Original research

Optimal measurement of gastric emptying of solids in gastroparesis or functional dyspepsia: evidence to establish standard test

Michael Camilleri, Ting Zheng, Kia Vosoughi, Camille Lupianez-Merly, Deborah Eckert, Irene Busciglio, Duane Burton, Saam Dilmaghani

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Gastroenterology, Mayo Clinic, Rochester, Minnesota, USA

Correspondence to
Dr Michael Camilleri, Gastroenterology, Mayo Clinic, Rochester, Minnesota, USA; camilleri.michael@mayo.edu

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ABSTRACT

Objective Symptoms in gastroparesis (Gp) and functional dyspepsia (FD) overlap; using egg protein substitute to measure gastric emptying of solids (GES), ~40% of patients are reclassified from Gp to FD, and vice versa. Our aim was to assess inter-individual and intra-individual coefficients of variation (COV) in GES in symptomatic patients with Gp or FD with documented slow or normal GES, respectively.

Design Scintigraphic GES ($T_{1/2}$ and GE% at 2 and 4 hours) using a 320 kcal real egg meal (30% fat) was tested in the following: single measurements in 20 patients with diabetes mellitus (10 each type 1 and type 2); repeat GES to estimate COV_{intra} measured: 3 days apart in 9 Gp, 4 weeks apart in 21 Gp and 18 with FD with normal GE assigned to placebo and in 70 patients at 94.3 weeks (median) apart.

Results COV_{inter} for GE% at 4 hours and GE $T_{1/2}$ were respectively 14.2% and 23.5% in FD and 27.5% and 33% in Gp; COV_{intra} for GE% at 4 hours and GE $T_{1/2}$ up to 4 weeks apart were 23.4% and 37.9% in FD and 20.1% and 33% in Gp. GE% at 2 hours showed less consistent results. However, >85% retained original diagnosis as normal or delayed. From clinical GES to baseline research for Gp group, repeat GES (after treatment) showed the COV_{intra} for GE% at 4 hours was 37.3% at median 94.3 weeks, with 26/70 changed diagnoses.

Conclusion The 320 kcal (30% fat) GES scintigraphic test provides consistent diagnosis in >85% and should be the standard test for suspected gastric emptying disorders.

WHAT IS ALREADY KNOWN KNOWN ON THIS TOPIC

⇒ Based on a published report on intra-individual variations in results of gastric emptying test using egg protein substitute, about 40% patients are reclassified from gastroparesis to functional dyspepsia and vice versa.

WHAT THIS STUDY ADDS

⇒ Using a 320 kcal, 30% fat real egg (standard size) meal, intra-individual variations are lower, especially percentage emptied at 4 hours, and 85% of patients are consistently diagnosed with gastroparesis (with slow gastric emptying) or functional dyspepsia with normal gastric emptying.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides further validation that policymakers should consider, specifically, that the real egg meal should become the clinical and research standard for assessing gastric emptying in patients with suspected gastroparesis or functional dyspepsia with normal gastric emptying.

INTRODUCTION

An optimal method to measure gastric emptying (GE) is of paramount importance for clinical practice and research. Earlier research suggested that GE delay and symptoms may not be correlated[1] or that symptomatic responses to treatment may not be associated with improved GE.[2] Other studies have demonstrated association of delayed GE and symptoms,[3] confirmed in an analysis of the literature for significant association of optimally measured GE with upper GI symptoms, particularly the individual symptoms of nausea and vomiting.[4] A meta-regression of therapeutic studies has shown a significant association of reduction in GE $T_{1/2}$ (ie, acceleration of GE) with a significant recognisable clinical improvement of upper GI symptoms.[5]

National societies[6] endorse measurement of GE of solids (GES) in clinical practice for identification of abnormalities in gastric motor functions, for investigation of pathophysiological mechanisms that might contribute to patients' symptoms, and for evaluation of efficacy of approved or unapproved prokinetic agents. Although stable isotope breath tests are also approved for clinical appraisal of patients with suspected GE delay,[7] scintigraphic measurement of GE continues to be the most commonly used method. However, among 339 patients referred to a tertiary centre for suspected gastroparesis, only 196 patients (57.8%) had been evaluated with a GE study; 130 of these patients (38.3%) had undergone a 4-hour GE study but only 23 patients (6.8%) ingested radiolabelled eggs as the test meal. Sixty-six patients (19.5%) were ultimately confirmed to have gastroparesis, whereas 273 (80.5%) received an alternative diagnosis.[8]

Optimisation of GE measurement is therefore critically important. Performance characteristics of

the measurements of GES in healthy adult participants have been previously documented in the literature[9 10] based on the emptying of a 320 kcal, 30% fat egg meal. The latter study[10] also provided information regarding inter-individual and intra-individual coefficients of variation (COV) in 319 healthy adults (214 females, 105 males), which were predictably lowest for the per cent emptied from the stomach at 4 hours (GE4h (COV_{inter}, 9.6%)); the overall COV_{intra} for GE $T_{1/2}$ was 23.8% and for GE4h was 12.6%.[10] An alternative meal composed of egg-protein substitute (Egg Beaters) used in many studies[11] uses >10% retained at 4 hours as a cut-off for diagnosing delayed GE based on the 95 percentile in 100 healthy volunteers studied at multiple centres. Others have determined that this test has not been widely adopted and instead proposed use of the Nottingham Test Meal (NTM) consisting of 400 mL liquid nutrient (0.75 kcal/mL with ^{111}In radiolabel) and an optional solid component (12 solid agar-beads, 0 kcal, with ^{99m}Tc radiolabel).[12] With this test meal, the GE $T_{1/2}$ with the liquid-component and solid-component NTM was median 44 min (95% CI of the mean in 74 healthy adults of 28–78 min) and 162 min (144–193 min), respectively.[13] This approach has been applied using liquid GE alone in 330 consecutive adult, patients without diabetes with dyspeptic symptoms and estimated the IQR for $T_{1/2}$ from 61 healthy controls (38–56 min) and revealed frequently observed patterns included normal early phase with slow late-phase (25%) and fast early phase with slow late-phase emptying (27%).[14] There is evidence that such a caloric liquid meal empties at approximately the same rate with the same pattern of emptying as the Egg Beaters meal.[15]

