Measurement of oro-caecal transit time by magnetic resonance imaging

Savarino, Edoardo; Savarino, Vincenzo; Fox, Mark; Di Leo, Giovanni; Furnari, Manuele; Marabotto, Elisa; Gemignani, Lorenzo; Bruzzone, Luca; Moscatelli, Alessandro; De Cassan, Chiara; Sardanelli, Francesco; Sconfienza, Luca Maria

Abstract: OBJECTIVES To assess prospectively the agreement of orocaecal transit time (OCTT) measurements by lactulose hydrogen breath test (LHBT) and magnetic resonance imaging (MRI) in healthy subjects. METHODS Volunteers underwent abdominal 1.5-T MRI using axial and coronal single-shot fast-spin-echo T2-weighted sequences, having fasted and after lactulose ingestion (10 g/125 mL). Imaging and H2 excretion gas-chromatography were performed concurrently every 15 min up to 180 min. MR images were analyzed using semiautomatic segmentation to calculate small bowel gas volume (SBGV) and visually to detect bolus arrival in the caecum. Agreement between MRI- and LHBT-OCTT was assessed. RESULTS Twenty-eight subjects (17 men/11 women; mean age ± standard deviation 30 ± 8 years) were evaluated. Two H2 non-producers on LHBT were excluded. OCTT measured by MRI and LHBT was concordant in 18/26 (69 %) subjects (excellent agreement, k = 0.924). Median SBGV was 49.0 mL (interquartile interval 44.1 - 51.6 mL). In 8/26 (31 %) subjects, MRI showed that the lactulose bolus was in the terminal ileum and not the caecum when H2E increased on LHBT. Median OCTT measured by MRI was significantly longer than OCTT measured by LHBT [135 min (120 - 150 min) vs. 127.5 min (105 - 150 min); p = 0.008]. Above baseline levels, correlation between [H2] and SBGV was significant (r = 0.964; p < 0.001). CONCLUSIONS MRI provides valid measurements of OCTT and gas production in the small bowel. KEY POINTS • MRI is a valid technique to measure OCTT. • Excellent agreement between MRI and LHBT was found. • Measuring gas production using MRI may provide evidence of small bowel fermentation.

DOI: https://doi.org/10.1007/s00330-014-3575-1

Measurement of Oro-Caecal Transit Time by Magnetic Resonance Imaging

Abstract

Objectives: To prospectively assess the agreement of oro-caecal transit time (OCTT) measurements by lactulose hydrogen breath test (LHBT) and magnetic resonance imaging (MRI) in healthy subjects.

Methods: Volunteers underwent abdominal 1.5-T MRI using axial and coronal single-shot fast-spin-echo T2-weighted sequences in the fasted condition and after lactulose ingestion (10g/125mL). Imaging and H_2 excretion gas-cromatography were performed concurrently every 15 minutes up to 180 minutes. MR images were analyzed using semiautomatic segmentation to calculate small bowel gas volume (SBGV) and visually to detect bolus arrival in the cecum. Agreement between MRI- and LHBT-OCTT was assessed.

Results: Twenty-eight subjects (17 males/11 females;mean age±standard deviation 30±8 years) were evaluated. Two H_2 non-producers on LHBT were excluded. OCTT measured by MRI and LHBT was concordant in 18/26 (69%) subjects (excellent agreement,k=0.924). Median SBGV was 49.0 mL (interquartile interval 44.1-51.6 mL). In 8/26 (31%) subjects, MRI showed the lactulose bolus was in the terminal ileum and not the cecum when H_2E increased on LHBT. Thus, median OCTT measured by MRI was significantly longer than that measured by LHBT [135min(120-150 min)vs.127.5(105-150min);p=0.008]. Above baseline levels, correlation between [H_2] and SBGV was significant (r=0.964;p<0.001).

Conclusions: MRI provides valid measurements of OCTT and gas production in the small bowel.

