Colon wall motility: comparison of novel quantitative semi-automatic measurements using cine-MRI

Journal:	*Neurogastroenterology and Motility*
Manuscript ID	NMO-00241-2015.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Hoad, Caroline; University of Nottingham, Sir Peter Mansfield Imaging Centre, School of Physics and Astronomy; Nottingham University Hospitals Trust and the University of Nottingham, NIHR Biomedical Research Unit in Gastrointestinal and Liver Diseases Menys, Alex; UCL, Centre for Medical Imaging Garsed, Klara; Nottingham University Hospitals NHS Trust and University of Nottingham, NIHR Biomedical Research Unit in Gastrointestinal and Liver Diseases Marciani, Luca; Nottingham University Hospitals NHS Trust and University of Nottingham, NIHR Biomedical Research Unit in Gastrointestinal and Liver Diseases; University of Nottingham, Nottingham Digestive Diseases Centre, School of Medicine Hamy, Valentin; UCL, Centre for Medical Imaging Murray, Kathryn; University of Nottingham, Sir Peter Mansfield Imaging Centre, School of Physics and Astronomy Costigan, Carolyn; University of Nottingham, Sir Peter Mansfield Imaging Centre, School of Physics and Astronomy Atkinson, David; UCL, Centre for Medical Imaging Major, Giles; Nottingham University Hospitals NHS Trust and University of Nottingham, NIHR Biomedical Research Unit in Gastrointestinal and Liver Diseases Spiller, Robin; Nottingham University Hospitals NHS Trust and University of Nottingham, NIHR Biomedical Research Unit in Gastrointestinal and Liver Diseases; University of Nottingham, Nottingham Digestive Diseases Centre, School of Medicine Taylor, Stuart; UCL, Centre for Medical Imaging Gowland, Penny; University of Nottingham, Sir Peter Mansfield Imaging Centre, School of Physics and Astronomy
Key Words:	Cine MRI, motility, imaging metric, ascending colon

Colon wall motility: comparison of novel quantitative semi-automatic measurements using cine-MRI

Running title: Colonic Wall Motility using cine-MRI

C.L. Hoad[1,2*], A. Menys[3], K. Garsed[2], L. Marciani[2,4], V. Hamy[3], K. Murray[1], C. Costigan[1], D. Atkinson[3], G. Major[2], R.C. Spiller[2,4], S.A. Taylor[3], P.A. Gowland[1]

[1] Sir Peter Mansfield Imaging Centre, School of Physics and Astronomy, University of Nottingham, Nottingham, UK

[2] NIHR Biomedical Research Unit in Gastrointestinal and Liver Diseases, Nottingham University Hospitals Trust and the University of Nottingham, Nottingham, UK

[3] Centre for Medical Imaging, Division of Medicine, University College London, UK

[4] Nottingham Digestive Diseases Centre, School of Medicine, University of Nottingham, Nottingham, UK

* Corresponding Author

Caroline Hoad, Sir Peter Mansfield Imaging Centre, School of Physics and Astronomy, University of Nottingham, University Park, Nottingham NG7 2RD

Email: Caroline.L.Hoad@nottingham.ac.uk

Tel: +44 (0)115 8466003

Fax: +44 (0)115 9515166

Author Contributions: CLH, LM, GM, RCS and PAG designed the study, KG, and CC acquired the data, AM, VH, DA, and SAT developed the registration

algorithms and designed the analysis interface, CLH, AM, KM analysed the data. CLH, AM, LM, GM, RCS, SAT and PAG interpreted the data. CLH and AM drafted the manuscript. CLH, AM, LM, RCS, SAT and PAG critically reviewed the manuscript. All authors approved the final version.

ABSTRACT

Background: Recently cine MRI has shown promise for visualising movement of the colonic wall, although assessment of data has been subjective and observer dependent. This study aimed to develop an objective and semi-automatic imaging metric of ascending colonic wall movement, using image registration techniques.

Methods: Cine balanced turbo field echo (bTFE) MRI images of ascending colonic motility were acquired over 2 minutes from 23 healthy volunteers (HVs) at baseline and following two different macrogol stimulus drinks (11 HVs drank 1L and 12 HVs drank 2 L). Motility metrics derived from large scale geometric and small scale pixel movement parameters following image registration were developed using the post-ingestion data and compared to observer grading of wall motion. Inter and intra-observer variability of the highest correlating metric was assessed using Bland-Altman analysis calculated from 2 separate observations on a subset of data.

Key Results: All the metrics tested showed significant correlation with the observer rating scores. Line analysis produced the highest correlation coefficient of 0.74 (95% CI 0.55-0.86), $p<0.001$, (Spearman Rho). Bland-Altman analysis of the inter- and intra-observer variability for the line analysis metric, showed almost zero bias and small limits of agreement between observations (-0.039-0.052 intra-observer and -0.051-0.054 inter-observer, range of measurement 0-0.353).

Conclusions and Inferences: The line analysis index of colonic motility derived from cine MRI registered data provides a quick, accurate and non-invasive method to detect wall motion within the ascending colon following a colonic stimulus in the form of a macrogol drink.

Keywords: Cine MRI, motility, imaging metric, ascending colon

Key Messages

Recent cine MRI has shown promise to visualise the movement of the colonic walls, however assessment has been limited to subjective and semi-automatic analysis.

This study reports the development of an objective metric of ascending colon motility derived from cine MRI data using image registration techniques to remove respiratory motion and parameterise bowel movements.

Data from 23 healthy volunteers, who had received a macrogol stimulus, were used to assess potential metrics, which were derived from cine MRI data. These metrics were compared to an observer score of motility.

The line analysis metric produced the highest correlation coefficient with the observer scoring. Inter- and intra-observer variability was low for this metric.

This study has shown that it is possible to generate objective semi-automatic metrics of colonic motility from cine MRI data using image registration techniques.

Assessment of colonic motor activity is difficult owing to its erratic nature and the inaccessibility of the colon for study. Previous methods have largely relied on procedures that are unpleasant for patients and demanding for staff; these involve placing pressure probes into the colon, which usually requires bowel cleansing, colonoscopy and often endoscopic clips to secure the probe, facilitating long term recordings (1). Recent developments with high resolution manometry have provided unprecedented detail on the different types of motor activity (2) but the technique remains difficult and expensive, limiting use to a few specialised centres. Scintigraphic methods allow accurate, reproducible assessment of transit and have been widely used to investigate pharmacologic modulation of gut transit (3). However scintigraphy only assesses bulk transit and does not allow detailed assessment of the motor patterns which may be relevant when studying disease or drugs which specifically target abnormal motility. More recently the Smart Pill has been introduced as a less invasive alternative while still allowing direct assessment of motor activity (4). Although better tolerated by patients, its use is limited by expense and it cannot be used to reliably assess specific regions of the colon because of the inability to control its position. This is also the case for the proposed Magnetic Tracking System (5) which again relies on the passage of a magnetic pill through the GI tract to assess the motor activity. Increasing data suggests dynamic motion capture "cine" MRI is acceptable to patients and could allow detailed evaluation of colonic motor activity. It has previously been shown that 1 litre of electrolyte macrogol solution provides a reliable stimulus with vigorous movements of the ascending colon (AC) in healthy volunteers (6) within an hour of ingestion. MRI scanners are now widely available in larger hospitals and costs for a short examination

(30 minutes) are similar to those of a nuclear medicine gastric emptying test and are considerably less than endoscopy and colonoscopy.

An important component to MR based motility assessment is automation and quantitative analysis, and non-linear image registration based techniques (7) can provide a range of quantitative measures for assessing bowel motion. Registration provides 1) parametric surrogate markers of motility and 2) allows automatic propagation of regions of interest (ROIs) through time series data once an ROI has been defined on a single image (7). This type of analysis has produced objective and repeatable metrics of global small bowel motility (8, 9). Until recently, the most widely used registration technique was only applicable to breath-held data (8, 10) as breathing produces additional motion within the images that is not related to the GI motion of interest, thus confounding the data, by mimicking bowel movement. This is problematic for colonic motility imaging as contractions are comparatively infrequent necessitating free-breathing protocols. Recent advances however have introduced a dual stage process that first corrects respiratory motion in extended free-breathing data sets (11) before performing motility assessment (12) facilitating data collection of longer time periods. Colonic motion has been recently studied using cine MRI (6, 13, 14), but analysis remains subjective and time consuming using semi-quantitative, subjective assessment of contractions, flow and bowel wall motion. To date there have been no reported investigations of objective imaging metrics of colonic motility derived from free breathing MRI data.

The aim of this study was to develop an objective imaging metric which quantifies movement in the ascending colon walls during free breathing cine

MRI, by applying image registration techniques to generate the metrics and validate these against observer rating scores of motility.

Materials and Methods

The data used for this work was a subset of that acquired from an open-label, parallel group design study in healthy volunteers using MRI to investigate the small bowel and colonic response to 1 and 2 litres of polyethylene glycol (PEG) (Macrogol 3550) electrolyte solution (Moviprep®, Norgine Pharmaceuticals Ltd, Harefield, UK) (6). Such PEG solutions are widely used in larger quantities than used here as bowel cleansing preparations prior to colonoscopy or barium enema examinations. The full study was registered on the EU Clinical Trials Register with EudraCT Number 2010-021879-85. It was approved by the National Research Ethics Service (approval 10/H0906/50), the NHS Trust R&D (approval 10GA018) and by the Medicines and Healthcare products Regulatory Agency (MHRA Clinical Trial Authorization CTA 03057/0045/001-0001, protocol 10050). All volunteers gave written consent before participating.

