Development and clinical applications of the time intensity curve shape analysis in dynamic contrast enhanced MRI: a pixel-by-pixel approach
Lavini, C.

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CHAPTER 9

Dynamic contrast enhanced MRI in determining disease activity in perianal fistulizing Crohn's disease.

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Stokkers PCF, Ponsioen CY, Stoker J.

Submitted
ABSTRACT

Purpose
To assess quantitative and qualitative analysis of dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) for the evaluation of disease activity and therapy response in perianal fistulizing Crohn’s disease.

Materials and Methods
Sixteen consecutive patients with perianal Crohn’s disease underwent pelvic MRI. A dynamic contrast enhanced sequence was performed at 3T (temporal resolution 4.2 seconds) during intravenous contrast injection. Maximum enhancement ($ME$), initial slope of increase ($ISI$), the volume transfer constant ($K_{trans}$) and the extravascular space fractional volume ($v_e$) were calculated within a Region of Interest drawn around the fistula. Perianal disease activity index (PDAI), C-reactive protein (CRP), and a MRI-based activity score were calculated. Six patients were scanned a second time after starting anti-Tumor Necrosis Factor α (anti-TNFα) treatment.

Results
PDAI moderately correlated to $ME$ ($r=0.669; p=0.005$) and $ISI$ ($r=0.582; p=0.018$) and volume of enhancing pixels ($r=0.786; p<0.001$), but not to $K_{trans}$ or $v_e$. Volume of enhancing pixels also correlated with CRP and the MRI-based score ($r=0.516; p=0.041$ and $r=0.786; p<0.001$ respectively). $K_{trans}$ values decreased significantly six weeks after starting anti-TNF-α therapy.

Conclusion
$ME$ and $ISI$ correlate with disease activity in perianal Crohn’s disease. $K_{trans}$ may be an indicator of effect of therapy in patients starting anti-TNFα treatment.
INTRODUCTION

Perianal fistulas are a common finding in patients with Crohn’s disease (1). To determine treatment strategy and response, the course of the perianal fistula and its inflammatory activity have to be evaluated. Magnetic Resonance Imaging (MRI) is now the recommended initial examination for assessing perianal fistulas (2). For assessing active inflammation, a $T_1$-weighted contrast enhanced sequence is performed. Enhancement indicates active inflammation as it reflects increased tissue perfusion and vascular permeability (3). Usually, enhancement is only assessed on conventional post-contrast imaging at one time-point and the grading is subjective. Subjective grading has intrinsic limitations while conventional post-contrast imaging at one time-point does not give information on microvascularisation. With dynamic contrast enhanced MR imaging (DCE-MRI), images are acquired during the delivery of the contrast agent in the tissue of interest, reflecting the dynamic response of the tissue to the inflow of blood. The signal intensity of the tissue on a $T_1$-weighted scan increases as a result of contrast leaking from the capillary into the extracellular extra-vascular space. By scanning dynamically, time intensity curves (TIC) are acquired, i.e. curves representing the signal intensity at each moment before and during contrast injection. DCE-MRI parameters such as TIC shapes and the volume transfer constant ($K_{\text{trans}}$) values have often been considered a mirror of the physiological parameters of the tissue (e.g. capillary permeability, tissue vascularisation) that are changed in inflammatory conditions (4). A previous study used qualitative DCE-MRI for the evaluation of perianal fistulas and showed significant correlations between absolute number of certain TIC shape types and the perianal disease activity index (PDAI) (5). However, quantitative information on fistula perfusion (i.e. $K_{\text{trans}}$) was not provided. In patients with rheumatoid arthritis of the wrist $K_{\text{trans}}$ values decreased 20% after anti Tumor necrosis factor- alpha (anti-TNFα), indicating a change in inflammatory activity that represents possibly therapy response (6). Anti-TNFα reduces short-term fistula drainage (7) and causes internal healing (8) possibly by inhibition of neo-angiogenesis.

The purpose of this study was to assess DCE-MRI parameters (both quantitative and qualitative) for the evaluation of disease activity and response to anti-TNFα treatment of perianal fistulizing Crohn’s disease.
MATERIALS AND METHODS

Study population
From August 2008 until December 2009 16 consecutive patients with known Crohn’s disease and suspected for perianal fistula who underwent pelvic MR imaging at the radiology department of a tertiary referral center were included in this prospective study. The indication for MRI was evaluation of perianal Crohn’s disease. The general exclusion criteria to MR imaging (e.g. pacemaker) were applicable. All patients provided written informed consent. Study approval was given by the institutional review board.

