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Comparison of gastric emptying of a nondigestible capsule to a radio-labelled meal in healthy and gastroparetic subjects

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SUMMARY

Background
Gastric emptying scintigraphy (GES) using a radio-labelled meal is used to measure gastric emptying. A nondigestible capsule, SmartPill, records luminal pH, temperature, and pressure during gastrointestinal transit providing a measure of gastric emptying time (GET).

Aims
To compare gastric emptying time and GES by assessing their correlation, and to compare GET and GES for discriminating healthy subjects from gastroparetics.

Methods
Eighty-seven healthy subjects and 61 gastroparetics enrolled with simultaneous SmartPill and GES. Fasted subjects were ingested capsule and [^{99m}Tc]-SC radio-labelled meal. Images were obtained every 30 min for 6 h. Gastric emptying time and percentage of meal remaining at 2/4 h were determined for each subject. The sensitivity/specificity and receiver operating characteristic analysis of each measure were determined for each subject.

Results
Correlation between GET and GES-4 h was 0.73 and GES-2 h was 0.63. The diagnostic accuracy from the receiver operating characteristic curve between gastroparetics and healthy subjects was GET = 0.83, GES-4 h = 0.82 and GES-2 h = 0.79. The 300-min cut-off time for GET gives sensitivity of 0.65 and specificity of 0.87 for diagnosis of gastroparesis. The corresponding sensitivity/specificity for 2 and 4 h standard GES measures were 0.34/0.93 and 0.44/0.93, respectively.

Conclusion
SmartPill GET correlates with GES and discriminates between healthy and gastroparetic subjects offering a nonradioactive, standardized, ambulatory alternative to scintigraphy.

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INTRODUCTION

Gastroparesis is a symptomatic chronic disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction.[1] Symptoms include nausea, vomiting, bloating, abdominal pain or discomfort and early satiety and may contribute to the common clinical symptom complex of dyspepsia, which cause frequent visits to primary care doctors and gastroenterologists.[2] Physiological studies can demonstrate delayed emptying of stomach contents, which may have some relationship to the symptoms.

Non-invasive diagnostic techniques for characterizing disturbances of gastric emptying include gastric emptying scintigraphy (GES) of a digestible solid meal, upper gastrointestinal (GI) barium series, ultrasonography of the stomach and breath testing.[3, 4] Scintigraphy is available to many clinicians as the current standard because of its physiological methodology, face validity and quantitative results.[3] Therefore, the applicability of any alternative approach for measuring gastric emptying should be gauged against scintigraphy. However, scintigraphy's full clinical value has been limited by the need for exposure to radiation, clinical practicality and diagnostic reliability from a lack of standardization between different centres. A test that offers a comparable diagnostic accuracy with fewer or none of these disadvantages might improve the speed of diagnostic evaluation and patient satisfaction.

A new method for characterizing gastric emptying is the SmartPill (SP) GI Monitoring System (The SmartPill Corporation, Buffalo, NY, USA).[5] This system consists of a nondigestible, wireless transmitting capsule, a receiver for acquiring and storing signals from the capsule and software for displaying data on a personal computer. The capsule samples and transmits pH, pressure and temperature data at regular intervals to a portable receiver worn by the subject. An abrupt change from an acid gastric pH to an alkaline duodenal pH associated with a burst of phasic contractions marks the passage of the capsule from the antrum through the pylorus into the duodenum.[5]

This study compared the gastric emptying time (GET) as measured by the nondigestible, wireless capsule system with two measures of GES by assessing the correlation between the two techniques and comparing the ability of the two methods to discriminate between healthy and gastroparetic subjects. We hypothesized a strong, positive correlation in gastric emptying measures between GET and GES and the comparable ability of the two methods to discriminate between healthy and gastroparetic subjects.

MATERIALS AND METHODS

This prospective study was conducted at seven medical centres from March 2005 to November 2005. Healthy subjects and subjects with a history of gastroparesis were enrolled. The protocol was approved by the Institutional Review Board of each centre. Each subject gave informed consent before enrolment.

General exclusion criteria – all subjects

Subjects with previous gastro-oesophageal surgery were excluded except those with uncomplicated appendectomy and/or laparoscopic cholecystectomy.

