LL sequence in the bowel quantitative assessment of contrast agent concentration is possible, thus permitting objective evaluation of physiological changes in actively inflamed tissue in an area that suffers from motion problems.
INTRODUCTION

Crohn’s disease (CD), a transmural, granulomatous inflammatory bowel disease typically runs a chronic relapsing and remitting course (1). Prevalence in many developed countries is estimated at 0.1 % (2).

Grading of disease severity is important in CD in order to be able to optimally determine treatment strategy and response to treatment (3). In clinical practice, assessment of activity can be done by the Crohn’s Disease Activity Index (CDAI) (4), laboratory investigations (e.g. C-reactive protein) (5, 6) and/or endoscopy (scored in the Crohn’s Disease Endoscopic Index of Severity (CDEIS)) (7). Ideally, an activity score should be objective, reproducible, quantifiable and non-invasive. However, to none of the abovementioned methods all four criteria are applicable; the CDAI is a clinical index that incorporates subjective elements, laboratory findings can be unchanged in the presence of active disease (8), and endoscopy is an invasive procedure. Moreover, none of the abovementioned methods allow transmural and extraintestinal evaluation of disease.

With abdominal MRI the trans- and extramural extent of CD can accurately be assessed (9-11). On MRI one of the characteristics of active CD is a pathological increase in bowel wall signal intensity (enhancement) after intravenous administration of Gadolinium (11-15).

However, with conventional MR imaging techniques signal intensity is expressed on an arbitrary scale that differs from one imaging examination to another and therefore is unsuitable for direct signal quantification. Furthermore, signal enhancement at higher fields strengths can be affected by incomplete fat suppression and B1-inhomogeneities (16), thus compromising the clinical evaluation of signal enhancement.

The increase of the longitudinal relaxation rate (1/T1) is directly proportional to the tissue concentration of the contrast medium (17). Therefore, calculation of the absolute T1-values in tissue before and after intravenous injection of Gadolinium would provide objective measurements of the Gadolinium-uptake. As there is a correlation between mesenteric vascularisation and permeability and disease severity (18, 19), calculation of contrast agent concentration for every pixel in a parametric image (i.e. a T1-map) could possibly provide an objective, quantifiable, and reproducible means of determination of CD activity. However, the making of T1-maps in the bowel is a challenging task due to the long times required for T1-mapping and the short time frame available for scanning due to respiration and bowel peristalsis (20).

Thus, the purpose of our study was to determine the feasibility and value of T1-mapping in abdominal MRI for CD.
MATERIALS AND METHODS

Patients
Ten patients with known CD were enrolled in our study, which was performed at the Radiology department of a tertiary referral center. Patients were eligible for participation if they were scheduled to undergo MR enterography (MRE) for evaluation of either known or suspected CD activity of the small bowel and if at ileocolonoscopy (CS) active CD was seen. The study was approved by the local ethics committee, and written informed consent was obtained from all patients. The general exclusion criteria to MR imaging (e.g. pregnancy, pacemaker) were applicable.

Imaging protocol
Patients were instructed to fast for four hours preceding the scan. In the hour preceding the MRE patients were instructed to ingest 1600 ml of a 2.5% mannitol-solution at a steady rate.
MRE was performed on a Philips 3.0 Tesla Intera scanner using a 6-channel phased array cardiac coil with patients in supine position. A respiratory triggered T2-weighted Turbo Spin Echo sequence was performed in the transversal and coronal plane (TE/TR 60/1000 ms, matrix 304x244, FOV 455x275 cm, 5 mm slice thickness, no gap). After intravenous administration of 20mg of Buscopan (butylscopolamine bromide; Boehringer-Ingelheim, Ingelheim, Germany) to diminish bowel peristalsis, T1-measurements were performed in a single breath hold using the classical Look-Locker (LL) sequence in combination with a segmented 3D Turbo Field Echo sequence with a matrix size of 128x128, slice thickness of 7 mm and flip angle of 8 degrees. Twenty alpha pulses with an interpulse interval of 197 ms were applied within a TR of 4.0 s. In total, 4 inversion pulses (shots) were used, resulting in an overall scan time of 16 seconds. The total number of slices in the acquired volume amounted to 14 with the volume positioned at the most proximal affected bowel loop that was assessed at CS (for complete CS that would be the terminal ileum).
The accuracy of the Look Locker T1-determination was assessed by measuring T1-values in the range 300-1500 ms in small tubes with different Gadolinium-concentrations. There appeared to be a consistent underestimation of the T1-values of up to 10% for T1 values as large as 1500 ms. This underestimation of T1-values is comparable to the underestimation of T1-values for other fast T1-determination schemes (21).
Seventy seconds after intravenous administration of 0.15 ml/kg of bodyweight Gadolinium-DTPA-BMA (Gadodiamide, Omniscan, General Electric Healthcare, Chalfont St. Giles, United Kingdom) by bolus injection (3 ml/sec) using an automated injection pump (Spectris Solaris; Medrad Inc, Warrendale, PA) a second T1-map was acquired with identical settings. After acquisition of the T1-maps, post contrast 3D T1-weighted images were acquired in coronal and transversal planes (TE/TR 1.7/3.4 ms, FOV 380x285 mm, matrix 252x187, slice thickness 4 mm).
Reconstruction of T\textsubscript{1}-Maps
T1-maps were produced off-line using home-written software that interpolates the LL recovery curves and calculates T1-values pre- and post-Gadolinium injection. Calculation of the Gadolinium-concentration per voxel was performed by using the following formula:

