Author’s response to reviews

Title: Gastric emptying and small intestinal transit time and motility assessed by a magnet tracking system

Authors:

Jonas Worsoe (jonas.worsoe@gmail.com)
Lotte Fynne (lfynne@hotmail.com)
Tine Gregersen (tine_gregersen@hotmail.com)
Vincent Schlageter (vincent.schlageter@motilis.com)
Lisbet A. Christensen (lisbchte@rm.dk)
Jens F. Dahlerup (jensdahl@rm.dk)
Nico J.M. Rijkhoff (nr@hst.aau.dk)
Søren Laurberg (SOERLAUR@rm.dk)
Klaus Krogh (klaukrog@rm.dk)

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Author’s response to reviews: see over
Aarhus September 5th. 2011

Dear

Tim Shipley, PhD
Executive Editor of BMC-series journals

On behalf of the co-writers and I, I wish to thank the reviewer for taking the time to assess our manuscript and comment on it. We have done our best to address the issues raised by the reviewers and by doing so we feel that the manuscript has improved. A authors’ contribution section is added. The manuscript has been subject to professional revision of the language by American Journal Experts (certificate attached). We hereby re-submit a revised version of the manuscript:

“Gastric transit and small intestinal transit time and motility assessed by a magnet tracking system.”

Please find below a systematic list addressing all questions raised by the reviewers.

Yours Sincerely,

Jonas Worsøe
Response to the reviewers:

Reviewer: Andreas Steingoetter

Reviewer’s report:

This is an interesting and well performed study. Unfortunately, the manuscript has many shortcomings with regard to definition of used terms, completeness, data presentation and analysis and reference literature.

- Major Compulsory Revisions

1

The reviewer does not agree with many definitions and nomenclatures regarding gastrointestinal physiology used in this manuscript. Gastric emptying, gastric emptying time, motility index, contraction amplitude have been wrongly used in the manuscript.

This methodology assessed gastric and intestinal transit rather than gastric emptying. The term gastric emptying should be confined to the emptying of meals and macronutrients, however in this study no meal was ingested together with the pill. Furthermore, the authors should also differentiate between solid emptying (with the solid having a nutrient content), or the emptying of an indigestible solid (see Discussion). Please use gastric transit time and gastric transit instead of gastric emptying.

The term motility index is given in the attached tables, however has never been defined or mentioned in the manuscript text. This term has been defined and established based on the manometry data (e.g. see Hansen MB Physiol Res 2002) and should not simply be overwritten or newly defined to avoid confusion and allow for consistent parameter interpretation in future studies. Moreover, this parameter does not add any additional information to the tables or presented data. Please omit this term or provide a different term.
The terms have been corrected as suggested. We omit the term motility index and use the term 2 hour mean velocity instead.

2

*Analysis was partly based on the detected contraction amplitude. It is unclear to the reviewer how this contraction amplitude was derived from the presented data.*

The local variations of position can be measured precisely, and is linked to the resolution of the MTS-1 system. The amplitude of small back-and-forth movements can be measured very accurately (e.g. 1mm/0.5°). It is the assumed that small intestinal contraction amplitude is reflected on the magnetic pill.

3

*How could the amplitude be separated from overlaying breathing movement?*

An adaptive algorithm is used to filter out the movements due to breathing; the reference signal is recorded by an external sensor (belt).

A key feature is that we do not filter out all the activity with frequencies close to the breathing frequency, but only the movements in phase with the breathing.

4

*No information on the applied statistical analysis methods is provided.*

The following paragraph has been added:

“*Statistics*

Numerical data are given as means and standard deviations and non-gaussian distributed data are given as medians and total range. Statistical significance was tested with Wilcoxon’s test (non-parametric test for paired data), and the level of significance was set at 0.05.”

5/6

*MRI has been proven to a valid tool for the noninvasive assessment of gastrointestinal function. Recently, fluorine MRI has been shown to be feasible for real time tracking of an ingested capsule and the assessment of small intestinal motility patterns (Hahn T. et al Magn Reson Med. 2011 Mar 4). The*
reviewer is highly surprised about no citation or mentioning of this versatile imaging technique allowing concurrent determination of the underlying anatomical information in the manuscript.