The details of the study protocol have been already published (5). In brief 24 healthy volunteers were divided into two age matched groups of 12 subjects. Group 1 received 1 litre of PEG electrolyte solution at 1pm on day 1 following a 6 hour fast and a further 1 litre at 8am the next morning. Group 2 were given a single dose of 2 litres PEG electrolyte solution at 8am on the study day following an overnight fast. Group 1 was given 1 hour to ingest the solution and Group 2 was given 2 hours. Time 0 was then defined as the time of the first MRI scan immediately after ingestion of the PEG electrolyte solution. Baseline scans (performed according to the protocol described below) were acquired before the

PEG electrolyte solutions were ingested and then further scans were acquired hourly for 4 hours following ingestion. Subjects spent around 15-20 minutes in the scanner at each time point and sat upright for the rest of the time. 1 subject from Group 1 withdrew from the study. To provide a range of motility data, only the baseline and first two post ingestion time points were considered (baseline, T=0, T=60 min). To identify potential motility metrics, the post-ingestion data from group 1 and group 2 were combined to provide a range of motility responses as it has previously been shown that the motility response (assessed by an observer) was dose dependent (6).

Imaging was carried out using a 1.5 T Philips Achieva Scanner. Each volunteer was positioned supine in the scanner with a 4 element parallel imaging body coil wrapped around the abdomen. The colonic motility scan was one of a range of scans acquired to characterise the response of the gastrointestinal tract to the PEG solution; information on all the sequences used can be found in (6). The colonic motility scan comprised of a single sagittal slice, balanced turbo field echo (bTFE) positioned by the radiographer centrally through the AC with field of view 330 x 228 mm^2, in-plane resolution 1.5 x 1.5 mm, slice thickness 15 mm, flip angle 70°, repetition time/echo time 3.0/1.5 ms. A cine dataset was acquired using this sequence every second for 2 minutes. Subjects were asked to shallow breath throughout the acquisition.

The data was registered using the DRAM methodology (12) performed at a different laboratory, blind to the subject preparation. In brief, effects of respiratory motion on the data were first removed by registering using Robust Data Decomposition Registration(11). The resulting images were then

subsequently non-linearly registered using an optic flow technique (7) to generate the deformation fields which define how each image maps onto a median image generated from the entire data series.

Following registration, in-house software written using Matlab® (The Mathworks Inc) was used to allow an observer to define regions of interest (ROI) and lines across the single median image of the AC (Figure 1). This information was then used to automatically derive both small scale pixel-based and large scale geometry-based metrics, from the registration parameters.

Four potential imaging metrics were investigated, two based on small scale pixel deformation fields and two based on large scale geometry changes. A single observer (CH) defined all the ROIs to generate the different metrics.

(A)***SD_JAC***: The standard deviation (SD) of the Jacobian, representing the fractional area change of each pixel due to deformation, averaged over an ROI encompassing the whole AC (drawn by an observer), a measure which has previously been used to quantify small bowel motility (8). Each image in the time series is registered to a target image, so that each pixel has a displacement field associated with it for each time point. Distortions that do not result in a local change of area have a Jacobian value of 1. If the local area decreases, the value of the Jacobian will decrease towards zero and if the area expands its value will increase above 1. Therefore, when we report a SD Jacobian of 0.34 for a given pixel we are saying that for 68% of time points, the total fractional area change falls within 0.34 units of 1 (with 1 being no displacement). The larger the SD Jac the greater the variation in fractional area and hence more movement of the

pixels. SD_JAC, generated pixel by pixel (through the time series), was averaged over a ROI drawn by an observer covering the whole AC to generate the metric. Example maps of SD_JAC are shown in figure 2A

(B) ***SD_I***: The standard deviation of the variation in intensity, linked to flow due to movement of the colonic contents generated by wall movement. SD_I generated pixel by pixel was averaged over a ROI drawn by an observer covering the whole AC.

(C)***LA:*** Line analysis index. The AC was divided into three regions (bottom-section including cecum, mid-section and top-section up to the hepatic flexure) and in each region an observer drew either 3 or 5 lines perpendicular to the main axis of the AC, depending on the overall length of the AC (Figure 1a). These lines were automatically propagated through the time series using the deformation fields from the registration and the length of each line at each time point was saved for subsequent analysis, giving between 9 and 15 time series. The time series were smoothed using a moving average of 5 data points. Example smoothed time series are shown in figure 2B. For additional visualisation of motility, colour motility plots were generated of (a) absolute difference in length from mean for points along AC against time (Figure 2C) and (b) change in length between consecutive time points (wall velocity- Figure 2 D). A series of LA Motility Indices were defined as the percentage of the time series line analysis data which had a change in length (i.e. wall velocity) between consecutive time points of greater than 0.25, 0.5 and 0.75 mms^{-1} after smoothing ($LA_{0.25mms^{-1}}$, $LA_{0.5mms^{-1}}$ and $LA_{0.75mms^{-1}}$).

(D) ***NAC:*** The Normalised Area Change across the time series was defined by first splitting the AC into three regions of interest (ROIs)

(Figure 1b) drawn by an observer; 3 regions were chosen to help identify smaller wall movements which may have been missed if using a large ROI of the whole AC. The ROIs were then automatically propagated through the time series data using the deformation fields defined during registration and the areas of the ROIs were plotted against time, and the resulting time course was smoothed using a moving average of 5 points. Each time course was normalised to its mean value and the number of time points which were more than 3, 5 and 10% different from the mean were counted and summed over all 3 regions to give three NAC Motility Indices ($NAC_{3\%}$, $NAC_{5\%}$ and $NAC_{10\%}$).

These different measures were compared to an observer rating which was carried out on the raw, unregistered data. The Observer Rating Score (6) was defined as the duration of wall motion multiplied by the number of sections of the ascending colon showing motion (with the AC being divided into 3 sections). Thus if motion was observed involving the whole AC for 15 seconds and later involving only 1 third of the AC for 20 seconds the corresponding observer rating score would be (15 x 3)+(20 x 1) = 65 in units of segment x s. This was estimated by a single observer (CH). This measure was used as the comparator as it had shown to differentiate between low and high motility previously (6). Motility plots using the LA data were used to define the different types of contractions observed.

Inter and intra-observer variations of the highest correlating metric were obtained from data acquired by 2 observers (CH with over 15 years experience of analysing GI MR images and KM with 4 years experience) and 1 observer on 2 occasions (CH) with the analysis separated by a 3 month period, respectively.

Observers were required to draw on the median image only of a subset of the total data (N=33 from 11 subjects) and all subsequent analysis and generation of the metrics were automated. KM was shown how to interact with the analysis software (i.e. draw regions on the anatomy, save outputs etc.) by CH.

As a demonstration of the utility of the best correlating metric to differentiate between different colonic motor activity, the differences over time (including baseline data) between the two different macrogol stimuli (1L and 2L) were investigated. Previous manually observed scoring of this data showed distinct differences with time and between the stimuli. (6).

Statistics

Statistical analysis was carried out using SPSS 20.0 (IBM) and GraphPad Prism 6.0 (GraphPad Software, La Jolla California USA). All data were tested for normality using the Shapiro-Wilks test.

As the observer rating score was non-normally distributed, all potential metrics were correlated to it using Spearman Rho correlation coefficients, statistical significance was set at $p<0.05$. The parameter with the highest correlation to the observer rating score was then used to determine the observer variability of the measurement.

To assess the inter and intra-observer variability, Bland-Altman limits of agreement between observers were calculated (15) and correlation between observations was assessed by the intra-class correlation coefficient.

Results

After registration to remove respiratory motion, a small amount of data still showed large scale movements of the whole abdomen, which when registered using the optic flow technique, translated into large changes in the images not associated with specific motion of the bowel. This mis-registration led to errors in the metrics generated due to additional global distortions of the anatomy (from respiratory motion) producing large scale changes to the deformation fields, and hence overestimating motility. Data sets which showed large scale breathing distortions on the images post registration were excluded from subsequent analysis. These were identified using organs such as the liver and kidney which should normally be static after image registration to correct for respiration. As a result 7 data sets (15 %) were excluded from post-ingestion data and a further 4 data sets (17 %) from the baseline data.

Demographics of the subject groups used for metric correlation and inter-observer measurements are given in Table 1. Example images and 2D motility plots are shown in Figure 2. All proposed measures showed significant correlation with the observer rating scoring, however only a few metrics (SD_JAC and line analysis) showed highly significant correlation ($p < 0.01$) and this is summarised in Table 2 and Figure 3. The normalised area change indices and SD_I showed very weak correlation with the observer rating score. The $LA_{0.25mms^{-1}}$ and $LA_{0.5mms^{-1}}$ indices showed the highest correlation with the observer rating score and this metric was therefore investigated for the inter- and intra-observer measurements.

The line analysis plots of displacement and velocity also provided additional information as to the types of contractions seen following this stimulus. Examples of the different types of contractions are shown in Figure 4. Using the plots to define the contractions, there were 5 types of contractions seen: segmental antegrade and retrograde contractions, whole AC antegrade and retrograde contractions and near simultaneous large amplitude contractions. The last type of contraction appears to significantly change the whole lumen diameter rapidly and over a very short period of time (typically < 20 s). All these types of contraction could be visually seen by observing the cine data if displayed as a movie. Dilation of the lumen was also observed on many of the datasets (Figure 4 B and C).

Inter and intra-observer Bland-Altman measurements and Intra-class correlation coefficients are summarised in Table 3 for the $LA_{0.25mms^{-1}}$ and $LA_{0.5mms^{-1}}$ indices These data show that there was very little bias between observations for the inter- and intra-observer measurements of line analysis with small limits of agreement compared to the range of values measured (limits of agreement Inter-obs $LA_{0.5mms^{-1}}$: -0.051 to0.054, range of measurement: 0.000-0.353).. Intra-class correlation coefficients were statistically significant (and coefficients above 0.9) for both LA indices calculated.

The variation of the colonic motility activity (as assessed with $LA_{0.5mms^{-1}}$ index) with both time and macrogol stimulus is shown graphically in Figure 5. Baseline motility was low compared to the post-stimulus data, with the 2 L having a larger effect immediately after ingestion.

