Functional MRI of the small bowel

*Fundamentals of MRI motility measurements*

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Chapter 2

Evaluation of gastrointestinal motility with MRI: advances challenges and opportunities

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ABSTRACT

Dynamic magnetic resonance imaging (MRI) of gastrointestinal motility has developed rapidly over the past few years. The non-invasive and non-ionizing character of MRI is an important advantage together with the fact that it is fast and can visualize the entire gastrointestinal tract. Advances in imaging and quantification techniques have facilitated assessment of gastric, small intestinal and colonic motility in a clinical setting. Automated quantitative motility assessment using dynamic MRI meets the need for non-invasive techniques. Recently, studies have begun to examine this technique in patients, including those with IBD, pseudo-obstruction and functional bowel disorders. Remaining challenges for clinical implementation are processing the large amount of data, standardization and validation of the numerous MRI metrics and subsequently assessment of the potential role of dynamic MRI. This review examines the methods, advances and remaining challenges of evaluation of gastrointestinal motility with MRI. It accompanies an article by Khalaf et al. in this journal that describes a new protocol for assessment of pan-intestinal motility in fasted and fed state in a single MRI session.
INTRODUCTION

Abdominal magnetic resonance imaging (MRI) is very well suited to image fluids and gastrointestinal volumes in the gastrointestinal tract. Newly developed MRI parameters, previously described in this journal1, provide functional information like volumes, transit time and small bowel water content measurements, but this review focuses on the imaging of gastrointestinal motility.

Dynamic MRI, also referred to as cine MRI, is a MRI technique in which sequences of images are acquired in order to obtain movies. By using post-processing techniques local or global movements in the gastrointestinal tract can be quantified. Approximately 30 years ago dynamic MRI was introduced2 as a method for the assessment of gastrointestinal motility. Only recently quantification techniques for motility assessment have matured to a level that allows for clinical evaluation.

Dynamic MRI is used in the stomach to measure frequency and amplitude of antral contractions3–5. It is used for the small bowel to look at segmental and global motility using frequency measures and surrogate measures6–12. In the colon it has been applied to assess motion and velocity of contents, wall motion and to study motility using surrogate measures13–17. So far there has been a paucity of validation studies. To our knowledge there is only one study in which dynamic MRI findings were compared to manometry, demonstrating 100% correlation between visualized colonic movements and intraluminal pressure changes.17 The clinical value of dynamic MRI is under evaluation for pathologies like inflammatory bowel disease (IBD), chronic intestinal pseudo-obstruction (CIPO) and constipation.

In this issue of Neurogastroenterology and Motility, Khalaf et al. introduce a protocol for assessment of pan-intestinal motility in fasted and fed state in a single session of MRI. As part of their novel approach they quantified small bowel motility using dynamic MRI.18 In this review we discuss the challenges and opportunities in evaluating gastrointestinal motility with dynamic MRI. The first part of this review summarizes the technical aspects of the dynamic MRI technique, the second part discusses the observations made by applying the described techniques to gastrointestinal physiology, diseases and disorders.

ACQUISITION AND POST-PROCESSING METHODS

Image acquisition

There is no standard imaging protocol available yet for dynamic GI motility imaging. Most studies use two-dimensional (2D) scans (i.e. one single slice) acquired in prone or supine position. Securing good temporal and spatial resolution of the images, MRI scanners with field strengths of 1.5T and 3T from several vendors can be used. The preferred MRI sequence depends on the quantitative imaging analysis used, but
is one that displays the bowel wall clearly, with the ability of fast acquisition in order to acquire at a high frame rate, like the commonly used bFFE sequence (balanced steady-state free procession gradient echo sequence) (see figure 1 and movie\textsuperscript{19}).

Until now limited data exists to optimize imaging protocols with respect to quantitative imaging analysis. Spatial resolution requirements are based on the lower limit of bowel wall thickness, 1-3 mm in healthy subjects. Manometric, electromyographic and radiographic studies have shown that the fastest contractions occur in the small bowel, between 9 and 12 contractions per minute\textsuperscript{20}, indicating that at least a temporal resolution of 1 frame every 2.5 seconds is required to capture motility.

