Characterization of gastric volume responses and liquid emptying in functional dyspepsia and health by MRI or Barostat and simultaneous 13C-acetate breath test

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Abstract

The assessment of gastric accommodation and emptying by different methodologies provides inconsistent results. OBJECTIVES: To compare magnetic resonance imaging (MRI), barostat and 13C acetate breath-test (BT) for the assessment of gastric volume responses and emptying in healthy controls (HC) and patients with functional dyspepsia (FD). METHODS: Eight HC and eight FD patients underwent: (1) continuous BT with simultaneous MRI in the upright position after ingestion of isocaloric, 300 kcal, 200 ml, and 800 ml meals, both labeled with 100 mg of 13C-acetate, (2) BT with gastric barostat after ingestion of the 200 ml meal. MRI measured total gastric volume and gastric content volume (GCV) at baseline, after filling and during emptying. Meal emptying half-times (T½) for MRI and BT were calculated (mean±SD). RESULTS: (1) Initial GCV was lower in FD than in HC (762±22ml vs. 810±52ml, p<0.04) after the 800 ml meal but not the 200 ml meal. T½MRI was shorter for the 800ml than the 200ml meal (p<0.001), but similar in HC and FD (200ml: HC 117±30min vs. FD 138±42min, NS; 800ml: HC 71±16min vs. FD 78±27min, NS). In contrast, T½BT was similar between meals and groups (200 ml: HC 111±11min vs. FD 116±19min; 800ml: HC 114±14min vs. FD: 113±17min). (2) Barostat measurements showed similar postprandial volume increases between groups. CONCLUSIONS: Direct measurements by MRI provide a sensitive, non-invasive assessment of gastric accommodation and emptying after a meal. In contrast to MRI, BT did not detect faster emptying of high-volume compared to low-volume liquid nutrient meals in HC or FD.
Characterization of Gastric Volume Responses and Liquid Emptying in Functional Dyspepsia and Health by MRI or Barostat and Simultaneous $^{13}$C-Acetate Breath Test

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Keywords: MRI, $^{13}$C-sodium acetate breath test, gastric barostat, gastric emptying, gastric volume response, functional dyspepsia

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### ABREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>BT</td>
<td>$^{13}$C-acetate breath test</td>
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<td>FD</td>
<td>Patients with functional dyspepsia</td>
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<td>GAV</td>
<td>Gastric Air Volume (=TGV-GCV)</td>
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<td>GAV$_{fasting}$</td>
<td>GAV in fasting condition (baseline)</td>
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<td>GAV$_{pp}$</td>
<td>GAV directly after meal administration (measured)</td>
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<td>GAV$_{relaxation}$</td>
<td>Volume difference between GAV$<em>{pp}$ and GAV$</em>{fasting}$</td>
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<td>GCV</td>
<td>Gastric Content Volume</td>
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<td>GCV$_{fasting}$</td>
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<td>Gastric Emptying</td>
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<td>HC</td>
<td>Healthy Controls</td>
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<td>$\kappa$</td>
<td>Coefficient for postprandial volume increase (<em>regression estimated</em>)</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>T½$_{MRI/BT}$</td>
<td>Meal emptying half-times as assessed by MRI / BT</td>
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<td>TGV</td>
<td>Total Gastric Volume</td>
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<td>TGV$_{0}$</td>
<td>Total Gastric Volume directly after meal administration (<em>regression estimated</em>)</td>
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ABSTRACT

The assessment of gastric accommodation and emptying by different methodologies provides inconsistent results.

**OBJECTIVES**: To compare magnetic resonance imaging (MRI), barostat and $^{13}$C-acetate breath-test (BT) for the assessment of gastric volume responses and emptying in healthy controls (HC) and patients with functional dyspepsia (FD).

**METHODS**: Eight HC and eight FD patients underwent: (1) continuous BT with simultaneous MRI in the upright position after ingestion of isocaloric, 300 kcal, 200 ml, and 800 ml meals, both labeled with 100 mg of $^{13}$C-acetate, (2) BT with gastric barostat after ingestion of the 200 ml meal. MRI measured total gastric volume and gastric content volume (GCV) at baseline, after filling and during emptying. Meal emptying half-times (T½) for MRI and BT were calculated (mean±SD).

**RESULTS**: (1) Initial GCV was lower in FD than in HC (762±22ml vs. 810±52ml, $p<0.04$) after the 800 ml meal but not the 200 ml meal. T½MRI was shorter for the 800ml than the 200ml meal ($p<0.001$), but similar in HC and FD (200ml: HC 117±30min vs. FD 138±42min, NS; 800ml: HC 71±16min vs. FD 78±27min, NS). In contrast, T½BT was similar between meals and groups (200 ml: HC 111±11min vs. FD 116±19min; 800ml: HC 114±14min vs. FD: 113±17min). (2) Barostat measurements showed similar postprandial volume increases between groups.

