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Regional gastrointestinal contractility parameters using the wireless motility capsule: inter-observer reproducibility and influence of age, gender and study country

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Summary

Background: The wireless motility capsule concurrently measures temperature, pH and pressure as it traverses the gastrointestinal tract.

Aims: To describe normative values for motility/contractility parameters across age, gender and testing centres.

Methods: Healthy participants underwent a standardised wireless motility capsule assessment following an overnight fast and consumption of a meal of known nutritional content. Traces were divided into regions of interest and analysed using 2 software packages (MotiliGI and GIMS Data Viewer). Inter-observer agreement was independently assessed by 2 investigators.

Results: Normative data for motility/contractility parameters (maximum amplitude, mean peak amplitude, contraction frequency and motility index) are presented for 107 individuals (62 male, median age 40 years, range 18-78). MotiliGI-Gastric, small bowel and colonic maximal contraction amplitude correlated with age ($r = .24$, $P = .01$; $r = .22$, $P = .02$; and $r = .2$, $P = .04$ respectively). Small bowel motility index was higher in females than males (150.4 ± 12 vs 122 ± 7.6, $P = .04$). Inter-observer agreement was excellent for transit times, pH and contractility/motility parameters. GIMS Data viewer-Gastric, small bowel and colonic $\log_e$ motility index correlated with the respective area under the contraction curve, total contractions, sum of amplitudes and contraction frequency (all $r > .35$, $P < .0003$) but not with transit times.

Conclusions: Our analysis provides normative data for motility/contractility parameters. Log motility index summarises a number of measures. In future, the measurement of contractile activity with the wireless motility capsule may potentially aid in the diagnosis of disease states such as visceral myopathic disorders.

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1 | INTRODUCTION

Gastrointestinal (GI) motility can be considered as movements within the digestive system and transit of contents across the absorptive and secretary surface. This process is coordinated and regulated through a complex circuitous interaction between a numbers of system including, but not limited to, the enteric, autonomic and central nervous systems. When aberrancies occur in any of these, it may result in disruption of the coordination of propulsive peristalsis, potentially leading to dysmotility and ultimately symptoms.[1] However, dysmotility has been used to describe a plethora of abnormalities, which are not purely limited to alterations in transit but may also result in changes in GI sensorimotor activity.[2]

Currently, our understanding of GI motility, both in health and disease, has been limited by the relative inaccessibility of certain portions of the GI tract.[3] Although several techniques are available to evaluate such regions, many of these primarily measure only transit times, although it is well recognised that these poorly predict symptoms.[4] Technological developments, such as those seen with high-resolution manometric techniques, have facilitated the concurrent evaluation of both motility as well as contractility patterns.[5,6] While these techniques are considered to be the gold standard, by definition they necessitate the placement of an intraluminal catheter which can cause a transient disturbance in the underlying regulatory neural systems that control motility.[7] Furthermore, particularly for the assessment of large bowel function, studies need to be of relatively long duration (>24 hours), can necessitate colonoscopy and sedation (that may potentially influence motility) and require the subject under study to be confined to the laboratory.[8]

Therefore, techniques that measure both contractility and motility that do not require an intraluminal catheter provide an alternative and more attractive method of describing normal and abnormal GI physiology.[5,9] To be clinically applicable, such techniques should be standardised, reproducible and easily interpretable as well as acceptable to the patient. In this regard, the wireless motility capsule has a number of salient advantages.[10,11] For instance, it is minimally invasive, ambulatory and does not require exposure to ionising radiation. Additionally, the wireless motility capsule has been demonstrated to be sensitive and specific technique in measuring pan-enteric and regional transit is comparable to conventional methods and has robust normal ranges for transit times and pH.[11-13] The wireless motility capsule has been approved for use in the USA by the Food and Drug Administration for investigating suspected delayed gastric emptying and chronic constipation.[14] In addition to measuring temperature and pH, the wireless motility capsule also measures intraluminal pressure as it traverses the GI tract.[10,14] However, this has received scant attention in the literature to date. Moreover, the inter-observer agreement of contractility measures has not been comprehensively described.[15] The primary aim of this study was to define normative ranges for regional and contractility/motility measures. Our secondary aims were to evaluate the inter-observer agreement between transit times, pH profile and contractility/motility parameters as well as investigating the co-relationship between these and the motility index.

