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**MAIN TITLE**

# Normative values for gastric motility assessed with the 3D-transit electromagnetic tracking system

**RUNNING TITLE**

Normative values for gastric motility patterns

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**Abstract**

**Background**

The Motilis 3D-Transit system allows ambulatory description of transit patterns throughout the gastrointestinal tract and offers an alternative method for studying gastric motility. We aimed to establish normative values for gastric motility assessed with the method.

**Method**

A total of 132 healthy volunteers ingested the 3D-Transit capsule for assessment of gastrointestinal transit times. Recordings from 125 subjects were used for definition of normative values. 46 subjects were studied on two consecutive days. Recordings were reanalysed using newly developed software providing information on gastric emptying (GE) as well as contraction frequency and movement during gastric contractions.

**Results**

The median GE time was 2.7 hours (range 0.1-21.2). In 89% of subjects, the capsule passed the pylorus within a post-ingestion period of 6 hours. The median frequency of gastric contractions was 3.1 per minute (range 2.6-3.8). The frequency was higher in women (3.2, range 2.7-3.8) than in men (3.0, range 2.6-3.5) and increased with age (0.004 per year) ($p<0.05$). The median amplitudes were 35° (range 4-85) when based on rotation of the capsule and 11 mm (range 6-31) when based on capsule change in position. The rotation amplitude was higher in women and decreased with increasing BMI ($p<0.05$). The position amplitude was also higher in women and increased with the amount of calories in the test meal, but decreased with increasing BMI and age ($p<0.05$). Day-to-day variation ($p>0.05$) was considerable while inter-rater variability was small.

**Conclusion & inferences**

We have established normative values for gastric motility assessed with the 3D-Transit system.

**KEYWORDS**

Gastroenterology, Neurogastroenterology, Gastrointestinal motility, Gastric Motility

**ABBREVIATIONS**

GE: Gastric emptying; BMI: Body Mass Index,

## Introduction

Gastroparesis is defined as delayed gastric emptying with absence of mechanical obstruction. The most common aetiologies are diabetes mellitus, surgery, neurological disorders and viral infections[1, 2]. However, in a significant proportion of patients, gastroparesis remains idiopathic[1, 2]. Symptoms are usually non-specific, such as nausea, vomiting, bloating, upper abdominal discomfort, pain, postprandial fullness and early satiety[3]. Even though symptoms vary, nausea and vomiting are predominant symptoms in diabetic gastroparesis whereas abdominal pain is more common in idiopathic gastroparesis[1, 4]. Likewise the severity of symptoms varies[5] with severe cases having reduced quality of life and frequent hospitalisation due to the cardinal symptoms or dehydration and poor glycaemic control[1, 3, 4, 6, 7]. In the United States of America, prevalence is estimated at 19.6 per 100.000 men and 37.8 per 100.000 women[8], though gastroparesis likely remains unrecognised in many subjects[8, 9].

Gastric emptying assessed by scintigraphy is currently the gold standard for diagnosis of gastroparesis. The method quantifies the emptying of a solid-phase, egg-based, radiolabelled meal that is imaged after 30 minutes and thereafter every hour for at least 4 hours[10]. The validity of scintigraphy requires that internationally accepted protocols are strictly followed[11]. Nevertheless, the clinical use of results from scintigraphy is widely debated and results do not predict response to treatment[12, 13]. This limitation could be because scintigraphy only describes gastric emptying while other parameters of gastric motility (e.g parameters of contractile activity) could be equally important. Furthermore, scintigraphy is expensive, requires the intake of radioactive isotopes and only determines passage from the stomach. The latter is a major limitation as many motility disorders are pan-enteric and not restricted to a single region of the gastrointestinal tract[14].

Gastric emptying can also be determined by breath test measuring the stable isotope $^{13}C$.[15] This test can be performed in an ambulatory setting without use of extensive equipment and the exposure to irradiation[16, 17]. The wireless motility capsule (Smartpill™ Medtronic Corporation, Buffalo, NY, USA) is a US Food and Drug Administration and European Union-approved capsule system for ambulatory investigation of total and regional gastrointestinal transit times. The system measures pH, pressure and temperature throughout the gastrointestinal tract. However, the interpretation of pressure data is complicated as the capsule advances in the gut on the same pressure events that it seeks to record and the exact location of the capsule on a minute-to-minute basis is unknown[18-20].