For the liquid nutrient and the Egg Beaters meal, there are, to date, no reported intra-individual variations reported. Intra-individual variations among patients with gastroparesis have scarcely been documented in the literature. A prior study documented the intersubject and intrasubject variability of GES, but the sample size was only 26, with 14 patients with diabetes and 12 healthy controls.[16] In 61 patients with upper GI symptoms (21 patients with diabetes) who underwent GE measurements twice with the same 320 kcal, 30% fat egg meal, performed with an average interval of 15 days apart, the COV_{inter} for GE $T_{1/2}$ was 40% and the COV_{intra} was 20%. These COV measurements were similar in patients with diabetes and in those who did not have diabetes.[17] It is worth noting, however, that the COV_{intra} for GE $T_{1/2}$ was higher in patients with rapid (28%) GE than in those with delayed (18%) GE or those with normal GE (12%). Conversely, the COV_{intra} for GE% emptied at 4 hours was lower (3%) in patients with rapid emptying compared with 19% with delayed emptying and 12% with normal emptying.[17]

The National Institutes of Health Gastroparesis Consortium documented symptom overlap in patients with gastroparesis and functional dyspepsia, and the symptoms were associated with differences in GE measurements[18] at 4 hours that used the lower calorie and low fat (2%) meal (Egg Beaters). The study showed that, over 48 weeks, 42% of patients with an initial diagnosis of gastroparesis were reclassified as having functional dyspepsia based on normalisation of GE results (<10% retained at 4 hours) at 48 weeks after receiving treatment for gastroparesis; conversely, 37% of patients with functional dyspepsia were reclassified as having gastroparesis based on >10% retained at 4 hours on GE test at 48 weeks.[18]

Given these findings, it is necessary to further characterise the variations between and within patients with upper GI symptoms, particularly in patients with diabetes mellitus and in patients with the prior diagnosis of gastroparesis based on slow GE or functional dyspepsia with normal GE. The current cohort studied differs from our prior study of patients with upper GI symptoms,[17] in that the current study of intrasubject COV was conducted in patients with confirmed gastroparesis based on slow GE as well as in patients with functional dyspepsia with normal GE.[17] Thus, our aims were to assess COV_{inter} of scintigraphic measurements of GE conducted in prior studies in patients with type 1 diabetes or idiopathic gastroparesis and in patients with type 2 diabetes and gastroduodenal symptoms,[19 20] and to measure COV_{intra} in patients with proven gastroparesis by comparing results at baseline and after treatment for 3 days with placebo in a randomised, parallel-group design trial of the effects of felcisetrag[21] or after treatment for 4 weeks[22 23] in randomised, parallel-group design trials of the effects of cannabidiol (CBD).

MATERIALS AND METHODS

Data source

We retrospectively obtained data from a database of published GE studies conducted in patients with type 1 or 2 diabetes[19 20] who reported having gastroduodenal symptoms and who had previously participated in placebo-controlled, crossover trials of the effects of RM-131 (relamorelin). A second cohort[21] consisted of patients with an established diagnosis of gastroparesis (seven idiopathic, three diabetic) who had previously participated in a parallel-group, randomised, controlled trial of felcisetrag. Two additional cohorts with documented GE of the same 320 kcal, 30% fat meal with gastroparesis[23] or functional dyspepsia with normal GE[22] who participated in a placebo-controlled, parallel-group, 4-week duration study of CBD were also included in the current analysis. These cohorts are summarised in table 1.

For all these participants, only the data from the placebo treatment arm were used, and for the patients with gastroparesis in the felcisetrag and CBD studies and those with functional

Table 1 Overview of cohorts and data used for analysis of performance of gastric emptying studies

Study cohort	Disease/Condition	Medication	Design of placebo-controlled RCT	Data used	N for intersubject analysis	N for intrasubject analysis
Cohort 1 (RM-131 (relamorelin) study)	Type 1 or 2 DM with gastroduodenal symptoms	RM-131 (relamorelin)	Crossover	Placebo arm (baseline only)	20 (10 DM1, 10 DM2)	NA
Cohort 2 (felcisetrag study)	Gastroparesis	Felcisetrag	Parallel group	Placebo arm (baseline and day 3)	10*	9
Cohort 3 (CBD study—gastroparesis)	Gastroparesis	CBD	Parallel group	Placebo arm (baseline and week 4)	23	21
Cohort 4 (CBD study—functional dyspepsia)	Functional dyspepsia	CBD	Parallel group	Placebo arm (baseline and week 4)	18	18

*One participant had incomplete data during placebo treatment and was excluded from the intrasubject analysis.
CBD, cannabidiol; DM, diabetes mellitus; NA, not available; RCT, randomised controlled trial.

dyspepsia in the CBD study, we used both sets of data at baseline and at the end of treatment during which participants had been randomised in a blinded manner to placebo.

For 70 patients who participated in the studies, we also compared the results of the diagnostic GES test performed in the clinical nuclear medicine lab with the baseline GES performed in the research lab.