2 | MATERIALS AND METHODS

2.1 | Study population

The study population consisted of 109 healthy participants who underwent wireless motility capsule testing in studies performed in the UK (14/109), Sweden (22/109) and the USA (73/109). The data from the USA were collected during a multi-centre clinical trial evaluating GI transit as measured by the wireless motility capsule in comparison to radio-opaque markers and has been published elsewhere.[16] The data from Sweden were collected as part of the process for deriving normative transit values.[12] The data from the UK were derived from the baseline recordings in healthy subjects of a clinical trial programme investigating the promotile drug camicinal.[17] The respective Institutional Review Boards, or Ethical Committees, approved all studies at the study centres. Each participant provided written informed consent. Participants were included if they were between 18 and 80 years old, with no concurrent or past medical history of cardiovascular, endocrine, renal, gastroenterological, liver, respiratory or any other chronic disease or currently taking any medications (prescribed or over the counter). Participants were also required to have a normal bowel habit, defined as a complete spontaneous bowel movement at least once per 48 hours for the purposes of this study. Participants were excluded if there was a known absolute or relative contraindication to undergoing a wireless motility capsule study (such as previous GI surgery, clinical evidence of diverticulitis), if there was a history of GI symptoms or if they had a body mass index >35 kg/m^2, were pregnant or had a planned magnetic resonance imaging (MRI) procedure during the study. Participants were instructed to refrain from tobacco and alcohol use for 24 hours prior to wireless motility capsule ingestion and during the study period.

2.2 | Wireless motility capsule

The wireless motility capsule (SmartPill, Medtronic, Minneapolis, USA) has been described elsewhere.[13,18] In brief, the wireless motility capsule system consists of an indigestible single-use capsule, an external portable data receiver, a docking station and bespoke display and analysis software. The wireless motility capsule contains 3 sensors: (1) a pH sensor capable of measuring pH in the range of 0.5 to 9.0 pH units with an accuracy ± 0.5, (2) a pressure transducer capable of measuring pressures ranging from 0 to 350 mm Hg with an accuracy of ± 5 mm Hg below 100 mm Hg and ± 10 mm Hg at, or above, 100 mm Hg and (3) a temperature sensor capable of measuring temperatures ranging from 25 to 49°C with an accuracy of ± 1°C. After activation, calibration and ingestion, pH, pressure and temperature are continuously measured as the wireless motility capsule traverses the GI tract. Data from the sensors are transmitted at 434 MHz to the portable data receiver worn by the participants.

Data are stored within the receiver and can be downloaded to a personal computer, using a USB docking station, for subsequent analysis.

2.3 | Wireless motility capsule testing protocol

After an overnight fast, participants ingested a standardised meal consisting of known nutritional content (SmartBar®, Medtronic, Minneapolis, USA, 260-kcal, composed of 3% fat, 21% protein and 75% carbohydrate, 3% of which as fibre) with 50 mL of water. Following this meal, participants ingested the wireless motility capsule which had been previously calibrated and activated as per the manufacturer's instructions. Participants were then asked to refrain from eating for the next 6 hours and avoid strenuous physical activity. After 6 hours, participants were permitted to resume their daily activities and diet. During the recording period, participants were asked to record bowel movements, food intake/meal times, GI symptoms (if any) and sleeping times on the portable data receiver.

2.4 | Wireless motility capsule data analysis

2.4.1 | Definition of anatomical landmarks

Each participant's wireless motility capsule data were downloaded onto a personal computer (Dell, Bracknell, Berkshire, UK) and analysed using the manufacturer supplied analysis software (MotiliGI, version 3.0.20, Medtronic, Minneapolis, USA). The GI tract was divided into 3 regions based on the identification of stereotypical landmarks, based on pH and temperature measures, as per the method proposed by Sarosiek et al.[19] In brief, the gastric region and gastric emptying time were defined from capsule ingestion, which is associated with a sharp temperature rise to 37°C, until a steep pH rise (>3 pH units) from gastric baseline to a pH greater than 4.0 pH units, reflecting passage across the pylorus. The small bowel region and small bowel transit time were defined as from this point until passage across the ileocaecal junction (ICJ), characterised a sustained drop in pH greater than 1 pH unit, and sustained for at least 10 minutes.[18] Finally, the colonic region and colonic transit time were defined from this point until capsule expulsion, verified by a characteristic temperature drop from body temperature to room temperature, see Figure 1.