Discussion

This study has shown that objective metrics of ascending colon motility can be generated non-invasively with minimal observer input using cine MRI combined with registration techniques. The line analysis (LA) indices proved to be the most robust measures of those examined, correlating well with the subjective scoring of wall movement (6). In addition the motility plots of wall deformation and wall velocity allowed a quick visual assessment of any contractions including smaller movements which were occurring, in a similar way to pressure changing maps generated by high resolution manometry. Five different types of contraction were observed both visually, and from the motility plots, following the macrogol stimulus, both segmental over short distances in the AC as well as encompassing the whole AC region. Retrograde and antegrade and near simultaneous wall movements were observed and were a result of the colonic response to the large fluid content from the stimulus drink. These contractions were probably induced to aid mixing and absorption the fluid within the chyme. The most common type of wall movement was segmental retrograde, however it is beyond the scope of this paper to define all the contractions observed throughout the datasets. By using image registration to correct for breathing effects, data could be acquired over extended time periods, without any additional observer analysis time needed. The recording period of 2 minutes used in this study could be extended to allow more sporadic motility patterns to be investigated. The imaging sequences are available on all modern scanners hence the technique could be widely used in clinical practice. As colonic wall movement occurs on a longer time scale than a breath hold (2) the image registration is important if these methods are to be of clinical use. Typical computing time for the registration for

a 2 minute cine-MRI dataset would be 15 mins, with observer drawing and metric calculations taking a further 2-3 minutes. In comparison manual assessment of the motility from a single 2 minute cine could take up to 10 minutes, depending on the number of contractions present, and this would increase with longer acquisition periods. Inter and intra-observer variability was extremely low, with excellent correlation between the 2 measurements acquired, reflecting the objective nature of this registration-based approach which is crucial for clinical practice.

This study showed that an influx of fluid into the AC stimulates rapid contractions which can be detected over a short recording period. Different amounts of ingested fluid, elicit different responses, with the tendency of larger amounts of fluid to initially stimulate more wall movement. A previous study by Kirchhoff et al (14) demonstrated that MRI is extremely accurate in detecting high amplitude propagation pressure waves as defined by manometry when the data are acquired simultaneously. They also noted that MRI showed increases in luminal diameter which were not detected by the manometry probe, as already observed by Wright et al (16) who carried out simultaneous measurements in the stomach. This increased sensitivity to wall activity provided by MRI, may provide a greater understanding of the physiology of the colon in terms of mixing its contents and propelling them towards the rectum. Recent work using high resolution manometry by Dinning et al (17, 18) has shown that the motor patterns within the colon are far more complicated than previously thought, and the crude spacing of conventional manometry sensors resulted in mis-interpretation of the actual motor patterns. Cine MRI with image registration could now provide an alternative, non-invasive approach to viewing the colonic

walls. This could provide further information on the basic physiology of the colon, without disturbing the natural environment. This technique can also be extended to other segments of the colon and in defining objective clinical information in constipation patients. Further studies are needed to determine both optimal timings of MRI assessment of colonic motility following PEG ingestion and the optimal volume of stimulating drink to ingest. However it could be envisaged that a protocol similar to that used for MR imaging of the small bowel in Crohn's disease could be developed. Subjects would arrive at the MRI unit and be given the stimulating drink. A period of time later they would have a short 20-30 minute MRI scan where measurements of colonic motility could be made.

There are limitations to the proposed technique. The validation of the metrics was based on observer scores of motility and is therefore not a 'gold standard' measure for comparison although the observers did have extensive experience of imaging the colon using MRI. However it is also possible that the computer algorithm will detect motion in the colon not visualised by the observer. The line analysis metric showed good consistency across different subjects with a wide range of observed motility scores. Acquisition of the data is currently from a single slice positioned within the AC and thus results could be influenced by poor positioning of the slice, or anatomy which is not easily visualised in a single plane. Multislice acquisition, to gain greater coverage of the anatomy, is possible with reduced temporal or spatial resolution and would allow investigation of other less straight colonic regions such as the descending and sigmoid colon. Over estimation of motility from imperfect registration of the data occurred, if the raw data showed large movements of all internal organs from respiration.

From the subjects studied here 14-18% of the data was corrupted with mis-registration errors and was discarded. However in future studies, these errors can be minimised by training of the subjects to breath in a shallow manner during data acquisition and with active monitoring of the data collected; an approach not available with this data, which was looked at retrospectively. It is also possible that other more sophisticated metrics may provide greater correlation to the motility seen in the AC; however a simplistic approach was taken for this study to allow fast generation of the metrics studied.

In conclusion the line analysis index of colonic motility derived from cine MRI registered data provides a quick, accurate and non-invasive method to detect wall motion within the ascending colon following a colonic stimulus in the form of a macrogol drink.

Acknowledgements, funding and disclosures

This is a summary of independent research funded by the National Institute for Health Research Biomedical Research Unit. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

AM is a director and shareholder of Motilent Ltd. All other authors have no conflicts of interest to disclose.

Abbreviations:

AC – Ascending colon

bTFE – balanced Turbo Field Echo

HV – Healthy volunteers

LA – Line analysis

MRI – Magnetic Resonance Imaging

NAC – Normalised Area Change

PEG - polyethylene glycol

ROI – Region of Interest

SD_JAC – Standard deviation of the Jacobian

SD_I – Standard deviation of Intensity

References:

1. Bampton PA, Dinning PG, Kennedy ML, Lubowski DZ, Cook IJ. Prolonged multi-point recording of colonic manometry in the unprepared human colon: Providing insight into potentially relevant pressure wave parameters. American Journal of Gastroenterology, 2001; 96(6): 1838-1848.
2. Dinning PG, Wiklendt L, Maslen L, Gibbins I, Patton V, Arkwright JW, Lubowski DZ, O'Grady G, et al. Quantification of in vivo colonic motor patterns in healthy humans before and after a meal revealed by high-resolution fiber-optic manometry. Neurogastroenterol Motil, 2014; 26(10): 1443-57.
3. Deiteren A, Camilleri M, Bharucha AE, Burton D, McKinzie S, Rao AS, Zinsmeister AR. Performance characteristics of scintigraphic colon transit measurement in health and irritable bowel syndrome and relationship to bowel functions. Neurogastroenterol Motil, 2010; 22(4): 415-23, e95.
4. Rao SS, Kuo B, McCallum RW, Chey WD, DiBaise JK, Hasler WL, Koch KL, Lackner JM, et al. Investigation of colonic and whole-gut transit with wireless motility capsule and radiopaque markers in constipation. Clin Gastroenterol Hepatol, 2009; 7(5): 537-44.
5. Hiroz P, Schlageter V, Givel JC, Kucera P. Colonic movements in healthy subjects as monitored by a Magnet Tracking System. Neurogastroenterol Motil, 2009; 21(8): 838-e57.
6. Marciani L, Garsed KC, Hoad CL, Fields A, Fordham I, Pritchard SE, Placidi E, Murray K, et al. Stimulation of colonic motility by oral PEG electrolyte bowel preparation assessed by MRI: comparison of split vs single dose. Neurogastroenterology and Motility, 2014; 26(10): 1426-1436.
7. Odille F, Menys A, Ahmed A, Punwani S, Taylor SA, Atkinson D. Quantitative assessment of small bowel motility by nonrigid registration of dynamic MR images. Magnetic Resonance in Medicine, 2012; 68(3): 783-793.
8. Menys A, Taylor SA, Emmanuel A, Ahmed A, Plumb AA, Odille F, Alam A, Halligan S, et al. Global Small Bowel Motility: Assessment with Dynamic MR Imaging. Radiology, 2013; 269(2): 442-449.
9. Hahnemann ML, Nensa F, Kinner S, Kohler J, Gerken G, Umutlu L, Lauenstein TC. Quantitative assessment of small bowel motility in patients with Crohn's disease using dynamic MRI. Neurogastroenterol Motil, 2015.
10. Hahnemann ML, Nensa F, Kinner S, Gerken G, Lauenstein TC. Motility Mapping as Evaluation Tool for Bowel Motility: Initial Results on the Development of an Automated Color-Coding Algorithm in Cine MRI. Journal of Magnetic Resonance Imaging, 2015; 41(2): 354-360.
11. Hamy V, Menys A, Helbren E, Odille F, Punwani S, Taylor S, Atkinson D. Respiratory Motion Correction in Dynamic-MRI: Application to Small Bowel Motility Quantification during Free Breathing. Medical Image Computing and Computer-Assisted Intervention - Miccai 2013, Pt Ii, 2013; 8150: 132-140.
12. Menys A, Hamy V, Makanyanga J, Hoad C, Gowland P, Odille F, Taylor SA, Atkinson D. Dual registration of abdominal motion for motility assessment in free-breathing data sets acquired using dynamic MRI. Physics in Medicine and Biology, 2014; 59(16): 4603-4619.
13. Buhmann S, Kirchhoff C, Wielage C, Mussack T, Reiser MF, Lienemann A. Assessment of large bowel motility by cine magnetic resonance imaging using two different prokinetic agents - A feasibility study. Investigative Radiology, 2005; 40(11): 689-694.
14. Kirchhoff S, Nicolaus M, Schirra J, Reiser MF, Goke B, Lienemann A. Assessment of colon motility using simultaneous manometric and functional cine-MRI analysis: preliminary results. Abdominal Imaging, 2011; 36(1): 24-30.
15. Bland JM and Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res, 1999; 8(2): 135-60.
16. Wright J, Evans D, Gowland P, Mansfield P. Validation of antroduodenal motility measurements made by echo-planar magnetic resonance imaging. Neurogastroenterol Motil, 1999; 11(1): 19-25.

17. Dinning PG, Wiklendt L, Gibbins I, Patton V, Bampton P, Lubowski DZ, Cook IJ, Arkwright JW. Low-resolution colonic manometry leads to a gross misinterpretation of the frequency and polarity of propagating sequences: Initial results from fiber-optic high-resolution manometry studies. Neurogastroenterology and Motility, 2013; 25(10): E640-E649.
18. Dinning PG, Wiklendt L, Patton VE, Bampton PA, Cook IJ, Gibbins I, Lubowski DZ, Arkwright JW. Spatial Aliasing of Colonic Manometry Data: What Have We Been Missing or Mislabeling? Gastroenterology, 2013; 144(5): S919-S919.