Our research team (gastroenterologists, nurses, technologists, study coordinators) evaluated all the participants in specific studies conducted by our research team in our Clinical Research Trials Unit. All participants underwent clinical evaluations including physical examination and review of their medical records to be sure there were no additional confounders that could alter their GE results such as opioid use or concomitant treatment with agents that could retard GE. Additional details regarding the clinical manifestations of the participants are included in the previously published articles.[19–23]

Gastric emptying study

We measured GE by our established, validated scintigraphic method.[10] Patients ate a ^{99m}Tc-labelled meal of two scrambled eggs (standard size), one slice of whole wheat bread and one glass (240 mL) of skim (<1% fat) milk (320 kcal, 30% fat) after fasting overnight for at least 8 hours. Abdominal images were obtained with a gamma camera, each for a duration of 2 min. The images were taken with an anterior view and a posterior view immediately after eating the radiolabelled egg meal. Additional anterior and posterior images were then obtained at specified times over the next 4 hours: every 15 min during the first 2 hours, and every 30 min during the last 2 hours. All clinical diagnostic studies included at least GE results at 1 hour, 2 hours and 4 hours. In preparation for the GE studies performed in the clinical diagnostic lab, or the research lab, all study participants were informed not to take any prescription or over-the-counter medications that could interfere with GE for at least 48 hours before and during their tests. Patients with diabetes participating in research GE tests undergo measurement of fasting blood glucose with correction of levels >250 mg/dL with short-acting insulin SQ, based on a standard algorithm.

Data collection

We quantified transit measurements based on ^{99m}Tc counts measured within a 140 keV (±20%) window. To quantify the counts in the stomach, we used a variable region of interest programme, and all regions of interest were drawn by one technologist (DB). Our primary end point was the GE $T_{1/2}$, which was estimated from a plot that linearly interpolated the imaging data obtained during the 4 hours after eating the radiolabelled meal. We also quantitated the GE results by the per cent (%) emptied from the stomach at 1 hour, 2 hours, 3 hours and 4 hours after eating the radiolabelled meal. This was consistent with previous publication that such data provide clinically relevant information,[11 24] providing the basis for the consensus recommendations of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine.[6] These end points were shown to be relevant as optimal measurement of GE that correlated with upper GI symptoms and responsiveness to prokinetic agents.[4 5]

Assessments of inter-individual and intra-individual variations in gastric emptying measurements

The intersubject variations (COV_{inter}) were estimated from the transit parameters (GE $T_{1/2}$, GE2h and GE4h) among 20 participants with type 1 or type 2 diabetes with gastroduodenal symptoms when they received placebo in the crossover studies. In the parallel-group designed studies with felcisetrag[21] and CBD,[22 23] the baseline measurement was used to estimate the COV_{inter} for the patients with functional dyspepsia or gastroparesis.

Intrasubject variations (COV_{intra}) were derived from the two transit values obtained 3 days apart for the 9 patients with gastroparesis (felcisetrag trial[21] in which one participant had incomplete data during placebo treatment and was excluded from the intrasubject analysis), 21 patients with gastroparesis (CBD trial[23]) and 18 patients with FD (CBD trial[22]) who were blindly randomised to placebo treatment. COV_{intra} was also calculated for 70 patients in whom there was measurement of GES using the same method in the clinical diagnostic practice and compared with the measurement obtained during placebo treatment in the respective clinical trials. For these patients, we also estimated the time lag in weeks between the two measurements.

Statistical analysis

We used descriptive statistics to summarise participant demographics in each of the three groups as well as GE end points; all these data are mean±SEM.

The COV_{inter} were calculated by the SD divided by the mean and expressed as a per cent. The COV_{intra} was calculated for the patients with functional dyspepsia or gastroparesis randomly assigned to treatment with placebo who were studied on two occasions (at baseline and at the end of treatment with placebo) by dividing the SD of the within-subject differences by the overall (grand) mean of the corresponding transit measurements[10] and expressed as a per cent. Bland-Altman plots[25] were used to assess visually the intrasubject variations in GE. Spearman's correlations were performed to assess correlations, for example, between measurements at baseline and after placebo treatment. All statistical analyses were conducted using SigmaPlot V.12 (Systat Software, San Jose, California, USA).

RESULTS

Inter-individual coefficient of variation

Table 2 summarises the demographic features of the patient cohorts and COV_{inter} for each group of patients in the different studies. The first group of 20 patients with diabetes included those with or without gastroparesis, and their clinical characteristics as described in the original trials are available in online supplemental table 1. Their COV_{inter} reflected the prior clinical diagnoses, with higher COV_{inter} compared with the more defined cohorts with functional dyspepsia or established gastroparesis. This is illustrated by the COV_{inter} of 44.9% compared with 23.5% in functional dyspepsia and 33% in gastroparesis. For all groups, the COV_{inter} was lowest for GE% emptied at 4 hours, and highest for GE% emptied at 2 hours.

Intra-individual coefficient of variation between baseline, and end of placebo treatment

Figure 1 shows the parameters of GE $T_{1/2}$ and per cent emptied at 2 hours and 4 hours in 17 patients with functional dyspepsia and documented normal GE. The correlation curves with 95% CI show consistent results, and the upper limits of normal range (174 min for GE $T_{1/2}$, 25% for GE at 2 hours and 75% for GE at 4 hours) document the misclassification of GE on repeat tests in only three patients. Bland-Altman plot (figure 2) shows consistency of GE data for the majority of patients with functional dyspepsia, with the vast majority of the replicate data within

Table 2 Gastric emptying results at first (or baseline) measurement of different groups as well as COV_{inter}