Keypoints:

- *MRI is a valid technique to measure OCTT.*
- *Excellent agreement between MRI and LHBT was found.*
- *Measuring gas production using MRI may provide evidence of small bowel fermentation.*

Keywords: magnetic resonance imaging; small bowel; lactulose hydrogen breath test; oro-caecal

transit time; irritable bowel syndrome

Introduction

Recent clinical investigations have documented abnormal GI function and oro-cecal transit time (OCTT) in many patients with "functional" GI diseases (1-3) such as irritable bowel syndrome (IBS) (4-6). Indeed, IBS studies have revealed enteric dysmotility that may cause symptoms either directly as a result of altered OCTT or as a consequence of impaired clearance and overgrowth of colonic bacteria in the small bowel (7). However routine clinical investigations of GI function are not, at present, able to identify the underlying causes of symptoms and disease (8). Moreover, the evaluation of OCTT is controversial due to important problems of the available techniques, such as lactulose hydrogen breath testing (LHBT), sequential scintigraphy with isotope-marked meals, or by magnetic resonance imaging (MRI) (9-17).

Another important condition that is frequently linked to IBS and in which abnormal gas production and metabolism are implicated is small intestine bacterial overgrowth (SIBO), characterized by fermentation of substrates in the small bowel due to bacterial contamination from the caecum (18-19). Patients with SIBO complain of similar symptoms to IBS and a proportion of IBS patients have notable symptoms relief after antibiotic therapy (20,21). At present, the diagnosis of SIBO is challenging. Aspiration and culture of jejunal aspirates represent the reference standard, but this method is invasive, can be affected by contamination during intubation, and may be falsely negative as a result of a patchy bacterial distribution within the gut (22). In this setting, LHBT has been used to detect abnormal hydrogen excretion (H_2E) due to altered bacterial distribution in the GI tract (23-24); recent research demonstrated that this methodology is accurate to detect OCCT, but has suboptimal sensitivity and specificity for SIBO detection (24,25).

On this basis, we performed a prospective, comparative diagnostic study to assess the agreement of OCTT measurements by LHBT and MRI in healthy subjects. We also compared small bowel gas volume (SBGV) measured using MRI to the increase in H_2 excretion on LHBT to assess whether imaging can detect the presence of SIBO.

Materials and Methods

Study Population

The study protocol was approved by the local Ethics Committee and all participants gave written informed consent.

Asymptomatic healthy subjects were prospectively screened to undergo LHBT and MRI evaluation of the small bowel. Exclusion criteria were: co-morbidity requiring active treatment (e.g. use of laxative, antispasmodics, drugs that affect gastric emptying, narcotics or sedatives, antibiotics, or anti-secretory drugs), previous abdominal surgery, contraindications to MRI examination and reported adverse events to lactulose.

Study Protocol

Before LHBT and MRI assessment, each subject underwent physical and clinical evaluation (including stool examination) and a detailed medical history. Volunteers completed a previously validated structured questionnaire taking into account 11 GI symptoms, each carrying a score from 0 (no symptoms) to 3 (severe), as previously described (26). A global symptomatic score (GSS), calculated as the sum of all symptom scores, was assigned to each subject (maximum score=33).

Thereafter, subjects were requested to eat a light dinner the day preceding the examination (21) and to fast until the examination. They were also asked to refrain from smoking and from physical activity the day before the test.

MRI

MRI was performed using a 1.5-T MR system (Signa Excite, General Electric, Medical Systems, Milwaukee, IL) equipped with a surface phased-array coil (TorsoPA, General Electrics Medical Systems, Milwaukee, IL). Axial and coronal T2-weighted breath-hold sequences (single-shot fast spin-echo, TE=90 ms, TR= 1147 ms, field of view=380×380 mm^2, slice thickness=7 mm, two slabs of 20 slices, acquisition time 22 s per slab) were acquired. First acquisition served as baseline.

Subjects with baseline abnormal amount of fluids in the stomach stopped the examination and repeated the test after a longer period of fasting (i.e. at least 12-15 hours). After the baseline acquisition, subjects were asked to use 30 mL of chlorexidine-based antiseptic oral solution (chlorexidine gluconate 0.12%, Oral-B, Procter & Gamble, Pomezia, Italy) to eliminate the possibility of oropharyngeal bacterial fermentation and, after providing a baseline H_2 breath sample, were orally administered 10 g of lactulose (15 g of Lattulac® 66.7g/100 mL, Sofar, Milan, Italy) diluted in 125 mL of still water. Subsequently, MRI sequences and breath samples were acquired every 15 minutes (one time point) up to 180 minutes from lactulose administration.