**CONCLUSIONS**: Direct measurements by MRI provide a sensitive, non-invasive assessment of gastric accommodation and emptying after a meal. In contrast to MRI, BT did not detect faster emptying of high-volume compared to low-volume liquid nutrient meals in HC or FD.
INTRODUCTION

Abnormal gastric function has been implicated as a cause of gastrointestinal symptoms and disease. For example, gastric volume responses after a meal (e.g. accommodation) and gastric emptying are abnormal in a significant proportion of patients with functional dyspepsia (FD).(1) Conventional measurement techniques tend to focus on a single aspect of gastric function and do not provide a comprehensive description of the gastric response to feeding, hence the association between abnormal gastric function and the occurrence of dyspeptic symptoms is still poorly understood.(2) Moreover these techniques may involve exposure to radioactive isotopes (e.g. scintigraphy, SPECT), be invasive and potentially disturbing to gastric physiology (e.g. barostat), or user dependent (e.g. ultrasound).(2) The use of magnetic resonance imaging (MRI) for the assessment of GI function in the clinical and research setting addresses many of these shortcomings. MRI provides non-invasive evaluation of gastric function and meal emptying with high spatial and temporal resolution in real time without exposure to ionizing radiation.(3, 4) The technique follows both gastric volume changes and emptying of gastric contents independently and can differentiate between the ingested meal, gastric secretion and intragastric gas.(5, 6) It is reproducible,(7) and has been validated for measurement of gastric volume(8) and gastric emptying (GE).(3, 4)

Initial validation studies have shown good correlation between MRI and barostat measurements of gastric accommodation in healthy volunteers;(8) however, important differences in absolute volume responses and early gastric emptying were also observed.(9) It is unclear whether comparisons between the two techniques are valid across a range of experimental conditions (e.g. meal volume) and in patients
with abnormal gastric function (e.g. dyspepsia). Similarly, breath tests using substrates labeled with stable $^{13}$C have been used to measure GE,(10, 11) but it remains uncertain whether BT results in different experimental conditions can be compared.(12) The BT technique is based on the principle, that postgastric substrate processing is uniform and therefore GE is the rate limiting step of $^{13}$CO$_2$ breath excretion. If this is a valid assumption, then the dynamic process of GE should be closely correlated to the $^{13}$CO$_2$/$^{12}$CO$_2$ ratio in the breath, if a high sampling frequency is obtained.(13, 14) The recently developed method of a continuous (1 sample / 3 minutes) and automatic breath collection and analysis system using molecular correlation spectroscopy facilitates this approach.(14, 15)

The aim of the present study was to compare and contrast gastric MRI and barostat measurements of postprandial gastric volume responses with simultaneous $^{13}$C-acetate breath test (BT) measurements of gastric emptying in different experimental conditions (isocaloric 200ml and 800ml test meal). These investigations were performed in both health and FD patients with predominant early satiety (known to have a high prevalence of impaired accommodation).(1) Since the intragastric distribution of a liquid meal affects gastric function, data on gastric volume responses and emptying were obtained in the physiological upright, seated position.(16, 17) We hypothesized (1) that MRI and continuous BT measurements would provide equivalent measurements of gastric emptying, (2) that impaired gastric volume responses would be most evident on gastric barostat, but that this invasive technique would disturb the gastric emptying process and (3) that impaired accommodation in FD patients would accelerate gastric emptying, especially at larger volumes.
SUBJECTS AND METHODS

Subjects
Eight HC and eight FD patients with early satiety as a predominant symptom(1) participated in the study. Groups were matched for demographic variables (Table 1) and all subjects had a similar dietary history within two weeks prior to the study.(18) HC were screened and had no evidence of gastrointestinal disease on investigation. Diagnosis of functional dyspepsia was based on Rome II criteria and normal endoscopy.(19) Patients with predominant reflux symptoms, diabetes mellitus, prior abdominal surgery except appendectomy, cholecystectomy, hysterectomy or hernia repair, use of medications known to influence gastrointestinal motor function or nutrient metabolism within one week prior to the start of the study, and females with inadequate contraception were excluded from the study.

Written informed consent was obtained from each participant prior to entry into the study. The study was carried out according to Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the local Ethics Committee of the Department of Internal Medicine at the University Hospital Zurich, Switzerland (EK-Nr. 905).

Study design
The study followed a prospective, randomized design. Each subject was investigated on three different morning sessions, separated by one week. On separate study days, BT and simultaneous gastric MRI were performed prior to and after administration of a low volume liquid nutrient meal and an isocaloric high volume meal. On a separate study day subjects underwent BT and simultaneous gastric
barostat study after administration of the low volume meal. All tests were performed in randomized order after an eight-hour overnight fast and in a relaxed sitting position. Physical activity was restricted during the test.

**Meal compositions**

The low volume nutrient liquid meal consisted of 200 ml Ensure® plus Vanilla (300 kcal, 53% carbohydrate, 32% fat, 15% protein, caloric density 1.5 kcal/ml; Abbott AG, Baar, Switzerland). The isocaloric high volume meal (800 ml) consisted of 200 ml Ensure® plus Vanilla and 600 ml water (caloric density 0.375 kcal/ml). Test meals were labeled with 100 mg $^{13}$C-sodium acetate (acetic acid-1-$^{13}$C, sodium salt, chemical purity of 99.1 %, isotopic purity minimum 99 atom% $^{13}$C; Isotec, Miamisburg, OH, U.S.A.) and, for MRI studies, with 0.5 mM Gd-DOTA (Dotarem®, Guerbet, Roissy CdG Cedex, France) to enhance image contrast. Meals were ingested via a drinking straw to avoid air swallowing within 5 minutes.