Tables

Table 1. Demographics of the two subject groups, data presented as mean (std dev)

	Total Cohort (N=23)	Inter-observer Group (N=11)
Gender M / F	11/12	3/8
Mean Age (yrs)	27.1 (8.5)	26.7 (10.2)
Age Range (yrs)	19-50	20-50
BMI (kgm^{-2})	23.2 (2.4)	23.2 (2.3)

Table 2. Correlation of potential metrics with the observer rating score.

	Post Ingestion N= 39		
Metric	Spearman Rho correlation	95% Confidence interval of coefficient	p-value
SD_JAC	0.492	0.199-0.704	0.002
SD_I	0.368	0.050-0.619	0.021
$LA_{0.25mms^{-1}}$ Index	0.673	0.447-0.819	<0.001
$LA_{0.5mms^{-1}}$ Index	0.739	0.545-0.858	<0.001
$LA_{0.75mms^{-1}}$ Index	0.649	0.411-0.804	<0.001
$NAC_{3\%}$ Index	0.366	0.047-0.617	0.022
$NAC_{5\%}$ Index	0.353	0.032-0.608	0.028
$NAC_{10\%}$ Index	0.329	0.006-0.590	0.041

Table 3. Bland-Altman Limits of Agreement and Intra class correlation coefficients for intra- and inter-observer measurements of the LA metrics (N=33).

Metric (range of observation 1)	Intra-observer			Inter-observer		
	Bias	95% Limits of Agreement	ICC	Bias	95% Limits of Agreement	ICC
$LA_{0.25mms^{-1}}$ Index (0.009-0.625)	0.014	-0.046-0.074	0.981 *	-0.005	-0.096-0.085	0.956 *
$LA_{0.5mms^{-1}}$ Index (0.000-0.353)	0.007	-0.039-0.052	0.964 *	0.001	-0.051-0.054	0.947 *

* $p<0.001$

Figure Legends

Figure 1. Sagittal images through the AC showing; (A) Placement of lines for line analysis (LA) index (B) Position of ROIs for normalised area change (NAC) index

Figure 2. (A) Example images from cine MRI data showing overlay (red/blue) of standard deviation of Jacobian. Original data as insert. (B) Example single smoothed line length plot from mid AC. (C) Wall displacement motility plots from line analysis, colour bar indicates change in length of smoothed line length from mean. (D) Wall velocity motility plot, colour bar indicates change in consecutive line lengths after smoothing.

Figure 3. Graphs showing correlation between motility metrics and observer rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) $LA_{0.5\ mms^{-1}}$ motility index, (D) $NAC_{5\%}$ motility index.

Figure 4. Examples of different types of colonic motility shown on line analysis plots of displacement and velocity. (A) 3 retrograde segmental contractions – black arrow heads. (B) 2 whole AC retrograde contractions – grey arrow. (C) Near simultaneous high amplitude whole AC contraction – black arrow. (D) Low amplitude retrograde contraction – Grey arrow heads. Red regions on the displacement maps represent an large increase in the lumen diameter compared to the mean value. This is highlighted by the white arrow heads on B and C.

Figure 5. Box and whisker plot showing the variation of $LA_{0.5\ mms^{-1}}$ with both time and macrogol stimulus. Groups N=11 1L drink, N=12 2L drink. Missing data

due to breathing artefacts baseline: N=2 1L, N=2 2L; T=0 mins: N=2 1L, N=3 2L; T=60 mins: N=1 1L, N=1 2L.

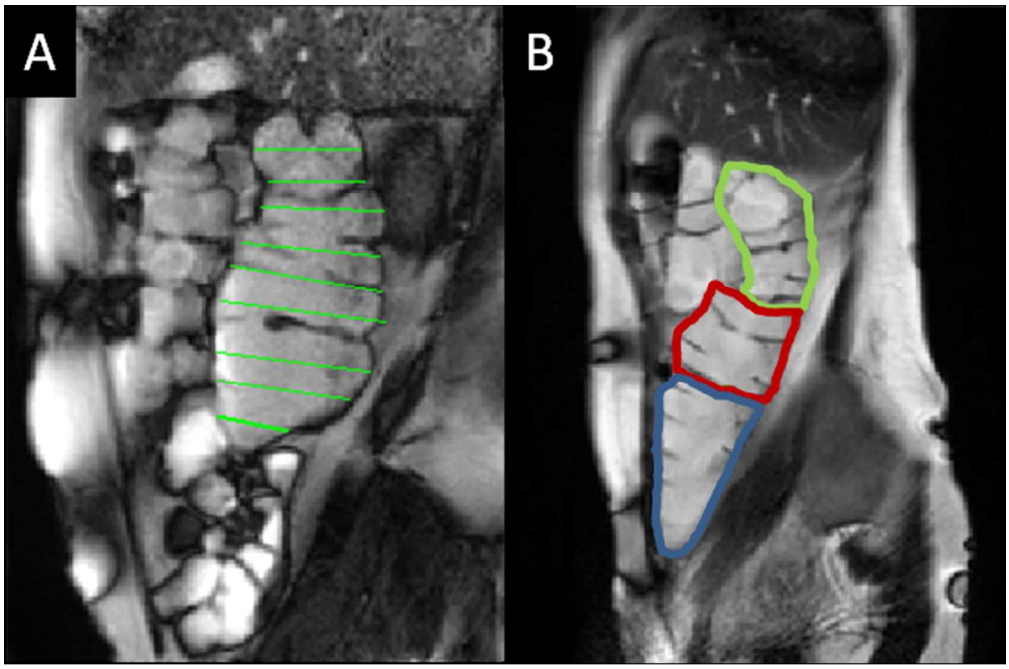

Figure 1. Sagittal images through the AC showing; (A) Placement of lines for line analysis (LA) index (B) Position of ROIs for normalised area change (NAC) index
90x59mm (300 x 300 DPI)

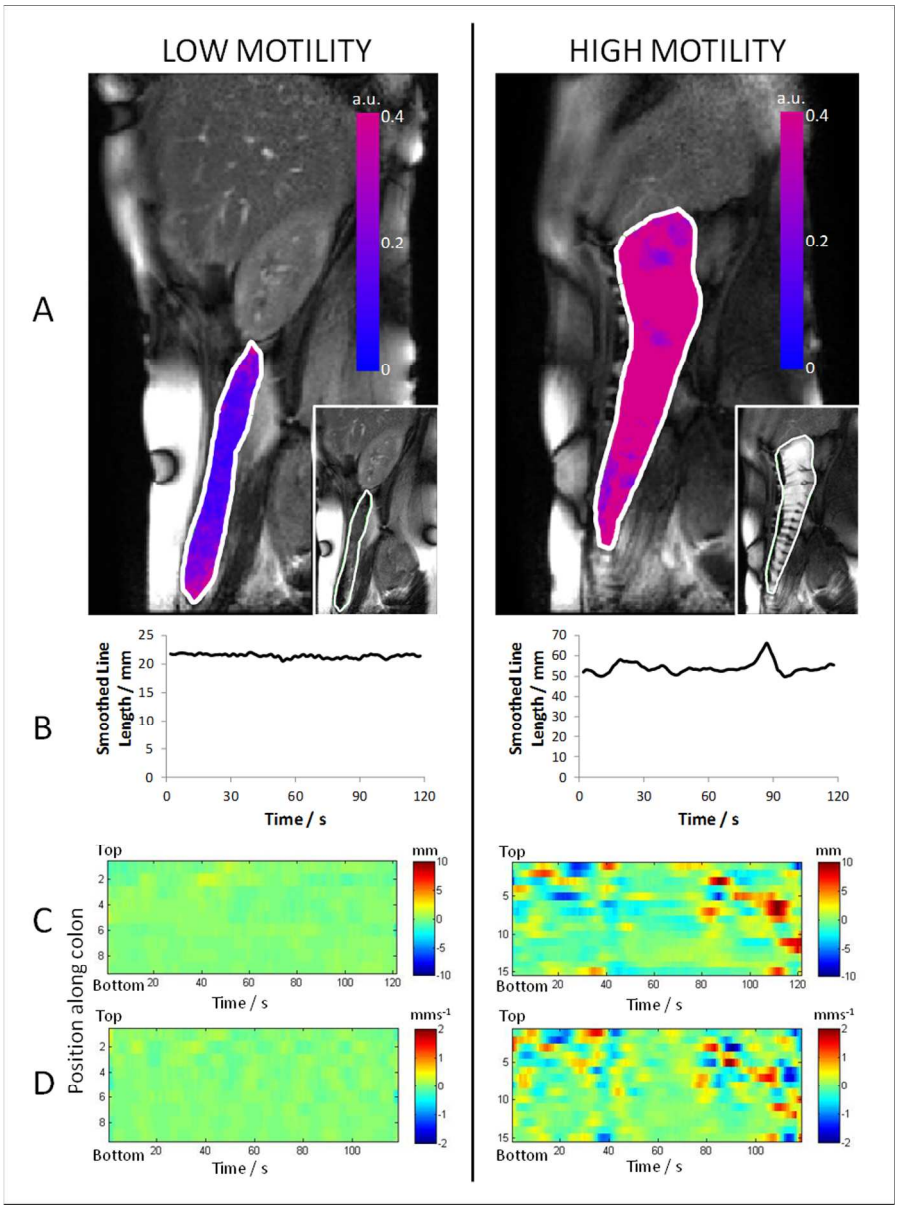

Figure 2. (A) Example images from cine MRI data showing overlay (red/blue) of standard deviation of Jacobian. Original data as insert. (B) Example single smoothed line length plot from mid AC. (C) Wall displacement motility plots from line analysis, colour bar indicates change in length of smoothed line length from mean. (D) Wall velocity motility plot, colour bar indicates change in consecutive line lengths after smoothing.
148x199mm (300 x 300 DPI)