LHBT Evaluation

Gas-cromatography breath analysis was performed immediately before each MRI acquisition. Every 15 minutes, we collected a sample of alveolar air using a system with two pockets connected by a T-shape valve. One 500-mL pocket was used to exclude anatomical dead space air, while the second was used to collect the air sample. For such purpose, subjects were instructed to take a deep breath, to hold it for 15 s, and then perform a forced expiration in the mouthpiece connected to the pockets system. Volunteers were not removed from MRI scanner during these measurements. Breath samples were then collected from the relevant pocket using a 30 mL syringe closed with a stopcock and immediately injected into a gas-chromatographer (Quintron MicroLizer™ DP plus, Milwaukee, IL). For each time point, H_2 and CH_4 concentration ([H_2] and [CH_4]), measured in parts per million (ppm) was noted. OCTT measured by LHBT (BT-OCTT) was defined as the time corresponding to an increase in breath [H_2] of >10 ppm above the baseline value, within the 3 hours (12).

LHBT results were interpreted by an experienced gastroenterologist who was blinded to the results of the MRI. Data were analyzed in order to detect the presence of an asymptomatic SIBO, using both traditional double peak criteria (i.e., abnormal test was defined by a 12 ppm [H_2] increase in breath over baseline with ≥5 ppm decrease at two or more points before the second

peak) (11) and Pimentel criteria (i.e. an abnormal test was defined by a [H_2] rise within 90 minutes or an absolute change >20 ppm within 180 min) (20).

MRI Analysis

Using T2-weighed sequences, the lactulose fluid bolus appears hyperintense within an empty GI tract and the passage of the bolus can be tracked easily by visual inspection on sequential axial images during MRI examination (Figure 1). Coronal images were used to confirm bolus progression only when axial images analysis was uncertain. Bolus detection was performed by two radiologists with more than eight and three years' experience in abdominal MRI who were blinded to LHBT results. OCTT obtained using MRI (MR-OCTT) was defined as the time elapsed between lactulose ingestion and its detection in the caecum.

Gas appears as signal void within the bowel. To calculate SBGV, we analysed each single MR image separately using a freeware software (OsiriX, v. 3.6.1, Pixmeo SARL, Bern, Switzerland) that allows for drawing grow segmentation regions with a semi-automatic method. The cursor was placed in the middle of the signal void area and the software automatically creates a region of interest that includes all pixels with grey levels similar to those selected. The threshold interval of grey levels to be included could be modified by the operator to make the analysis taking into account the highest area of signal void pixels (Figure 2). The area obtained with this segmentation were multiplied by the thickness of each slice (7 mm) to obtain the SBGV. Image processing was performed by the same radiologist with more than eight years' experience in abdominal MR and image elaboration who were blinded to LHBT results.

Statistical Analysis

Age and body mass index were reported as mean±standard deviation. Other continuous variables with non-parametric distribution were reported as median and interquartile range. These included, [H_2], [CH_4], and SBGV. BT-OCTT and MR-OCTT were considered as a discrete variables, being

measured in steps of 15 minutes.

The primary analysis compared BT-OCTT to the MR-OCTT using the Wilcoxon signed rank test, while agreement between these variables was estimated using the Cohen kappa statistics. A preliminary inspection of the data revealed that the relationship between breath [H_2] above baseline levels (i.e. <5ppm) and the SBGV above baseline levels (i.e. <5ml, see results) was linear. The data at each time point was fitted using a linear regression. Correlation between [CH_4] and SBGV was estimated using the Pearson correlation coefficient. Interobserver variability in MR-OCTT detection at MR was assessed by Cohen kappa statistics with a value of >0.8 representing near perfect agreement.

Calculations were performed using SPSS Statistics v. 17 (SPSS, Chicago, IL) and Excel (Microsoft 2007, Redmond, WA). A *P*-value less than 0.05 was considered as significant.