2.4.2 | Motility and contractility measures

Motility and contractility measures were calculated using 2 pieces of proprietary software (MOTILIGI, version 3.0.20, and GIMS Data Viewer, version 3.0.0, Medtronic, Minneapolis, USA). MotiliGI—the contractility and motility measures provided by the software include maximum amplitude of contractions, mean peak amplitude of contractions, contractions per minute and the MI. The MI combines a number of pressure measures into one metric. The MI is determined according to the method proposed by Ouyang et al whereby the summation of the area under the amplitude curve for contractions about 10 mm Hg above baseline, calculated as the amplitude of the reading multiplied by the duration of the reading divided by the time window and expressed in units of mm Hg*second/minute.[20] This is equivalent to the sum of the amplitudes of all the contractions multiplied by their duration in a given segment, thus providing a time-based summary measure. MotiliGI is user friendly and provides a "wizard" which aids in the performance of semi-automated analysis. *GIMS* Data viewer provides total number of contractions, frequency of contractions, area under of the curve (AUC) of contractions, sum of amplitudes and $\log_e$ MI. The AUC represents the integral of the contraction amplitudes over time. The $\log_e$ MI is derived from the natural log of the (sum of amplitudes x number of contractions +1) as determined by Camilleri et al in healthy individuals in whom concomitant antral manometry and scintigraphy was undertaken after ingestion of a radiolabelled solid and liquid meal.[21] The software calculates $\log_e$ MI over the segment of interest, ie, gastric, small bowel and colon, as previous studies have suggested that the cumulated slope is linear.[22] The $\log_e$ MI therefore provides amplitude-based summary measure. GIMS Data viewer has been designed for research use. Pan-enteric data are shown in the Data S1.

2.5 | Inter-observer agreement

Inter-observer agreement was assessed in all participants. Traces were independently analysed by 2 observers (ADF and CBH).

2.6 | Statistical analysis

The motility/contractility measures are summarised using the number of observations, mean and standard deviation. To evaluate the effect of gender, age and study country on the study endpoints, a multiple linear regression model was used. Reference ranges for the motility parameters were derived from the 5th to 95th percentiles. Agreement between observers was compared using the intra-class correlation coefficient, and Bland-Altman's limits of agreement. A 2-way, random effects, single measure intra-class correlation coefficient model was used and interpreted according to Yen et al. using the following criteria: <0.40 = poor, 0.40-0.59 = fair, 0.60-0.74 = good, 0.75-1.00 = excellent.[23] Limits of agreement includes both random error (precision) and systematic error (bias), providing a useful measure for comparing the difference between 2 observations and is expressed as a 95% confidence interval of the difference. Correlational analyses were performed to investigate the contribution of contractility parameters to MI and transit times and are reported using Pearson's (r) or Spearman's coefficient (r_s) dependant on data distribution. Given that this analysis was exploratory, we did not correct for multiple testing. Two-tailed tests were used throughout. $P < .05$ was adopted as the criterion for statistical significance. All analyses were performed using proprietary software (STATA, Version 14, College Station, TX, USA).

