ORIGINAL RESEARCH

Gastrointestinal motility during sleep assessed by tracking of telemetric capsules combined with polysomnography – a pilot study

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Abstract: Studies of gastrointestinal function during sleep are hampered by lack of applicable techniques. Recent development of a novel ambulatory telemetric capsule system, which can be used in conjunction with polysomnography, offers a solution to this problem. The 3D-Transit system consists of ingestible electromagnetic capsules traceable through a portable extracorporeal receiver while traversing the gut. During sleep monitored by polysomnography, gastrointestinal motility was concurrently investigated using 3D-Transit in nine healthy subjects. Overall, the amplitude of gastric contractions decreased with depth of sleep (light sleep, N2 versus deep sleep, N3; $P<0.05$). Progression through the small intestine did not change with depth of sleep (Kruskal–Wallis probability =0.1), and there was no association between nocturnal awakenings or arousals and the occurrence of colonic or small intestinal propagating movements. Basal colonic activity was suppressed during both deep sleep ($P<0.05$) and light sleep ($P<0.05$) when compared with nocturnal wake periods. In conclusion, the novel ambulatory 3D-Transit system combined with polysomnography allows minimally invasive and completely ambulatory investigation of associations between sleep patterns and gastrointestinal motility.

Keywords: colonic movement, gastric contractions, sleep assessment, ingestible capsule, circadian motility, sleep stage

Introduction

Sleep has a profound inhibitory effect on gastrointestinal (GI) motility,[1] with suppression of both gastric and colonic motilities clearly demonstrated in several studies.[2–5] However, the lack of applicable methods and the relative inaccessibility of the GI tract have made routine investigation of whole gut motility during sleep very difficult. Nevertheless, by means of a novel telemetric capsule system[6] – 3D-Transit system (Motilis Medica SA, Neuchatel, Switzerland) – it is now possible to investigate whole gut circadian motility. Simultaneous recordings from up to three capsules, positioned in various gut segments, make this feasible. In this pilot study, we hypothesize that by combining polysomnography and 3D-Transit, it is possible to investigate the relationship between regional GI motility patterns and sleep stages in a single examination in healthy subjects.

Subjects and methods

Sixteen healthy subjects (nine females and seven males; median age, 34 years; range, 24–52), with no history or current symptoms of GI, psychological, or sleep disorders, were included after providing informed written consent. In addition, previous major

abdominal surgery, medication affecting GI motility, pregnancy, and breast feeding were exclusion criteria.

Detailed information regarding GI motility profiles of these volunteers has previously been published.[6]

The study was conducted according to the Declaration of Helsinki and approved by the local ethics committee and the Danish Medicines Agency (reference numbers: M-20100267 and 2011123594).

Methods

3D-Transit

The 3D-Transit system is a novel, ambulatory system providing whole gut transit times and various motility patterns.[6] The system includes wireless telemetric capsules for ingestion, an extracorporeal receiver, and 3D-Transit software. The latter is for data analysis and real-time display (Figure 1B). The subjects wear the receiver in an abdominal belt throughout the study period (Figure 1A). Each capsule (diameter, 8 mm; length, 21 mm; density, 1.6 g/cm^3) incorporates a miniature battery (allowing ~60 hours recording) and an electromagnet. Following activation, the electromagnetic field continuously emitted by each capsule while traversing the gut is converted into space–time coordinates (x; y; z; Φ; θ) using the analysis software after download. The coordinates x; y; z express the distance (frontal, transversal, and sagittal planes) and the Φ; θ express the angular orientation (rotations) of each capsule with respect to the receiver (Figure 1B). Thus, changes in position, velocity, and orientation of the capsules reflect the contractile activity and progression dynamics. In order to determine capsule location, the system exploits the fact that the GI contraction frequency varies throughout the gut. The rotations of the capsule mirror the contractions of the gut. Hence, changes in the contraction frequency displayed in the raw data will, together with a matching localization of the capsule viewed in the 2D display (Figure 1B, inset), determine the shift from one GI segment to the other.