Results

Study Population

It comprised 28 healthy volunteers (30±8 years; 17 males [30±7 years]; 11 females [30±9 years]). Mean body mass index was 22±3 kg/m^2, 4/28 (14%) were alcohol consumers, 3/28 (11%) were coffee consumers, and 15/28 (54%) were smokers. All subjects were asymptomatic (GSS score=0).

No adverse reactions were reported. In two cases, the test was postponed due to the presence of abnormal quantity of fluids in the stomach and was performed by prolonging the fasting period. No subject complained of any symptoms during the testing period.

LHBT Data

Among 28 subjects, 26 were H_2 producers and 8 CH_4 producers. The median baseline H_2 concentration was 2 ppm (1-4 ppm) and increases of [H_2] above 5 ppm were considered significant (8). The baseline CH_4 concentration was 0 ppm (0-8 ppm).

Median BT-OCTT was 127.5 minutes (105-150 min). The two non-H_2 producers were excluded from this analysis. Median excretion values of H_2 and CH_4 over time are shown in Figure 3.

Based on traditional double peak criteria, SIBO was present in 3/28 (11%) subjects, while based on Pimentel criteria, SIBO was present in 5/28 (18%) individuals.

MRI Data

Interobserver agreement for MR-OCTT detection was excellent (Cohen k=0.92) between the two observers. Median MR-OCTT was 135 minutes (120-150 minutes). In the two patients that were non-H_2 producers, MR-OCTT was 105 and 180 minutes, while LHBT was blinded for this assessment.

At baseline, MRI detected a median SBGV of 49.0 mL (interquartile interval 44.1-51.6 mL). Oral administration of lactulose solution was followed by a progressive increase of SBGV (Figure

4).

Correlation Analysis

In 2/28 (8%) cases, MR-OCTT and BT-OCTT could not be compared because patients were H_2 non-producers. In the remaining 26 subjects, median MR-OCTT (135 minutes) was significantly longer (*P*=0.008) than the median BT-OCTT (127.5 minutes) (Figure 5). However, the difference (7.5 minutes) was lower than the interval between two measurement time points. Agreement between BT-OCTT and MR-OCTT was almost perfect (k=0.924). Lactulose bolus reaching the caecum was detected at the same time by MRI and LHBT in 18/26 (69%) subjects. In the remaining 8/26 (31%) individuals with discordant results, MR-OCTT was longer than BT-OCTT. In each of these 8 cases, MRI showed that the lactulose bolus was in the terminal ileum and not yet in the caecum and MR-OCTT was longer than BT-OCTT by one (n=6) or two (n=2) time points.

Considering SIBO individuals diagnosed by LHBT in detail: in 3/26 (12%) subjects, SIBO was identified using the traditional double peak criteria and MRI confirmed the diagnosis in 2 cases, since the initial H_2E peak during the LHBT appeared before the lactulose bolus entered the cecum on MRI. Regarding the third subject, the initial H_2E peak was associated to the lactulose bolus detection into the caecum in the presence of accelerated MR-OCCT (i.e., false positive). In 5/26 (19%) individuals, SIBO was identified by Pimentel criteria and MRI confirmed the diagnosis in three, while two cases were false positive due to an accelerated OCCT. Thus, the LHBT diagnosis of SIBO was confirmed by the combined test in 5 cases, whereas 3/8 (38%) subjects had false-positive LHBT due to rapid transit.

The significant correlation between [H_2] and SBGV is shown in Figure 6, where each dot represents medians at a given timepoint starting from 105 minutes after lactulose ingestion (r=0.964, *P*<0.001). No correlation between [CH_4] and SBGV was found (r=0.168, *P*=0.573) in CH_4 producers patients.

Discussion

This study demonstrates high agreement for measurements of MR-OCTT and BT-OCTT with 69% of cases showing the same value and 92% of patients showing a difference between the two observed values of only one time point (i.e., <15 minutes). Additionally, correlation between the increase in H_2E in the breath during LHBT and SBGV measured by MRI was significant. This implies that MRI is both a valid method for measurement of OCTT and also provides direct evidence of bacterial fermentation in the small bowel and a novel diagnostic test for SIBO.