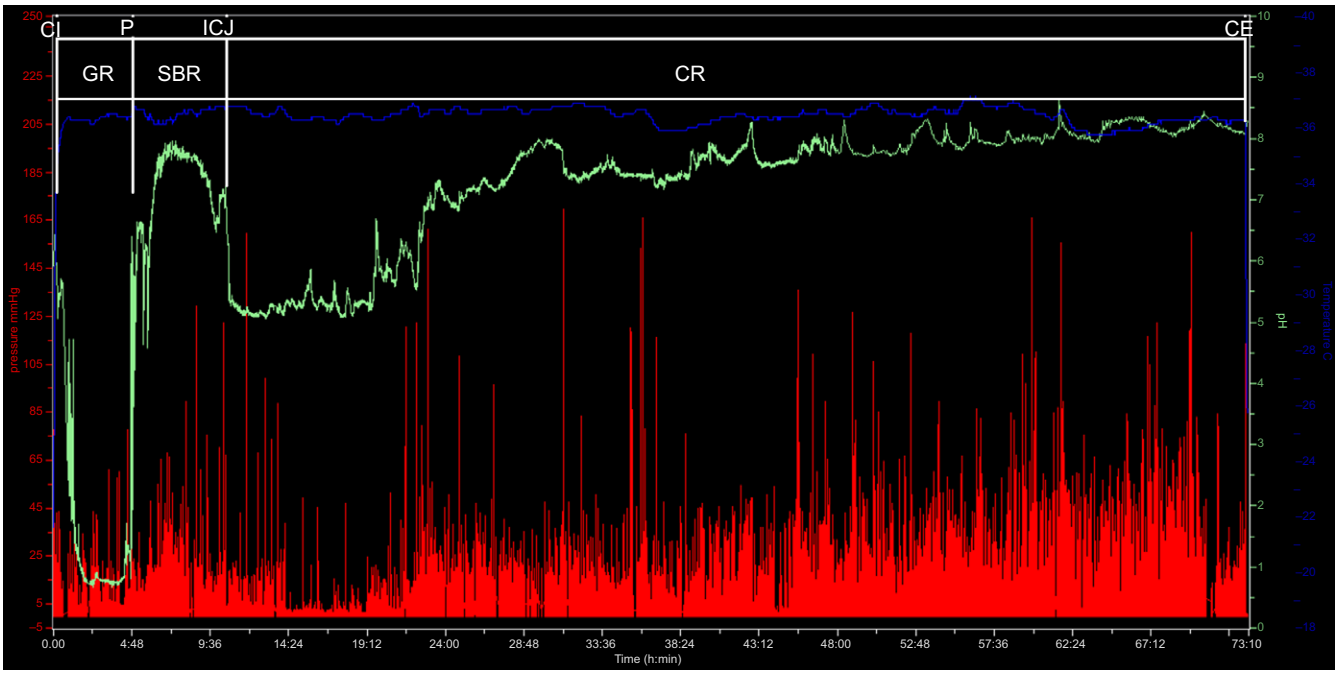

FIGURE 1 A typical tracing from a wireless motility capsule study. Time is recorded on the *x*-axis, pressure on the y1-axis (red line) and pH on the y2-axis (green line) and temperature (blue line). The gastric region (GR), small bowel region (SBR) and colonic region (CR) are illustrated. CI, capsule ingestion, P, pylorus, ICJ, ileocaecal junction, CE, capsule expulsion

3 | RESULTS

3.1 | Participant characteristics

A total of 109 individual wireless motility capsule data files were available. Of these, 2 were excluded due to major signal loss. Of the remaining 107 individual wireless motility capsule data files, 62 were male with a median age of 40 years, range 20-78, and 45 females with a median age of 38 years, range 18-74.

3.2 | Regional transit times and pH profile

The mean gastric emptying time, small bowel transit time, colonic transit time and whole gut transit time were 194 ± 118 minutes, 262 ± 107 minutes, 1474 ± 1112 minutes and 1930 ± 1158 minutes respectively. There were no gender or country differences in gastric emptying time, small bowel transit time, colonic transit time and whole gut transit time. Age weakly positively correlated with prolonged wireless motility capsule ($r = .2$, $P = .04$). The mean gastric, small bowel and colonic pH were 2.4 ± 1.5, 6.9 ± 1 and 6.8 ± 1.1 respectively. No gender, age or country differences were seen.

3.3 | Motility/contractility measures—MotiliGI

Motility and contractility measures derived from MotiliGI are shown in Table 1. Gastric ($r = .24$, $P = .01$), small bowel ($r = .22$, $P = .02$) and colonic ($r = 0.2$, $P = .04$) maximal pressures correlated with age. The small bowel motility index was higher in females than males (150.4 ± 12 vs 122 ± 7.6, $P = .04$). No other gender or country differences were evident. As expected based on their calculations, the respective gastric, small bowel and colonic motility indices correlated with the gastric ($r = .65$, $P < .0001$), small bowel ($r = .6$, $P < .0001$) and colonic ($r = .6$, $P < .0001$) mean contraction amplitude. As expected based on their calculations, the gastric, small bowel and colonic MI correlated with their respective gastric ($r = .72$, $P < .0001$), small bowel ($r = .8$, $P < .0001$) and colonic ($r = .5$, $P < .0001$) mean contraction frequency. Gastric emptying time correlated with gastric MI ($r = .4$, $P < .0001$). Small bowel transit time and colonic transit time did not correlate with their respective MI.