The 3D-Transit system (Motilis Medica SA, Lausanne, Switzerland) is an ambulatory minimally invasive, radiation-free capsule system that allows detailed investigation of the entire gastrointestinal tract as it tracks the precise position and orientation of an electromagnetic capsule. Examinations can be performed at home under near-normal conditions and provide information on gastric emptying time, small intestinal transit time, total and segmental colonic transit time, and movement patterns within the colon[21].

Recent development of software for analysis of recordings obtained by 3D-Transit now enables assessment of the frequency and amplitude of either rotation or change in position of the capsule within the stomach. As the 3D-Transit is a relatively novel research tool, it is important to define normal ranges of motility parameters described by the method. Therefore, the aim of the present study was to establish normative data for gastric emptying and gastric contractile activity assessed with the 3D-Transit system. Furthermore, we aimed to determine if gastric emptying and gastric contractions were affected by age, gender, body mass index (BMI), or the content of the test meal taken with the 3D-Transit capsule.

## Material and Methods

### Study population

For the present study, we reanalysed 3D-Transit data from 132 volunteers who had served as healthy controls in previous studies at Aarhus and Aalborg University Hospitals, Denmark, and Queen Mary University London, UK. Among the 132 subjects, 46 had ingested capsules on two consecutive days. All studies were carried out in accordance with the declaration of Helsinki and after approval by local Research Ethical Committees (reference numbers: 1-10-72-54-15, 2016101143; N-2013-0030, 2013070299; M-2010-0276, 2011-123594; 1-10-72-356-12, 2012-003939-27; 1-10-72-255-14, 2014-112300; M-2014-213-14, 2014-080548, 2015-033891; 1-10-72-211-15, 2015-093124 and 15/LO/1039)(see appendix A). Data for GE times in some of the subjects have been published previously[21-26]. Informed consent was obtained from all participants before enrolment.

All subjects were without previous history of serious gastrointestinal disease or other conditions affecting bowel function and none took medication affecting gastrointestinal motility.

### The 3D-Transit system

The 3D-Transit system consists of an electromagnetic capsule (21.5 millimetres x 8.3 millimetres, 1.6 gram per $cm^3$), an extracorporeal detector containing four sensors to register the electromagnetic field emitted by the capsule, and software for display and analysis of data. The battery lifetime of the capsule is approximately 60 hours at 10 Hertz sampling rate. However, the sampling rate is adjustable and in most of the studies above it was set at 5 Hertz to prolong battery lifetime. After ingestion of the capsule, the electromagnetic field emitted is monitored in real time by means of Bluetooth communication and stored within the detector for later analysis by dedicated software. Capsules do not interfere with each other and up to three capsules can be followed simultaneously.

When the electromagnetic field is registered by the detector, data is converted into coordinates (x,y,z,$\Phi$,$\theta$) via an iterative algorithm. The x,y,z coordinates represent distance in the 3-dimentional planes, while the $\Phi$,$\theta$ express the angular position of the capsule relative to the detector and thereby the rotation of the capsule. Thus, changes in position, velocity of movements, and orientation of the capsule can be studied with respect to anatomical information. Thereby, contractile activity and progression dynamics can be studied throughout the entire gastrointestinal tract. Artefacts due to breathing and posture changes are recorded by a thoracic belt and accelerometer inside the detector. Electromagnetic noise from the surrounding environment affects the capsule signal to the detector. Thus, the minimal distance allowable from external electronic devices (e.g. computers) is approximately 40 centimetres. Further details about the system have been published previously[21, 23].

**Study protocol**

All subjects arrived at the research facility in the morning after an overnight fast. Prior to ingestion, the capsule was activated and the wireless connection between detector and capsule was confirmed. Study participants swallowed the capsule immediately after ingestion of a standardized meal and a glass of water. There were slight variations in the content and number of calories within the meal taken in the various studies (Appendix B supplementary material)[21-26].