Currently, evaluation of OCTT is challenging because of the important drawbacks of the available techniques (9-17). LHBT is a simple, non-invasive and widely-used test that provides indirect measurement of OCTT based on the time from lactulose ingestion to metabolism by colonic microbiota and an increase in breath H_2E; however, it can be confounded by the presence of SIBO and H_2 non-producers (i.e., colonic microbiota that does not produce H_2) (10,11,22,23,27). Scintigraphy requires ingestion of a radioactive meal, evaluated with sequential scans over several hours. Scintigraphy has good sensitivity and specificity providing similar measurements of OCTT by using both solid and liquid meal (28), but is time consuming, relatively costly, sometimes difficult to interpret due to overlapping loops of small intestine and the caecum, and utilizes ionizing radiations (8,28). MRI was recently applied to evaluate GI structure and function (29-31) and to detect the presence of gas or liquids and the movement of fluid through the GI tract (32-34). In particular, Chaddock et al. measured OCTT using MRI and lactose-ureide breath test, showing poor correlation between these methods when analyzed after administration of a meal (15).

In our series, OCTT measurements varied widely between 90 and 180 minutes; however, agreement between the two techniques was maintained across the observed range. Overall, there was a small but significant difference between BT-OCTT and MR-OCTT. This difference was within the temporal resolution of measurement acquisition (15 minutes) and would normally be considered clinically irrelevant; however, it is of interest because it reflects a systematic difference between the two investigations. The >10ppm increase in breath hydrogen that occurred in 31% of

subjects *before* MRI documented the arrival of the lactulose fluid bolus in the cecum indicates that bacterial colonization was present in the small bowel in a proportion of subjects as previously suggested (35,36). Detailed examination of the LHBT and MRI results revealed that in all cases the "early" increase in breath hydrogen occurred during 15 to maximum 30 minutes stasis of the lactulose fluid bolus in the terminal ileum. This finding confirms that SIBO limited to the terminal ileum should be considered normal. However, more extensive SIBO that causes a rise in breath hydrogen >30 minutes before arrival of contrast in the cecum may indicate clinically relevant SIBO in patients with enteric dysmotility (e.g. systemic sclerosis) or functional gastrointestinal disease (26). This issue may be clinically relevant, as this may also identify patients with IBS with diarrhea that respond to antibiotic therapy (8).

The presence of H_2 non-producers in 8% of the population (2% - 43% reported in the literature) (11,22,37,38), the high degree of variability in OCTT and the discrepancy between OCTT measurements documented by LHBT and MRI in some individuals, all indicate that LHBT alone does not provide an accurate measurement of gastrointestinal function. Moreover, addition of CH_4 measurements were "positive" in only a small number of individuals and a distinct increase of CH_4 on entry into the caecum was not present. The combined LHBT-MRI test is not affected by these limitations and may potentially represent a good alternative approach. Indeed, MRI observations revealed that in about half of the healthy volunteers in whom SIBO was "diagnosed" on the basis of LHBT results were confounded by variation in OCTT and were not due abnormal distribution of bacteria in the small bowel. These data are in agreement with those reported by Yu et al. (2) and Zhao et al. (8) in IBS patients using combined 99mTc scintigraphy and LHBT , showing that an "abnormal LHBT" using any of the published criteria cannot distinguish rapid OCTT from SIBO (39).

Our observations suggest that MRI can provide also a direct assessment of gas production in the small bowel. Our data allowed us to evaluate the relationship between the H_2E and the SBGV over time. After 90 minutes, the rapid rise in H_2 excretion and SBGV was likely related to

fermentation in the large bowel (± distal small bowel) with subsequent, retrograde passage of gas into the small bowel. A similar relationship was not observed between CH_4 measurements and SBGV in those patients that produced methane. Clinically, these data suggest the potential to use MRI to estimate the amount of gas in the gut, that represents a crucial issue in patients with IBS and other GI disorders with abnormal gas dynamics. Additionally, MRI may facilitate assessment of the effect of drugs on gas production and transit within the gut.