Group	N	Age (year)	Sex (F/M)	BMI (kg/m^2)	GE2h (%)	GE4h (%)	$T_{1/2}$ (min)
DM1 or IG+GD symptoms	10	45.7±4.4	8/2	24.1±1.1	22.0±3.7	68.0±5.7	206±27
DM2+GD symptoms	10	51.8±2.5	10/0	31.1±1.7	51.7±10.8	83.8±4.7	128±19
COV_{inter} DM1, IG and DM2	20				60.0%	22.6%	44.9%
Functional dyspepsia (CBD trial)	18	33.6±2.8	13/5	25.40±1.18	47.2±7.5	86.1±2.9	140.6±7.8
COV_{inter} functional dyspepsia	18				39.9%	14.2%	23.5%
Gastroparesis (felcisetrag trial)	10	46.7±5.0	8/2	24.63±1.75	21.7±3.4	68.3±5.4	206±22
Gastroparesis (CBD trial)	23	42.3±3.0	18/5	27.44±1.04	25.0±3.3	68.1±4.0	209±14
Combined gastroparesis (felceistrag+CBD trial)	33	43.6±2.5	26/7	26.59±0.91	24.0±2.5	68.2±4.7	208±12
COV_{inter} gastroparesis	33				60.6%	27.5%	33.0%

Data are mean±SEM or per cent variation.
BMI, body mass index; CBD, cannabidiol; COV_{inter}, intersubject coefficient of variation; DM, diabetes mellitus, type 1 or type 2; F, female; GD, gastroduodenal; GE, gastric emptying; IG, idiopathic gastroparesis; M, male.

40 min difference for GE $T_{1/2}$, 20% difference for GE at 2 hours and 10% difference for GE at 4 hours. The COV_{intra} are also documented in table 3, in which it is noted that the data are more consistent for GE% emptied at 4 hours (16.6%) and GE $T_{1/2}$ (21.2%), compared with GE% emptied at 2 hours (33.1%).

Figure 3 shows combined data for the patients with gastroparesis and previously documented delayed GE who received placebo when they participated in parallel-group, randomised treatment trials with felcisetrag[21] (3 days) and CBD[22 23] (4 weeks). As shown in the lower panel of figure 3, correlations with 95% CI of the regression line document the general trends of the correlations between the two measurements for all three end points. In addition, in comparison with the upper limit of normal ranges shown by interrupted lines (174 min for GE $T_{1/2}$, 25% for GE at 2 hours and 75% for GE at 4 hours), it is noted that one patient had normal GE on repeat testing using GE $T_{1/2}$, and that four patients had normal GE% emptied at 2 hours, and three patients had normal GE% emptied at 4 hours with two of these three patients being within 5% of the cut-off value of 75% emptied.

Figure 4 is a Bland-Altman plot showing consistency of GE data for the majority of patients with gastroparesis. The vast majority of the replicate data are within 60 min difference for GE $T_{1/2}$, 20% difference for GE at 2 hours and 20% difference for GE at 4 hours. Importantly, despite the variation, only four patients were inconsistently classified on repeat testing (see regression analysis in figure 3), with two patients having data close to the cut-off values.

Table 3 also documents the consistent intra-individual measurements for the patients with gastroparesis. Thus, for the entire group with gastroparesis, COV_{intra} was 20.1% for GE% emptied at 4 hours and 33.1% for GE $T_{1/2}$. As in the patients with functional dyspepsia, the COV_{intra} in patients with gastroparesis was numerically higher for GE% at 2 hours (49.7%).

Comparison of data obtained during clinical diagnostic test and research test

For 70 patients, data were available to compare GE% at 2 hours and 4 hours, based on the same GE test conducted in the clinical diagnostic laboratory and the subsequent measurement of GE at baseline in the research laboratory. The age of the patients was 54.3±2.5 (SEM) years, and BMI was 26.3±0.6 kg/m^2. The two tests were conducted with a median interval of 94.3 weeks (10th

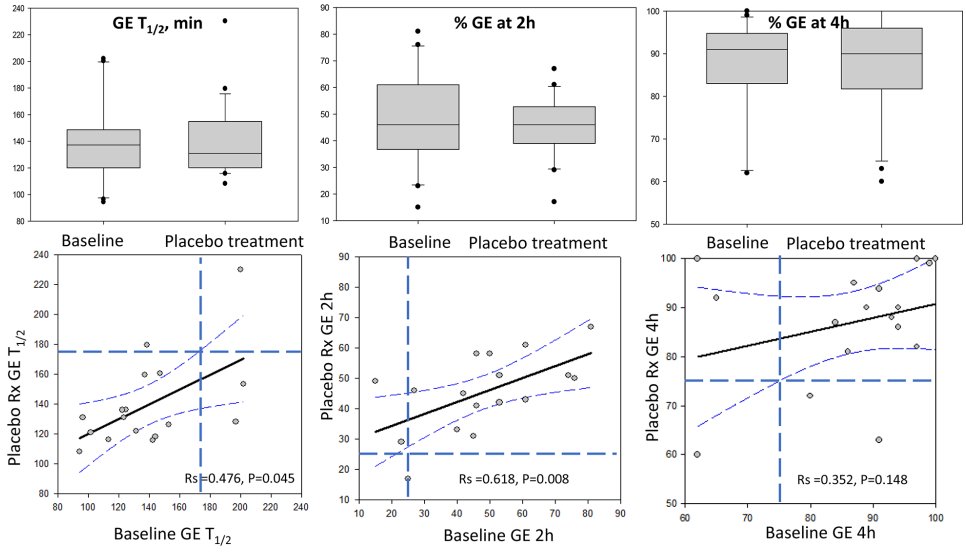

Figure 1 Parameters of gastric emptying (GE) of solids in patients with functional dyspepsia and documented normal GE showing IQR, 5% and 95% CI and outliers at baseline and after treatment with placebo for 4 weeks (upper panel). Lower panel shows correlations with 95% CI of regression and upper limit of normal range shown by interrupted lines (174 min for GE $T_{1/2}$, 25% for GE at 2 hours and 75% for GE at 4 hours). Note three patients had delayed emptying on repeat test.