**Magnetic Resonance Imaging (MRI)**

MRI studies were performed in the upright seated position using an open configuration MRI system (0.5 T, Signa SP/l, GE, Milwaukee, Wi, USA) as recently described.(20) Volume scans covering the complete gastric region were performed to assess fasting and, after ingestion of the test meal, postprandial volumes every three minutes until 15 min, every 10 min until 60 min, and finally every 15 min until 120 min. Total gastric volume (TGV), gastric content volume, (GCV) and gastric air volume (GAV (=TGV-GCV)) were identified and plotted over time to generate volume curves (Fig. 1A, B).(20) MRI gastric emptying rates (ml/min) were calculated by dividing the change in GCV during each time interval after meal ingestion by the
duration of the time interval. For analysis of gastric relaxation and emptying, volume data was were fitted to a novel, three parameter GE model (13, 21-23)

\[ V(t) = V_0 \cdot (1 + \kappa \cdot t / t_{empt}) \cdot e^{-t/(t_{empt})} \]

with \( V(t) \) the volume \((V)\) at time \( t \) in min. \( V_0 \), \( \kappa \) and \( t_{empt} \) are regression estimated constants, defining the total gastric volume \((TGV_0)\) and gastric content volume \((GCV_0)\) directly after meal administration, the initial volume increase after meal ingestion during a lag phase \((\kappa)\) and the rate at which the stomach empties \((t_{empt})\).

Gastric relaxation \((TGV_{relaxation})\) was defined as the volume difference between the (measured) initial postprandial TGV and the baseline TGV in fasting condition \((TGV_{fasting})\) and plotted versus the increase in GAV \((\text{Fig. 2})\), defined as the difference between pre- and postprandial gastric air volume \((GAV_{relaxation})\). The emptying half-times \((T_{1/2}^{\text{MRI}})\) for TGV and GCV were determined from \( \kappa \) and \( t_{empt} \) by Newton approximation.

**Simultaneous \(^{13}\text{C}-\text{sodium acetate breath test and breath test analysis}**

Subjects were connected to the BT-device (BreathID Ltd., Jerusalem, Israel) by means of a single use tubing system, enabling the continuous collection of breath samples via a nasal cannula directly from the patient’s nostrils. Measurements were started before substrate administration (baseline) and continued for up to 3.5 hours after meal administration. The \(^{13}\text{C}/^{12}\text{C}\) isotope ratio of the breath samples was continuously analyzed using molecular correlation spectroscopy and displayed in real-time. The results were expressed as delta \((\delta)\) over baseline \((\text{dob} = \delta_s - \delta_0)\). (14)

To assess the proportion of \(^{13}\text{C}\)-sodium acetate given by mouth that is metabolized, the results were expressed as a percentage dose of \(^{13}\text{C}\) recovered (PDR) over time for each time interval (Fig. 1C), from which the cumulative PDR (cPDR) obtained by
numerical integration from PDR values for each time interval was calculated. (24, 25)

The evaluation of the BT for GE was done by non-linear regression analysis of the $^{13}$CO$_2$-excretion curves (PDR), (24, 25) resulting in the gastric emptying coefficient (GEC), a reliable parameter describing the rate at which stomach empties. In addition, gastric emptying half-time ($T_{1/2}$BT) and lag phase ($t_{lag}$) were calculated as previously described. (24-26) The $^{13}$C-acetate delivery rates into the duodenum were calculated by following the intragastric $^{13}$C-acetate dose and concentration during the initial volume changes and the postprandial emptying process as assessed by MRI.

**Gastric barostat measurements**

The gastric barostat assembly comprising a double-lumen polyvinyl tube (Dentsleeve Pty Ltd., Wayville, SA, Australia) attached to a polyethylene bag (1000 ml capacity, infinitely compliant at the inflation volumes obtained in this study), was positioned in the stomach and connected to a programmable barostat device (Distender Series II, G&J Electronics Inc., Willowdale (Toronto), Ontario, Canada) as described previously. (27) After determining the minimal intra-balloon distending pressure (MDP) (1, 28-30) and a subsequent 15-minute adaptation period, the intra-balloon pressure was increased 2 mmHg above MDP for measurement of gastric tone, whilst the corresponding intra-balloon volume was being recorded. Measurements started 20 minutes before oral administration of the 200 ml meal and continued for up to 3.5 hours postprandially.

Pre- and postprandial gastric tone was calculated based on the mean balloon volumes at consecutive 5-minute intervals; in the early postprandial phase (0-15 min after meal ingestion) the mean intra-balloon volume was calculated for 3-minute intervals (Fig. 3A). The meal-induced gastric relaxation ($\Delta$ intragastric balloon volume) was quantified as the difference between the average volumes during 20
minutes before (preprandial volume) and 35 minutes after meal administration (postprandial volume). The time interval at which maximum relaxation occurred was also recorded. The lower range of normal (mean – 2SD) for the meal-induced increase in intragastric balloon volume in HC was used as a cut-off to indicate impaired gastric accommodation in FD patients (Fig. 3B).

**Gastrointestinal sensory responses**

Patients were asked to rate their perception of fullness, nausea, bloating, and abdominal discomfort/pain on a 100 mm visual analogue scale (VAS) before and 0, 6, 15, 25, 35, 45 min after administration of the meal and then every 15 minutes until 210 minutes had elapsed. During the gastric barostat study, preprandial measurements were performed every 10 minutes starting 20 minutes before meal administration.