Both breath-hold and free-breathing protocols are being explored. The short observation periods associated with breath-hold protocols may seem inadequate to measure GI motility, but have shown good initial results\textsuperscript{4,10,16,21–27} and are very practical for clinical use. Recent work showed that in breath-hold scanning, using a displacement mapping quantification technique (described below), a temporal resolution of at least 1 image per second and a duration of 15 seconds is required for robust assessment of motility.\textsuperscript{28} Free-breathing scans provide more information due to longer scanning times, but the breathing artifacts in the scans and the amount of data for processing still pose a burden to handle.

Three-dimensional (3D) motility imaging gains interest since it provides more coverage to assess movement in all directions, excluding ‘out of plane’ movement, but challenges lie on both the acquisition and the post-processing side. Development of a MRI sequence that meets the temporal and spatial resolution requirements is ongoing; processing the large amount of data acquired and developing automatic 3D data analysis software is a step that has not been taken yet.

Until this moment, in most MRI motility studies the subjects were given bowel preparation with an oral solution, to create good contrast and distention in the GI tract for optimal visualization.\textsuperscript{29} Lately interest has emerged in assessing the bowel in an unprepared state because this allows evaluation of fasted (interdigestive) motility and the response to food.\textsuperscript{18}

Although acquisition techniques require further refinement, it is safe to say that at this moment in time, we are able to visualize motility with dynamic MRI with good resolution. The main hurdle evaluating its clinical value has been the absence of a robust automatic quantification method. Therefore several post-processing/quantification techniques are in development to provide standardization and to overcome the obstacle of manual data processing.
Quantification methods

All methods described below can be used for gastric, small intestinal and colonic measurements. Their advantages and disadvantages are summarized in table 1.

Table 1. Advantages and disadvantages of quantification techniques

<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Visual assessment</td>
<td>• Straight-forward</td>
<td>• Labor-intensive scoring</td>
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<td></td>
<td>• Local and global assessment</td>
<td>• Training required</td>
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<tr>
<td></td>
<td>• Easy to use in clinic (no additional means necessary)</td>
<td>• Does not provide actual quantification of motility</td>
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<td></td>
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<td>• Through-plane movement can cause false-positive contractility*</td>
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<td></td>
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<td>• Prone to interpersonal and intrapersonal variations</td>
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<td>• Requires bowel preparation</td>
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<tr>
<td></td>
<td></td>
<td>• Limited validation studies available</td>
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<tr>
<td>Diameter measurements</td>
<td>• Provides quantification of peristaltic contractions</td>
<td>• Manual measurements are labor-intensive</td>
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<td></td>
<td>• Can be implemented in semi-automatic software for fast and standardized measurements</td>
<td>• Semi-automated software not widely available yet</td>
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<td></td>
<td>• Easy to use in clinic (manual measurements)</td>
<td>• Provides only local assessment</td>
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<tr>
<td></td>
<td></td>
<td>• Through-plane movement can cause false-positive contractility*</td>
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<td></td>
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<td>• Requires bowel preparation</td>
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<tr>
<td></td>
<td></td>
<td>• Semi-automated analysis</td>
</tr>
<tr>
<td>Displacement mapping</td>
<td>• Provides local and global motility measures.</td>
<td>• Metric is a surrogate outcome measure, it does not separately quantify individual measures of contractile activity (e.g. contraction frequency and amplitude)</td>
</tr>
<tr>
<td></td>
<td>• Results presented in easily readable color maps</td>
<td>• Semi-automated analysis</td>
</tr>
<tr>
<td></td>
<td>• No bowel preparation required</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Software commercially available</td>
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<tr>
<td>GI Tagging</td>
<td>• Fully automated analysis</td>
<td>• Long scan durations (minutes) needed for frequency measurement</td>
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<td></td>
<td>• No bowel preparation required</td>
<td>• Software not available</td>
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<tr>
<td></td>
<td>• Works with breath-hold and free-breathing data</td>
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</tr>
<tr>
<td></td>
<td>• Enables assessment of motion over prolonged periods</td>
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</table>