Drugs such as cisapride, domperidone, metoclopromide, macrolide antibiotics, $5HT_4$ partial agonists such as tegaserod and antiemetics including anticholinergics and $5HT_3$ antagonists were held accordingly. No narcotic drugs for 1 week were allowed before the start of the study. Prescription medications such as antilipidaemics, antidepressants or birth control pills were permitted, if the condition and the dose were stable for 6 months prior to enrolment in the study. Nonsteroidal anti-inflammatory drugs were stopped 1 week prior to the study and other over-the-counter drugs were stopped 3 days before.

Healthy subjects

Males and females between ages 18 and 65 years with no GI disease as screened by the Mayo GI Disease Screening Questionnaire[6] and no cardiovascular, endocrine, renal and chronic disease were recruited as healthy volunteers. Additional criteria included: average bowel movement frequency of at least one per 48 h, no pregnancy, no surgery within the past 3 months, no clinical evidence of diverticulitis as evidenced by the absence of chronic or acute abdominal pain, no medications or over-the-counter agents that could influence GI motility, no tobacco use within 8 h before and after capsule ingestion, no alcohol use 24 h before capsule ingestion and during the monitoring period and a body mass index <35.

Subjects with history of gastroparesis

Males and females between ages 18 and 65 years with history of nausea and vomiting, early satiety, epigastric pain or discomfort for at least 6 months and documented abnormal scintigraphy as defined by local medical centre standards within 2 years were enrolled as gastroparetic subjects. Gastroparetics with excessively delayed GET (>90% of a standard egg meal retained after 2 h), average bowel movement frequencies exceeding 72 h, evidence of gastric bezoar within the last 3 years, stricture, peptic ulcer, severe dysphagia to solid food and pills, severe vomiting, severe abdominal pain, severe weight loss (>4.5 kg in last 2 months), or diabetes with a haemoglobin A1C >10 were excluded. Proton pump inhibitors were stopped for 1 week, histamine-2 blockers for 2 days and antacids for 1 day. Medications that affect gastric motility were stopped 48 h before the start of the study unless the subject was on the medication during the previous scintigraphy.

Pressure and pH monitoring

Measurements were made of pH and pressure using the wireless capsule system. The capsule houses sensors for pH, temperature and pressure and transmits sensed data at 434 MHz. Capsule size is nearly identical to the imaging capsule from Given Imaging Ltd (Yoqneam, Israel).

According to manufacturer's information (SmartPill Corporation, Buffalo, NY, USA; smartpillcorp.com), the single use capsule measures pH from 0.5 to 9.0 pH units with an accuracy of $\pm$0.5 pH units; pressure from 0 to 350 mmHg with an accuracy of $\pm$5 mmHg and temperature from 25 to 49°C with an accuracy of $\pm$1°C. The data receiver has rechargeable batteries; data are downloaded from the data receiver through a docking station/battery charger via USB connection to a Windows PC compatible laptop (Dell Latitude Centrino, Dell Corporation, Round Rock, TX, USA).[19]

Capsule gastric emptying time

Capsule GET is defined as the duration of time from capsule ingestion to an abrupt pH rise (usually >3 pH units) from gastric baseline to a pH >4 as the capsule passes from the acidic antrum to the more alkaline duodenum.[7–10] GET for each subject was determined by two independent reviewers and by computer software (MOTILIGI). Discrepancies in observed or software determined GET were resolved by further review and consultation with an additional reviewer.

Gastric scintigraphy

The standardized scintigraphy meal consisted of a scrambled egg substitute mixed with 1 mCi ^{99m}Tc sulphur-colloid marker (120 g Egg Beater, 60 kcal), two slices of bread (120 kcal), strawberry jam (30 g, 74 kcal), and water (120 mL), total caloric value of 255 kcal (72% carbohydrate, 24% protein, 2% fat and 2% fibre).[11] The subjects completed the meal within 20 min of ingesting the capsule.

Scintigraphic images were taken in the 140 keV ^{99}Tc peak with a 20% window (140 keV $\pm$ 10%); 1 min of anterior and 1 min of posterior measurements were taken for each scan. Data were corrected for time decay of technetium. The region of interest was drawn around the image of the stomach for each time frame and the geometric mean was calculated as the square root of the product of the counts measured on the anterior and posterior images. Data were expressed as per cent of the meal retained at 2 h (GES-2 h) and per cent of the meal retained at 4 h (GES-4 h) which are standardized from the literature.[11]

Experimental protocol

Females underwent a urine pregnancy test on the morning of the study before exposure to any radiation. Diabetic gastroparetic subjects on insulin were administered half the regular dose of their normal morning injection.