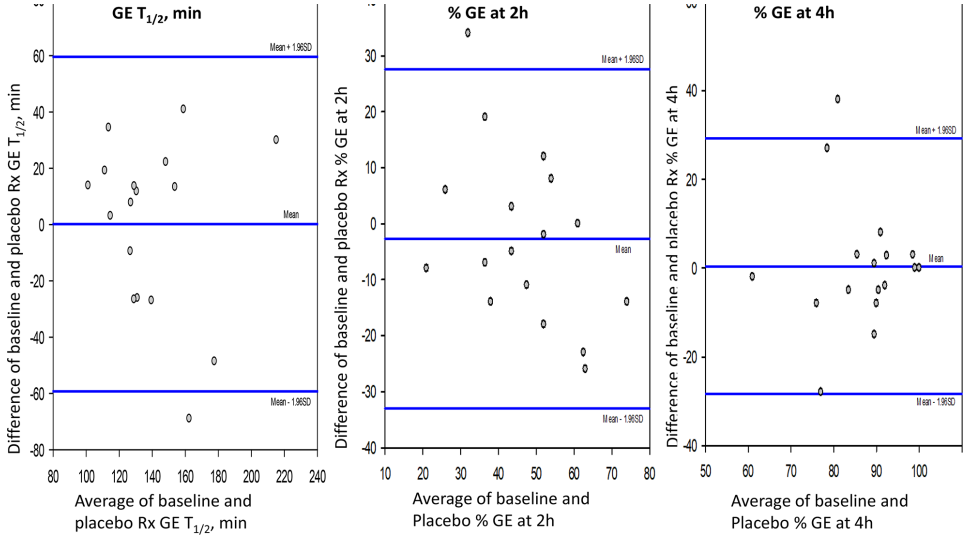

Figure 2 Bland-Altman plot showing consistency of gastric emptying (GE) data for the majority of patients with functional dyspepsia. The vast majority of the replicate data are within 40 min difference for GE $T_{1/2}$, 20% difference for GE at 2 hours and 10% difference for GE at 4 hours.

and 90th percentile of 6–499 weeks). Figure 5 shows there was no significant difference in GE% at 2 hours ($p=0.145$ on signed rank test); however, there was a significant difference in GE% at 4 hours ($p<0.001$). The lower panel also shows the GE% at 4 hours data are consistent between the two tests in 46/70 patients, and the majority of variations are observed in the 24 patients shown in the left upper quadrant of the figure where the second estimate showed normal results, reflecting either variation over a median 94 weeks or effects of therapeutic interventions administered over the time interval between the diagnostic test and subsequent participation in the research trial.

Figure 6 shows consistency in the difference in GE% at 4 hours over the interval in weeks between the two tests (clinical diagnostic vs research). The consistency of the difference is best demonstrated in the time interval 0–200 weeks.

DISCUSSION

Our data document the COV_{inter} and COV_{intra} in GE parameters in patients with symptoms consistent with gastroparesis or functional dyspepsia when using a 320 kcal, 30% fat meal. The data also show that, in all groups studied, the per cent variations were greater for GE% at 2 hours, and the parameter with the lowest COV_{inter} and COV_{intra} was GE% at 4 hours. Nevertheless, GE $T_{1/2}$ showed better performance characteristics than GE% at 2 hours and, given the clinical significance of this parameter, it appears to be a useful assessment of GE. To amplify the significance of COV_{intra} of 20.1% for GE% emptied at 4 hours in a patient with gastroparesis indicates that repeating the GE test in the same individual would be expected to vary by approximately 20.1% from the average measurement. For example, if the first result was 60% emptied at 4 hours, the repeat test result would be expected to be in the range 48−72% (both of which would still indicate delayed GE% at 4 hours (<75%)). Applying the COV_{intra} of 16.6% for GE% at 4 hours in a patient with functional dyspepsia whose GE% was at the group's mean value of 86.1% emptied, the repeat test result would be expected to be in the range 72%–100%, that is, the vast majority of GE% at 4 hours would again be in the normal range. Similarly, based on COV_{intra} of 33.1% for GE $T_{1/2}$ in patients with gastroparesis, if one assesses the impact on the group mean of 214.4 min, the repeat test result would be expected to be in the range 143.4–281 min, with the vast majority with slow GE $T_{1/2}$ (≥175 min).

Indeed, another extremely valid observation is that, when assessed over 3 days or 4 weeks, these GE data (GE% at 4 hours and $T_{1/2}$) are sufficiently consistent to be associated with the same diagnosis in about 85% of either delayed GE in gastroparesis or normal GE in patients with functional dyspepsia selected based on previously documented normal GE. This contrasts with the report of approximately 40% of GE results swinging from delayed to normal or vice versa observed in the NIH Consortium

Table 3 GE results at first (or baseline) measurement of different groups as well as COV_{intra} based on change postplacebo treatment

COV_{intra} for group	N	Age (year)	Sex (F/M)	BMI (kg/m^2)	GE2h (%)	GE4h (%)	$T_{1/2}$ (min)
Functional dyspepsia	18*	33.6±2.8	13/5	25.40±1.18	47.2±7.5	86.1±2.9	140.6±7.8
COV_{intra} functional dyspepsia					33.1%	16.6%	21.2%
Gastroparesis (felcisetrag trial)	9	45.7±5.4	7/2	24.61±1.95	21.7±3.8	69.8±5.8	204.1±24.9
COV_{intra} gastroparesis (felcisetrag)					44.0%	23.4%	37.9%
Gastroparesis (CBD trial)	21	42.4±3.2	17/4	27.86±1.09	23.4±3.4	67.1±4.3	214.4±15.2
COV_{intra} gastroparesis (CBD trial)					51.2%	19.1%	31.5%
Combined gastroparesis (felcisetrag+CBD trial)	30	43.4±2.7	24/6	26.88±0.98	22.9±2.6	67.9±3.4	211.3±12.8
COV_{intra} gastroparesis (felcisetrag+CBD trial)					49.7%	20.1%	33.1%

Data are mean±SEM or % variation.
*One missing value at GE 2 hours, % emptied.
BMI, body mass index; CBD, cannabidiol; COV_{inter}, intersubject coefficient of variation; F, female; GE, gastric emptying; M, male.