In the first 6 hour period following capsule and test meal ingestion, the subject was instructed not to consume any food and only a small quantity of water if required. After leaving the research facility, subjects were allowed to perform their normal daily routine and activities, but hard physical work and sports were prohibited. Participants wore the detector belt at all times during the study, except when showering and changing clothes. The 3D-Transit system was worn until capsule expulsion or battery power expired.

**Intragastric movements**

The two investigators (NS and MWK) performing the data analysis were both very experienced in the practical use of the 3D-transit system, including use of the basic software and assessment of total and regional gastrointestinal transit times. To enable them to clear artefacts and mark contractions manually, they spent two days with the manufacturer in Switzerland. During that stay, they performed supervised analysis of data from approximately 30 recordings.

Gastric emptying time was defined as time from ingestion to pyloric passage. The latter was determined by a combination of visual identification of the duodenal arch and a change in contraction pattern from 3 contractions/minute to 9-12 contractions/minute[21, 27].

As described in a previous publication from our group, all fast capsule movements, physiological or non-physiological, were identified with an automated algorithm developed by Motilis Media SA. Fast capsule movements were defined as displacements longer than 4 cm with an average velocity of more than 4 cm/minute[28]. The majority of these would be artefacts. Such displacements were compared to data from the accelerometer to identify artefacts due to changes in body position. Very fast movements (>2 cm/second) or movements where the capsule returned to the exact same position the main characteristics of artefacts. Every single contraction of the stomach was manually marked to calculate its amplitude and the frequency (figure 1). The computation was done for the three-dimensional movement of the capsule as well as its rotation. Hence, surrogate markers for the amplitude of gastric contraction were position amplitude, based on capsule movement in millimetres (mm) and rotation amplitude based on capsule rotation around its own axis in degrees ($^{o}$). Furthermore, periods with clearly visible contractions were separated from those with uncertain or no contractions, thereby giving a percentage of time with detectable contractions in each subject. Unless the capsule had passed the pylorus earlier, the analysis of intragastric movements was restricted to first the 6 hours following the index meal.

**Statistical analysis**

Statistical analysis was performed in STATA15 (Stata Release 15, College Station, StataCorp LLC, TX, USA and SPSS Statistics Version 25, IBM, NY, USA). Because data were non-Gaussian, all analyses were non-parametric and data are presented as median and (range). A multivariate analysis was performed to explore associations between gastric emptying or contractions and demographics or the content of the standardized meal. Day-to-day variation for the 46 subjects who had ingested capsules on two consecutive days is given as coefficient of variation (difference/mean) and illustrated by Bland-Altman plot. The interobserver variation for 16 randomly chosen recordings is also given as coefficient of variation (difference/mean) and illustrated by Bland-Altman plots (figure 3), $p<0.05$ was considered statistically significant.

**Results**

Use of the 3D-Transit system was well tolerated without any adverse events or discomfort. From a total of 185 recordings from 132 healthy volunteers, 14 recordings (8%) from 7 volunteers (5%) were discarded due to poor quality of data. Hence, recordings from 125 volunteers (56 males and 69 females, median age of 39 years (20-88), median BMI of 24 (19-

41)) were available for further analysis. Among these, 46 subjects had ingested capsules on two consecutive days. In the 46 subjects who ingested two capsules, only the first recording was included as normative data and for analysis of association with background variables. During its stay in the stomach, the capsule was located in the antrum or corpus most of the time with a relatively quick passage through the fundus (example shown in figure 2). Gastric contractions were detectable for a median of 92% (5-100) of the time.

**Gastric emptying**

Median gastric emptying time was 2.7 hours (0.1 – 21). In 111 (89%) recordings, the capsule passed from the stomach to the duodenum during the 6 hours period following capsule ingestion with the standardized meal. We found no association between gastric emptying time and age, gender, BMI, calorie content or fat content of the test meal (all $p>0.05$). Normative values for gastric emptying and gastric contractions are shown in Table 1.

**Frequency of gastric contractions**

The median frequency of all gastric contractions was 3.1 per minute (2.6-3.9). The median frequency was lower in males (3.00 per minute (2.61-3.53)) than in females (3.16 per minute (2.70-3.80)) ($p=0.001$), but increased with age by 0.004 per year ($p<0.001$). Fat content, total number of calories of the meal and the BMI of the subject under study showed no associations with the frequency of gastric contractions (all $p>0.05$).