Subjects ingested the capsule with 50 cm^3 of water and afterwards began eating the standard meal with an additional 120 cm^3 of water. The first scintigraphic images were taken immediately following the meal ingestion and subsequently at 30-min intervals for 4 h. If 90% of the meal had not emptied after 4 h, an additional image was taken at 6 h. Subjects were ambulatory but were encouraged to sit. Sleeping was not permitted during the first 8 h of the test.

Six hours after capsule ingestion, subjects consumed 250 cm^3 Ensure (Abbott Laboratories, Abbott Park, IL, USA) and water was taken *ad libitum*. Diabetic subject's blood sugar levels were monitored using finger glucose monitoring and insulin administered according to the subject's normal protocol. Safety concerns regarding prolonged fasting especially in diabetic subjects prompted this second meal at 6 h thereby

imposing an upper limit time cap to the evaluation of the emptying of the test meal.

Approximately 8 h after capsule ingestion, subjects left the study centre with the data receiver to enable continued data acquisition from the capsule and a diary for recording bowel movements, food intake, sleep and GI symptoms (pain, nausea and cramping). Restrictions included no strenuous activities such as sit-ups, abdominal crunches and prolonged aerobic activity (>15 min), no alcohol and no GI medications that could affect motility. *Ad libitum* feeding was allowed from this point forward in the study. The clinical impracticality of maintaining the prolonged fasting more than 6 h to measure gastric emptying and the difficulties of maintaining a fixed dietary regimen also caused us to allow *ad libitum* feeding.

At 48–72 h postingestion, subjects returned with the data receiver and diary. Subjects retained the receiver until no more capsule signals were detected. Because of concerns of possible capsule retention, especially in subjects with GI motility disorders, capsule exit was confirmed for each subject by abdominal X-ray unless the subject retrieved and returned the capsule.[12–14]

Data analysis

The primary objective was to determine the correlation between GET and GES end points, GES-2 h and GES-4 h. Because GET and GES are measured on different scales (minutes and percentage points, respectively), we used the Pearson correlation as the measure of agreement. A nominal significance level of 0.05 was used in all hypothesis testing. If hypothesis tests failed to reject that the correlation between GET and GES was >0.70, the measures were deemed equivalent.

The GET times of <30 min were regarded as missing data because rapid emptying times have no relationship with emptying of a nondigestible solid after a caloric meal. The capsules are likely emptying prematurely with a random fasting migrating motor complex before the scintigraphic meal converts the stomach from fasting to fed state.

With the introduction of another meal for safety, the upper limit time for the capsule test was capped at 6 h. Because 26% of the GET times exceeded this upper limit, we employed maximum likelihood estimates (MLE) of the standard Pierson correlation to characterize the correlation of the two methods. MLE is routinely used to handle data with upper cut-off limits and accommodates the partial information conveyed by observations that have reached the upper limit in an unbiased fashion.[15] Correlations are reported along with corresponding 95% confidence intervals based upon bootstrap re-sampling.

The second objective was to assess the diagnostic utility of the two tests in discriminating normal subjects and patients with gastroparesis by calculating each method's sensitivity and specificity and generating receiver operating characteristic (ROC) curves. The areas under the ROC curves (*AUC*) and corresponding 95% bootstrap confidence interval are reported. The clinically ideal sensitivity and specificity of GET were calculated. Sensitivity and specificity for GES-2 h and GES-4 h are based on established cut-offs from the literature.[11] The cut-off used to define gastroparesis scintigraphically was >10% retained at 4 h.[11] All analyses were conducted using SAS (version 9.1.3).

The current clinical standard diagnosis of gastroparesis was initially based on previous history of symptoms and previous abnormal scintigraphy results. An additional analysis was performed to evaluate the discrimination performance characteristics of GET to GES where only healthy subjects with normal GES on day of study and patients with a previous history of disease and confirmed delayed scintigraphy on the day of the study were used. These results were utilized to determine the cut-off time periods to maximize clinically sensitivity and specificity of GET in diagnosing gastroparesis.

Determination of sample size

The power calculation was performed for the primary end point evaluation of the correlation between GES and GET. The original sample size of $n = 130$ was determined based on having 80% power in detecting a true correlation of 0.58.