MR imaging technique
MR imaging was performed on a 3.0 T-MRI (Intera, Philips Healthcare, Best, The Netherlands) using a 6-channel torso phased array body coil with patients in supine position. Sagittal, coronal and transversal $T_2$-weighted Fast Spin Echo sequences were performed with the coronal sequence angulated parallel and the transversal sequence angulated perpendicular to the anal canal ($TR/TE$ 3000/80ms, slice thickness 4mm, matrix 400x400, FOV 360x360mm). A fat suppressed $T_2$-weighted Fast Spin Echo sequence was performed in the transversal plane ($TR/TE$ 3000/70ms, flip angle 90 degrees, slice thickness 2mm, matrix 304x304, FOV 360x360mm). After completion of these series a $T_1$-measurement was performed using a classic Look Locker sequence in combination with a 3D Turbo Field Echo sequence. A dynamic transversal 3D $T_1$-weighted Fast Spoiled Gradient Echo sequence was performed, consisting of 70 consecutive scans with a temporal resolution of 4.2 seconds. Scan parameters were as follows: FOV 200x200x60mm, spatial resolution 1.38x1.38x4mm, scan matrix 144x144x15, TR/TE 5.12/2.3 ms, flip angle 30 degrees, bandwidth per pixel 433Hz. Orientation of the dynamic scan was perpendicular to the anal canal. Five seconds after the start of the scan 0.1 ml/kg bodyweight of contrast agent (Gadodiamide; Gadovist, 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 chase 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 transversal $T_1$-weighted Fast Spin Echo with fat saturation was acquired ($TR/TE$ 700/10ms, flip angle 90 degrees, slice thickness 4mm, 15
slices, FOV 300x300mm, matrix 256x256). Orientation of all transversal sequences was identical.

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**Location**

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<tr>
<td>Suprasphincteric</td>
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**Extension**

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<tr>
<td>Supralevatoric</td>
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**Hyperintensity on T2-weighted images**

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<tr>
<td>Pronounced</td>
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**Collections (cavities > 3 mm diameter)**

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<tr>
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**Rectal wall involvement**

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<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Thickened</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 1:** MRI-based score for the Severity of perianal Crohn’s Disease (9)

**Analysis of conventional MRI data**

All MRI examinations were evaluated by an experienced abdominal radiologist with prior experience in evaluation of pelvic MRI examinations (approximately 600 examinations for perianal fistulas). For determination of disease activity, the MRI-based score of disease severity was scored as developed by Van Assche (9). This score consists of both anatomical parameters and parameters indicative of active inflammation (table 1). Scores range from 0 to 22 with higher scores indicating more severe disease. This score does not include evaluation of contrast-enhanced sequences.

**Analysis of DCE-MRI**

The contour of the fistula was first assessed on the $T_2$ Fast Spin Echo image and
then a Region of Interest (ROI) was drawn around the fistula on the $T_1$-weighted 
dynamic scan by a research fellow [MLWZ].

We analyzed the DCE-MRI data both in a qualitative fashion and quantitative 
(model based) fashion. In each ROI we calculated the relative Maximum 
Enhancement ($ME$) and the Initial Slope of Increase ($ISI$). Subsequently TIC 
shapes were classified on a pixel-by-pixel basis. Seven different curve shapes, 
classified according to the scheme described by Lavini et al. (10), were each 
assigned a unique color (figure 1 and 2). The pixel-by-pixel TIC classification was 
then rendered in a color-coded map, providing a high resolution description of the 
curve shapes in the whole area of interest. We calculated the total number of pixel 
classified as each of the seven curve shapes together with the relative occurrence 
of each of these (number of pixel per shape/total number of pixel in the ROI). For 
the quantitative model based analysis we applied Tofts’ model (4) using a 
measured Arterial Input Function (AIF). The AIF was selected in the femoral artery 
or a branch thereof, and fitted to a model function as described in (11). We used 
Tofts’ model in its extended version

$$C_t(t) = C_p(t) + K^{trans} \int \tau C_p(\tau) e^{-K_{ep}(t-\tau)} d\tau$$

with $K^{trans} = K_{ep} v_e$ being the volume transfer constant, $C_t(t)$ the Concentration in the 
tissue and $C_p(t)$ being the plasma concentration or AIF. The Concentration-time 
curves were obtained from the $T_1$ maps, calculated from the Look Locker 
sequence. Conversion from signal intensity to concentration was performed as in 
(11). Average values of all quantitative parameters ($K^{trans}$, $v_e$, $K_{ep}$) and semi-
quantitative parameters ($ME$, $ISI$, volume of enhancing pixels) were then calculated 
across the ROI. We calculated the absolute and relative number of each TIC shape 
type within the ROI and the ratio of quickly enhancing types of TIC versus slowly 
enhancing TIC (ratio between TIC type 3, 4 and 5 versus 2). The DCE-MRI data 
were analyzed off-line using home-written software (12).