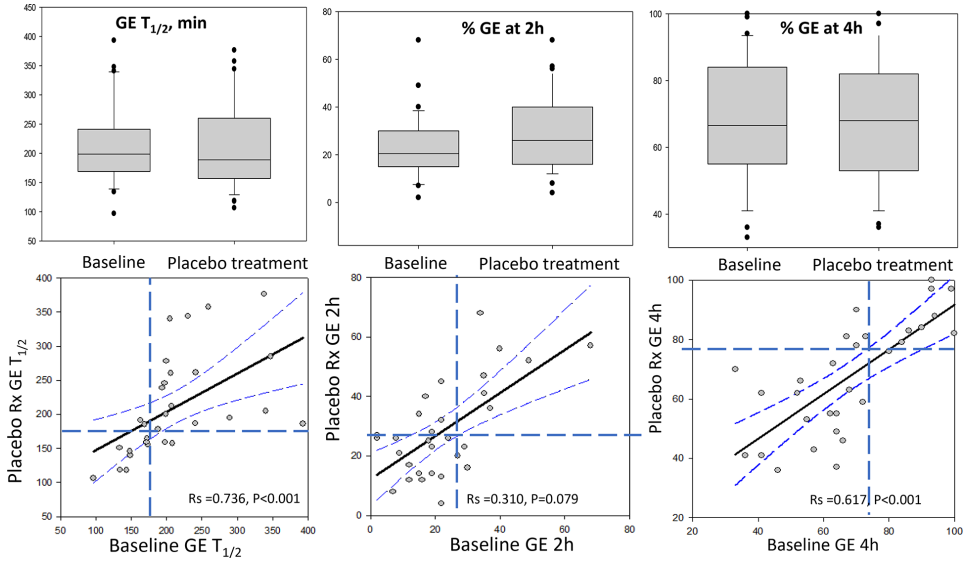

Figure 3 Parameters of gastric emptying (GE) of solids in patients with gastroparesis and documented slow GE showing IQR, 5% and 95% CI and outliers at baseline and after treatment with placebo for 4 weeks (upper panel). Lower panel shows correlations with 95% CI of regression and upper limit of normal range shown by interrupted lines (174 min for GE $T_{1/2}$, 25% for GE at 2 hours and 75% for GE at 4 hours). Note: very few patients' GE results are misclassified based on these parameters, in particular GE $T_{1/2}$ and GE at 4 hours.

study[18] that used the Egg Beaters meal. This was one of the two observations led to the perception that gastroparesis and functional dyspepsia are interchangeable conditions in tertiary care practice. This assessment was confounded by the fact that patients were receiving tricyclic antidepressants, cannabinoids, anticholinergics or opioids at entry to the study. Although they agreed to withhold these medications 72 hours before the GE tests, it is unclear whether the medications were 'washed-out' from neural structures controlling GE, even though the plasma levels may be reduced in accordance with the medications' half-times. It is therefore unclear whether these neuromodulators may have contributed, at least in part, to the intra-individual differences in GE measured with the Egg Beaters meal. The second rationale for the 'interchangeable' nature of gastroparesis and functional dyspepsia was based on the histopathological assessment of quantification of interstitial cells of Cajal and CD206 macrophages; however, this was shown to be insufficiently powered to conclude there were no differences between gastroparesis and functional dyspepsia.[26]

Overall, these data suggest that the standard meal used consisting of 320 kcal and 30% fat is valid and exhibits performance characteristics in disease states that are analogous to those observed and previously published in 215 healthy female volunteers and 104 healthy male volunteers.[10] In those 319 healthy participants, the median GE $T_{1/2}$ was 120 min, the 5th percentile was 78.4 min, the 95th percentile was 174.0 min and the COV_{inter} and COV_{intra} for GE $T_{1/2}$ were 24.5% and 23.8%, respectively.[10] Those COVs are similar to the ones observed in patients with gastroparesis in the current study, 33.1% and 31%, respectively. Based on the data of the 319 healthy participants,[10] in which

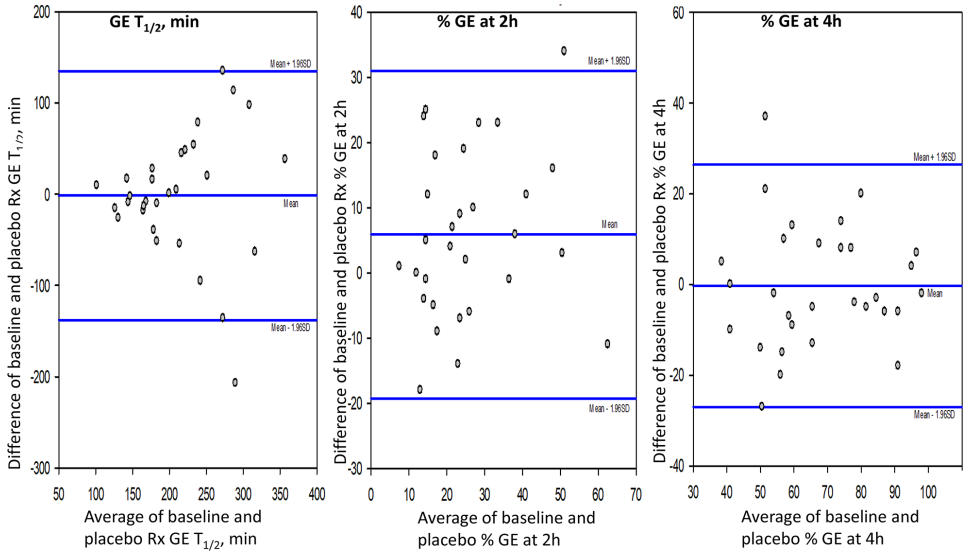

Figure 4 Bland-Altman plot showing consistency of gastric emptying (GE) data for the majority of patients with gastroparesis. The vast majority of the replicate data are within 60 min difference for GE $T_{1/2}$, 20% difference for GE at 2 hours and 20% difference for GE at 4 hours. Importantly, despite the variation, only two patients were inconsistently classified on repeat test (see regression analysis in figure 3).