\[
\Delta \left( \frac{1}{T_1} \right) = \frac{1}{T_{1,\text{post}}} - \frac{1}{T_{1,\text{pre}}} = R [Gd]
\]

in which T\textsubscript{1}\textsuperscript{*} is the effective T\textsubscript{1} as fitted from the recovery curves, R is the relaxivity value and [Gd] is the Gadolinium concentration. For the relaxivity R we used a value of 3.2 mM\textsuperscript{-1}s\textsuperscript{-1}L (22).

Reference parameters

**Ileocolonoscopy**
CS was performed by a gastroenterologist or a fellow gastroenterology under supervision of a gastroenterologist. The CDEIS, a validated endoscopic index of disease severity, was scored for all patients (7). The CDEIS scores the presence and extent of predefined CD-associated lesions (i.e. pseudopolyp, ulceration (healed, aphthoid, superficial/shallow, or deep), frank erythema, frankly swollen mucosa, stenosis (non-ulcerated or ulcerated) for the following segments: 1. rectum, 2. sigmoid and left colon, 3. transverse colon, 4. right colon and 5. ileum. As the CDEIS score reflects severity of disease for all evaluated bowel segments combined, a segmental CDEIS score was calculated for the most proximal affected bowel segment that could be visualized at CS.

**Histopathology**
Tissue samples were obtained for histopathological analysis of the most proximal bowel loop assessed at endoscopy. Also, biopsies were taken of other areas if inflammation was seen. Descriptive reports of histopathological results were provided by the histopathologist, in accordance with clinical practice.

**C-reactive protein**
CRP can be used as a marker for disease activity in CD (23). To distinguish between elevated and normal CRP-values a cut-off value of 5 mg/L was used, as is the cut-off value at our institution’s laboratory.

**Harvey-Bradshaw index**
The Harvey-Bradshaw Index (HBI) is a simplification of the Crohn’s Disease Activity Index that was developed in the 1970s to assess the degree of illness in individuals with CD. The HBI is a purely clinical disease activity index based on the patient’s symptoms in the previous 24 hours. Items that are scored are general well-being, abdominal pain,
frequency of liquid stools, abdominal mass and presence of complications of CD (e.g. uveitis, arthritis) (24). We considered a HBI-score of 4 or less as clinically inactive disease, with higher scores indicating active CD (25).

**Clinical evaluation**

In clinical practice, an assessment of disease activity on a per-patient basis can be made using a combination of endoscopic and histopathological results. In order to obtain a clinical evaluation of disease activity, disease was rated as either mild or marked, depending on endoscopic and histopathological results. If only erythema and aphthous ulcerations were seen at CS and the histopathologist rated disease as mildly active or did not observe any signs of active disease, clinical disease activity was rated as mild. If deep ulcerations or cobblestoning were seen at CS, and the histopathologist rated disease as active, activity was rated as marked.