Artifacts due to breathing and posture changes are recorded by a thoracic belt and an accelerometer (Figure 1A).

The 3D-Transit system has previously been validated for the measurement of gastric emptying, small bowel, and whole gut transit.[6,7] Further details on the technique and equipment have recently been published.[6]

Polysomnography

Sleep assessment was achieved by means of a standard technique.[8,9] Polysomnography (Natus Xltec Trex ambulatory polysomnography, Type II portable device) was performed as an overnight multihour study with six electroencephalography (EEG) channels, electrooculography, electrocardiography, and chin electromyography for registration of sleep states. Airflow, oxygen saturation, respiratory effort, and body movements were not assessed since the aim of the study was not to quantify pathology.

Protocol

Preceded by an overnight fast, 16 subjects ingested two capsules (C1 at 08:00 and C2 at 18:30).

Meals were standardized and consumed at set times. The last meal was ingested at 18:30.

After detailed instructions from an experienced neurophysiology assistant, application of the electrodes was done just before bedtime (approximately 23:00) by a trained health care worker or by the subjects themselves. Placement was done according to the international 10–20 system and accepted guidelines.[9]
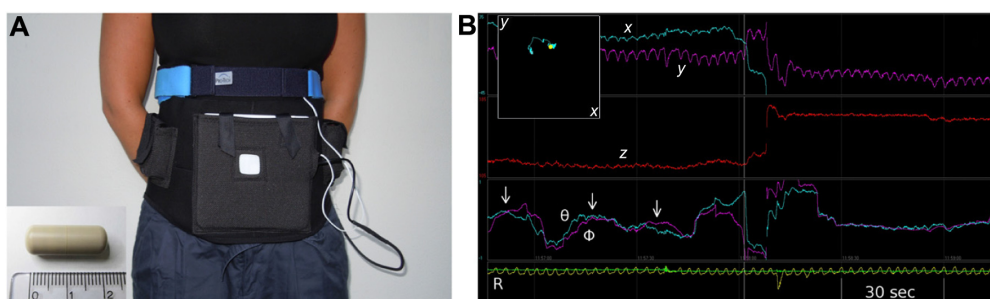

Figure 1 The 3D-Transit system

Notes: (**A**) Capsule containing an electromagnet and a battery (inset). The abdominal belt contains the 3D-Transit receiver and is worn by the subjects throughout the examination. Thoracic belt (blue) and an accelerometer inside the detector record artifacts owing to breathing and posture changes. The ruler is measuring in centimeters. (**B**) 3D-Transit visualization and analysis software. Changes in position and orientation of the capsules with respect to the receiver reflect gastrointestinal contractile activity and progression. Coordinates x, y, and z display capsule movements in a frontal, sagittal, and transversal plane, respectively. The Φ,θ coordinates describe capsule rotation, reflecting the contraction frequency (arrows mark individual contractions). The inset shows the actual movement of the capsule, which corresponds to the changes in the coordinates. The x-axis represents time.

Abbreviations: R, respiration; sec, seconds.

Data analysis

Sleep recordings (Sleep Works Natus XLTEK, Oakville, ON, Canada) were manually scored using 30-second epochs and staged as R (rapid eye movement [REM] sleep), N1 (drowsiness), N2 (light sleep), N3 (deep sleep/slow wave sleep), or W (wake) according to the American Academy of Sleep Medicine criteria.[9] Arousals, defined as changes in EEG frequency >3 seconds,[9] were marked. EEG data artifacts were defined as technical artifacts with 50 Hz noise due to poor EEG electrode placement with high impedance.

Data from the polysomnography and the 3D-Transit system were synchronized based on movement artifacts in the 3D-Transit recordings and the simultaneously increased heart rate registered by the electrocardiography electrodes comprised in the polysomnography (Figure 2).