3.4 | Motility/contractility measures—GIMS

Motility and contractility measures derived from GIMS are shown in Table 2. The number of contractions within a segment positively correlated with gastric emptying time, small bowel transit time and colonic transit time ($r_s = .36$, $P < .0001$; $r_s = .64$, $P < .0001$; and $r_s = .74$, $P < .0001$). The respective AUC correlated with gastric emptying time, small bowel transit time and colonic transit time ($r_s = .63$, $P = .0003$; $r_s = .51$, $P < .0001$; and $r_s = .69$, $P < .0001$). As expected based on their calculations, gastric $\log_e$ MI correlated with gastric AUC, total contractions, sum of amplitudes and frequency ($r = .86$ $P = .0001$; $r = .87$ $P = .0001$; $r = .88$ $P = .0001$; $r = .61$ $P = .0001$ respectively). Gastric emptying time did not correlate with gastric $\log_e$ MI. Female gender was associated with a higher gastric $\log_e$ MI (14 ± 1.5 vs 13.2 ± 1.4, $P = .002$) but there was no association with age or country. As expected based on their calculation, small bowel $\log_e$ MI correlated with small bowel AUC, total

TABLE 1 Normative regional wireless motility capsule motility/contractility data using MotiliGI showing all and gender-specific means, standard deviations, median and 5%-95% percentiles

Measure	Gender	Number	Mean	SD	5th percentile	50th percentile	95th percentile
Gastric							
Pressure maximum (mm Hg)	All	107	241	103	65	241	434
	Male	62	231	102	41	236	425
	Female	45	25	103	99	256	467
Mean peak amplitude (mm Hg)	All	107	3.3	3.3	1.8	2.7	6.6
	Male	62	3.2	2.1	1.8	2.7	5.6
	Female	45	3.6	2.4	1.8	3	9.9
Contractions per minute (number)	All	107	1.7	1.2	0.5	1.3	4.2
	Male	62	1.6	1.1	0.6	1.2	4.2
	Female	45	1.9	1.3	0.5	1.7	5.2
Motility index (mm Hg*second/min)	All	107	55	46	13	46	131
	Male	62	53	45	13	45	138
	Female	45	58	49	14	48	175
Small bowel							
Pressure maximum (mm Hg)	All	106	119	55	50	110	227
	Male	61	123	58	45	119	229
	Female	45	114	51	57	108	229
Mean peak amplitude (mm Hg)	All	106	3.9	1.9	2.2	3.8	7.1
	Male	61	3.6	1.2	1.6	3.6	5.5
	Female	45	4.4	2.4	2.4	3.9	7.5
Contractions per minute (number)	All	106	3.6	1.4	1.6	3.6	6.4
	Male	61	3.4	1.3	1.5	3.2	6.1
	Female	45	3.8	1.4	1.8	3.6	6.9
Motility index (mm Hg*second/min)	All	106	134	70	58	126	286
	Male	61	122	59	47	116	263
	Female	45	150	81	63	136	381
Colon							
Pressure maximum (mm Hg)	All	106	155	47	90	147	236
	Male	61	164	49	98	164	250
	Female	45	143	41	83	139	224
Mean peak amplitude (mm Hg)	All	106	4.5	1.9	2.1	4.2	7.2
	Male	61	4.3	1.4	2.2	4	7.2
	Female	45	4.7	2.4	2	4.5	8.3
Contractions per minute (number)	All	106	2.2	0.9	1.1	2.1	4.4
	Male	61	2.3	1	1.1	2	4.9
	Female	45	2.1	0.7	1.1	2.1	3.7
Motility index (mm Hg*second/min)	All	106	199	95	71	187	383
	Male	61	197	93	70	182	399
	Female	45	201	100	52	198	383

contractions, sum of amplitudes and frequency ($r = .84$ $P = .0001$; $r = .86$ $P = .0001$; $r = .91$ $P = .0001$; $r = .69$ $P = .0001$ respectively). Small bowel transit time did not correlate with small bowel $\log_e$ MI. Gender, age or country was not associated with small bowel $\log_e$ MI. As expected based on their calculations, colonic $\log_e$ MI correlated with colonic AUC, total contractions, sum of amplitudes and frequency ($r = .72$ $P = .0001$; $r = .87$ $P = .0001$; $r = .85$ $P = .0001$; $r = .35$ $P = .0003$ respectively). Colonic transit time did not correlate with colonic $\log_e$ MI, and gender, age or country was not associated with colonic $\log_e$ MI.