**Rotation and change in position of the capsule**

Median rotation amplitude was 35° (4-92) and median position amplitude was 11 mm (6-31). The rotation amplitude was higher in females (median 40°(14-85°)) than in males (median 30°

(4-77)) (p=0.001) and decreased with increasing BMI (p=0.001). It was not associated with age or the composition of the meal (all p>0.05). The position amplitude decreased with age (p=0.008), increased with the number of calories in the test meal (p=0.004), but it was not affected by BMI, gender or composition of the meal (p>0.05). Normative values for rotation and change in position of the capsule are shown in Table 1.

**Day-to-day variation**

Comparing the recordings from capsules taken at two consecutive days (n=46), there were no differences in gastric emptying, frequency of contractions, rotation amplitude or position amplitude (all p>0.05). The median coefficient of variation (difference/mean) was 0.76 for gastric emptying, 0.04 for frequency of contractions, 0.34 for rotation amplitude, 0.28 for position amplitude and 0.17 for percentage of time with visible contractions.

**Interobserver variation**

Comparing the 16 randomly chosen recordings assessed by two investigators (MWK and NS), there were no differences in contraction frequency, rotation amplitude, position amplitude or time with detectable contractions (all p>0.05). The coefficient of variation was 0.01 for frequency of contractions, 0.06 for rotation amplitude, 0.07 for position amplitude, and 0.13 for time with detectable contractions.

## Discussion

### Main findings of the study

In the present study, we found that the 3D-Transit system allows safe and ambulatory assessment of GE time and assessment of gastric contractions in healthy volunteers. Use of the system was well tolerated and useful data was obtained from 95% of subjects studied. Normative values for parameters of gastric motility were reported based on recordings from 125 healthy subjects.

### Methods for description of gastric motility

The pathophysiology behind gastroparesis is complicated and poorly understood. However, loss of interstitial cells of Cajal, disturbances in vagal function and neuropathy secondary to diabetes mellitus or neurodegenerative diseases may contribute[29, 30]. Gastric emptying scintigraphy is gold standard for assessment of gastric emptying. Gastric retention of >60% of the meal at 2 hours and/or >10% at 4 hours are criteria usually used to define gastroparesis[1, 10]. However, the association between symptoms of gastroparesis and results from scintigraphy is disputed and especially the quality of the methodology is of significance for the outcome[11, 30]. Furthermore, scintigraphy is expensive and exposes the subject under study to radiation. It is also time consuming and can only be applied in a specialized hospital setting. Finally, information obtained by GE scintigraphy is limited to the stomach. This is a major limitation as many motility disorders are panenteric[14]. However, protocols can be modified for assessment of transit through the whole gut [31, 32]. Other methods include: (1) barium gastric x-ray, which is useful to exclude mechanical obstruction, but it does not provide quantitative information on gastric emptying; (2) electrogastrography, which records gastric myoelectric activity by cutaneous electrodes on the anterior abdominal wall overlaying the stomach. Recordings are defined as abnormal when dysrhythmia exceeds 30% of the recording time and/or when the ingestion of a meal fails to initiate or increase the amplitude of the signal[33]. However, electrogastrography provides no information on GE and there has never been widely uptake of the method. (3) The wireless motility capsule, which records pressure, pH and temperature during its passage through the gastrointestinal tract[34-38]The method is well-validated, it is easy to use and robust normative data for overall and regional transit times as well as measure of contractile activity are available [34-36]. However, the wireless motility capsule provides no information on the exact position of the capsule at a given point of time.

**Comparison of results from 3D-transit with those of other methods**

In the present study, median GE time of the 3D-Transit capsule was 2.7 hours. This is very close to results from the wireless motility capsule (where median gastric emptying was 3.2, 3.23 and 3.25 hours[21, 37, 38] even though the size of the wireless motility capsule is significantly larger than the 3D-Transit capsule (3D-Transit capsule 8.3 x 21.5milimitres; wireless motility capsule 11.7 x 26.8 millimetres) [37, 38].