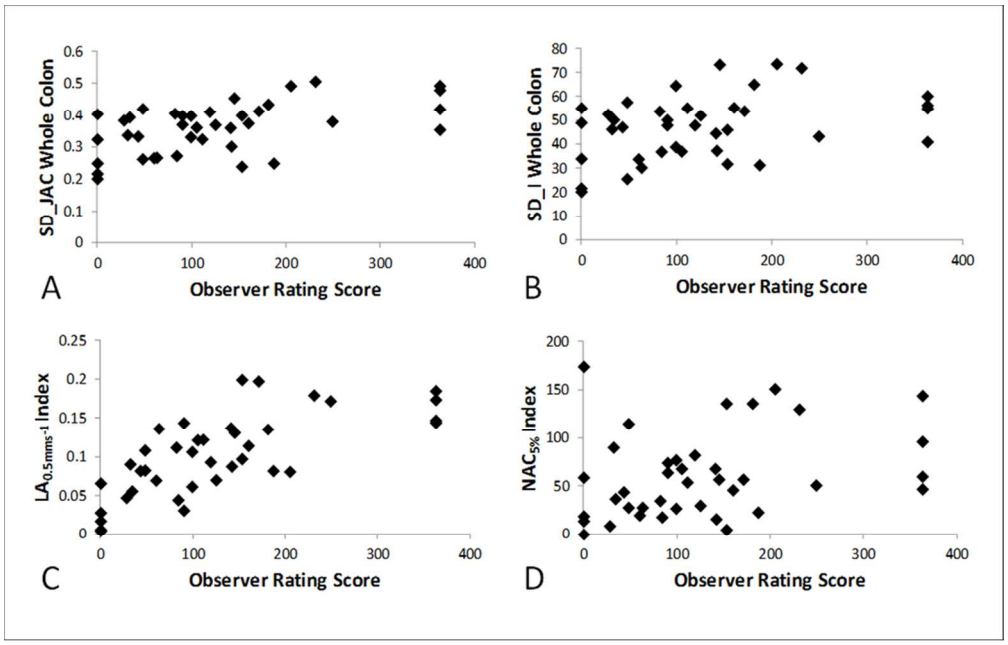

Figure 3. Graphs showing correlation between motility metrics and observer rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) $LA_{0.5\ mms\text{-}1}$ motility index, (D) $NAC_{5\%}$ motility index.
95x60mm (300 x 300 DPI)

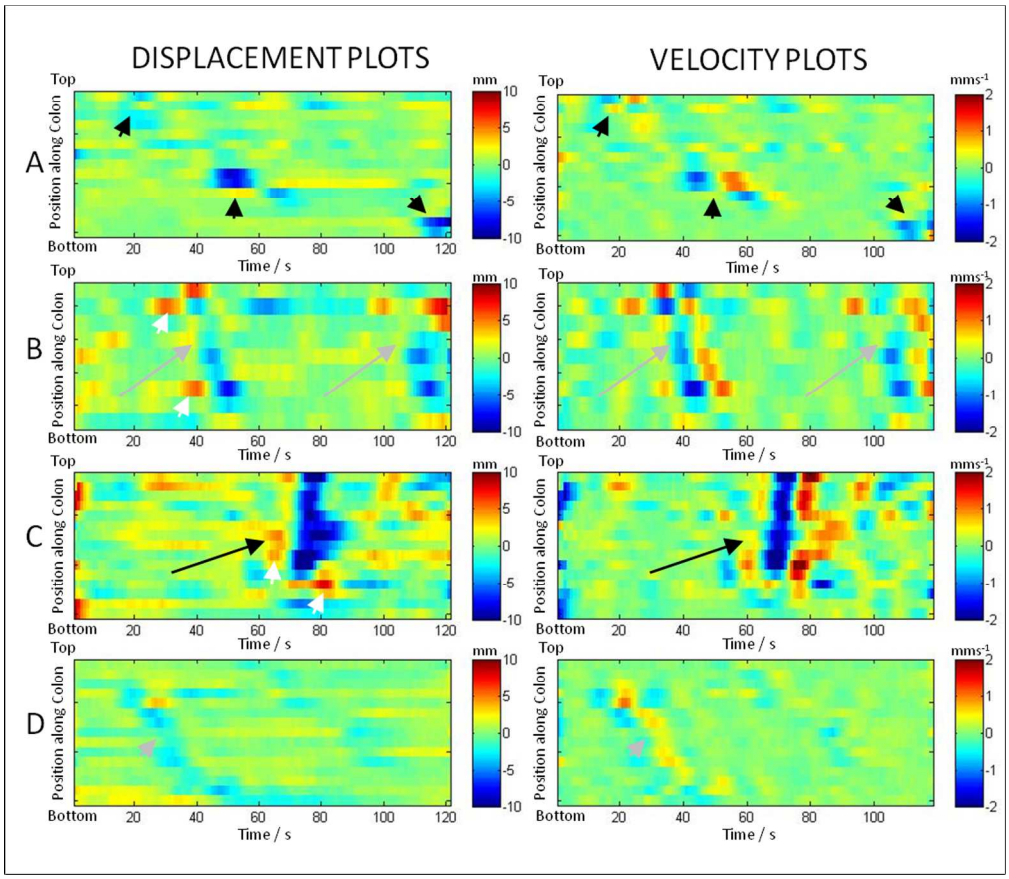

Figure 4. Examples of different types of colonic motility shown on line analysis plots of displacement and velocity. (A) 3 retrograde segmental contractions – black arrow heads. (B) 2 whole AC retrograde contractions – grey arrow. (C) Near simultaneous high amplitude whole AC contraction – black arrow. (D) Low amplitude retrograde contraction – Grey arrow heads. Red regions on the displacement maps represent an large increase in the lumen diameter compared to the mean value. This is highlighted by the white arrow heads on B and C.
180x156mm (300 x 300 DPI)

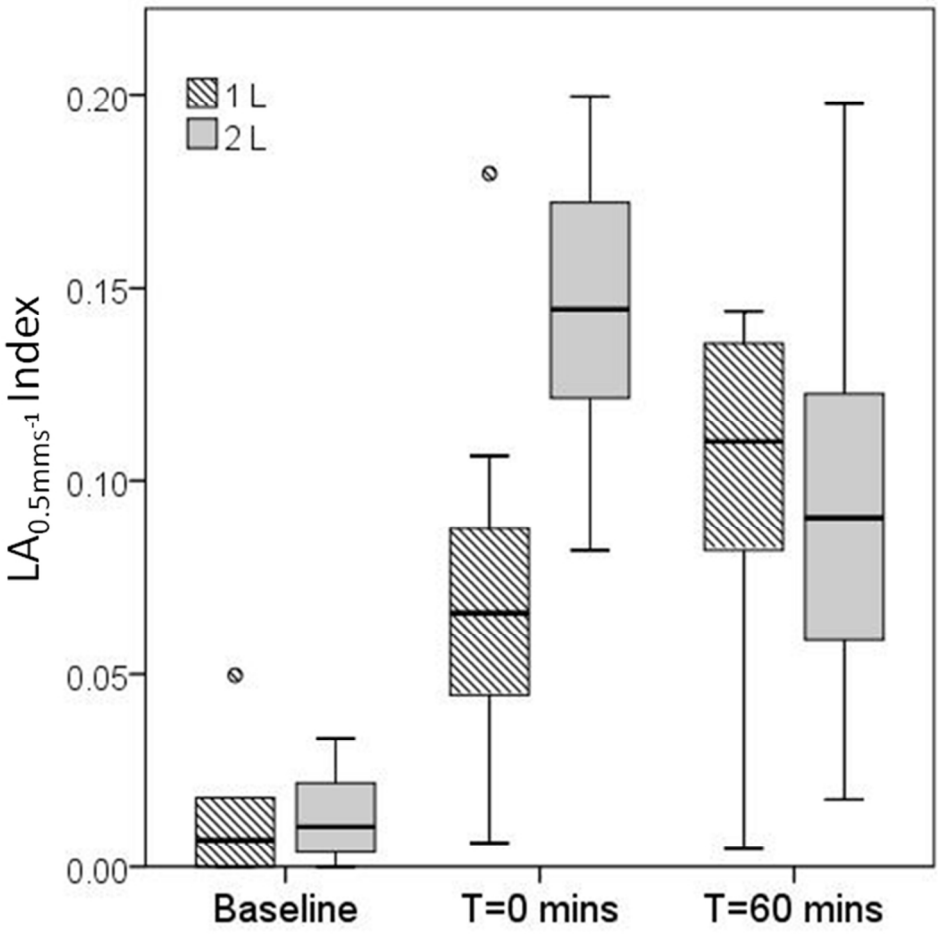

Figure 5. Box and whisker plot showing the variation of $LA_{0.5\ mms\text{-}1}$ with both time and macrogol stimulus. Groups N=11 1L drink, N=12 2L drink. Missing data due to breathing artefacts baseline: N=2 1L, N=2 2L; T=0 mins: N=2 1L, N=3 2L; T=60 mins: N=1 1L, N=1 2L.
85x82mm (300 x 300 DPI)

Colon wall motility: comparison of novel quantitative semi-automatic measurements using cine-MRI

Running title: Colonic Wall Motility using cine-MRI

C.L. Hoad[1,2*], A. Menys[3], K. Garsed[2], L. Marciani[2,4], V. Hamy[3], K. Murray[1], C. Costigan[1], D. Atkinson[3], G. Major[2], R.C. Spiller[2,4], S.A. Taylor[3], P.A. Gowland[1]

[1] Sir Peter Mansfield Imaging Centre, School of Physics and Astronomy, University of Nottingham, Nottingham, UK

[2] NIHR Biomedical Research Unit in Gastrointestinal and Liver Diseases, Nottingham University Hospitals Trust and the University of Nottingham, Nottingham, UK

[3] Centre for Medical Imaging, Division of Medicine, University College London, UK

[4] Nottingham Digestive Diseases Centre, School of Medicine, University of Nottingham, Nottingham, UK

* Corresponding Author

Caroline Hoad, Sir Peter Mansfield Imaging Centre, School of Physics and Astronomy, University of Nottingham, University Park, Nottingham NG7 2RD

Email: Caroline.L.Hoad@nottingham.ac.uk

Tel: +44 (0)115 8466003

Fax: +44 (0)115 9515166

Author Contributions: CLH, LM, GM, RCS and PAG designed the study, KG, and CC acquired the data, AM, VH, DA, and SAT developed the registration

algorithms and designed the analysis interface, CLH, AM, KM analysed the data. CLH, AM, LM, GM, RCS, SAT and PAG interpreted the data. CLH and AM drafted the manuscript. CLH, AM, LM, RCS, SAT and PAG critically reviewed the manuscript. All authors approved the final version.