TABLE 2 Normative regional wireless motility capsule motility/contractility data using GIMS showing all and gender specific means, standard deviations, median and 5%-95% percentiles

Measure	Gender	Number	Mean	SD	5th percentile	50th percentile	95th percentile
Gastric							
Total contractions (number)	All	107	268	254	63	195	792
	Male	62	208	160	63	153	556
	Female	45	353	330	94	231	1045
Contraction per minute (number)	All	107	1.5	1.3	0.4	1.2	3.9
	Male	62	1.5	1	0.5	1.1	3.9
	Female	45	1.7	1.5	0.4	1.4	3.6
Area under the curve	All	107	9619	8771	1544	6471	32629
	Male	62	7659	6537	1503	5930	21296
	Female	45	12400	10683	3418	7106.7	33492
Motility index-natural log	All	107	13.6	1.5	11.3	13.6	16.3
	Male	62	13.3	1.4	11.3	13.2	14.1
	Female	45	14.2	1.5	12.3	13.9	16.8
Sum of amplitudes	All	107	5702	5030	2610	4146	6881
	Male	62	4458	3345	1367	3563	11418
	Female	45	7466	6373	2311	4716.8	18689
Small bowel							
Total contractions (number)	All	106	781	417	242	729	1567
	Male	61	741	395	229	677	1486
	Female	45	837	445	287	851	1821
Contraction per minute (number)	All	106	3.5	1.5	1.5	3.3	6.4
	Male	61	3.3	1.5	1.5	2.9	6.3
	Female	45	3.7	1.5	2	3.6	6.3
Area under the curve	All	106	26046	15161	7529	24799	56821
	Male	61	24196	13841	8819	22189	54915
	Female	45	28669	16672	9312	26631	56860
Motility index-natural log	All	106	15.9	1.2	13.9	16.1	17.7
	Male	61	15.8	1.3	13.8	15.9	17.5
	Female	45	16.1	1.1	14.2	16.3	17.9
Sum of amplitudes	All	106	14485	8068	4505	13361	30628
	Male	61	13737	7631	4450	12203	27088
	Female	45	15545	8629	5494	14421	32458
Colon							
Total contractions (number)	All	106	622	489	87	497	820
	Male	61	559	408	102	464	1377
	Female	45	712	579	61	577	1717
Contraction per minute (number)	All	106	0.6	0.3	0.2	0.5	1.3
	Male	61	0.6	0.3	0.3	0.6	1.3
	Female	45	0.5	0.2	0.1	0.5	0.9
Area under the curve	All	106	107640	119598	9095	73696	375574
	Male	61	94570	116647	9916	58201	265957
	Female	45	126181	122638	5137	97202	402153
Motility index-natural log	All	106	16	1.7	12.6	16.2	18.5
	Male	61	15.9	1.6	12.9	15.9	18.1
	Female	45	16.2	1.9	11.9	16.6	18.9

(Continues)

TABLE 2 (Continued)

Measure	Gender	Number	Mean	SD	5th percentile	50th percentile	95th percentile
Sum of amplitudes	All	106	26532	22376	3407	21587	67049
	Male	61	23790	4138	4138	18597	54229

3.5 | Inter-observer agreement

Inter-observer agreement was assessed all participants, Table 3. Intra-class correlation coefficient and limits of agreement showed excellent reproducibility for majority of the measures.

4 | DISCUSSION

To date, this is the largest and most comprehensive dataset that describes normative regional and motility/contractility parameters using the wireless motility capsule. The wireless motility capsule has become a popular method for measuring transit times due to is minimally invasive nature in an ambulatory setting. However, normative data only exist with regard to only a proportion of the wireless motility capsule's capabilities, ie transit times and regional pH.[12] Despite this, the wireless motility capsule also provides direct measurements of regional motility/contractility measures, which may also be potentially more useful clinically in evaluating GI motility. Nevertheless, these have been largely ignored in the literature to date. In this study, we have shown that the regional $\log_e$ MI is a particularly useful summary measure of contractility parameters given its robust correlations with other regional measures such as AUC, total contractions, sum of amplitudes and contraction frequency. Log_e MI as reported in this study, ie derived from the wireless motility capsule, is numerically similar to that reported using an intraluminal catheter.[21] Furthermore, we demonstrate that many of these parameters have good inter-observer agreement. Notably, it is clear from many of the motility/contractility measures that there is a large variation in the normal ranges presumably reflecting the diversity of "normal" GI tract physiology.