RESULTS

Study subjects and demographics

Eighty-seven healthy (55 male, 32 female; 69 Caucasian, seven Black, five A/P Island, four Hispanic; two Others) and 61 gastroparetic (10 male, 51 female; 50 Caucasian, seven Black, four Hispanic) subjects (total of 148 subjects) were enrolled. Two subjects failed to participate in the test after enrolment. A total of 146 subjects had complete GES data and were included in the analyses for scintigraphy. Of these, 16 had missing GET data because of prototype equipment malfunctions and

five additional subjects had GET times regarded as missing because the emptying time was <30 min. As a result, 125 subjects were included in the analyses for GET.

Quantitative observations

Figure 1a,b are examples from study subjects and depict the relationship between gastric emptying of the scintigraphic meal and the changes in gastric pH measurements used to determine GET. Figure 1a shows the relationship in a healthy subject and Figure 1b in a gastroparetic subject. In both figures, the radio-labelled meal empties completely before the capsule empties.

Emptying times above 360 min were capped at 360 min because an Ensure meal was given at 360 min postingestion. Introduction of the Ensure meal further delays the emptying of the original meal and the capsule if still present in the stomach. Hence, inclusion of GET values >360 min would not be an accurate reflection on the emptying of the capsule relative to the original test meal. Thirty-two subjects (26 gastroparetic and six healthy) had GET times that exceeded 360 min. Table 1 provides the median and 95% confidence interval times for GES-2 h and GES-4 h in the 87 healthy and 59 gastroparetic subjects (total 146 subjects) and GET for 77 healthy and 48 gastroparetic subjects (total 125 subjects). Box and whisker plots are illustrated in Figure 2 for the three measurements. Measurements of GES-2 h, GES-4 h and GET from the healthy subjects were statistically