Comparison of Gadolinium-concentrations with reference parameters

Comparison of the Gadolinium-concentrations with reference parameters was twofold:
1) The Gadolinium-concentration of the most severely affected bowel loop was compared with CRP, HBI and clinical disease activity. To this end, a Region of Interest (ROI) was drawn using electronic calipers around the most severely affected bowel loop as judged by the gastroenterologist at CS.
2) For comparison of Gadolinium-concentrations with CDEIS-values a ROI was drawn around the most proximal bowel loop assessed at CS.

**RESULTS**

Ten consecutive patients were included in this study. One patient suffered from claustrophobia, leading to an incomplete examination and exclusion from analysis. Therefore, nine patients (8 female, 1 male) could be evaluated, of whom characteristics are displayed in Table 1.

CS was performed in all patients: in seven patients the terminal ileum could be inspected, in one patient only the rectosigmoid and descending colon could be inspected due to the presence of an impassable ulcerated stenosis, and in one patient intubation of the terminal ileum was not possible due to fecal contamination of the cecum. The most

<table>
<thead>
<tr>
<th>Table 1: characteristics of the 9 evaluated patients</th>
<th>Mean±SD (range)</th>
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<tbody>
<tr>
<td>Age</td>
<td>33.9 ± 13.5, (20-58)</td>
</tr>
<tr>
<td>CDEIS</td>
<td>11.0 ± 10.5 (1.0-30.0)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>37.2 ± 60.1 (1.1-176.4)</td>
</tr>
<tr>
<td>Harvey-Bradshaw Index</td>
<td>5.4 ± 7.1 (0-22)</td>
</tr>
</tbody>
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proximal bowel loop that could be assessed at CS was inflamed in all patients and biopsies of these inflamed areas were obtained in all patients.

MRI examinations were carried out within a median of 6 days of CS. The time frame between MRE and CS was 1 week in seven patients, 3 weeks in 1 patient and 21 weeks in one patient. In this last patient clinical and radiological disease activity was rated as very mild and no medication changes were effected between MRE and CS. In all patients acquisition of T1-maps before and after Gadolinium-administration was feasible and we could calculate Gadolinium-concentrations from these T1-maps (Fig. 1). In some cases

**Figure. 1:** 29-year old female patient with active CD.

- **a.** Post-contrast T1-weighted transversal image with inflamed bowel loop (arrowheads)
- **b.** Identical post-contrast T1-weighted transversal image with Gadolinium-map displayed as overlay. Concentrations in the actively inflamed bowel loop are as high as 0.5 mmol/l.
- **c.** Endoscopic view of the severely inflamed bowel of the patient.
Figure 2: Mean Gadolinium-concentrations with confidence intervals in patients with mild disease (n=3) versus patients with marked disease (n=6).

Figure 3: Mean Gadolinium-concentrations with confidence intervals in patients with inactive disease (n=5) versus active disease (n=4), as defined by the Harvey-Bradshaw Index.

Figure 4: Mean Gadolinium-concentrations with confidence intervals of patients categorized with normal (n=5) versus elevated (n=4) CRP-values.
bowel motion in between the consecutive T1-acquisitions resulted in misregistration and thus in artificial Gadolinium-concentrations. These misregistrations could easily be identified by visual inspection of the respective T1-maps and the resulting Gadolinium-map. However, for none of the patients misregistration was observed in the bowel loops that we used for calculation of the Gadolinium-concentrations.

In six patients the most proximal bowel loop that was assessed was also the most severely affected bowel loop (in all six the terminal ileum), meaning that only 1 ROI was drawn for each patient. In 1 patient the terminal ileum was mildly inflamed, but the colon was severely affected; in 1 patient the cecum was the most proximal bowel loop that was assessed, but the descending colon was most severely affected and in 1 patient the rectosigmoid and descending colon were evaluated, but disease was most severe in the inaccessible region of the terminal ileum, as was confirmed at subsequent surgery and histopathological examination of the resected bowel. In these three patients 1 ROI was drawn around the most proximal bowel loop assessed at CS for comparison with the CDEIS, and a second ROI was drawn to delineate the most severely inflamed bowel. The Gadolinium-concentrations of the most severely affected bowel loop were compared with the clinical disease activity as determined by endoscopy and histopathology (in 1 patient with surgery and histopathology), the CRP and the HBI. Mean Gadolinium-concentrations of the most severely affected bowel loop were higher in patients who had marked disease than in patients with mild disease (Figure 2). Also, mean Gadolinium-concentrations were higher in patients with active disease than in patients with inactive disease, as defined by the CRP (Figure 3) and the HBI (Figure 4).