Magnetic Marker Monitoring has been mentioned in the introduction, however no reference is provided to the most recent publication by Goodmann K et al. 2010 (Eur J Pharm Biopharm. 2010 Jan;74(1):84-92) showing the potential of this technique for the assessment intestinal motility. As general request, an update and optimization of the cited literature is of need.

Regarding a mentioning of MRI techniques for investigation of motility, the following is added: “Magnetic resonance imaging have also been used to measure gastric and small intestinal motility [(2303 Schwizer,W. 2006; 2304 Froehlich,J.M. 2005)]. MRI has also been used to track the position of fluorine labeled capsules giving information about small intestinal motility patterns and this can be combined with anatomical data [(2301 Hahn,T. 2011)].”

The literature is updated

7

Most of the presented figures have poor quality (especially Figure 1 and 3). Figure 3 is not readable.

Fig. 3 has been improved and figure 1 appearing in the first submission has been discarded.

8

Figure legend 4B. Regarding the statement “Most distance through the small intestine is covered during the period just after pyloric passage and during the period just before ileocecal passage. These two periods, separated by approximately 90 minutes, likely reflect phase III of the MMC.”

The conclusion of these observations should depend on the ingestion time point of the used meals, i.e. the study arm. It is unclear if this data is representative for all study arms, i.e. also for study arm 3, where the meal was ingested directly after pyloric passage?
Comments on MMC with respect to the meal.

The following is added: “It was anticipated that MTS-1 could be used for identification of phase III in the migrating motor complexes (MMC) and in the recordings during fasting we saw several examples of suggested MMC phase III (Fig. 4B). However, no statistical difference in the distribution of fast movements which could represent phase III MMC was seen when comparing fasting and postprandial motility data.”

9

The second last paragraph in the Discussion tries to highlight the underlying inaccuracy of the MTS-1 system. It would be of interest to get a rough idea on the accuracy of the derived parameters by the MTS-1 system considering the mentioned inaccuracy.

This sentence is added: “The absolute accuracy is approximately 1-2 cm, which is sufficient for anatomical localization. The amplitude of small back and forth movements can be measured more accurately (1-2 mm) as it is relying on the resolution of the MTS-1.”

Please make sure to provide correct figure numbers and figure captions.

- Minor Essential Revisions

10

I very much appreciate the presentation of individual data in the tables. However, the authors should think about a more compact representation of the data. Namely, to skip depend parameters like progression and motility index, therefore including individual frequency and velocity. Showing the data agreement using Bland-Altman plots may be useful.

As suggested individual mean contraction frequencies have been added. Though a Bland Altman plot often gives a good presentation, we are not sure that it would really contribute much information to our relative limited data.

11

Page 9 please check wording in first paragraph

The last sentence is changed: “Likewise in the postprandial state, 60 % (range: 42-74%) of the distance occurred with very fast movements in median 3% (range: 2-7%) of the time.”
Please also provide the density of the applied magnetic pill, the PillCam and the magnet-PillCam

P9 1. Paragraph:

Additional data given: “Subjects ingested a small magnetic pill (dimensions: 6x15 mm, weight: 1.62 g, density: 1.8 g cm⁻³, magnetic moment 0.2 Am²),…”

12

Figure 4 should be changed to a 3D surface plot for better visualization and understanding.

Different representations have been tried, including 3D plots. Finally the best visualization was obtained with the classical 2D representation.

13

Could the authors please comment on the use of two different meals for study arms two and three?

Use of different meals: In study arm two, the meal was a Danish standard breakfast served in the morning, and in study arm three the meal was given after lunch and a sandwich was served. Motility influenced by two different meals are not compared as mentioned in the protocol section.

- Discretionary Revisions

14

Page 12. The last sentence of paragraph two includes 8 references but adds no additional information to the first sentence of this paragraph.