**Statistical analysis**

**MRI**

Parameters $V_0$, $\kappa$, $t_{emp}$ of the GE model were estimated from a single statistical fit to the volume data within each study group (HC and FD patients) using the R library `nlme`.\(^{(31)}\) Average volume curves over all subjects for each meal were calculated (Fig. 1A, B). Effects of GCV and GAV were compared using a mixed effects model ANOVA, with ‘subject’ as a random variable and ‘treatment’ (low / high volume meal) and ‘GCV / TGV’ or ‘GAV’ as fixed variables.\(^{(32)}\) Interaction terms were included, if required, based on an AIC criterion.\(^{(33)}\) Student’s paired $t$-test for the assessment of differences in postprandial to preprandial parameters within groups was applied as appropriate.
Statistical analysis was first carried out as a descriptive evaluation of $\delta$ (‰), PDR (%/h), cPDR (%), GEC, $T_{1/2}^{BT}$ (min), $t_{lag}$ (min) and characteristics of patients and volunteers (mean ± SD). Effects of meals and barostat were compared using a mixed effects model ANOVA, with ‘subject’ as a random variable and ‘treatment’ (MRI low volume meal / MRI high volume meal / barostat) as fixed variables.(32)

**Gastric barostat**

Barostat results in HC and FD patients were compared by Student’s $t$-test. The normal range (mean ± 2SD) for the meal-induced gastric relaxation was calculated from the data in HC (Fig. 3B). Subsequently, patients were divided into those with normal and those with insufficient meal-induced relaxation.

**Gastrointestinal sensory scores**

Sensory scores were offset-log transformed by $y = \log(x+3)$ to handle heteroscedasticity, stabilize variances and for linear volume/score regression.(34, 35) Postprandial scores immediately after meal administration were compared to preprandial scores in each group and on all test days by paired t-test. The area under the curves (AUC [min]) of the offset-log-transformed symptom self report scores over 120 minutes (AUC0-120) was calculated using the trapezoid method and used to compare the effects of different meal volumes during MRI or gastric barostat on fullness, nausea, bloating or discomfort/pain between HC and FD patients. Effects on postprandial scores and AUC0-120 of sensory scores were compared using a mixed effects model ANOVA, with 2 levels of ‘subject’ (HC/FD) as a random variable and three levels of ‘treatment’ (MRI low volume meal / MRI high volume meal / barostat) as fixed variables.(32) The average symptom scores at each time point were plotted
against gastric content volumes (Fig. 4). Linear regression analysis was used to assess the relationship between symptom scores and gastric content and the coefficient of correlation (r) was calculated.

Statistical curve fits and mixed effect model ANOVA were performed using the data analysis and graphics package R.(31) Descriptive statistics, linear regression analysis and t-tests were calculated by SPSS® for Windows 10.0.7 (SPSS Inc., Chicago, IL, USA). Graphs were plotted by Graphpad Prism for Windows 4.02 (GraphPad Software Inc., San Diego, CA, USA).

All data were considered to be significant at alpha < 0.05. Demographic data and quantitative variables are presented as mean ± SD, unless otherwise indicated. The results presented in some tables are group mean averages calculated by the mixed effects model ANOVA and may slightly differ from the raw data presented in the figures.
RESULTS

Gastric barostat
Barostat measurements with simultaneous BT were performed in 7 HC and 7 FD patients. One patient and one control did not tolerate the gastric barostat assembly. In both groups, MDP was 8 ± 2 mm Hg. The mean preprandial intragastric balloon volume at MDP ± 2 mm Hg was not significantly different in HC and FD patients (HC 205 ± 109 ml vs. FD 122 ± 59 ml, \( p = 0.10 \)). In all subjects, ingestion of the meal caused an immediate and sustained relaxation of the proximal stomach, reflected by a significant increase in intragastric balloon volume (Fig. 3A). During the first 35 minutes after meal ingestion, the mean intragastric balloon volume was 549 ± 109 ml in HC and 438 ± 154 ml in FD (\( p < 0.002 \) as compared to preprandial volumes), corresponding to an increase of 344 ± 91 ml and 316 ± 154 ml, respectively (\( p = 0.68 \) between HC and FD groups; Fig. 3B). In FD patients, the maximum gastric relaxation occurred at a later time interval as compared to HC (33 ± 18 vs. 12 ± 6 min; \( p < 0.02; \) Fig. 3A). Only one patient with FD (FD #5) had a clearly impaired meal-induced increase in intragastric balloon volume, indicating impaired accommodation as described by other groups (Fig. 3B).(1)

MRI and breath test
Gastric volumes
MR image acquisition and simultaneous BT were performed successfully in all subjects. TGV, residual GCV and GAV in fasting condition were similar in both groups and on both occasions (Tables 2, 3). After meal ingestion all MR images showed homogeneous gastric contents and no disintegration or layering of the test meal. GCV\(_0\) after ingestion of the 800 ml meal was lower in FD patients than in HC
(762 ± 22 vs. 810 ± 52 ml; p < 0.05), indicating faster GE during meal ingestion. There was also a trend for a smaller relaxation volume in FD patients than in HC (p = 0.08; Table 2). GAV$_{pp}$ was larger for the 800 ml meal than for the 200 ml meal (p < 0.05) with a trend to greater increase in GAV$_{relaxation}$ after administration of the high volume meal (p = 0.06, Table 3). GAV$_{pp}$ after ingestion of the high volume meal was significantly higher compared to fasting condition only in HC (p < 0.05). TGV$_{relaxation}$ correlated with GAV$_{relaxation}$ in HC and FD after ingestion of the 200 ml meal (HC: r = 0.87, p < 0.01; FD: r = 0.75, p < 0.05) and in FD patients after ingestion of the 800 ml meal (HC: r = 0.38, p = 0.35; FD: r = 0.72, p < 0.05; Fig. 2). In both, HC and FD patients, the TGV and GCV curves after ingestion of the 200 ml meal were characterized by a prominent initial volume increase (higher coefficient $\kappa$), which was followed by a typical pattern of GE in all patients (Fig. 1A, B). This initial volume increase was less pronounced after ingestion of the high volume meal (Fig. 1A, B), as indicated by the lower coefficient $\kappa$ (p < 0.001, Table 2).