Two advantages of MRI over LHBT for assessment of OCTT should be emphasized. First, previous studies documented that lactulose may influence small bowel secretion that significantly accelerate OCTT (40). As MRI can detect most aqueous material within the gut, other material may be used to assess MR-OCTT; however these substrates should either retain sufficient intra-luminal fluid or be otherwise visualized moving through the bowel by MRI. Then, it is known that LHBT evaluation can be impaired by large residual stomach content (14); however, to date, no tools are available to evaluate whether stomach is empty or not prior to the test. As demonstrated in two participants, MRI is able to overcome this limitation by detecting excess gastric content at baseline. On the other hand, using MRI to measure OCTT has disadvantages. The long time needed to detect lactulose bolus in the caecum during MR make this method fairly expensive. Moreover, claustrophobia and contraindications to MRI may somewhat limit the applicability in clinical practice.

This study has limitations. First, the sample size is relatively low; however, this represents the first report of combined MRI and LHBT to investigate gastrointestinal function. Also, the use of LHBT as reference standard can be questioned, but since there is no consensus on which is the best technique for measuring OCTT we opted to use it because it is safe, cheap and easy-to-perform in combination with MRI compared to other methods (e.g., scintigraphy) and because the lactulose fluid bolus represents a good substrate to follow using MRI. It may be relevant that the MR examination is performed in supine position. In this series, the median BT-OCTT was longer than 101 min obtained in a previous study in a large number of healthy volunteers in the seated position

(26). An upright position may promote gastric emptying and bolus transit through the small intestine as documented by previous MRI studies (30,31); however any effect is likely to be small and unlikely to confound diagnosis of SIBO using the combined technique. Finally, inter observer agreement of MR-OCTT measurements was near perfect, but we did not test reproducibility of combined MRI-LHBT examination.

In conclusion, our study demonstrates that MRI represents a valid, non-invasive, radiation-free modality that provides a direct measurement of OCTT; its combination with LHBT may also allow non-invasive detection of patients with SIBO. Moreover, measurement of gas production in the small bowel by MRI after ingestion of lactulose may provide direct evidence of bacterial fermentation. Ongoing studies will examine whether the combined LHBT-MRI technique detects clinically relevant abnormalities of small bowel function and transit in patients with functional GI diseases that may be amenable to specific treatments.

References

1. Suarez FL, Levitt MD (2002) Intestinal gas. In: Feldman M, Friedman LS, Sleisenger MH, eds. Gastrointestinal and liver diseases: pathophysiology/diagnosis/management. Philadelphia, PA: WB Sanders Co:155–163.
2. Azpiroz F, Malagelada J-R (2005) Abdominal bloating. Gastroenterology 129:1060–78
3. Lembo A, Ameen VZ, Drossman DA (2005) Irritable bowel syndrome: toward an understanding of severity. Clin Gastroenterol Hepatol 3:717e25
4. Vanner SJ, Depew WT, Paterson WG, et al (1999) Predictive value of the Rome criteria for diagnosing the irritable bowel syndrome. Am J Gastroenterol 94:2912e17
5. Barbara G, Stanghellini V, Brandi G, et al (2005) Interactions between commensal bacteria and gut sensorimotor function in health and disease. Am J Gastroenterol 100:2560e8
6. Gilmore IT (1990) Orocaecal transit time in health and disease. Gut 31:250:251
7. Longstreth GF, Thompson WG, Chey WD, et al (2006) Functional bowel disorders. Gastroenterology 130: 1480–1491
8. Zhao J, Zheng X, Chu H, et al (2014) A study of the methodological and clinical validity of the combined lactulose hydrogen breath test with scintigraphic oro-cecal transit test for diagnosing small intestinal bacterial overgrowth in IBS patients. Neurogastroenterol Motil 26:794-802.
9. Rao SS, Camilleri M, Hasler WL, et al (2011) Evaluation of gastrointestinal transit in clinical practice: position paper of the American and European Neurogastroenterology and Motility Societies. Neurogastroenterol Motil. 23:8-23.
10. Hasler WL (2003) Lactulose breath testing, bacterial overgrowth, and IBS: just a lot of hot air? Gastroenterology 125:1898e900
11. Bond JH, Levitt MD (1975) Investigation of small bowel transit time in man utilizing pulmonary hydrogen (H2) measurements. J Lab Clin Med 85:546 -555