Running power spectral analysis was done to assess mean gastric contraction frequency and amplitude for each 1-minute period (MATLAB software). Speed of progression in the small intestine was also calculated for each 1-minute period. Colonic and small intestinal propagating movements (PMs) (≥3 cm anterograde displacement of the capsule at ≥1.5 cm/min) and basal colonic activity (mean standard deviation of the position of capsules during displacement of <3 cm) were assessed. For each subject, the aforementioned parameters were analyzed for every sleep stage and nocturnal wake periods.

All analyses were performed using STATA Version 12 (StataCorp LP, College Station, TX, USA). Data related to all study end points were nonparametric and therefore presented as median and range. Kruskal–Wallis test was performed to test whether the mean ranks were the same in the different groups. Difference between groups was tested for statistical significance with Wilcoxon rank-sum test (nonparametric test for unpaired data). Level of statistical significance was set at 0.05.

Results

In six of the 16 experiments (38%), missing sleep data precluded interpretation. All electrodes were correctly located on the scalp and face, but poor contact between the electrodes and the skin emerged during night, leading to artifacts. In another study, 3D-Transit failure prevented synchronization. In the remaining nine examinations, median total sleep time was 6.6 hours (range, 5.1–7.5 hours), with a median arousal index of 7.6 per hour sleep (range, 5.0–16.9 arousals/hr) and a median sleep efficiency (total sleep time/time in bed ×100) of 79% (range, 37%–96%). Median percentage of total sleep time was 4.1% in stage N1, 51.5% in stage N2, 16.7% in stage N3, and 26.4% in REM stage. Further data on sleep structure are shown in Table 1.

During sleep, C1 was located in the colon in all subjects. In four subjects, C2 was initially located in the stomach and moved to the small intestine. In five subjects, C2 was located in the distal part of the small intestine crossing over to the cecum during sleep.

Gastric contractions

As depicted in Table 2, gastric contraction frequency was significantly higher during nocturnal wake periods than during N2 and REM sleep. Compared with wake periods,
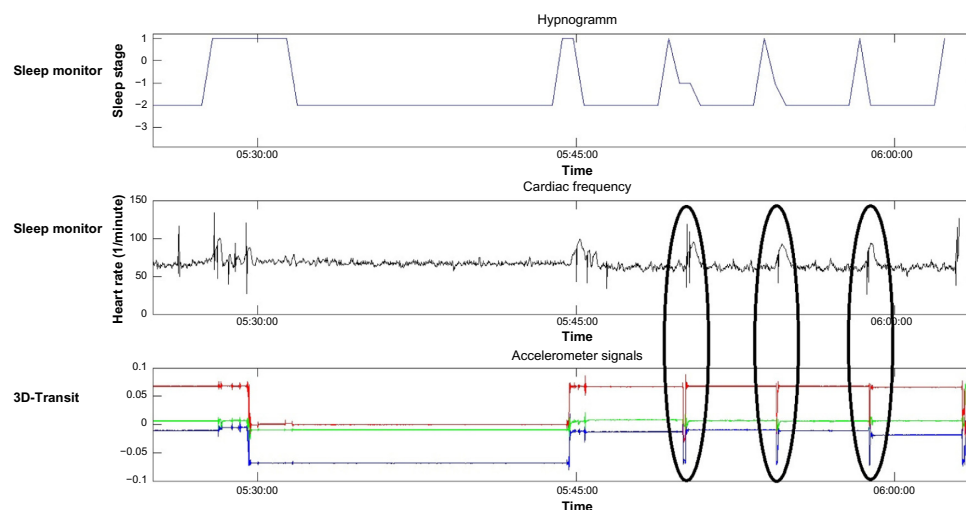

Figure 2 Data synchronization.
Notes: Posture changes obtained through the accelerometer inside the 3D-Transit receiver (red, green, and blue lines) are associated with an increased heart rate achieved through the portable sleep monitor. This way data were easily time-linked (ovals).