In the stomach, slow wave contractions usually start in the fundus and spread towards the antrum. Their frequency has been described in detail, especially by electrogastrography and antro-duodenal manometry, and corresponds very well to the average 3.1 per minute frequency observed in the present study[39, 40]. Based on electrogastrography, contractions with a frequency <2 per minute have been used to define “bradygastria” while frequencies > 4 per minute have defined “tachygastria”. In the present study, the average frequency of contractions within a single subject ranged from 2.6 to 3.9.

Hence, none of our 125 healthy would be defined as having an abnormal frequency of gastric contractions[41].

Data from electrogastrography suggest that some patients with gastroparesis have a reduced amplitude of gastric contractions[41]. The amplitude of contractions assessed with 3D-Transit is not directly comparable to the amplitude determined by electrogastrography. We do however consider the position amplitude, determined by movement, or the rotation amplitude of a capsule within the stomach a more direct measure than the amplitude of an electrical signal registered on the surface of the abdomen.

In the present study, GE time was not associated with age, gender, BMI or the minor differences in the composition of the meal given with the capsule. Hence, we consider our normative data on gastric emptying robust. In contrast, the contraction frequency of 3.1 per minute *was* affected by gender and age while position and rotation amplitudes were associated with gender, BMI and calorific content of the meal. This has to be considered when future studies with the 3D-Transit system are designed.

**Pan-enteric assessment**

Motility disorders are usually not confined to one region of the gastrointestinal tract. A major advantage with the wireless motility capsule and the 3D-Transit system is that they allow ambulatory assessment of whole gut and regional gastrointestinal transit times. This is important both for research and in a clinical setting. Compared to the wireless motility capsule, the major advantage with the 3D-Transit system is that it defines the precise location and orientation of the capsule within the gastrointestinal tract. This allows for assessment of segmental colonic transit times and details on progression through the colon[28, 42, 43]. Based on region-specific contraction frequencies and anatomical characteristics, previous studies have compared regional transit times in healthy subjects and various patient groups[21-27, 44] . Recently, data analysis has been refined to allow detailed assessment of colonic motility patterns[28, 42]. As shown in the present study, the same investigations can now be further analysed to provide details on gastric motility. Future studies will show whether description of gastric contractions will add clinically relevant information to gastric emptying time.

**Limitations**

Gastric motility patterns depend on whether the subject is in the fasting or the postprandial state. Usually, an object with the dimensions of the 3D-Transit capsule will pass the pylorus in the fasting state during phase III of the migrating motor complex [40]. We aimed to study gastric motility and define normative values during a 6 hours post-ingestion period before *ad libitum* feeding was allowed. This was only partially achieved as 10% of capsules remained in the stomach at the end of the 6 hours. Hence, we restricted the analysis of gastric contractions to data obtained before subjects were allowed to eat again after 6 hours. The same was not possible for the gastric emptying time which may have been prolonged when subjects were allowed to eat freely. Studies with electrogastrography have shown that the frequency and amplitude of gastric contractions increase shortly after a meal[41]. This may have caused some variation in our data on contractility because the GE time, and thereby the recording time after the meal, varied considerably.

We do not know exactly how the signal amplitude of either rotation or change in position of the capsule reflect the true amplitude of gastric contractions. Hence, we have chosen to use the terms “rotation amplitude” and “position amplitude”. The definition of pyloric passage included a combination of change in contraction frequency and identification of the highly characteristic fast movement through the duodenal arch. This includes some subjective assessment. We have previously validated pyloric passage defined by magnet tracking against the same determined with PillCam and found that agreement was very good[27].

In accordance other methods for assessment of gastrointestinal motility, we found that that intersubjective and day-to-day variation were large for all parameters studied. This was especially true for gastric emptying time. Even though the large variation most likely reflects normal physiology, it may prove a limitation for the future use of the method as a diagnostic tool. Further studies are needed to determine whether 3D-Transit and the parameters of gastric contractility described in the present study will prove more sensitive than existing methods in distinguishing patients with various motility disorders from healthy subjects. Another limitation with use of the 3D-Transit system is the manual analysis of the recordings which is time-consuming and may depend on the experience of the investigator. The latter is probably of minor consequence as we found that interobserver variation was small.