* Through-plane movement is a limitation of all 2D techniques, but is a less prominent issue in displacement mapping and GI tagging techniques.
Visual assessment
The simplest method to interpret dynamic MR images is evaluation by visual assessment of propagation direction and incidence of phasic contractions at specified sites in the GI tract (Fig. 1A-B). This can be performed by a radiologist who observes all consecutive images of a bowel segment and grades the contractile activity on a 5-point scale or by using a classification system. Visual assessment is a relatively simple technique that can easily be used in daily clinical practice by trained radiologists when validated. However it is relatively labor-intensive and prone to inter- and intra-observer variations.

Diameter measurements
Another easily understandable method is the measurement of changes in the luminal diameter over time. This method requires satisfactory distension of the lumen and good visualization of the luminal boundaries. In selected bowel segments, a line is drawn perpendicular to the wall of the segment and copied to all sequential images of the dynamic 2D MRI. The length of this line is followed over time, representing the contractility of this specific bowel segment (Fig. 1C-D).

The drawing and copying of the diameter line to all sequential images can be performed manually, or semi-automatically with software like ‘Motasso’. This software-assisted method has been shown to be faster and have a higher measurement precision compared to the manual method. Adjustment of the software has made it possible to work with free-breathing data. An important limitation of the diameter measurement method is the through-plane movement of the segments that are measured. The software cannot distinguish this movement from a real contraction, leading to over-interpretation of contractility.

The diameter method is a relative simple technique, especially the manual method can be used clinically, but is a relatively time-consuming task. Unfortunately, to our knowledge, the semi-automatic ‘Motasso’ software is not available to other researchers and clinicians.

Displacement mapping
The displacement mapping method, also known as motility mapping, is based on the idea that contrast in the dynamic MR images changes over time due to motility and movement of luminal content. The motion of abdominal organs between two consecutive images in time can be estimated by an automated optical-flow based algorithm, providing displacement fields (Fig. 1E). Several surrogate measures for motility are then determined using these displacement fields. This method was optimized by two independent research groups.
Motility mapping provides the reader with a color-coded map (Fig. 1F) for a global assessment of motility in all segments of the MR image. Furthermore, a region of interest (ROI) can be delineated to obtain a single, numerical motility score for that area on the scan. It should be noted however that different groups have used different calculation techniques and that interpretation of the resulting color plots requires understanding of the technique. It is yet to be determined what metric will be clinically most valuable, this might even be disease-specific.

Displacement maps are preferably calculated from a 20-second breath-hold movie to avoid breathing artifacts and to limit data processing times, but a breath-hold protocol is not necessarily required for this technique.

The displacement mapping technique is more complex and less easy to understand than the previous two methods but it allows quantitative analysis of global and local GI motility. It has been automated for more repeatable and standardized results and it produces very easily readable color maps. The software has been used and validated in several studies and one software version is commercially available.

**GI Tagging**

Whereas the previous three techniques dealt with post-processing of conventionally acquired dynamic MRI data, the tagged MRI technique involves a dedicated type of MR acquisition. During image acquisition, taglines are applied to the tissue. These taglines are read-out with a delay and during this delay movement of the tagged tissue leads to deformation of the taglines. This deformation of the tag lines is thus related to motility.

With a quantification technique developed by Sprengers et al. the deformation of the taglines can be tracked in free-breathing scans to measure motility in multiple frequency bands in regions of interest (Fig. 1G). Assessment during free-breathing allows for longer monitoring i.e. minutes vs. seconds and assessing motility at frequencies as low as 2 contractions per minute. With the quantification technique developed by Pritchard et al. laminar flow velocity and direction can be measured.