ABSTRACT

Background: Recently cine MRI has shown promise for visualising movement of the colonic wall, although assessment of data has been subjective and observer dependent. This study aimed to develop an objective and semi-automatic imaging metric of ascending colonic wall movement, using image registration techniques.

Methods: Cine balanced turbo field echo (bTFE) MRI images of ascending colonic motility were acquired over 2 minutes from 23 healthy volunteers (HVs) at baseline and following two different macrogol stimulus drinks (11 HVs drank 1L and 12 HVs drank 2 L). Motility metrics derived from large scale geometric and small scale pixel movement parameters following image registration were developed using the post-ingestion data and compared to observer grading of wall motion. Inter and intra-observer variability of the highest correlating metric was assessed using Bland-Altman analysis calculated from 2 separate observations on a subset of data.

Key Results: All the metrics tested showed significant correlation with the observer rating scores. Line analysis produced the highest correlation coefficient of 0.74 (95% CI 0.55-0.86), $p<0.001$, (Spearman Rho). Bland-Altman analysis of the inter- and intra-observer variability for the line analysis metric, showed almost zero bias and small limits of agreement between observations (-0.039-0.052 intra-observer and -0.051-0.054 inter-observer, range of measurement 0-0.353).

Conclusions and Inferences: The line analysis index of colonic motility derived from cine MRI registered data provides a quick, accurate and non-invasive method to detect wall motion within the ascending colon following a colonic stimulus in the form of a macrogol drink.

Keywords: Cine MRI, motility, imaging metric, ascending colon

Key Messages

Recent cine MRI has shown promise to visualise the movement of the colonic walls, however assessment has been limited to subjective and semi-automatic analysis.

This study reports the development of an objective metric of ascending colon motility derived from cine MRI data using image registration techniques to remove respiratory motion and parameterise bowel movements.

Data from 23 healthy volunteers, who had received a macrogol stimulus, were used to assess potential metrics, which were derived from cine MRI data. These metrics were compared to an observer score of motility.

The line analysis metric produced the highest correlation coefficient with the observer scoring. Inter- and intra-observer variability was low for this metric.

This study has shown that it is possible to generate objective semi-automatic metrics of colonic motility from cine MRI data using image registration techniques.

Assessment of colonic motor activity is difficult owing to its erratic nature and the inaccessibility of the colon for study. Previous methods have largely relied on procedures that are unpleasant for patients and demanding for staff; these involve placing pressure probes into the colon, which usually requires bowel cleansing, colonoscopy and often endoscopic clips to secure the probe, facilitating long term recordings (1). Recent developments with high resolution manometry have provided unprecedented detail on the different types of motor activity (2) but the technique remains difficult and expensive, limiting use to a few specialised centres. Scintigraphic methods allow accurate, reproducible assessment of transit and have been widely used to investigate pharmacologic modulation of gut transit (3). However scintigraphy only assesses bulk transit and does not allow detailed assessment of the motor patterns which may be relevant when studying disease or drugs which specifically target abnormal motility. More recently the Smart Pill has been introduced as a less invasive alternative while still allowing direct assessment of motor activity (4). Although better tolerated by patients, its use is limited by expense and it cannot be used to reliably assess specific regions of the colon because of the inability to control its position. This is also the case for the proposed Magnetic Tracking System (5) which again relies on the passage of a magnetic pill through the GI tract to assess the motor activity. Increasing data suggests dynamic motion capture "cine" MRI is acceptable to patients and could allow detailed evaluation of colonic motor activity. It has previously been shown that 1 litre of electrolyte macrogol solution provides a reliable stimulus with vigorous movements of the ascending colon (AC) in healthy volunteers (6) within an hour of ingestion. MRI scanners are now widely available in larger hospitals and costs for a short examination

(30 minutes) are similar to those of a nuclear medicine gastric emptying test and are considerably less than endoscopy and colonoscopy.

An important component to MR based motility assessment is automation and quantitative analysis, and non-linear image registration based techniques (7) can provide a range of quantitative measures for assessing bowel motion. Registration provides 1) parametric surrogate markers of motility and 2) allows automatic propagation of regions of interest (ROIs) through time series data once an ROI has been defined on a single image (7). This type of analysis has produced objective and repeatable metrics of global small bowel motility (8, 9). Until recently, the most widely used registration technique was only applicable to breath-held data (8, 10) as breathing produces additional motion within the images that is not related to the GI motion of interest, thus confounding the data, by mimicking bowel movement. This is problematic for colonic motility imaging as contractions are comparatively infrequent necessitating free-breathing protocols. Recent advances however have introduced a dual stage process that first corrects respiratory motion in extended free-breathing data sets (11) before performing motility assessment (12) facilitating data collection of longer time periods. Colonic motion has been recently studied using cine MRI (6, 13, 14), but analysis remains subjective and time consuming using semi-quantitative, subjective assessment of contractions, flow and bowel wall motion. To date there have been no reported investigations of objective imaging metrics of colonic motility derived from free breathing MRI data.

The aim of this study was to develop an objective imaging metric which quantifies movement in the ascending colon walls during free breathing cine

MRI, by applying image registration techniques to generate the metrics and validate these against observer rating scores of motility.

Materials and Methods

The data used for this work was a subset of that acquired from an open-label, parallel group design study in healthy volunteers using MRI to investigate the small bowel and colonic response to 1 and 2 litres of polyethylene glycol (PEG) (Macrogol 3550) electrolyte solution (Moviprep®, Norgine Pharmaceuticals Ltd, Harefield, UK) (6). Such PEG solutions are widely used in larger quantities than used here as bowel cleansing preparations prior to colonoscopy or barium enema examinations. The full study was registered on the EU Clinical Trials Register with EudraCT Number 2010-021879-85. It was approved by the National Research Ethics Service (approval 10/H0906/50), the NHS Trust R&D (approval 10GA018) and by the Medicines and Healthcare products Regulatory Agency (MHRA Clinical Trial Authorization CTA 03057/0045/001-0001, protocol 10050). All volunteers gave written consent before participating.

The details of the study protocol have been already published (5). In brief 24 healthy volunteers were divided into two age matched groups of 12 subjects. Group 1 received 1 litre of PEG electrolyte solution at 1pm on day 1 following a 6 hour fast and a further 1 litre at 8am the next morning. Group 2 were given a single dose of 2 litres PEG electrolyte solution at 8am on the study day following an overnight fast. Group 1 was given 1 hour to ingest the solution and Group 2 was given 2 hours. Time 0 was then defined as the time of the first MRI scan immediately after ingestion of the PEG electrolyte solution. Baseline scans (performed according to the protocol described below) were acquired before the

PEG electrolyte solutions were ingested and then further scans were acquired hourly for 4 hours following ingestion. Subjects spent around 15-20 minutes in the scanner at each time point and sat upright for the rest of the time. 1 subject from Group 1 withdrew from the study. To provide a range of motility data, only the baseline and first two post ingestion time points were considered (baseline, T=0, T=60 min). To identify potential motility metrics, the post-ingestion data from group 1 and group 2 were combined to provide a range of motility responses as it has previously been shown that the motility response (assessed by an observer) was dose dependent (6).

Imaging was carried out using a 1.5 T Philips Achieva Scanner. Each volunteer was positioned supine in the scanner with a 4 element parallel imaging body coil wrapped around the abdomen. The colonic motility scan was one of a range of scans acquired to characterise the response of the gastrointestinal tract to the PEG solution; information on all the sequences used can be found in (6). The colonic motility scan comprised of a single sagittal slice, balanced turbo field echo (bTFE) positioned by the radiographer centrally through the AC with field of view 330 x 228 mm^2, in-plane resolution 1.5 x 1.5 mm, slice thickness 15 mm, flip angle 70°, repetition time/echo time 3.0/1.5 ms. A cine dataset was acquired using this sequence every second for 2 minutes. Subjects were asked to shallow breath throughout the acquisition.

The data was registered using the DRAM methodology (12) performed at a different laboratory, blind to the subject preparation. In brief, effects of respiratory motion on the data were first removed by registering using Robust Data Decomposition Registration(11). The resulting images were then

subsequently non-linearly registered using an optic flow technique (7) to generate the deformation fields which define how each image maps onto a median image generated from the entire data series.

Following registration, in-house software written using Matlab® (The Mathworks Inc) was used to allow an observer to define regions of interest (ROI) and lines across the single median image of the AC (Figure 1). This information was then used to automatically derive both small scale pixel-based and large scale geometry-based metrics, from the registration parameters.

Four potential imaging metrics were investigated, two based on small scale pixel deformation fields and two based on large scale geometry changes. A single observer (CH) defined all the ROIs to generate the different metrics.

(A)***SD_JAC***: The standard deviation (SD) of the Jacobian, representing the fractional area change of each pixel due to deformation, averaged over an ROI encompassing the whole AC (drawn by an observer), a measure which has previously been used to quantify small bowel motility (8). Each image in the time series is registered to a target image, so that each pixel has a displacement field associated with it for each time point. Distortions that do not result in a local change of area have a Jacobian value of 1. If the local area decreases, the value of the Jacobian will decrease towards zero and if the area expands its value will increase above 1. Therefore, when we report a SD Jacobian of 0.34 for a given pixel we are saying that for 68% of time points, the total fractional area change falls within 0.34 units of 1 (with 1 being no displacement). The larger the SD Jac the greater the variation in fractional area and hence more movement of the

pixels. SD_JAC, generated pixel by pixel (through the time series), was averaged over a ROI drawn by an observer covering the whole AC to generate the metric. Example maps of SD_JAC are shown in figure 2A

(B) ***SD_I***: The standard deviation of the variation in intensity, linked to flow due to movement of the colonic contents generated by wall movement. SD_I generated pixel by pixel was averaged over a ROI drawn by an observer covering the whole AC.