## Conclusions

In conclusion, the present study adds normative data on gastric contractility patterns and emptying time to those on region-specific transit times and motility patterns in the colon already available for the Motilis 3D-Transit system. Given the impact of age, gender and BMI, any future clinical study may have to take these into account and match patients accordingly.

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All other authors have no conflicts of interest to declare.

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*Author contributions:* Nanna Sutter: Collation of data, data analysis, statistical analysis, interpretation of data, drafting of the manuscript; Mette W Klinge: Data analysis and acquisition, revised the manuscript for important intellectual content. Esben Bolvig Mark: Development of algorithms for data analysis, revised the manuscript for important intellectual content; Anne-Mette Haase, Jakob Poulsen, Karoline Knudsen, Per Borghammer and Gursharan Nandhra: Data acquisition, revised the manuscript for important intellectual content. Vincent Schlageter: Technical support, revised the manuscript for important intellectual content; Malcolm Birch, Mark Scott, Asbjørn Mohr Drewes and Klaus Krogh: Study concept and design, study supervision, interpretation of data, critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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**Tables**

**Table 1**

| | Median | Range | Percentiles | | | | |
|---|---|---|---|---|---|---|---|
| | | | **5%** | **25%** | **75%** | **90%** | **95%*** |
| **Gastric emptying time** (all) n=125 (hours) | 2.7 | 0.1-21.2 | 0.6 | 2.0 | 4.1 | 5.8 | 8.7* |
| Male (n= 56) | 2.9 | 0.1-8.4 | 0.6 | 2.1 | 4.0 | 5.1 | 5.8* |
| Female (n=69) | 2.6 | 0.1-21.2 | 0.6 | 2.0 | 4.1 | 6.1 | 16.8* |
| Age 40 years or less (n=65) | 2.7 | 0.1-21.2 | 0.6 | 1.9 | 4.6 | 5.8 | 15.6* |
| Age above 40 years (n=62) | 2.7 | 0.1-17.6 | 1.3 | 2.0 | 4.0 | 5.8 | 6.1* |
| **Frequency of gastric contractions** (per minute) | 3.1 | 2.6-3.8 | 2.8 | 2.9 | 3.2 | 3.4 | 3.5 |
| Male | 3.0 | 2.6-3.5 | 2.8 | 2.9 | 3.1 | 3.2 | 3.3 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Female | 3.2 | 2.7-3.8 | 2.8 | 3.0 | 3.3 | 3.4 | 3.5 |
| Age 40 years or less | 3.0 | 2.8-3.4 | 2.8 | 2.9 | 3.2 | 3.3 | 3.3 |
| Age above 40 years | 3.1 | 2.6-3.8 | 2.8 | 3.0 | 3.3 | 3.5 | 3.5 |
| **Rotation amplitude** (degrees ) | 35 | 4-85 | 15 | 26 | 47 | 58 | 65 |
| Male | 30 | 4-77 | 14 | 23 | 40 | 48 | 61 |
| Female | 40 | 14-85 | 21 | 27 | 53 | 62 | 69 |
| Age 40 years or less | 34 | 13-85 | 21 | 26 | 48 | 64 | 69 |
| Age above 40 years | 35 | 4-70 | 15 | 26 | 46 | 54 | 58 |
| **Position amplitude** (millimeters) | 11 | 6-31 | 7 | 9 | 14 | 16 | 18 |
| Male | 11 | 6-31 | 7 | 9 | 14 | 16 | 18 |
| Female | 11 | 7-26 | 8 | 9 | 13 | 16 | 18 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Age 40 years or less | 11 | 8-26 | 8 | 10 | 14 | 17 | 19 |
| Age above 40 years | 10 | 6-31 | 7 | 9 | 13 | 15 | 18 |

**Table 1.** Normative values for parameters of gastric motility assessed with the electromagnetic 3D-Transit capsule system. *The upper 95 percentile for gastric emptying includes recordings from subjects in whom the capsule had not passed the pylorus within the 6 hours after its ingestion with the standardized meal, and who were allowed ad libitum feeding hereafter.