**Gastric emptying**

T½MRI was similar in HC and FD patients, but lower for the 800 ml meal as compared to the 200 ml meal (p < 0.001; Table 2, Fig. 1A, B), indicating faster GE of the high volume meal. In contrast, breath test parameters T½BT, GEC and t$_{lag}$ during simultaneous MRI were similar between meals and groups (Table 4, Fig. 1A, B). There was a weak but significant overall correlation in both groups for both meals between T½MRI and T½BT (Pearson’s correlation coefficient r = 0.53, p < 0.002; being r = 0.80, p < 0.001 for 200 ml meals and r = 0.65, p < 0.01 for 800 ml meals) During simultaneous barostat study GEC and t$_{lag}$ assessed by BT were significantly lower than during the corresponding MRI study, indicating a faster initial marker delivery into the duodenum (Table 4).
Mean MRI gastric emptying rates for HC and FD patients were 1.3±0.7 and 1.0±0.8 ml/min for the 200 ml meal and 6.3±1.8 and 5.6±1.6 ml/min for the 800 ml meal 15-90 minutes postprandially (p < 0.001 between meals). The mean intestinal delivery of $^{13}$C-acetate calculated from direct measurements of GE by MRI was 0.2 mg/min higher for the 800 ml meal compared to the 200 ml meal (p<0.01), with similar amounts of marker emptying from the stomach between HC and FD patients (HC: 800 ml: 0.7±0.2 vs. 200 ml: 0.5±0.2 mg/min; FD: 800 ml: 0.6±0.2 vs. 200 ml: 0.4±0.2 mg/min; p = NS).

**Sensory responses**

In both HC and FD patients, perception scores for fullness, nausea and bloating were significantly higher during gastric barostat than during the MRI study (p < 0.01, Table 4). This effect was present already prior to meal administration (p < 0.05, data not shown). Ingestion of the 800 ml meal caused a significant increase in fullness in HC and FD (p < 0.05) and in nausea only in FD (p < 0.05) as compared to preprandial scores (data not shown). In both groups fullness scores were higher for the 800 ml meal than for the 200 ml meal (p < 0.001, Table 4).

There was a linear correlation between mean fullness scores and mean GCV for both meals in HC and FD patients (200 ml meal in HC: r = 0.88, p < 0.001, in FD: r = 0.74, p < 0.01; 800 ml meal in HC: r = 0.99, p < 0.001, in FD: r = 0.99, p < 0.001; Fig. 4). In addition, mean nausea scores were strongly correlated to mean GCV in FD patients (200 ml meal: r = 0.72, p < 0.02; 800 ml meal: r = 0.90, p < 0.01), whereas in HC this correlation could only be demonstrated after ingestion of the 800 ml meal (200 ml meal: r = 0.34, p = 0.32; 800 ml meal: r = 0.78, p < 0.005). On all occasions, FD
patients had higher discomfort scores (AUC_{0-120}) than HC (p = 0.05, Table 4), which were most pronounced early after meal ingestion.
DISCUSSION

This prospective randomized controlled study compared non-invasive gastric MRI with gastric barostat and continuous $^{13}$C-acetate breath testing (BT) by simultaneously assessing gastric function and emptying in FD patients and healthy controls. Important methodological and pathophysiologically observations were made comparing and contrasting measurements acquired by these techniques.

Comparison of gastric emptying assessed by MRI and BT

MR image analysis showed faster gastric emptying (GE) for the high volume (800 ml) than for the isocaloric low volume (200ml) meal in both HC and FD patients. These findings correspond well with earlier reports and confirm that GE is more rapid for higher meal volumes and meals with lower caloric density.(36, 37) Hence, it is surprising that $^{13}$C-stable isotope BT failed to detect the more rapid GE of the high volume meal; $^{13}$CO$_2$ excretion curves were similar for both meals in HC and FD patients, resulting in identical BT emptying half-times. Although the $^{13}$C-acetate delivery rate of the $^{13}$C-marker into the duodenum calculated from direct measurements of GE by MRI was 0.2 mg/min higher for the high volume meal, this difference did not lead to a detectable change in $^{13}$CO$_2$ exhalation kinetics. This indicates that $^{13}$CO$_2$ exhalation depends on factors other than the rate of GE, such as meal volume, osmolarity and caloric density, as well as substrate dose and concentration or differences in metabolic capacity. These issues are being systematically addressed in further studies.(38) This work is essential if $^{13}$C-acetate BT are to be used to assess GE in health and disease using different meal volumes and compositions. The current results suggest that BT results can be compared only if identical test meals and conditions are applied.
Comparison of gastric emptying with and without gastric barostat

Using identical 200 ml meals for BT, a significantly lower GEC and tlag was detected during the concomitant gastric barostat study indicating faster initial gastric emptying; however there was no effect on T½BT. This finding is consistent with a recent report by de Zwaart et al.(9) and indicates that the presence of an intragastric barostat balloon interferes with normal gastric function and early postprandial delivery of nutrients (and 13C-substrate) into the duodenum. It is likely that rapid early gastric emptying is due to volume displacement caused by the large, pressurized intragastric balloon, factors that also explain increased dyspeptic symptoms during barostat studies. The fact that this did not affect T½BT suggests rapid delivery of nutrients to the duodenum early during the barostat study produces a more pronounced neurohormonal response (e.g. Vagal, CCK, GLP-1) and activation of the ‘ileal brake’ (i.e. small intestinal nutrient feedback). This mechanism would promote gastric relaxation and slow gastric emptying such that overall meal emptying half-times in MRI and gastric barostat studies remain similar.