(C)***LA:*** Line analysis index. The AC was divided into three regions (bottom-section including cecum, mid-section and top-section up to the hepatic flexure) and in each region an observer drew either 3 or 5 lines perpendicular to the main axis of the AC, depending on the overall length of the AC (Figure 1a). These lines were automatically propagated through the time series using the deformation fields from the registration and the length of each line at each time point was saved for subsequent analysis, giving between 9 and 15 time series. The time series were smoothed using a moving average of 5 data points. Example smoothed time series are shown in figure 2B. For additional visualisation of motility, colour motility plots were generated of (a) absolute difference in length from mean for points along AC against time (Figure 2C) and (b) change in length between consecutive time points (wall velocity- Figure 2 D). A series of LA Motility Indices were defined as the percentage of the time series line analysis data which had a change in length (i.e. wall velocity) between consecutive time points of greater than 0.25, 0.5 and 0.75 mms^{-1} after smoothing ($LA_{0.25mms^{-1}}$, $LA_{0.5mms^{-1}}$ and $LA_{0.75mms^{-1}}$).

(D) ***NAC:*** The Normalised Area Change across the time series was defined by first splitting the AC into three regions of interest (ROIs)

(Figure 1b) drawn by an observer; 3 regions were chosen to help identify smaller wall movements which may have been missed if using a large ROI of the whole AC. The ROIs were then automatically propagated through the time series data using the deformation fields defined during registration and the areas of the ROIs were plotted against time, and the resulting time course was smoothed using a moving average of 5 points. Each time course was normalised to its mean value and the number of time points which were more than 3, 5 and 10% different from the mean were counted and summed over all 3 regions to give three NAC Motility Indices ($NAC_{3\%}$, $NAC_{5\%}$ and $NAC_{10\%}$).

These different measures were compared to an observer rating which was carried out on the raw, unregistered data. The Observer Rating Score (6) was defined as the duration of wall motion multiplied by the number of sections of the ascending colon showing motion (with the AC being divided into 3 sections). Thus if motion was observed involving the whole AC for 15 seconds and later involving only 1 third of the AC for 20 seconds the corresponding observer rating score would be (15 x 3)+(20 x 1) = 65 in units of segment x s. This was estimated by a single observer (CH). This measure was used as the comparator as it had shown to differentiate between low and high motility previously (6). Motility plots using the LA data were used to define the different types of contractions observed.

Inter and intra-observer variations of the highest correlating metric were obtained from data acquired by 2 observers (CH with over 15 years experience of analysing GI MR images and KM with 4 years experience) and 1 observer on 2 occasions (CH) with the analysis separated by a 3 month period, respectively.

Observers were required to draw on the median image only of a subset of the total data (N=33 from 11 subjects) and all subsequent analysis and generation of the metrics were automated. KM was shown how to interact with the analysis software (i.e. draw regions on the anatomy, save outputs etc.) by CH.

As a demonstration of the utility of the best correlating metric to differentiate between different colonic motor activity, the differences over time (including baseline data) between the two different macrogol stimuli (1L and 2L) were investigated. Previous manually observed scoring of this data showed distinct differences with time and between the stimuli. (6).

Statistics

Statistical analysis was carried out using SPSS 20.0 (IBM) and GraphPad Prism 6.0 (GraphPad Software, La Jolla California USA). All data were tested for normality using the Shapiro-Wilks test.

As the observer rating score was non-normally distributed, all potential metrics were correlated to it using Spearman Rho correlation coefficients, statistical significance was set at $p<0.05$. The parameter with the highest correlation to the observer rating score was then used to determine the observer variability of the measurement.

To assess the inter and intra-observer variability, Bland-Altman limits of agreement between observers were calculated (15) and correlation between observations was assessed by the intra-class correlation coefficient.

Results

After registration to remove respiratory motion, a small amount of data still showed large scale movements of the whole abdomen, which when registered using the optic flow technique, translated into large changes in the images not associated with specific motion of the bowel. This mis-registration led to errors in the metrics generated due to additional global distortions of the anatomy (from respiratory motion) producing large scale changes to the deformation fields, and hence overestimating motility. Data sets which showed large scale breathing distortions on the images post registration were excluded from subsequent analysis. These were identified using organs such as the liver and kidney which should normally be static after image registration to correct for respiration. As a result 7 data sets (15 %) were excluded from post-ingestion data and a further 4 data sets (17 %) from the baseline data.

Demographics of the subject groups used for metric correlation and inter-observer measurements are given in Table 1. Example images and 2D motility plots are shown in Figure 2. All proposed measures showed significant correlation with the observer rating scoring, however only a few metrics (SD_JAC and line analysis) showed highly significant correlation ($p < 0.01$) and this is summarised in Table 2 and Figure 3. The normalised area change indices and SD_I showed very weak correlation with the observer rating score. The $LA_{0.25mms^{-1}}$ and $LA_{0.5mms^{-1}}$ indices showed the highest correlation with the observer rating score and this metric was therefore investigated for the inter- and intra-observer measurements.

The line analysis plots of displacement and velocity also provided additional information as to the types of contractions seen following this stimulus. Examples of the different types of contractions are shown in Figure 4. Using the plots to define the contractions, there were 5 types of contractions seen: segmental antegrade and retrograde contractions, whole AC antegrade and retrograde contractions and near simultaneous large amplitude contractions. The last type of contraction appears to significantly change the whole lumen diameter rapidly and over a very short period of time (typically < 20 s). All these types of contraction could be visually seen by observing the cine data if displayed as a movie. Dilation of the lumen was also observed on many of the datasets (Figure 4 B and C).

Inter and intra-observer Bland-Altman measurements and Intra-class correlation coefficients are summarised in Table 3 for the $LA_{0.25mms^{-1}}$ and $LA_{0.5mms^{-1}}$ indices These data show that there was very little bias between observations for the inter- and intra-observer measurements of line analysis with small limits of agreement compared to the range of values measured (limits of agreement Inter-obs $LA_{0.5mms^{-1}}$: -0.051 to0.054, range of measurement: 0.000-0.353).. Intra-class correlation coefficients were statistically significant (and coefficients above 0.9) for both LA indices calculated.

The variation of the colonic motility activity (as assessed with $LA_{0.5mms^{-1}}$ index) with both time and macrogol stimulus is shown graphically in Figure 5. Baseline motility was low compared to the post-stimulus data, with the 2 L having a larger effect immediately after ingestion.

Discussion

This study has shown that objective metrics of ascending colon motility can be generated non-invasively with minimal observer input using cine MRI combined with registration techniques. The line analysis (LA) indices proved to be the most robust measures of those examined, correlating well with the subjective scoring of wall movement (6). In addition the motility plots of wall deformation and wall velocity allowed a quick visual assessment of any contractions including smaller movements which were occurring, in a similar way to pressure changing maps generated by high resolution manometry. Five different types of contraction were observed both visually, and from the motility plots, following the macrogol stimulus, both segmental over short distances in the AC as well as encompassing the whole AC region. Retrograde and antegrade and near simultaneous wall movements were observed and were a result of the colonic response to the large fluid content from the stimulus drink. These contractions were probably induced to aid mixing and absorption the fluid within the chyme. The most common type of wall movement was segmental retrograde, however it is beyond the scope of this paper to define all the contractions observed throughout the datasets. By using image registration to correct for breathing effects, data could be acquired over extended time periods, without any additional observer analysis time needed. The recording period of 2 minutes used in this study could be extended to allow more sporadic motility patterns to be investigated. The imaging sequences are available on all modern scanners hence the technique could be widely used in clinical practice. As colonic wall movement occurs on a longer time scale than a breath hold (2) the image registration is important if these methods are to be of clinical use. Typical computing time for the registration for

a 2 minute cine-MRI dataset would be 15 mins, with observer drawing and metric calculations taking a further 2-3 minutes. In comparison manual assessment of the motility from a single 2 minute cine could take up to 10 minutes, depending on the number of contractions present, and this would increase with longer acquisition periods. Inter and intra-observer variability was extremely low, with excellent correlation between the 2 measurements acquired, reflecting the objective nature of this registration-based approach which is crucial for clinical practice.

This study showed that an influx of fluid into the AC stimulates rapid contractions which can be detected over a short recording period. Different amounts of ingested fluid, elicit different responses, with the tendency of larger amounts of fluid to initially stimulate more wall movement. A previous study by Kirchhoff et al (14) demonstrated that MRI is extremely accurate in detecting high amplitude propagation pressure waves as defined by manometry when the data are acquired simultaneously. They also noted that MRI showed increases in luminal diameter which were not detected by the manometry probe, as already observed by Wright et al (16) who carried out simultaneous measurements in the stomach. This increased sensitivity to wall activity provided by MRI, may provide a greater understanding of the physiology of the colon in terms of mixing its contents and propelling them towards the rectum. Recent work using high resolution manometry by Dinning et al (17, 18) has shown that the motor patterns within the colon are far more complicated than previously thought, and the crude spacing of conventional manometry sensors resulted in mis-interpretation of the actual motor patterns. Cine MRI with image registration could now provide an alternative, non-invasive approach to viewing the colonic

walls. This could provide further information on the basic physiology of the colon, without disturbing the natural environment. This technique can also be extended to other segments of the colon and in defining objective clinical information in constipation patients. Further studies are needed to determine both optimal timings of MRI assessment of colonic motility following PEG ingestion and the optimal volume of stimulating drink to ingest. However it could be envisaged that a protocol similar to that used for MR imaging of the small bowel in Crohn's disease could be developed. Subjects would arrive at the MRI unit and be given the stimulating drink. A period of time later they would have a short 20-30 minute MRI scan where measurements of colonic motility could be made.