The GI tract is a complex organ, large parts of which are relatively inaccessible, thus making it a challenge to assess in detail.[3] A number of other methods to assess transit times are currently available, such as scintigraphy,[24] radio-opaque markers,[25] the 3-D magnetic transit system,[3] MRI[26] and the wireless motility capsule.[15] However, transit times *per se* may represent a blunt tool for evaluating GI motility as abnormalities that lead to symptoms can be more subtle.[3] Despite the functionality of the wireless motility capsule to record pressure as it traverses the GI tract, the majority of studies to date have not presented these data, arguably due to at least 3 factors. Firstly, due to the lack of availability of normative data, secondly due to challenges in calculating/extracting these parameters and finally their relevance to symptoms. However, a recent study by Barshop et al demonstrated that duodenal area under the pressure curve was strongly and reproducibly associated with symptom severity in patients with both idiopathic and diabetic gastroparesis; these findings warrant confirmation in larger more homogenous patient groups.[27] However, based on the normative data we present herein, the values that they report would be within the normative range for this metric, Table 2. Nevertheless, such detailed measures may provide alternative relevant physiological endpoints in clinical trials as it is well described that transit times are not optimal to correlate with symptoms.[28] A number of techniques have been developed and studied over the last 50 years utilising a variety of free-floating capsule techniques including those containing radiopharmaceuticals and pressure sensors.[29,30] A more recently developed method is the 3D transit system which, using an electromagnetic capsule, can delineate pan-enteric and regional GI motility[3]. The marked advantage of this system is that the location, velocity and direction of travel of the capsule, relative to the receiver plate, is known at all times.[4] While this is a minimally invasive and ambulatory technique, the interpretation is labour-intensive and has yet to be validated in a large cohort of healthy subjects and remains a research tool.[3]

There was little correlation between transit times and other contractility measures. These data suggest that regional contractility and transit times are not inextricably linked as measured using the wireless motility capsule. In a previous study reported by Hasler and colleagues, of 56 healthy controls and 36 constipated subjects, it was demonstrated that colonic pressure activity increased from the proximal to distal colonic segments in all groups.[31] However, when considering those subjects with the most severe slow transit constipation, there was a marked reduction in this increase in pressure activity albeit not associated with transit times.

We have demonstrated that the inter-observer agreement was excellent for the majority of measures. This is in agreement with the report by Rao et al who have previously described the intra-class correlation coefficient for regional and whole gut transit times in 45 traces, composed of 10 healthy participants, 10 patients with gastroparesis and 25 patients with constipation.[32] The authors demonstrated excellent intra-class correlation coefficients between 3 independent observers. However, this study, to the best of our knowledge, has only been published in abstract form and did not encompass other motility/contractility measures derived from the wireless motility capsule. Moreover, intra-class correlation coefficients in isolation cannot provide a complete picture of inter-observer agreement and should be accompanied by other parameters such as limits of agreement, as included in our study.[33]

The process of analysing wireless motility capsule traces using MotiliGI is relatively straightforward as it includes an analysis "wizard" which guides the clinician. While GIMS does not include this feature, it does have enhanced functionality and provides a more detailed analysis of wireless motility capsule traces in comparison to MotiliGI. Thus, we would propose for routine clinical practice that there is an inherent temporal advantage of using MotiliGI rather

TABLE 3 Inter-observer agreement of wireless motility capsule parameters showing observer median and inter-quartile range (IQR), intra-class correlation coefficient (ICC) and Bland-Altman's 95% limits of agreement (LOA)