Comparison of gastric volume and meal responses in FD patients and controls

Consistent with the study hypothesis, gastric content volumes measured by MRI immediately after ingestion of the 800 ml meal were lower in FD patients than in HC. TGV₀ and GCV₀ and gastric relaxation after both meals showed a clear trend to lower values in the patient group. These findings indicate more rapid GE during and immediately after meal ingestion in FD patients. This is likely caused by impaired initial gastric relaxation (i.e. accommodation), which is the most commonly reported gastric dysfunction observed in FD patients with early satiety.(1, 39) Similarly gastric barostat measurements revealed that gastric relaxation was slower in FD patients
than in healthy controls with the maximum gastric volume achieved later (although ultimately there was no significant difference in maximum bag volume) (Fig. 3A).

Delayed increase in TGV was the functional correlate on MRI for impaired accommodation detected by barostat in this group of FD patients. These findings suggest that non-invasive MRI assessment of gastric content volumes and total gastric volumes after ingestion of a high volume meal provide a more physiological, sensitive and well-tolerated method to identify disturbed gastric function in FD patients than barostat investigations.

In both, HC and FD patients, the dynamic change of TGV and GCV after ingestion of the 200 ml meal were characterized by a prominent initial volume increase (high coefficient $\kappa$), reflecting a higher rate of gastric secretion than gastric emptying in the early postprandial period. (40, 41) This was not seen after ingestion of the isocaloric high volume meal (Fig. 1A, B), as indicated by the lower coefficient $\kappa$ (Table 2). In both groups, the proceeding pattern of GE was characterized by similar dynamics of TGV, GCV and GAV (Table 3). These findings demonstrate that ingestion of the 800 ml meal is followed by more rapid GE than a 200ml meal, although it cannot be excluded that the low caloric density, low osmolarity meal also stimulated less secretion.

Relationship between gastric volumes and postprandial symptoms

Baseline symptoms before meal ingestion were similar between groups (entry criteria were based on postprandial symptoms with early satiety as a predominant symptom). A significant correlation between gastric content volumes assessed by MRI and fullness for both meals in both groups was present (Fig. 4). In contrast, nausea scores were correlated to mean gastric content volumes only in FD patients and in
HC after ingestion of the large volume meal. Activation of mechanoreceptors in the gastric body and fundus by balloon distension has been shown to induce the sensation of fullness. Consistent with this, perception scores for fullness, nausea and bloating were significantly higher during gastric barostat than during MRI (Table 4); an effect which could already be observed before the meal. The additional volume occupied by the intragastric barostat balloon (150 ml pre-, and 500 ml postprandial) appears to have a similar effect on gastric perception as that induced by higher gastric content volumes. Overall, FD patients and healthy controls had similar aggregate symptom scores during the tests, but despite the limited number of subjects there was a trend for higher dyspeptic symptoms such as discomfort scores in FD patients ($p = 0.053$).

In summary, consistent with the study hypothesis, MRI demonstrated rapid, early gastric emptying during and immediately after meal ingestion in FD patients, likely caused by impaired gastric relaxation in the early postprandial period (i.e. impaired accommodation). In addition, MRI demonstrated more rapid GE following a large compared to a small volume liquid nutrient meal. In contrast, $^{13}$C-acetate BT did not detect any difference between GE of the high and low volume test meals, or between HC and FD patients. We conclude that $^{13}$CO$_2$ exhalation depends on factors other than rate of gastric emptying. The current results suggest that BT results can be compared only if identical test meals and conditions are applied. The presence of a gastric barostat balloon triggered rapid, initial gastric emptying, altered the dynamics of gastric function and was associated with increased dyspeptic symptoms compared to non-invasive imaging. These findings endorse gastric MRI as the more physiological and valid method for the investigation of gastric function in clinical practice and for research purposes in health and disease, when measurements of
both, gastric motor function and emptying are required, for example in pharmacological studies of gastric function.

ACKNOWLEDGMENTS

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LEGENDS (Tables and Figures)

Table 1. Baseline characteristics among healthy controls (HC) and patients with functional dyspepsia (FD). Data are mean ± SD.

BMI, body mass index (kg m⁻²).
Denote: For all parameters $p > 0.05$ between groups.

Table 2. Effects of two different (200 ml vs. 800 ml) isocaloric mixed nutrient liquid meals on gastric volume responses in eight healthy controls (HC) and eight patients with functional dyspepsia (FD) in seated body position (Data are mean ± SD).

$V_{\text{fasting}}$, fasting volume prior to meal administration (ml); $V_0$, initial postprandial volume derived by the gastric emptying model (ml); $V_{\text{relaxation}}$, difference between (measured) initial postprandial volume and $V_{\text{fasting}}$ (ml); $\kappa$, regression estimated constant, defining the initial volume increase after meal ingestion during a lag phase; $T_{1/2\text{MRI}}$, gastric emptying half-time as assessed by MRI (min).

* $p < 0.05$ vs. HC (unpaired Student’s $t$-test)
^ $p = 0.07$ vs. HC
\( p = 0.08 \) vs. HC, all by linear mixed effects model

Denote: For all parameters $p < 0.05$ for GCV vs. TGV.
For all parameters, except for $V_{\text{fasting}}$, $p < 0.001$ for 800 ml vs. 200 ml.