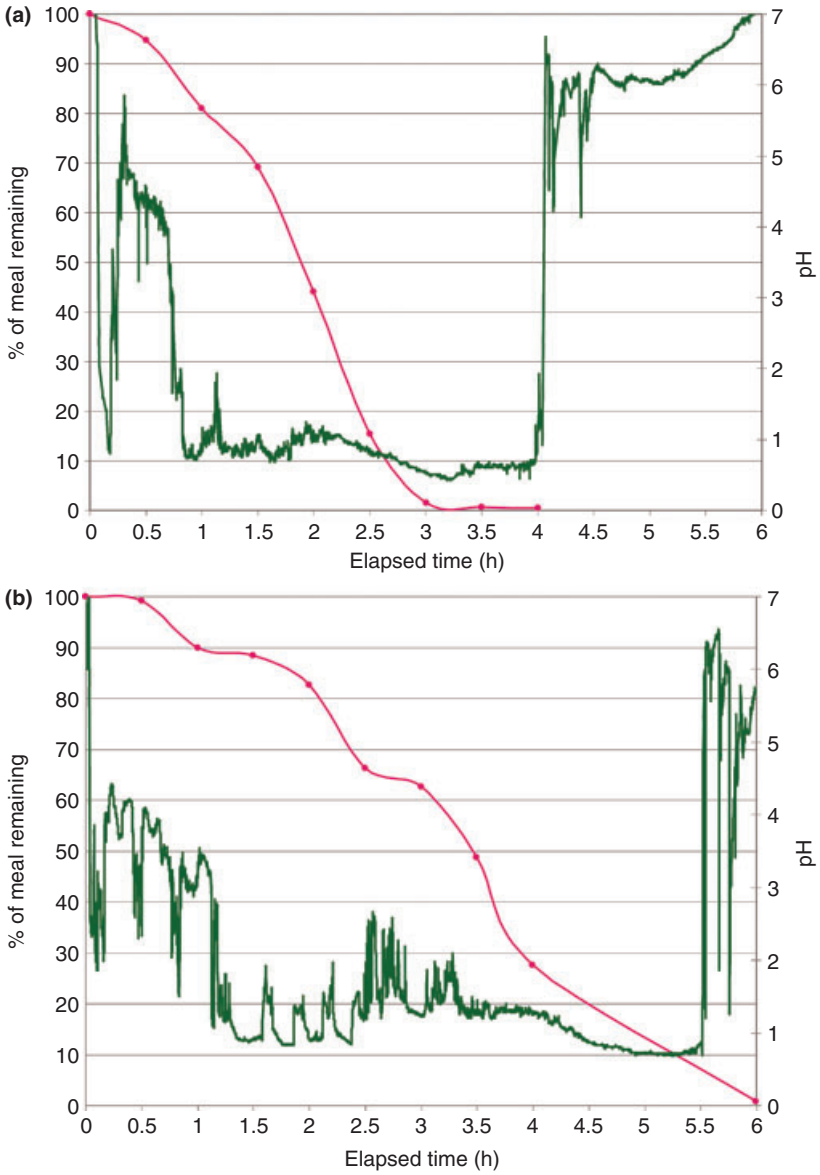


Figure 1. Relationship between scintigraphic empyting of a meal (gastric emptying scintigraphy) and gastric emptying time of the capsule. The magenta tracing and axis on the left show the per cent meal remaining over time. The green tracing and axis on the right show pH as measured by the capsule. The pH tracing shows the pH changes induced by the meal in the first hour followed by re-acidification of gastric pH. (a) Healthy subject. The emptying of the meal occurs almost completely by 3 h. Emptying of the capsule occurs at about 4 h (normal limit < 5 h) when the pH rapidly changes more than 3 pH units from the acidic gastric pH to the alkaline duodenum pH. (b) Gastroparetic subject shows more than 10% of the meal remaining at 4 h with the emptying of the capsule at 5.5 h.

Table 1. Median emptying times in minutes for gastric emptying time (GET) and median per cent of meal retained for GES-2 h and GES-4 h with corresponding 95% confidence intervals (CI)

Gastric emptying measure	Median (CI)	
	Healthy subjects	Gastroparetic subjects
GET (min)	215 (199–225), n = 77	>360 (320, >360), n = 48
GES-2 h (% of meal retained)	25% (23–37%), n = 87	51% (42–58%), n = 59
GES-4 h (% of meal retained)	1% (1–1.4%), n = 87	9% (4–13%), n = 59

different from those of the gastroparetic subjects ($P < 0.05$).

Correlation between GET and gastric emptying scintigraphy

To investigate the relationship between the emptying time of the standard radio-labelled meal and the non-digestible solid, we calculated the correlations between scintigraphy end points and GET. Correlation results between GET and the scintigraphic 2 and 4 h parameters are presented in Table 2. The correlation observed between GET and GES-4 h is 0.73, which exceeds the prespecified correlation target of 0.70. Scatter plots of GET with GES-2 h, and GES-4 h are provided in Figure 3 along with a fitted regression line and corresponding 95% confidence bands.

Discrimination properties of GES and GET with the diagnosis of clinical gastroparesis

Receiver operating characteristic curves were calculated to evaluate the clinical utility of the diagnostic tests for GET, and GES-2 h and GES-4 h cut-offs and are summarized in Table 2. The area under the ROC curve (*AUC*) and the sensitivity and specificity of the three diagnostic tests are reported. No statistically significant difference was observed between the *AUC*s for GET, and GES-4 h ($P > 0.05$). The ROC curves for each measure are illustrated in Figure 4.

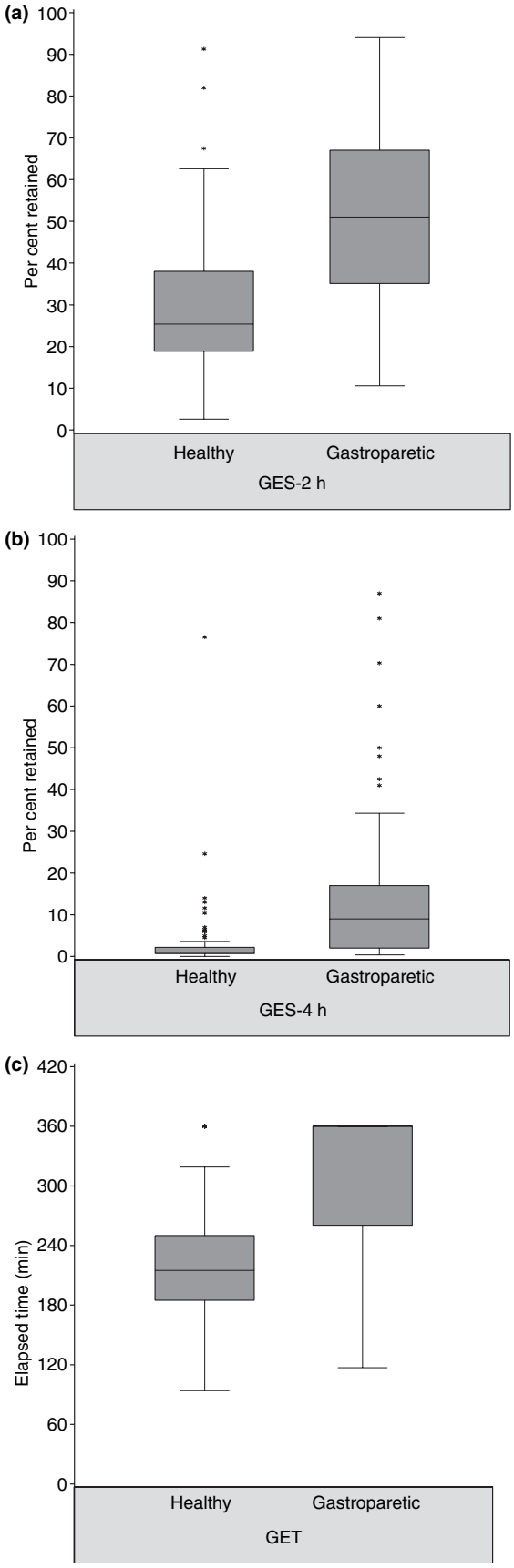
Discrimination performance of GET to GES with the diagnosis of gastroparesis and confirmed by day of test scintigraphy