GI tagging for GI applications is a new technique and the method and its clinical value are currently being explored. Therefore there is no software yet that is open to other researchers.
Figure 1. This figure visualizes the described quantification techniques. Coronal images A and B visualize the gastrointestinal tract at two moments in time (1 and 13 seconds) of a dynamic MRI movie used for visual assessment. A and B show contractility of the stomach (red arrows), several loops of the small bowel (green and blue arrows) and colon (yellow and orange arrows). Software-assisted (C) and manual (D) measurement of small bowel diameter are shown under the diameter measurement technique. The white circle marks the bowel segment used for analysis, below a plot of the calculated diameters representing motility. In E the deformation field of a coronal scan is visualized as a deformation grid used in the displacement mapping technique. Greater movement of underlying small bowel (delineated with green ROIs) occurs as greater distortion in the grid. F represents the analysis of a per-pixel deformation grid as a color-coded map. In G a coronal GI tagged image is visualized showing deformed taglines in the small bowel in green. In H a sagittal image shows movement within the colonic chime. The arrows highlight tag distortion (white arrow) and smearing and reduction of tag intensity (red arrow) due to movement. (Copyright granted)
STUDY PROTOCOLS

Assessment of GI motility with dynamic MRI can be carried out in various settings and protocols depending on the clinical question of interest.

It is important to note that there are fundamental differences between the motility patterns in the GI tract during fasting (interdigestive state) and after ingestion of a meal (postprandial state). In the interdigestive state, the motility pattern is characterized by an alternation of periods with intense contractile activity and periods with motor quiescence. This cyclic pattern starts in the stomach and propagates slowly to the terminal ileum, hence the name migrating motor complex (MMC). Immediately after a meal, the MMC is interrupted at all levels, to be replaced by the postprandial motor pattern.

In most dynamic MRI studies published so far, bowel preparation with a substantial volume of fluid, most often a mannitol solution, was given. It is likely that such preparation leads to induction of the postprandial motor pattern. Thus, the published results of MRI studies carried out until today pertain to a postprandial state induced by a non-physiological “meal”. This type of motility scan can be added to the standard abdomen MRI protocol and the motility can be quantified with one of the techniques described above. It has not yet been shown that the MMC can be detected with dynamic MRI, but it is likely that this is the case. Displacement mapping and MR tagging are techniques that can deal with the challenge of non-distended, “empty” bowel loops.

MRI motility imaging can also be used to evaluate the response to food or a pharmacological agent. This requires a MRI protocol designed specifically for this type of response testing. These protocols can be used as a complementary test for diagnosis, but also for pathophysiological studies and drug development.

In this edition Khalaf et al. introduce a protocol with which the pan-intestinal motor response to a physiological test meal can be measured in a single MRI session. In their study, in a healthy volunteer cohort, the authors not only explored pan-intestinal motility and transit, but also compared the imaging parameters to GI peptide responses and to symptoms. With this novel approach, several measures of interest for the assessment of gastrointestinal motility can be obtained in one measurement session. In their paper Khalaf and co-workers set normal limits for gallbladder and gastric volumes, small bowel motility and water content, whole gut transit, GI peptides and symptom data when using this test meal. Others have described an under 60 minutes MRI protocol to examine gastric motility, accommodation and emptying together with the duodenal response following a simple water stimulus. We have used a practical 30-minutes stimulation test for small bowel motility assessment, demonstrating a significant response to a caloric challenge in fasted healthy subjects within a time frame of less than 10 minutes.
CLINICAL IMPLEMENTATION

The conventional techniques for evaluation of motility and transit in the human GI tract are well established, but are often invasive, ionizing, lengthy and cannot measure in the less accessible regions of the small bowel and colon. Therefore MRI is an exciting novel technique that creates new opportunities for research, clinical diagnosis, treatment follow-up and drug development. The following are examples of clinical applications of this imaging technique.