Table 3. Effects of two different (200 ml vs. 800 ml) isocaloric mixed nutrient liquid meals on gastric air volume in eight healthy controls (HC) and eight patients with functional dyspepsia (FD) in seated body position (Data are mean ± SD).
GAV_{fasting}, gastric air volume prior to meal administration (ml); GAV_{pp}, initial postprandial gastric air volume (ml); GAV_{relaxation}, difference in postprandial and preprandial gastric air volume (GAV_{pp} - GAV_{fasting}, ml).

# $p < 0.05$ vs. GAV_{fasting}
* $p < 0.05$ vs. 200 ml
† $p = 0.06$ vs. 200 ml
§ $p = 0.07$ vs. 200 ml

**Table 4**: $^{13}$C-acetate breath test results (mean ± SD) and dyspeptic symptoms (mean AUC$_{0-120}$ ± SEM) after ingestion of two isocaloric mixed nutrient liquid meals of 200 and 800 ml volume, both labeled with 100 mg $^{13}$C-acetate, during simultaneous MRI or gastric barostat study in healthy controls (HC) and patients with functional dyspepsia (FD) in seated body position.

GEC, gastric emptying coefficient; $t_{lag}$, gastric emptying lag time (min); T$_{1/2}$, gastric emptying half-time as assessed by BT (min); AUC$_{0-120}$, area under the curve of the log-transformed VAS sensation scores (mm*min) for the whole measurement period of 120 min.

* $p < 0.05$ vs. MRI 200 ml by linear mixed effects model
** $p < 0.01$ vs. MRI 200 ml by linear mixed effects model
*** $p < 0.001$ vs. MRI 200 ml by linear mixed effects model
† $p = 0.053$ vs. HC
Figure 1. Gastric emptying after meal ingestion as assessed by MRI (A, B) and simultaneous $^{13}$C-acetate breath test (C). A) Average total gastric volumes (dotted lines) and gastric content volumes (solid lines) derived from the gastric emptying model after ingestion of the 800 ml mixed nutrient liquid meal (rectangles) and B) after administration of the isocaloric 200 ml meal (triangles), both in healthy controls (HC; open symbols) and patients with functional dyspepsia (FD; solid symbols). The dotted arrows indicate the average gastric content emptying half-times ($T_{1/2}^{MRI}$) which are lower for the 800 ml meal ($p < 0.001$), but similar in HC and FD. C) Similar average $^{13}$CO$_2$-excretion curves as assessed by breath test, expressed as percentage dose of $^{13}$C recovered (PDR). Each meal was labeled with 100 mg $^{13}$C-acetate. No significant difference was observed between the two test meal volumes.

Figure 2. Postprandial changes in gastric volumes. Correlation between change in gastric air volume ($GAV_{relaxation}$) and change in total gastric volume ($TGV_{relaxation}$) in healthy controls (HC, open symbols) and patients with functional dyspepsia (FD, solid symbols) after A) ingestion of the low volume (200 ml) mixed nutrient liquid meal and B) after administration of the isocaloric high volume (800 ml) meal. The unique markers indicate the corresponding data after both test meals in one healthy control (triangle, HC #1) and in one patient with functional dyspepsia (square, FD #5); the latter was shown to have “impaired accommodation” by barostat.

Figure 3. Results of barostat measurements. A) Mean intragastric balloon volume (± SEM) at distinct time intervals in seven healthy controls (HC, open symbols) and seven patients with functional dyspepsia (FD, solid symbols) Maximum relaxation of
the gastric fundus was reached earlier in HC than in FD (p < 0.02). B) Gastric accommodation to a meal was similar in healthy controls (HC) and patients with functional dyspepsia (FD). Individual values are shown as dots; mean and SD are shown as bars. Dotted line: lower normal range of meal-induced gastric relaxation (mean$_{HC} - 2$SD$_{HC}$).

Figure 4. Association between gastric content volume (GCV) and sensation of fullness in healthy controls (HC, open symbols) and patients with functional dyspepsia (FD, solid symbols) after A) ingestion of the low volume (200 ml) meal and B) after administration of the isocaloric high volume (800 ml) meal. Data are means (grouped by time point of measurement) with linear regression line and the 95% C.I..
Table 1. Baseline characteristics among healthy controls (HC) and patients with functional dyspepsia (FD). Data are mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>HC (n=8)</th>
<th>FD (n=8)</th>
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</thead>
<tbody>
<tr>
<td>Gender (m/w)</td>
<td>5 / 3</td>
<td>5 / 3</td>
</tr>
<tr>
<td>Age (y)</td>
<td>29 ± 5</td>
<td>34 ± 13</td>
</tr>
<tr>
<td>Weight (kg)</td>
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<td>67 ± 15</td>
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<td>Height (cm)</td>
<td>174 ± 6</td>
<td>173 ± 15</td>
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<tr>
<td>BMI (kg m⁻²)</td>
<td>21.4 ± 1.6</td>
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<tr>
<td>Fullness (VAS mm)</td>
<td>1.0 ± 2.6</td>
<td>4.8 ± 13.0</td>
</tr>
<tr>
<td>Nausea (VAS mm)</td>
<td>0.3 ± 0.5</td>
<td>1.3 ± 2.3</td>
</tr>
<tr>
<td>Bloating (VAS mm)</td>
<td>0.3 ± 0.5</td>
<td>5.6 ± 13.6</td>
</tr>
<tr>
<td>Discomfort (VAS mm)</td>
<td>0.3 ± 0.6</td>
<td>1.5 ± 1.8</td>
</tr>
</tbody>
</table>

BMI, body mass index (kg m⁻²).