Clinical evaluation

PDAI: The PDAI (table 2) was scored by a research fellow [MLWZ] at the time of 
the visit to the radiology department. The PDAI incorporates five elements: the presence or absence of discharge, pain or restriction of activities of daily living, restriction of sexual activity, the type of perianal disease, and the degree of induration (13). Scores range from 0 to 20, with higher scores indicating more severe disease.
**Figure 1.** Dynamic contrast enhanced MR imaging findings in a 24-year old female with a transsphincteric fistula and a seton in situ. A. Axial oblique fat-saturated T2-weighted fast spin-echo image shows perianal fistulizing disease. B, ME-map of the same section. ME of the perianal fistula is higher than that of the surrounding tissue. C TIC shape type map with in the fistula type 3 and 5 (fast rising pixels).

**Figure 2.** Dynamic contrast enhanced MR imaging findings in a 63-year old male with a transsphincteric fistula. A. Axial oblique fat-saturated \( T_2 \)-weighted fast spin-echo image shows perianal fistulizing disease. B, ME-map of the same section. ME of the perianal fistula is higher than that of the surrounding tissue. C TIC shape type map.

**C-reactive protein** C-reactive protein (CRP; mg/L) was determined as a biological marker of disease activity at the time of the MRI.

**Clinically active versus inactive disease** We divided the patients into two groups based on CRP-values and PDAI-values. We defined clinically inactive disease as a PDAI value < 5 combined with a CRP-value <5 mg/L, because 5 mg/L is used in our institution as a cut-off between normal and elevated CRP. For PDAI, no cut-off value between active perianal disease and remission has been established yet. We chose a cut-off value of 5, as used in a previous study on this topic (5), based on findings by Present et al (7).

**Clinical follow-up**
Follow-up data were collected for all patients for a minimum of 11 months (median 423 days, range 263-692). Three separate events were recorded: 1) if surgery had taken place for perianal Crohn’s disease; 2) if new abscess formation had taken place; 3) if a change in medication was necessary (addition of antibiotics and/or immunosuppressive medication and/or biologicals).
### Table 2: PDAI scores.

The patients who started with anti-TNFα treatment, either infliximab (Remicade; Schering-Plough) or adalimumab (Humira; Abbott laboratories) were scanned six weeks after starting treatment to assess initial treatment response.

**Statistical analysis**

Spearman’s rank correlation test was used to calculate correlation coefficients between DCE-MRI parameters and the reference parameters (PDAI, CRP and MRI-based score). 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 (14). The Mann-Whitney U test was used to calculate differences in DCE-MRI parameters between the predefined groups of patients. The Wilcoxon signed rank test was used for repeated measurements to
test for differences between $K_{\text{trans}}$ values before and after therapy. P-values <0.05 were considered to indicate statistical significance.

RESULTS
Sixteen patients were included in this study (7 males; 9 females), with a median age of 34.5 years (range 18-63) with perianal fistulizing Crohn’s disease. One patient used anti-TNFα (6%), two steroids (19%), four mercaptopurine (25%) and three 5-aminosalicylic acid (19%) for Crohn’s disease maintenance therapy. Two patients (13%) had a seton in situ. Six patients formed a subgroup of patients that started with anti-TNFα and were scanned a second time after six weeks. Patient baseline scores are depicted in table 3.

Clinical findings and DCE-MRI parameters
Nine patients had clinically active disease (PDAI >5 or CRP > 5). Patients with active disease had significantly higher ME and volume of enhancing pixels (p=0.017 and p=0.002 respectively).

PDAI was moderately correlated to ME ($r=0.669; p=0.005$) and ISI ($r=0.582; p=0.018$) and volume of enhancing pixels ($r=0.786; p<0.001$) (table 4). Absolute pixel counts of TIC type 2, 3, 4 and 5 showed moderate to strong correlations with PDAI. Relative pixel counts did not show a correlation with PDAI or CRP. For the quantitative parameters ($K_{\text{trans}}$, $v_e$ and $K_{ep}$) no correlations were found.