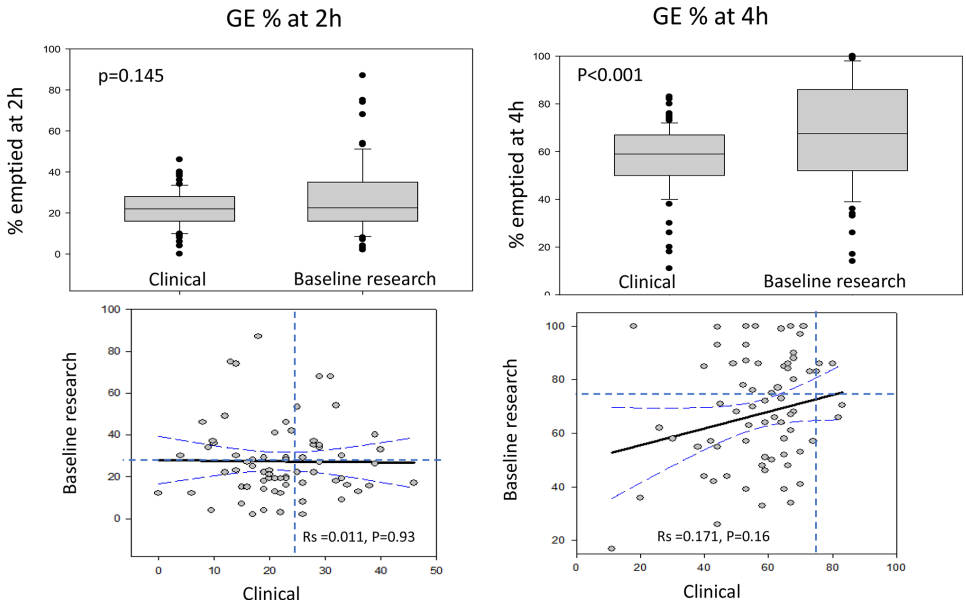

Figure 5 Comparison of earlier clinical diagnostic gastric emptying (GE) test conducted a median 94 weeks prior to the baseline test performed at entry to a research trial. Note significant difference in GE% at 4 hours (upper panel) with greater GE% emptied at the second test and the faster GE in 24 of the 70 patients (lower panel, right) during the second test.

males and females were virtually identical, the per cent emptied from the stomach of <75% at 4 hours (corresponding to the fifth percentile) is a valid criterion for identifying delayed GE, for both females and males. While it is expected that there are differences in GE between patients, the GE% at 4 hours with the lowest COV_{inter} of 27.5% and COV_{intra} of 20.1% suggests that this currently used criterion to identify normal GE >75% remains valid.

The comparison between the tests performed at the time of clinical diagnosis and participation in research trials provides useful insights on the range of GE over a median follow-up of 94 weeks. It demonstrates an overall consistent GE profile (as previously documented in extensive studies conducted in Adelaide, Australia showing consistency over time[27–29]) and the amelioration of GE% at 4 hours in a subset of patients (24/70). This improvement in GE% at 4 hours may reflect either spontaneous variation or faster GE, possibly as a result of therapy or even spontaneous improvement in the GE delay. It is known, for example, that follow-up of presumed postviral gastroparesis was associated with improved GE and complete or considerable symptom resolution over a mean follow-up of 32.3 months in seven patients.[30]

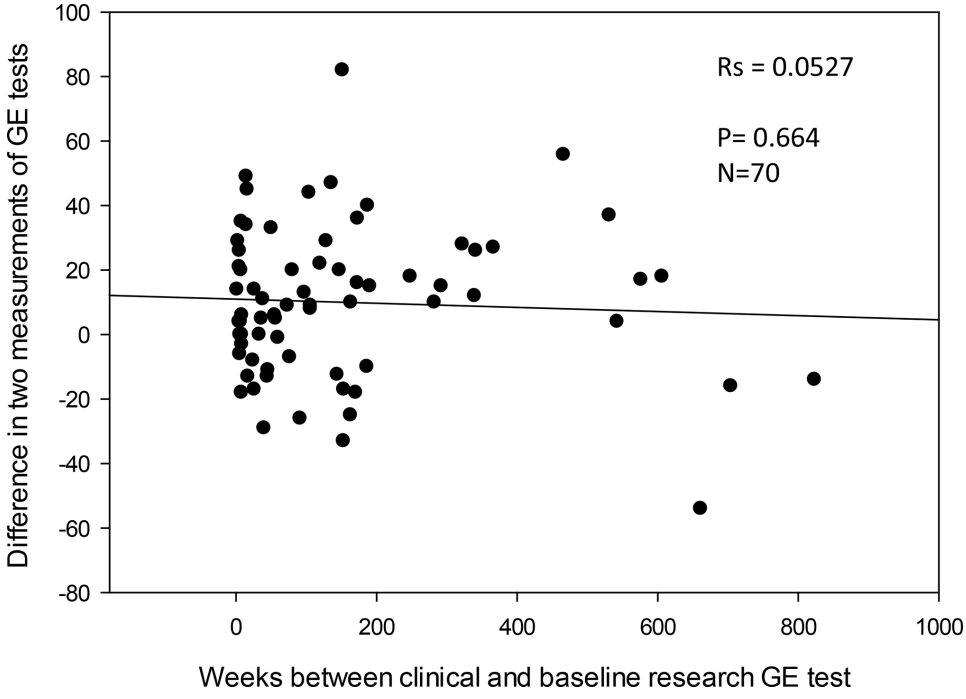

Figure 6 Plot showing difference in gastric emptying (GE) % at 4 hours based on interval in weeks between the two tests (clinical diagnostic vs research). Note: the consistency in the difference is best demonstrated in the time interval 0–200 weeks.