Measure	Observer A (median and (IQR))	Observer B (median and (IQR))	ICC (95% confidence interval)	Delta mean (LOA)
Gastric				
Pressure maximum (mm Hg)	241 (174-494)	240 (177-494)	0.99 (0.99-0.99)	0.02 ± 1.5
Mean peak amplitude (mm Hg)	2.7 (2.3-3.5)	2.8 (2.4-3.5)	0.99 (0.99-0.99)	0.08 ± 0.1
Contractions per minute	1.3 (1-2.1)	1.3 (1-2.1)	0.96 (0.91-0.99)	−0.02 ± 0.05
Motility index	46 (26-66)	46 (26-69)	0.99 (0.99-1.0)	−0.3 ± 0.3
Transit time	178 (132-221)	178 (136-221)	1 (1-1)	−0.1 ± 1.6
Median pH	2 (1.2-3.7)	2 (1.2-3.7)	0.99 (0.99-0.99)	−0.03 ± 0.05
Small bowel				
Pressure maximum (mm Hg)	110 (83-141)	109.9 (84-141)	0.99 (0.99-0.99)	−0.4 ± 1.5
Mean peak amplitude (mm Hg)	3.8 (3-4.3)	3.9 (3.1-4.3)	0.99 (0.99-0.99)	−0.01 ± 0.1
Contractions per minute	3.3 (2.6-4.4)	3.4 (2.7-4.4)	0.4 (0.1-0.6)	−0.1 ± 0.1
Motility index	125 (87-161)	126 (91-163)	0.99 (0.99-0.99)	−0.5 ± 2.4
Transit time	240 (196-293)	240 (196-293)	0.7 (0.6-0.84)	0.3 ± 0.8
Median pH	7 (6.6-7.4)	7 (6.7-7.4)	0.99 (0.99-0.99)	−0.02 ± 0.1
Colon				
Pressure maximum (mm Hg)	147 (118-184)	147.1 (117.8-183.9)	0.99 (0.99-0.99)	−0.1 ± 0.8
Mean peak amplitude (mm Hg)	4.2 (3.5-5.2)	4.2 (3.5-5.2)	0.99 (0.99-0.99)	−0.1 ± 0.08
Contractions per minute	2.1 (1.7-2.6)	2.1 (1.7-2.6	0.99 (0.99-0.99)	−0.1 ± 0.07
Motility index	187 (128-267)	188 (129-265)	0.99 (0.99-0.99)	−0.8 ± 2.5
Transit time	1129 (850-1987)	1129 (850-1987)	0.93 (0.87 -0.93)	0.4 ± 3
Median pH	6.9 (6.5-7.3)	6.9 (6.5-7.3)	0.99 (0.99-0.99)	−0.03 ± 0.06

than GIMS. For gastric emptying time, colonic transit time and whole gut transit time, both Wang et al and Diaz-Tartera et al have demonstrated a strong correlation between the results derived from manual evaluation of wireless motility capsule traces and those reported by an automated analysis from MotiliGI suggesting that such an analysis is robust for clinical practice.[12,34] In both of these studies, the agreement between the automated assessment of small bowel transit time was lower than the other transit measures arguably due to the relative difficulty of identification of the ICJ.

This study is not without limitations. In contrast to high-resolution manometry, the absolute interpretation of parameters derived from the wireless motility capsule is limited by the fact that it is currently not possible to detect a wave front, which represents a propulsive peristaltic pattern. Given that the wireless motility capsule is essentially a nonstatic "free-floating" pressure, pH and temperature transducer, the absolute clinical applicability of this normative dataset is limited to luminal pressures and transit times, but cannot detect the actual propagated pressure waves considered to be the primary mechanism for propulsive motility. Therefore, it could be cogently argued that the phasic contractile measurements delineated by the wireless motility capsule do not significantly add to the information of regional transit that can be measured by radio-opaque markers and/or scintigraphy. Although whole gut transit time can be measured with radio-opaque markers, which correlate reasonably well with wireless motility capsule derived transit times, the wireless motility capsule does offer the advantage of providing a regional motility profile, encompassing the entirety of the GI tract in a single ambulatory investigation.[15] In the clinical environment, whether any of these measures robustly and reproducibly associate with symptoms remains to be seen. The current study was undertaken using a standardised test meal, and while this improves external validity with respect to the normative data, no inferences can be made to these values with respect to other meals of differing nutritional content. A further limitation of our study was that we did not control for the individual female's stage of their menstrual cycle as this may influence GI motility.[35] We had previously shown that female gender was associated with longer gastric emptying time, colonic transit time and whole gut transit time,[12] although we did not demonstrate any associations between gender and transit times in this study. The reasons for this difference are unclear. Finally, the mean peak amplitudes were lower than we would have expected in comparison to previously reported stationary catheter studies[36,37] and may limit the identification of pathologically low amplitudes of contractions, such as what is seen in connective tissue disorders such as scleroderma.[38] In order to address this in future studies, an alternative approach which would be to use maximal amplitudes although further studies in clinical populations are needed.

In summary, this comprehensive analysis of the motility/contractility data provides normative motility/contractility data for the wireless motility capsule. Notably the $\log_e$ MI provides a summary

measure of many of these parameters. The measurement of contractile activity with the wireless motility capsule may advance our understanding of novel pharmacological agents[17] and potentially in the diagnosis of disease states association with alterations in contractile amplitude, such as what is seen in visceral myopathic disorders.

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SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

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