Table I Sleep distribution and efficiency

ID	N1 (min)	N1 (%)	N2 (min)	N2 (%)	N3 (min)	N3 (%)	REM (min)	REM (%)	SE (%)	WASO (min)	TST (min)	Arousals	Arousal index
1	13.5	3.4	208	52.3	83	20.9	93	23.4	37.7	84	397.5	50	7.5
2	14	3.1	249.5	55.6	66.5	14.8	118.5	26.4	96	14.5	448.5	37	5.0
3	15	4.1	200	54.7	51.5	14.1	99	27.1	89.4	12.5	365.5	34	5.6
4	11.5	3.7	156.5	50.8	67.5	21.9	72.5	23.5	78.6	7	308	87	16.9
5	17.5	4.8	173.5	47.5	55	15	119.5	32.7	71.1	29	365.5	51	8.4
6	22	5.4	189	46.8	88	21.8	105	26	39	27	404	62	9.2
7	15	5	176.5	58.5	31.5	10.4	78.5	26	67.5	38.5	301.5	73	14.5
8	12.5	3	205.5	49.5	77.5	18.7	119.5	28.8	95.7	16.5	415	39	5.6
9	15	4.4	175.5	51.5	56.5	16.7	93	27.4	90.5	26	339	43	7.6
Median	15	4.1	189	51.5	66.5	16.7	99	26.4	78.6	26	365.5	50	8.2
Range	11.5–15	3–5.4	156.5–249.5	46.0–58.5	31.5–88	10.4–21.9	72.5–119.5	23.4–32.7	37.7–96	7–84	301.5–448.5	34–87	5.0–16.9

Abbreviations: N1, drowsiness; min, minutes; N2, light sleep; N3, slow wave (deep) sleep; REM, rapid eye movement; SE, sleep efficiency (total sleep time/time in bed ×100); WASO, wake after sleep onset; TST, total sleep time; Arousal index, arousals per hour sleep; ID, identification.

the amplitude of contractions decreased significantly during sleep. Furthermore, the amplitude during N3 sleep was significantly lower than during the other sleep stages.

Progression through the GI tract

Progression through the small intestine did not change with depth of sleep when compared with wake periods (Kruskal–Wallis probability >0.05). Among 136 PMs (119 in the small intestine and 21 in the colon), 12 (9%) occurred within 30 seconds after an arousal, 10 (7%) during wake periods, and 114 (84%) during stable sleep.

It is evident from Table 2 that basal colonic activity decreased significantly across sleep stages. Basal colonic activity was also significantly less during N3 and N2 sleep compared with wake periods.

Discussion

This pilot study has shown that simultaneous recording of whole gut GI motility and sleep states is technically possible. This holds great potential for future clinical studies exploring the relationship between sleep and GI function. By way of example, this is highly relevant in the case of inflammatory bowel disease, where a relationship between subjective sleep disturbances and disease relapse[10] and subclinical inflammation appears.[11–15] The method may also be useful in Parkinson's disease and irritable bowel syndrome where both GI dysmotility and sleep disorders may appear.[16,17]

Our results regarding sleep structure are consistent with those found in a recent population-based study.[18] However, sleep efficiency tended to be lower compared with other "first night" polysomnography studies, with two of the subjects having very low sleep efficiency. A more pronounced "first night effect" due to both the polysomnography and the 3D-Transit system may have influenced the result.[19] However, we believe that a full ambulatory setting, as provided by the 3D-Transit system, facilitates experiments in the home environment of the subjects, which comes closer to normal physiologic conditions than previous methods for mapping GI function employing manometry catheters or nasogastric tubes.[2,20] Two consecutive nights of polysomnographic and 3D-Transit recordings may reduce the "first night effect".[19]

By timing capsule ingestion and meal times, it is possible to "tailor" the position of the capsules within the GI regions of interest by the time of sleep onset.[6] In a previous pilot study among 20 healthy volunteers, the 3D-Transit system was found to be safe. 3D-Transit validation studies are limited by small sample sizes, and larger studies including studies on

Table 2 Gastric contractions and basal colonic activity during sleep and nocturnal awakenings