There are limitations to the proposed technique. The validation of the metrics was based on observer scores of motility and is therefore not a 'gold standard' measure for comparison although the observers did have extensive experience of imaging the colon using MRI. However it is also possible that the computer algorithm will detect motion in the colon not visualised by the observer. The line analysis metric showed good consistency across different subjects with a wide range of observed motility scores. Acquisition of the data is currently from a single slice positioned within the AC and thus results could be influenced by poor positioning of the slice, or anatomy which is not easily visualised in a single plane. Multislice acquisition, to gain greater coverage of the anatomy, is possible with reduced temporal or spatial resolution and would allow investigation of other less straight colonic regions such as the descending and sigmoid colon. Over estimation of motility from imperfect registration of the data occurred, if the raw data showed large movements of all internal organs from respiration.

From the subjects studied here 14-18% of the data was corrupted with mis-registration errors and was discarded. However in future studies, these errors can be minimised by training of the subjects to breath in a shallow manner during data acquisition and with active monitoring of the data collected; an approach not available with this data, which was looked at retrospectively. It is also possible that other more sophisticated metrics may provide greater correlation to the motility seen in the AC; however a simplistic approach was taken for this study to allow fast generation of the metrics studied.

In conclusion the line analysis index of colonic motility derived from cine MRI registered data provides a quick, accurate and non-invasive method to detect wall motion within the ascending colon following a colonic stimulus in the form of a macrogol drink.

Acknowledgements, funding and disclosures

This is a summary of independent research funded by the National Institute for Health Research Biomedical Research Unit. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

AM is a director and shareholder of Motilent Ltd. All other authors have no conflicts of interest to disclose.

Abbreviations:

AC – Ascending colon

bTFE – balanced Turbo Field Echo

HV – Healthy volunteers

LA – Line analysis

MRI – Magnetic Resonance Imaging

NAC – Normalised Area Change

PEG - polyethylene glycol

ROI – Region of Interest

SD_JAC – Standard deviation of the Jacobian

SD_I – Standard deviation of Intensity

References:

1. Bampton PA, Dinning PG, Kennedy ML, Lubowski DZ, Cook IJ. Prolonged multi-point recording of colonic manometry in the unprepared human colon: Providing insight into potentially relevant pressure wave parameters. American Journal of Gastroenterology, 2001; 96(6): 1838-1848.
2. Dinning PG, Wiklendt L, Maslen L, Gibbins I, Patton V, Arkwright JW, Lubowski DZ, O'Grady G, et al. Quantification of in vivo colonic motor patterns in healthy humans before and after a meal revealed by high-resolution fiber-optic manometry. Neurogastroenterol Motil, 2014; 26(10): 1443-57.
3. Deiteren A, Camilleri M, Bharucha AE, Burton D, McKinzie S, Rao AS, Zinsmeister AR. Performance characteristics of scintigraphic colon transit measurement in health and irritable bowel syndrome and relationship to bowel functions. Neurogastroenterol Motil, 2010; 22(4): 415-23, e95.
4. Rao SS, Kuo B, McCallum RW, Chey WD, DiBaise JK, Hasler WL, Koch KL, Lackner JM, et al. Investigation of colonic and whole-gut transit with wireless motility capsule and radiopaque markers in constipation. Clin Gastroenterol Hepatol, 2009; 7(5): 537-44.
5. Hiroz P, Schlageter V, Givel JC, Kucera P. Colonic movements in healthy subjects as monitored by a Magnet Tracking System. Neurogastroenterol Motil, 2009; 21(8): 838-e57.
6. Marciani L, Garsed KC, Hoad CL, Fields A, Fordham I, Pritchard SE, Placidi E, Murray K, et al. Stimulation of colonic motility by oral PEG electrolyte bowel preparation assessed by MRI: comparison of split vs single dose. Neurogastroenterology and Motility, 2014; 26(10): 1426-1436.
7. Odille F, Menys A, Ahmed A, Punwani S, Taylor SA, Atkinson D. Quantitative assessment of small bowel motility by nonrigid registration of dynamic MR images. Magnetic Resonance in Medicine, 2012; 68(3): 783-793.
8. Menys A, Taylor SA, Emmanuel A, Ahmed A, Plumb AA, Odille F, Alam A, Halligan S, et al. Global Small Bowel Motility: Assessment with Dynamic MR Imaging. Radiology, 2013; 269(2): 442-449.
9. Hahnemann ML, Nensa F, Kinner S, Kohler J, Gerken G, Umutlu L, Lauenstein TC. Quantitative assessment of small bowel motility in patients with Crohn's disease using dynamic MRI. Neurogastroenterol Motil, 2015.
10. Hahnemann ML, Nensa F, Kinner S, Gerken G, Lauenstein TC. Motility Mapping as Evaluation Tool for Bowel Motility: Initial Results on the Development of an Automated Color-Coding Algorithm in Cine MRI. Journal of Magnetic Resonance Imaging, 2015; 41(2): 354-360.
11. Hamy V, Menys A, Helbren E, Odille F, Punwani S, Taylor S, Atkinson D. Respiratory Motion Correction in Dynamic-MRI: Application to Small Bowel Motility Quantification during Free Breathing. Medical Image Computing and Computer-Assisted Intervention - Miccai 2013, Pt Ii, 2013; 8150: 132-140.
12. Menys A, Hamy V, Makanyanga J, Hoad C, Gowland P, Odille F, Taylor SA, Atkinson D. Dual registration of abdominal motion for motility assessment in free-breathing data sets acquired using dynamic MRI. Physics in Medicine and Biology, 2014; 59(16): 4603-4619.
13. Buhmann S, Kirchhoff C, Wielage C, Mussack T, Reiser MF, Lienemann A. Assessment of large bowel motility by cine magnetic resonance imaging using two different prokinetic agents - A feasibility study. Investigative Radiology, 2005; 40(11): 689-694.
14. Kirchhoff S, Nicolaus M, Schirra J, Reiser MF, Goke B, Lienemann A. Assessment of colon motility using simultaneous manometric and functional cine-MRI analysis: preliminary results. Abdominal Imaging, 2011; 36(1): 24-30.
15. Bland JM and Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res, 1999; 8(2): 135-60.
16. Wright J, Evans D, Gowland P, Mansfield P. Validation of antroduodenal motility measurements made by echo-planar magnetic resonance imaging. Neurogastroenterol Motil, 1999; 11(1): 19-25.

17. Dinning PG, Wiklendt L, Gibbins I, Patton V, Bampton P, Lubowski DZ, Cook IJ, Arkwright JW. Low-resolution colonic manometry leads to a gross misinterpretation of the frequency and polarity of propagating sequences: Initial results from fiber-optic high-resolution manometry studies. Neurogastroenterology and Motility, 2013; 25(10): E640-E649.
18. Dinning PG, Wiklendt L, Patton VE, Bampton PA, Cook IJ, Gibbins I, Lubowski DZ, Arkwright JW. Spatial Aliasing of Colonic Manometry Data: What Have We Been Missing or Mislabeling? Gastroenterology, 2013; 144(5): S919-S919.

Tables

Table 1. Demographics of the two subject groups, data presented as mean (std dev)

	Total Cohort (N=23)	Inter-observer Group (N=11)
Gender M / F	11/12	3/8
Mean Age (yrs)	27.1 (8.5)	26.7 (10.2)
Age Range (yrs)	19-50	20-50
BMI (kgm^{-2})	23.2 (2.4)	23.2 (2.3)

Table 2. Correlation of potential metrics with the observer rating score.

	Post Ingestion N= 39		
Metric	Spearman Rho correlation	95% Confidence interval of coefficient	p-value
SD_JAC	0.492	0.199-0.704	0.002
SD_I	0.368	0.050-0.619	0.021
$LA_{0.25mms^{-1}}$ Index	0.673	0.447-0.819	<0.001
$LA_{0.5mms^{-1}}$ Index	0.739	0.545-0.858	<0.001
$LA_{0.75mms^{-1}}$ Index	0.649	0.411-0.804	<0.001
$NAC_{3\%}$ Index	0.366	0.047-0.617	0.022
$NAC_{5\%}$ Index	0.353	0.032-0.608	0.028
$NAC_{10\%}$ Index	0.329	0.006-0.590	0.041

Table 3. Bland-Altman Limits of Agreement and Intra class correlation coefficients for intra- and inter-observer measurements of the LA metrics (N=33).

Metric (range of observation 1)	Intra-observer			Inter-observer		
	Bias	95% Limits of Agreement	ICC	Bias	95% Limits of Agreement	ICC
$LA_{0.25mms^{-1}}$ Index (0.009-0.625)	0.014	-0.046-0.074	0.981 *	-0.005	-0.096-0.085	0.956 *
$LA_{0.5mms^{-1}}$ Index (0.000-0.353)	0.007	-0.039-0.052	0.964 *	0.001	-0.051-0.054	0.947 *

* $p<0.001$

Figure Legends

Figure 1. Sagittal images through the AC showing; (A) Placement of lines for line analysis (LA) index (B) Position of ROIs for normalised area change (NAC) index

Figure 2. (A) Example images from cine MRI data showing overlay (red/blue) of standard deviation of Jacobian. Original data as insert. (B) Example single smoothed line length plot from mid AC. (C) Wall displacement motility plots from line analysis, colour bar indicates change in length of smoothed line length from mean. (D) Wall velocity motility plot, colour bar indicates change in consecutive line lengths after smoothing.

Figure 3. Graphs showing correlation between motility metrics and observer rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) $LA_{0.5\ mms^{-1}}$ motility index, (D) $NAC_{5\%}$ motility index.

Figure 4. Examples of different types of colonic motility shown on line analysis plots of displacement and velocity. (A) 3 retrograde segmental contractions – black arrow heads. (B) 2 whole AC retrograde contractions – grey arrow. (C) Near simultaneous high amplitude whole AC contraction – black arrow. (D) Low amplitude retrograde contraction – Grey arrow heads. Red regions on the displacement maps represent an large increase in the lumen diameter compared to the mean value. This is highlighted by the white arrow heads on B and C.

Figure 5. Box and whisker plot showing the variation of $LA_{0.5mms^{-1}}$ with both time and macrogol stimulus. Groups N=11 1L drink, N=12 2L drink. Missing data

due to breathing artefacts baseline: N=2 1L, N=2 2L; T=0 mins: N=2 1L, N=3 2L; T=60 mins: N=1 1L, N=1 2L.