There are limitations to our study including the short interval between the replicate tests of GE in the cohort of patients who had gastroparesis; however, the observations in the patients with gastroparesis (n=21) and in the patients with functional dyspepsia (n=18) studied 4 weeks apart and the observations in 70 patients at a median interval of 94 weeks provide reasonable sample sizes, relative to the only other two papers in the literature that evaluated 14 patients with diabetes[16] and 60 patients with upper GI symptoms.[17] A second limitation pertains to generalisability. Since several other medical centres use the low-fat Egg Beaters meal preferentially for estimating GE, our data may not necessarily be generalisable to the anticipated performance of the GE test at other centres.

There are also potential confounders related to glycaemic control, test meal composition and the potential effect of placebo in such studies. Study inclusion required confirmation that patients with diabetes did not have severely uncontrolled disease by haemoglobin A1c measurement (HbA1c >12%, as noted in online supplemental table 1). In addition, fasting blood glucose was measured before the GE test in the research studies, with standard treatment algorithm-based administration of short-acting insulin for all studies involving patients with diabetes in the Clinical Research Trials Unit (algorithm established by endocrinology division). Effect of hyperglycaemia may be relevant for blood glusose >250 mg/dL,[31 32] although other studies suggest that higher fasting blood glucose levels are associated with faster GE, and in type 2 diabetes, 6 months of intensive therapy for the diabetes (with mean HbA1c decrease from 10.6% to 9%) did not result in significant change in mean GE $T_{1/2}$ (from 92 min before to 92 min after improved glycaemic control).[33] Since blood glucose measurements are not done routinely with the clinical GE measurements, hyperglycaemia may be a confounder in the data obtained for the comparison of GE studies in the clinical lab and subsequently in the research labs. Nevertheless, the consistency of the COV_{intra} illustrated in figure 6 suggests that glycaemic control was unlikely to be contributing to the COV_{intra}. However, for the placebo-controlled research studies in patients with diabetes, it is unlikely that HbA1c would have differed significantly over 3 (felcisetrag trial) to 28 (CBD trial) days.

Potential confounders in the meal composition are addressed by selection of standard egg size, and use of skim (low, <1% fat) milk. Although it is acknowledged that lactase deficiency is extremely prevalent in different ethnicities, the effect of lactase deficiency on GE of solids is unproven, and incomplete hydrolysis of lactose results in accelerated emptying of liquids.[34] In addition, even patients with significant lactase deficiency have no symptoms as long as the lactose load ingested with a meal is not large at any one time.[35] It is relevant to note that the lactose content of 240 mL of skim milk is 12–13 g, which is well within the 'safety' limits when ingested with a meal.[35] Another confounder is the potential that placebo may have neuroendocrine and biological effects[36] that could alter GE, and we chose to study COV_{intra} in patients on placebo. In fact, the observed consistency of the results obtained at baseline and on placebo strengthens the claim of the reproducibility of the test meal and method proposed.

In summary, availability of an optimal GE measurement is necessary for clinical diagnosis as well as for categorising patients for clinical trials. The standard 320 kcal, 30% fat egg meal used in our study has a composition which is closer to a typical American meal than the Egg Beaters alternative meal. More importantly, the data presented here validate the extensive utilisation of this test in clinical practice for >30 years at our clinic as well as having provided the opportunity to appraise the efficacy of medications in proof-of-concept pharmacodynamic studies assessing the effects of agents such as the ghrelin receptor agonist, relamorelin[19 20] and the 5-HT_4 receptor, felcisetrag.[21]

In conclusion, we believe that this unparalleled body of data should lead to further discussion by gastroenterology, motility and nuclear medicine organisations to standardise a robust method to measure GE in clinical and research practice. This goal can be achieved by simply replacing the egg protein substitute with two real eggs and then obtaining images at least at baseline, as well as at 1, 2 and 4 hours after the meal. Modern programmes available in gamma cameras are able to accurately estimate GE $T_{1/2}$ using these simple parameters of GE.[37]

Twitter Ting Zheng @JohnnyTingZheng

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Competing interests MC is an Associate Editor of *Gut*. Data in these studies were acquired in previously published reports on the effects of relamorelin and felcisetrag, which were performed with funding from Rhythm Pharmaceuticals and Takeda, respectively and studies of effects of cannabidiol.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by Mayo Clinic Institutional Review Board (IRB #21-003438). The medical records of any patients who had denied authorisation of use of their medical (including research) records for research purposes were not used in the analysis in the current study, as required by the Institutional Review Board.Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All relevant data are included in the paper and/or in the online supplemental materials. Only deidentified participant data are provided. Additional related documents will be available, if deemed appropriate, by request to the senior author with investigator support, after approval of a proposal, with a signed data access agreement. And if applicable: data will be available, consistent with data sharing NIH policy for studies supported by NIH (in this case, R01-DK122280).

ORCID iDs
Michael Camilleri http://orcid.org/0000-0001-6472-7514
Kia Vosoughi http://orcid.org/0000-0002-6797-9386
Saam Dilmaghani http://orcid.org/0000-0003-2027-7405

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