Sleep stage	Gastric contractions (contractions per min) (median; range)	P-value	Gastric contractions (amplitude, mm) (median; range)	P-value	Colonic activity (mean SD, mm) (median; range)	P-value
N1	2.8 (2.4–3.3)	NS*	2.5 (1.4–8.6)	0.03* 0.05**	1.40 (0.5–10.4)	NS* <0.0001**
N2	2.6 (2.2–3.8)	<0.0001*	2.7 (0.8–9.6)	0.0006* <0.0001**	1.15 (0.3–14.5)	<0.0001* <0.0001**
N3	2.8 (2.2–3.5)	NS*	2.0 (0.2–8.5)	<0.001*	0.88 (0.3–12.1)	<0.0001*
REM	2.6 (2.4–3.1)	<0.0001*	2.7 (1.2–5.5)	<0.0001* 0.009**	1.59 (0.5–19.2)	NS* <0.0001**
Wake	2.9 (2.2–3.4)	–	5.1 (1.3–9.7)	–	1.69 (0.5–13.5)	–

Notes: *Sleep stage compared with nocturnal wake period; **N3 compared with other sleep stages.
Abbreviations: min, minutes; N1, drowsiness; NS, not significant; N2, light sleep; N3, slow wave (deep) sleep; REM, rapid eye movement; Wake, wake periods.

different groups are needed to support our previous data. The system is, however, minimally invasive, and there is no need for bowel preparation.[6] The main concern using 3D-Transit is the risk of capsule retention and thus, potentially, GI obstruction. Previous studies with capsule endoscopy have found a low risk of retention even among patients suspected of having small intestinal disease (1.4%).[21] The 3D-Transit capsule is smaller than the one used for capsule endoscopy, and we therefore argue that the risk of retention using the present device will be even lower.

Polysomnography is usually carried out in a sleep laboratory, but unattended monitoring as demonstrated here is possible.[22] The main limitation of this study was exclusion of data from six subjects (38%) due to artifacts caused by poor contact between the EEG electrodes and the scalp. Nevertheless, other studies using unattended polysomnography have recorded similar dropout rates.[23] However, correct placement of the electrodes with impedance measurement by a sleep technologist should markedly reduce data loss in the future.

The small number of subjects recruited to the present pilot study does not allow us to draw firm conclusions about sleep and GI physiology. However, in accordance with a previous study using electrogastrography, we found that the amplitude of gastric contractions decreased with the depth of sleep.[4] Yet, gastric contraction frequency did not exceed 2–4 cpm at any point in contrast to the findings of Elsenbruch et al.[4]

Also, in contrast to earlier studies employing small intestinal manometry, we found no change in the progression through the small intestine comparing sleep and nocturnal wake periods.[20,24] This might be due to the short duration of the nocturnal wake periods. Diurnal recordings for comparison might be better for evaluating this specific end point. Future studies evaluating circadian motility patterns are required to confirm this. Also, further validation steps are

required to better assess the migrating motor complex and the influence of sleep.[20]

Colonic motility has been shown to be generally suppressed during sleep,[3,25,26] and we found increasing suppression of basal colonic activity with increasing depth of sleep and when compared to nocturnal wakening.

Contradictory results regarding the association between PMs and arousals or wake periods have previously been published.[2,3] We found no association between these phenomena in this study. This could be a type II error, and larger future studies are required.

Conclusion
In conclusion, polysomnography in combination with 3D-Transit holds promise for ambulatory assessment of GI function during sleep.

Author contributions
All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work. AMH contributed to the study design, data interpretation and analysis, preparation of the manuscript, and critical review. She is the guarantor of the article. SF contributed to the data analysis and technical review. MO contributed to the study design, data interpretation and analysis, and critical review. SMS contributed to critical review. VS contributed to technical support and technical review. KK contributed to the study design, data interpretation, preparation of manuscript, and critical review. All authors read and approved the final paper.

Disclosure
V Schlageter is a co-owner of Motilis Medica SA and a technical partner in terms of improving the system prototype. The authors report no other conflicts of interest in this work.

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