Crohn’s disease

Several studies show that small bowel motility quantified with dynamic MRI can be used as a biomarker of inflammatory activity in Crohn’s disease and to differentiate healthy from diseased bowel.\textsuperscript{21,27,32,43,49} The motility in the terminal ileum was lower in Crohn’s patients in comparison to healthy subjects.\textsuperscript{43} It has been shown that the lesion detection rate is increased when static and dynamic MRI are combined.\textsuperscript{26,50} The motility patterns in Crohn’s disease revealed reduced contraction-wave frequencies, amplitudes, and decreased luminal occlusion rates.\textsuperscript{21,25} Bowel motility was inversely correlated with bowel diameter proximal to the stenosed segment.\textsuperscript{23} Motility changes of the terminal ileum showed correlation with histopathological findings both in active (P=0.006) and chronic Crohn’s disease (p=0.01).\textsuperscript{49} It was also shown that aberrant motility in Crohn’s disease is linked to inflammatory burden and patient symptoms.\textsuperscript{42}

The first follow-up study in patients with Crohn’s disease receiving anti-TNFα treatment showed that MRI of small bowel motility accurately detects response to anti-TNFα therapy as early as 12 weeks. This suggests that the method allows for personalized medicine since it permits relatively early identification of nonresponse to anti-TNFα agents.\textsuperscript{41}

These observations indicate that including the evaluation of small bowel motility in standard MRI of patients with Crohn’s disease may improve management.

GI motility disorders and functional bowel disorders

A retrospective dynamic MRI study compared small bowel motility of patients with chronic intestinal pseudo-obstruction (CIPO) and patients with irritable bowel syndrome (IBS) to healthy subjects. The small bowel contractions in CIPO patients were found to be significantly weakened compared to IBS patients and healthy subjects.\textsuperscript{51} The results of a subsequent study in CIPO patients suggest that dynamic MRI is useful for the evaluation of the severity of CIPO by the prediction of severe clinical features.\textsuperscript{52} These findings were confirmed by a study in which the reader was blind to any clinical information, demonstrating a significantly decreased small bowel motility in CIPO patients compared to controls.\textsuperscript{24} Additionally, it was found that the response to a prokinetic drug may differ according to disease phenotype.
A study in Ehlers-Danlos syndrome-Hypermobility type patients and controls showed that the increase in gastric motility following a water challenge was significantly lower in Ehlers-Danlos syndrome-Hypermobility type patients with functional dyspepsia compared to controls.\textsuperscript{4}

In constipated patients a response assessment with an oral preparation stimulus revealed a significant difference in colonic motility between patients and healthy controls 60 minutes after ingestion.\textsuperscript{16}

**FUTURE PERSPECTIVES**

In 1994 it was stated that MRI of the real-time motion of the gastrointestinal tract was in the embryonic state.\textsuperscript{53} Currently we can say that adolescence has been reached when it comes to the acquisition of the scans. However, the clinical field is in need of standardization and validation of the outcome metrics and subsequently assessment of the potential role of dynamic MRI. Up until this moment, motility MRI is rarely used in clinical routine but the body of (positive) evidence is growing and is opening doors to allow a widespread translational application.

Future research should be aimed at improving our understanding of the pathophysiological postprandial GI response and validating the numerous MRI metrics in a range of disorders for diagnostic potential, treatment follow-up and drug development. On a technical note, more research into 3D acquisition and improved post-processing analysis techniques is eagerly awaited.

Meanwhile, software must be further refined to stimulate translation into clinical routine. Ideally, the software will be fully automated, able to work with vast quantities of data, widely available and is designed with an intuitive user interface. Additionally, the software should offer the user a motility metric toolbox for local and global measurements.

**CONCLUSIONS**

There is a clinical need for a non-invasive technique that can assess motility and transit in the entire GI tract. Automated quantitative bowel motility assessment using dynamic MRI is likely to meet some of the hitherto unmet needs. Incorporated in clinical MRI protocols, or in the form of specifically designed motility-provoking protocols, dynamic MRI has potential as a future tool to investigate gastrointestinal motility disorders.
REFERENCES