We agree and the sentence has been deleted
- Discretionary Revisions

15

Was the correction of the respiratory motion always accurate and successful?
The time window for StFT was always shifted by 10 samples, i.e. by 1 second correct?
Time window
Correction of breathing was always successful.

Reviewer: Werner Weitschies
Reviewer’s report:
It is an interesting idea to compare pill cam transit data with magnetic marker monitoring data. However the scientific quality of the manuscript needs to be improved.

Major Comments:

1) How can the authors prove that the magnets that were ingested before the meal passed the small intestine with the meal? At least the gastric emptying times and the dimensions of the swallowed magnet have to be presented and carefully discussed (see minor comments). In the submitted version this essential and critical point is completely ignored.

1: It is correct that we cannot prove that the magnet passed the small intestine together with the meal. However our purpose was not to track the bolus: in the first setting the meal should not interfere with the comparison between the Magnet and the PillCam. It would have blurred the PillCam data if the meal was given simultaneously. Regarding comparison between the second and the third setting, the meal was given after pyloric passage of the magnet only to stimulate a postprandial pattern. We did not wish to “follow” the bolus through the small intestine. Therefore data on gastric emptying of the meal was not collected. The paragraph has been changed in the discussion: “Compared to scintigraphy, MTS-1 has no risk of radiation exposure; this is especially important if children are investigated. Scintigraphy, however, allows determination of gastric emptying for both solids and liquids (i.e. meals and macronutrients), whereas magnetic tracking only determines transit of the magnetic pill, since a small solid will leave the stomach with a phase III MMC {{2244 Cassilly,D. 2008}}. In this study the meal was only given to induce the postprandial small intestinal motility pattern.”
More information have been added: “Subjects ingested a small magnetic pill (dimensions: 6x15 mm, weight: 1.62 g, density: 1.8 g cm$^{-3}$, magnetic moment 0.2 Am$^2$), which was tracked by a matrix of 4x4 magnetic field sensors separated by 5 cm and placed over the abdomen (Fig. 1).”

2) What is the scientific basis for the three motility categories chosen: Fast movements, slow movements, very slow movements?

2: The following sentence is added: “An initial analysis of velocity histograms identified a trimodal distribution of velocities and the cut offs were made to separate the three types of movements velocities”

3) How can a progression in cm be calculated when the subjects were not permanently measured?

4) How can the authors be sure that the calculated progression is movement of the magnet in the intestine and not movement of the intestines with the pill inside

3 and 4: That is correct. We have commented on it in the discussion. “A problem with the MTS-1 is that movement of the small intestine inside the abdomen affects the measurements. This can only be overcome with simultaneous collection of anatomical data (computer tomography), not included in this protocol. A shortcoming of our protocol was that short breaks were allowed during the investigation, potentially influencing measurements of distance and calculation of total distance travelled in the small intestine. However, using the positioning of the sensor with respect to anatomical landmarks indicated that this error was very little.”

5) Was one baseline measurement used for the complete recording?

5: The laboratory where experiments were conducted was without any movable ferromagnetic objects. A calibration of the sensors and a “baseline measurement” without introduction of the magnetic pill was made before all experiments to check for any disturbance that could affect measurements.

7) The included data are uncomplete. The tables are not supplementary material but essential (they are also cited in the manuscript).

7: Tables are included.
8) A description of the magnet is completely missing (dimensions, material, magnetic moment) but essential (see major comments).

8: Further description of the magnetic pill is added, see above.

9) What data are presented in Table 1? Fasting or fed conditions? All transit data need be listed.

9: The data presented in table 1 is obtained under similar conditions: the magnet or magnet-PillCam unit was ingested during fast and a meal was served after four hours. Small intestinal transit data were not available in all investigations if ileocecal passage did not occur within the 8-hour protocol.

Reviewer: Phil Dinning

Reviewer’s report:

Comments to Authors.

This paper represents another stage in the use and validation of the magnetic pill. In this instance it has been validated against “Pillcam” for the measurement of gastric emptying and small bowel transit. Specific comments and questions are listed below in the sections required by the journal:

Major Compulsory Revisions

1. On page 3 in the opening paragraph of the introduction you state that manometry has “unreliable measurement in non-sphincteric regions”. What is your justification for this comment? Do you have any evidence to suggest that it is unreliable?