ISI and volume of enhancing pixels were significantly higher in patients with elevated CRP (p=0.030 and p=0.039 respectively). CRP level was moderately correlated to ME ($r=0.566; p=0.022$), ISI ($r=0.602; p=0.014$) and volume of enhancing pixels ($r=0.516; p=0.041$) (table 3). No correlations were found between CRP and the quantitative parameters.

MRI-based score
Patients with clinically active disease had a significantly higher MRI-based score (p=0.029). The MRI-based score showed a weak to moderate correlation with ME and volume of enhancing pixels (table 3). Total pixel counts of the individual TIC curve types 2, 3, 5 showed moderate to strong correlations with the MRI-based score.

Follow-up
One year follow-up was available for 15 of 16 patients. One patient was lost to follow-up due to emigration. Eight patients needed an intervention (53%); three patients developed an abscess, one patient needed surgical treatment and two
changed medication within the follow-up time. There was a significantly larger volume of enhancing pixels in patients were an event occurred (p=0.028), all other parameters were not significantly correlated.

In the subgroup of patients with anti-TNFα treatment, six weeks after starting anti-TNFα therapy $K_{\text{trans}}$ values were significantly lower in these six patients (mean $K_{\text{trans}}$ 0.509 versus 0.320; p=0.027) (figure 3). $K_{ep}$ (p=0.116), $v_e$ (p=0.173), ME (p=0.345), ISI (p=0.345), volume of enhancing pixels (p=0.075) and PDAI (p=0.257) were not significantly different between patients who needed an intervention and those who did not.

![Figure 3](image.png)

**Figure 3.** $K_{\text{trans}}$ values before and six weeks after start of anti-TNFα therapy. All $K_{\text{trans}}$ values decrease after anti-TNFα therapy.

**DISCUSSION**

Our study is the first to provide both qualitative and quantitative DCE analysis parameters of fistulas in patients with perianal Crohn’s disease. Our most important finding was that in patients with anti-TNFα therapy, $K_{\text{trans}}$ values were significantly lower six weeks after starting treatment. In addition, ME and ISI and volume of enhancing pixels showed a significant, moderate correlation with PDAI and CRP. The quantitative parameters $K_{\text{trans}}$, $v_e$ and $K_{ep}$ did not correlate with PDAI, CRP and MRI-based score. For the different shape curves only correlations of PDAI with absolute amount of certain curve types were found. Relative pixel counts of any of the curve shapes did not correlate with any of the reference standards, which is consistent with an earlier study (5).

DCE-MRI is primarily applied in cancer studies where patients receive treatment with antiangiogenic agents (15). Chronic inflammation also causes neoangiogenesis (16) and permeability of the vascular endothelium increases. This increased permeability is highlighted by a high $K_{\text{trans}}$ (17). Neo-angiogenesis and
vascular remodeling are often present in Crohn’s disease patients (18) and the TNFα inhibitor Infliximab reduces this inflammation-induced angiogenesis in Crohn’s disease patients (19) $K^{\text{trans}}$ values decreased significantly six weeks after starting anti-TNFα therapy, indicating changes in vessel permeability and thus a reduction of angiogenesis and a possible initial effect of therapy in these patients. Yet, it has to be stressed that these results were obtained with a small cohort (only six patients had a follow-up scan) and further research has to be conducted to see if this can predict clinical response.

$ME$ and $ISI$ showed moderate correlations with the reference standards. This is likely caused by increased perfusion due to high vascularisation of the inflamed tissue. A previous study, however, did not find this correlation (5), but did not use the same DCE-MRI protocol (which differed in field strength, scan type (2D/3D), scan parameters, and in the fact that we analyzed the whole lesion volume instead of a single slice).

No correlation was found between $K^{\text{trans}}$ and the reference standards. This might be due to the deficiencies in the clinical scoring systems or that $K^{\text{trans}}$ is not representative of the severity of inflammation.

A number of study limitations have to be taken into account to understand the validity of this study. One of those is certainly the limited sample size of the overall cohort and especially the number of patients with a follow-up scan. It was not possible to compare clinical response in these patients as not all patients continued with the anti-TNFα for a whole year (for various reasons, pregnancy, side effects etc).