The gadolinium-concentrations of the ROIs drawn around the most proximal bowel loop and the segmental CDEIS did not show a significant correlation.

DISCUSSION

We have conducted this study to determine the feasibility of T1-mapping and calculation of Gadolinium-concentrations in the abdominal region. We have proven that T1-mapping is feasible in the abdominal region and that higher Gadolinium-concentrations are present in more active disease.

Pathological enhancement is considered one of the most important criteria of active CD on MRI. While in some studies the degree of enhancement has been found to correlate with clinical disease activity (10, 11, 13, 15), in other studies no significant correlation was observed (26, 27). Our study is the first to prove that measured Gadolinium-concentrations are higher in more active CD, underscoring the importance of pathological enhancement as criterion for active disease.

Although the results of our study were encouraging, we have only included a very limited number of patients in our feasibility study and have not included any patients without active disease to determine Gadolinium-concentrations in this group of patients. We did include patients with mild disease and patients with marked disease in our study.
small proportion of patients had mild disease; it would have been interesting to perform T1-mapping in a larger group of patients with equal distributions among the different disease categories (i.e. mild and marked disease), in addition including patients in remission. Clinically, the distinction is sometimes made between remission, mild, moderate and severe disease; analysis of a larger and heterogeneous group of patients might elucidate how Gadolinium-concentrations vary between these four disease categories.

T1-mapping has been performed in a large number of studies, but all these studies regarded anatomical regions that are not or only limitedly affected by motion, e.g. the brain (28). In this study we performed T1-mapping of the abdomen, a region that is strongly affected by peristalsis and respiration, requiring acquisition of T1-maps in one breath hold. However, even if imaging is performed within a comfortable breath hold and antispasmyotic medication is administered before scanning, misregistration of pre-and post-gadolinium maps can still occur. We performed analysis of selected bowel loops in which no misregistration was seen, in this way precluding use of artificial Gadolinium-concentrations. Nevertheless, it would still be very interesting to be able to calculate Gadolinium-concentrations for all bowel loops in the Field of View, which cannot be done at present. While misregistration is less likely to occur in actively inflamed bowel loops due to the transmural nature of the inflammatory process (affected bowel loops will be more fixated in the surrounding fatty tissue), unaffected bowel loops would probably be more prone to misregistration due to their mobility. Gadolinium maps would become more accurate if the resolution of the T1-maps could be increased, thus permitting non-linear registration between T1-maps.

Another limitation of our study is the fact that we could only scan 14 slices due to the limited time window available in a breath hold. We chose to position these slices at the location of the most proximal bowel loop that was assessed at CS, which was the terminal ileum in most patients. Although not in all patients the most proximal bowel loop was the most severely affected bowel loop, in all patients the most proximal bowel loop did show inflammation to some extent. We did perform analysis of the most severely diseased bowel loop included in the 14 slices and compared findings in these loops with clinical activity.

We compared MRI findings with several clinical parameters; while all are used in clinical practice and are validated parameters for assessment of disease activity, they each have their limitations. The Harvey-Bradshaw Index is a clinical index that partly relies on patients’ subjective evaluation of disease (e.g. general well-being, abdominal pain) which does not necessarily correlate with the presence of active inflammation. The CRP is often elevated when active disease is present, but can be normal even if macroscopic inflammation is present (8). With histopathology only small tissue samples are obtained for analysis when taking biopsies during CS. Sampling bias might occur this way. The CDEIS is an index that has been validated and has been shown to be reliable and reproducible. However, scoring the CDEIS is rather time-consuming and to calculate scores analogue scale transformation
of endoscopic findings is required. These characteristics make this endoscopic score unsuitable for everyday clinical practice. It will be informative to perform pre-operative T1-mapping in patients who will undergo surgery for resection of inflamed bowel; in this way, comparison with macroscopic appearance of all bowel wall layers and histopathological examination of the resection specimen is possible, making comparison of MRI findings with clinical parameters more straightforward. This is especially important as clinical disease severity may depend more upon transmural inflammation typical of CD than upon superficial lesions accessible by the endoscopist.

In conclusion, by using a breath hold LL sequence in the bowel quantitative assessment of contrast agent concentration is possible, thus permitting objective evaluation of physiological changes in actively inflamed tissue in an area that suffers from motion problems.

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