Denote: For all parameters p > 0.05 between groups.
Table 2. Effects of two different (200 ml vs. 800 ml) isocaloric mixed nutrient liquid meals on gastric volume responses in eight healthy controls (HC) and eight patients with functional dyspepsia (FD) in seated body position (Data are mean ± SD).

<table>
<thead>
<tr>
<th>Units</th>
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<td></td>
<td>TGV</td>
<td>GCV</td>
<td>TGV</td>
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<tr>
<td>V\text{fasting}</td>
<td>[ml]</td>
<td>152±41</td>
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<td>V\text{relaxation}</td>
<td>[ml]</td>
<td>203±22</td>
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<tr>
<td>V\text{0}</td>
<td>[ml]</td>
<td>346±47</td>
<td>26±18</td>
<td>927±108</td>
</tr>
<tr>
<td>\kappa</td>
<td></td>
<td>1.40±0.36</td>
<td>1.48±0.21</td>
<td>0.81±0.32</td>
</tr>
<tr>
<td>T\text{\textsubscript{1/2}}\text{MRI}</td>
<td>[min]</td>
<td>137±37</td>
<td>117±30</td>
<td>74±12</td>
</tr>
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</table>

V\text{fasting}, fasting volume prior to meal administration (ml); V\text{0}, initial postprandial volume derived by the gastric emptying model (ml); V\text{relaxation}, difference between (measured) initial postprandial volume and V\text{fasting} (ml); \kappa, regression estimated constant, defining the initial volume increase after meal ingestion during a lag phase; T\text{\textsubscript{1/2}}\text{MRI}, gastric emptying half-time as assessed by MRI (min).

* $p < 0.05$ vs. HC (unpaired Student’s t-test)

\* $p = 0.07$ vs. HC

\*\* $p = 0.08$ vs. HC, all by linear mixed effects model

Denote: For all parameters $p < 0.05$ for GCV vs. TGV.

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**Table 3.** Effects of two different (200 ml vs. 800 ml) isocaloric mixed nutrient liquid meals on gastric air volume in eight healthy controls (HC) and eight patients with functional dyspepsia (FD) in seated body position (Data are mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>HC</th>
<th>FC</th>
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</thead>
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<tr>
<td></td>
<td>200</td>
<td>800</td>
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<tr>
<td>GAV_{fasting}</td>
<td>85±50</td>
<td>75±62</td>
</tr>
<tr>
<td>GAV_{pp}</td>
<td>94±45</td>
<td>114±54**</td>
</tr>
<tr>
<td>GAV_{relaxation}</td>
<td>8± 31</td>
<td>39±42†</td>
</tr>
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GAV_{fasting}, gastric air volume prior to meal administration (ml); GAV_{pp}, initial postprandial gastric air volume (ml); GAV_{relaxation}, difference in postprandial and preprandial gastric air volume (GAV_{pp} - GAV_{fasting}, ml).

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<table>
<thead>
<tr>
<th></th>
<th>HC Barostat 200 ml (n=7)</th>
<th>HC MRI 200 ml (n=8)</th>
<th>HC Barostat 800 ml (n=8)</th>
<th>HC MRI 200 ml (n=7)</th>
<th>HC MRI 800 ml (n=8)</th>
<th>FD Barostat 200 ml (n=8)</th>
<th>FD MRI 200 ml (n=8)</th>
<th>FD Barostat 800 ml (n=8)</th>
<th>FD MRI 800 ml (n=8)</th>
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<tr>
<td>GEC</td>
<td>3.7 ± 0.2 *</td>
<td>3.9 ± 0.4</td>
<td>3.8 ± 0.1</td>
<td>3.5 ± 0.3 *</td>
<td>3.8 ± 0.2</td>
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<tr>
<td>t$_{lag}$</td>
<td>60 ± 11 **</td>
<td>69 ± 10</td>
<td>71 ± 14</td>
<td>66 ± 20 **</td>
<td>71 ± 15</td>
<td>65 ± 12</td>
<td></td>
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<tr>
<td>T½BT</td>
<td>110 ± 12</td>
<td>111 ± 11</td>
<td>114 ± 14</td>
<td>130 ± 11</td>
<td>116 ± 19</td>
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<tr>
<td>Fullness</td>
<td>126 ± 10</td>
<td>87 ± 17</td>
<td>132 ± 10</td>
<td>128 ± 10</td>
<td>89 ± 23</td>
<td>134 ± 10</td>
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<tr>
<td>Nausea</td>
<td>99 ± 11 **</td>
<td>66 ± 12</td>
<td>62 ± 11</td>
<td>112 ± 11 **</td>
<td>80 ± 15</td>
<td>76 ± 11</td>
<td></td>
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<tr>
<td>Bloating</td>
<td>91 ± 10 **</td>
<td>62 ± 16</td>
<td>79 ± 9</td>
<td>124 ± 10 **</td>
<td>95 ± 21</td>
<td>112 ± 9</td>
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<tr>
<td>Discomfort</td>
<td>64 ± 7</td>
<td>63 ± 7</td>
<td>63 ± 6</td>
<td>80 ± 7 †</td>
<td>80 ± 8 †</td>
<td>79 ± 6 †</td>
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</table>

GEC, gastric emptying coefficient; t$_{lag}$, gastric emptying lag time (min); T½BT, gastric emptying half-time as assessed by BT (min); AUC$_{0-120}$, area under the curve of the log-transformed VAS sensation scores (mm*min) for the whole measurement period of 120 min.

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