12. Rana SV, Malik A (2014) Breath tests and irritable bowel syndrome. World J Gastroenterol. 28;20:7587-7601
13. Metcalf AM, Phillips SF, Zinsmeister AR, et al (1987) Simplified assessment of segmental colonic transit. Gastroenterology 92:40-47
14. Schwizer, W., A. Steingoetter, Fox M (2006) Magnetic resonance imaging for the assessment of gastrointestinal function. Scand J Gastroenterol 41:1245-1260
15. Chaddock G, Lam C, Hoad CL, et al (2014) Novel MRI tests of orocecal transit time and whole gut transit time: studies in normal subjects. Neurogastroenterol Motil. 26:205-214
16. Hahn T, Kozerke S, Schwizer W, et al (2012) 19F MR imaging golden angle-based capsule tracking for intestinal transit and catheter tracking: initial in vivo experience. Radiology 265:917-925
17. Worsøe J1, Fynne L, Gregersen T, et al (2011) Gastric transit and small intestinal transit time and motility assessed by a magnet tracking system. BMC Gastroenterol. 29;11:145.
18. Pimentel M, Lezcano S (2007) Irritable bowel syndrome: bacterial overgrowth - what's known and what to do. Curr Treat Options Gastroenterol 10:328e37
19. Vanner S (2008) The small intestinal bacterial overgrowth. Irritable bowel syndrome hypothesis: implications for treatment. Gut 57:1315e21
20. Pimentel M, Chow EJ, Lin HC (2000) Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. Am J Gastroenterol 95:3503e6
21. Furnari M, Parodi A, Gemignani L, et al (2010) Clinical trial: the combination of rifaximin with partially hydrolysed guar gum is more effective than rifaximin alone in eradicating small intestinal bacterial overgrowth. Aliment Pharmacol Ther 32:1000–1006
22. Gasbarrini A, Corazza GR, Gasbarrini G, et al (2009) Methodology and indications of H2-breath testing in gastrointestinal diseases: the Rome Consensus Conference. Aliment Pharmacol Ther. 29(Suppl 1):1-49

23. Pimentel M, Chow EJ, Lin HC (2003) Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. a double-blind, randomized, placebo-controlled study. Am J Gastroenterol 98:412e19
24. Jahng J, Jung IS, Choi EJ, Conklin JL, Park H (2012) The effects of methane and hydrogen gases produced by enteric bacteria on ileal motility and colonic transit time. Neurogastroenterol Motil. 24:185-190
25. Yu D, Cheeseman F, Vanner S (2011) Combined oro-caecal scintigraphy and lactulose hydrogen breath testing demonstrate that breath testing detects oro-caecal transit, not small intestinal bacterial overgrowth in patients with IBS. Gut 60:334-340
26. Parodi A, Sessarego M, Greco A, et al (2008) Small intestinal bacterial overgrowth in patients suffering from scleroderma: clinical effectiveness of its eradication. Am J Gastroenterol.103:1257-1262
27. Gemignani L, Savarino V, Ghio M, et al (2013) Lactulose breath test to assess oro-cecal transit delay and estimate esophageal dysmotility in scleroderma patients. Semin Arthritis Rheum. 42:522-529
28. Bennink R, Peeters M, Van den Maegdenbergh V, et al (1999). Evaluation of small-bowel transit for solid and liquid test meal in healthy men and women. Eur J Nucl Med. 26:1560-1566.
29. Xu HM, Han JG, Na Y, Zhao B, Ma HC, Wang ZJ (2011) Colonic transit time in patient with slow-transit constipation: comparison of radiopaque markers and barium suspension method. Eur J Radiol. 79:211-213
30. Kwiatek MA, Menne D, Steingoetter A, et al (2009) Effect of meal volume and calorie load on postprandial gastric function and emptying: studies under physiological conditions by combined fiber-optic pressure measurement and MRI. Am J Physiol Gastrointest Liver Physiol. 297:G894-901
31. Kwiatek, MA, Fox MR, Steingoetter A, et al (2009) Effects of clonidine and sumatriptan

on postprandial gastric volume response, antral contraction waves and emptying: an MRI study. Neurogastroenterol Motil 21: 928-e971