Theoretically measurements of contractions in non-sphincteric regions will be a mix of intraluminal pressure (water or air) and muscle contraction, whereas measurements in sphincteric regions are a good indication of muscle force.

2. In the data analysis section there are a host of techniques described. I would like some information on how they were validated. For example how did you decide on the definitions for the frequency data? Has the fast Fourier transform
**analysis been validated? What does weight=0 and weight=1 mean?**

The power spectral density is estimated by and FFT on a short segment of data (3min) using a Hamming window. This window is then shift with step of 1s to analyze all the data, leading to a time-frequency map. At each instant, peaks detection is applied to select main present frequencies. Then only steady values are considered (extreme values are not considered based on Bayesian algorithms). This approach is classical in the study of time-frequency maps. Weight 0 and 1: This means that some frequency measured have not been taken into account (weight 0). The criteria is the following: when there is no progression of the capsule (weight 1), the real contraction frequency (electrical slow waves frequency) is measured; otherwise (weight 0), at each contraction the capsule is at a different place, thus the frequency seen is also function of the velocity of progression of the capsule along the GIT (Doppler effect). We have changed the manuscript: “A standard approach for analysis of time-frequency maps was used. The power spectral density is estimated by and fast fourier transform on a short segment of data. A time frame of 3 min was used, and a Hamming window was applied. Calculations for the sliding window were conducted every 10 samples giving a time-frequency map. At each instant, peak detection is applied to select main present frequencies. Only steady values were considered and extreme values were omitted based on Bayesian algorithms.”

3. **In the results the frequency data has been presented collectively for the entire small bowel. Did frequencies differ between the proximal and distal small bowel?**

**What was the frequency of contraction in the ascending colon or caecum? You must have those data if you can confirm the ileocaecal transit. Is there a significant drop in the frequency of contraction between the distal ileum and the proximal colon.**

Small intestinal contraction frequency decreased along the small intestine. This is described in fig. 7. With these data it is difficult to report colonic motility. We observed that the small intestinal contraction pattern ceased, and the magnet remained immobile in the cecum. Our data from the colon cannot be used for analysis since they were incomplete.

4. **It is mentioned in both the introduction and discussion that Pillcam may effect contractions and transit? No references are provided in either instance. What evidence do you have for this statement?**

It would appear likely to us that the size and shape could influence GI function. It is supported by Baek et al. who investigated capsules of different shape and dimensions and found that frictional resistance characteristic depended upon these parameters.

5. **There is mention in the discussion that it was anticipated that the MTS-1 would be able to measure MMC phase III activity. Why was this not mentioned in the**
Introduction as a potential aim?

Addition to the introduction: “Furthermore, motility patterns recorded with MTS-1 in the fasting state and in the postprandial state were compared for identification of migrating motor complex phase III during fast”.

6. Overall, while the technique correlates well with Pillcam, the paper fails to provide any clear reason for why this technique would provide clinical or research benefit over any of the other “transit’ pills. As pointed out in the paper SmartPill already measures transit in the stomach, small bowel and colon and it is completely ambulatory. The magnet pill requires someone to sit still for up to 8 hrs. It is mentioned in the discussion that MTS-1 can define segmental colonic transit times but that isn’t the point of this paper. Can you detail any advantage in using your technique over Smartpill? One of the real benefits seems to be the ability to track the exact location of the pill.

Measurements of contraction patterns either with manometry (SmartPill) or movement of a small magnet (MTS) are both proxy measurements of what is really investigated. With MTS-1 it is possible exactly to locate the magnetic pill, and therefore antegrade and retrograde movements can be separated in immobile bowel segments (colon). The Smartpill does not give information about the exact position and cannot separate antegrade and or retrograde movements. As you point out this paper does not investigate colonic movements, so our goal was simply to validate the gastric transit and small intestinal transit measured with MTS-1.

Minor Essential Revisions

1. There are 7 figs and only 5 figure legends.

The figures have been renumbered with matching legends