More importantly, our study does not have a perfect reference standard. PDAI is commonly used in these studies, but is based on clinical parameters that are partly made up of the patient’s subjective experience of the disease, rather than objective inflammatory or anatomical parameters. CRP is the most widely used biochemical marker of inflammation in Crohn’s disease, but is not specific for perianal fistulas, and can reflect and other inflammatory process occurring at the time of the investigation. MRI-based score is an activity score based on anatomical and inflammatory MRI-parameters (9).

Other limitations come from the DCE-MRI technique, and apply to all the studies in general which make use of this technique. The analysis of DCE-MRI data can be done with different degree of complexity ranging from a simple analysis of the parameters of the TIC (qualitative analysis) to complex pharmacokinetic modelling.
(quantitative analysis). Both were used in this study, together with a heuristic method of classifying the TIC shapes. The parameters obtained by the qualitative analysis (represented in the study by $ME$ and $ISI$) are completely dependent on the parameters chosen for the MR scan, and cannot be compared between studies.

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<th>Clinically active</th>
<th>Clinically inactive</th>
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<td>11 (6-15)</td>
<td>3 (1-5)</td>
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<tr>
<td>MRI-based score</td>
<td>11 (4-18)</td>
<td>16 (4-18)</td>
<td>9 (4-17)</td>
</tr>
<tr>
<td>CRP</td>
<td>4.5 (0-116)</td>
<td>23.4 (2.2 – 116)</td>
<td>1.3 (0 - 4.2)</td>
</tr>
</tbody>
</table>

**Table 3:** severity indexes of the study population

<table>
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<th>PDAI</th>
<th>CRP</th>
<th>MRI-based score</th>
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<tbody>
<tr>
<td>ME</td>
<td>$r=0.669$  ($p=0.005$)</td>
<td>$r=0.566$ ($p=0.022$)</td>
<td>$r=0.466$ ($p=0.069$)</td>
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<tr>
<td>ISI</td>
<td>$r=0.582$  ($p=0.018$)</td>
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<td>$K_{trans}$</td>
<td>$r=0.281$ ($p=0.292$)</td>
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<td>$K_{ep}$</td>
<td>$r=0.196$  ($p=0.467$)</td>
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<td>$v_e$</td>
<td>$r=0.127$  ($p=0.639$)</td>
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<tr>
<td>Volume of enhancing pixels</td>
<td>$r=0.786$ ($p&lt;0.001$)</td>
<td>$r=0.516$ ($p=0.041$)</td>
<td>$r=0.786$ ($p&lt;0.001$)</td>
</tr>
</tbody>
</table>

**Table 4:** DCE-MRI versus reference parameters.

In this study we were careful to keep the scan protocol the same across the whole study (this including not only the same scan parameters, but also injection rates, dosage etc), in this way trying to minimize the scan-related variations. The quantitative analysis suffers from a number of problems related to the model chosen. In this paper we chose to use Tofts’ model. This model uses contrast agent concentration as input, and depends on the choice of the AIF. It is known that the choice of the AIF plays a pivotal role in the modeling, and that small variation of the AIF can lead to large variations in the calculated parameters ($K_{trans}$ and $v_e$). We have chosen a patient dependent AIF because inflow of contrast agent depends on variables such as cardiac output and it therefore more reliable than a measured patient average (11). Still there are unknowns in the calculation of the AIF. The real $T_1$ value of blood cannot be extracted from the Look Locker sequence because of flow problems, and the blood $T_1$ value had to be inserted “manually”. We chose a $T_1$ value of 1700 ms for all the patients, though we are
aware that the $T_i$ can significantly change according to the blood’s hematocrit, which is unknown. All these uncertainties result in variations in the measured $K_{\text{trans}}$ which are difficult to estimate. The TIC shape analysis we performed was done on a pixel-by-pixel basis. Though this has been shown to be a robust method, it is important to realize that classification is dependent on some arbitrary choices in DCE-MRI parameters such as AIF and noise ratio threshold.

In conclusion, the semi-quantitative parameters $ME$ and $ISI$ can be used to evaluate disease activity in patients with perianal Crohn’s disease. The quantitative parameter $K_{\text{trans}}$ may be an indicator of effect of therapy.

REFERENCES

8. Ng SC, Plamondon S, Gupta A, et al. Prospective evaluation of anti-tumor necrosis factor therapy guided by magnetic resonance imaging for Crohn’s