32. Marciani L, Cox EF, Hoad CL, et al (2010) Postprandial changes in small bowel water content in healthy subjects and patients with irritable bowel syndrome. Gastroenterology 138:469-477.
33. Murray K, Wilkinson-Smith V, Hoad C, et al (2014) Differential effects of FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) on small and large intestinal contents in healthy subjects shown by MRI. Am J Gastroenterol. 109:110-119
34. Marciani L (2014) Assessment of gastrointestinal motor functions by MRI: a comprehensive review. Neurogastroenterol Motil 23:399–407
35. Hao WL, Lee YK (2004) Microflora of the gastrointestinal tract: a review. Methods Mol Biol 268: 491–502
36. Bratten JR, Spanier J, Jones MP (2008) Lactulose breath testing does not discriminate patients with irritable bowel syndrome from healthy controls. Am J Gastroenterol 103:958e63
37. Cloarec D, Bornet F, Gouilloud S, et al (1990) Breath hydrogen response to lactulose in healthy subjects: relationship to methane producing status. Gut 31: 300–304
38. Furnari M1, Savarino E, Bruzzone L, et al (2012) Reassessment of the role of methane production between irritable bowel syndrome and functional constipation. J Gastrointestin Liver Dis. 21:157-163.
39. Zhao J, Fox M, Cong Y, et al (2010) Lactose intolerance in patients with chronic functional diarrhoea: the role of small intestinal bacterial overgrowth. Aliment Pharmacol Ther. 31:892-900
40. Hammer HF, Santa Ana CA, Schiller LR, et al (1989) Studies of osmotic diarrhea induced in normal subjects by ingestion of polyethylene glycol and lactulose. J Clin Invest. 84:1056-1062

Figure Legends

Figure 1. Magnetic resonance evaluation of the upper and lower abdomen, axial T2-weighted steady-state fast spin-echo sequences, performed in a 32 year-old asymptomatic subject. (a) baseline, pelvic scan. Some small bowel loops are distended by gas (red line) while others have virtual lumen (asterisks); caecum is distended by stool (green dotted line). (b) upper abdomen scan performed immediately after oral administration of lactulose. The stomach is distended (blue dashed line) and a gas-fluid level can be seen (A=air; F=fluid). (c) pelvic scan performed 75 minutes after oral administration of lactulose. Some small bowel loops are distended by fluid (red dashed line), while others have virtual lumen (asterisks); caecum (green dashed line) and the colon-sigma junction (yellow dashed line) are distended by stool. (d) pelvic scan performed 135 minutes after oral administration of lactulose. Some small bowel loops are distended by fluid (red dashed line), while others have virtual lumen; air can be seen in other loops (asterisks). Compared to (c), high signal can be appreciated inside the caecum (green line), indicating that the fluid bolus has entered the caecum. The colon-sigma junction is distended by stool (yellow dashed line).

Figure 2. Semi-automatic segmentation of gas within small bowel lumen. The green line represents the area selected for volume calculation.

Figure 3. Median H_2 (a) and CH_4 (b) excretion over time in asymptomatic subjects after oral administration of a bolus of diluted lactulose. Bars refer to interquartile ranges.

Figure 4. Median small bowel gas volume (SBGV) over time measured using MRI in asymptomatic subjects after oral administration of a bolus of diluted lactulose.

Figure 5. Comparison between oro-caecal transit time (OCTT) measured in min using LHBT and

MRI in asymptomatic subjects after oral administration of a bolus of diluted lactulose. Bars refer to standard deviations. Data are expressed in minutes.

Figure 6. Graph showing the relationship between H_2 excretion and the small-bowel gas volume (SBGV). Each dot represents the medians at a given timepoint, starting from 105 minutes.