Seventy-two of 77 healthy subjects had normal scintigraphic emptying on the day of the test as defined by GES-4 h[11] 23 of the 48 gastroparetic had an abnormal scintigraphic emptying on the day of the test as defined by GES-4 h. We further analysed this data set for *AUC*, sensitivity and specificity after reclassifying subjects as gastroparetic or normal based on their 4 h scintigraphic day of study results. The *AUC* for GET was 0.94, the sensitivity was 0.87, and the specificity was 0.92. Utilizing this analysis, the cut-off point for GET that provides an optimum balance of sensitivity and specificity for clinical use was found to be 300 min.

Adverse events

Passage of the capsule was confirmed in all subjects by either retrieval of the capsule or KUB. One subject could not swallow the capsule and was discharged from the study. Forty-six per cent of the subjects had a KUB to evaluate capsule presence because the capsule was not returned by the subject. Surprisingly, over 50% of subjects from the study recovered the capsule and returned it to the study site. Of the subjects that did not return the capsule (n = 67), 84% demonstrated that the capsule had been evacuated within 5 days of ingestion and thus before the first KUB. Only five subjects had a repeat KUB and there were no capsules retained upon follow-up radiological examinations.

Ten adverse events were reported. Six of the 10 were not related to the study device, three were probably not related and one was related. No serious adverse events or unanticipated device-related adverse events occurred. Two of the reported events (one not device related and one probably not device related) were reports of vomiting. However, both these occurred well after capsule ingestion and did not result in vomiting of the capsule. The one related adverse event occurred in a gastroparetic subject who had ingested Citrucel, a bulk forming laxative that subsequently entrapped the capsule in a jelly-like, viscous mass. An endoscopy was performed, but was not able to retrieve the capsule from the viscous mass. Erythromycin IV (200 mg) was administered, and the capsule subsequently emptied



the stomach after 30 min. All adverse events are described in Table 3.

DISCUSSION

Efforts to improve GES by standardizing meals, diagnostic cut-offs and test duration times have been implemented at academic centres. However, there still remains the relative inaccessibility of standardized test for gastric emptying to community gastroenterologists to whom a vast majority of symptomatic patients are referred.

In this study, we simultaneously applied GES and the ingestion of a pH and pressure sensing capsule to compare the two measures of gastric emptying in healthy subjects and symptomatic subjects with a history of gastroparesis. We observed a correlation of 0.73 and a sensitivity and specificity similar to GES-4 h suggesting that this method is reasonable for clinical evaluation of delayed gastric emptying.

Although the two techniques measure different aspects of gastric function, GES-4 h and GET are strongly related because they probably occur in succession. We found that the digestible meal must empty almost completely (over 90%) before the capsule empties with the return of the fasting state and migrating motor complex (MMC). Therefore, when the emptying of the meal is delayed, a corresponding delay in emptying a nondigestible solid from the stomach is likely.

The use of nondigestible solids to assess gastric emptying has been reported. Feldman demonstrated that the gastric emptying of nondigestible radio-opaque NG tube pieces was delayed in patients with gastroparesis following the consumption of a high fat meal of donuts and 7UP (Dr Pepper/Seven Up, Plano, TX, USA).[16] Using a liquid fatty meal, Mojavarian reported a 0.72 correlation with 50% emptying of the scintigraphic meal and the time required to empty a nondigestible capsule that measured luminal pH.[7, 8]

Figure 2. Box and Whisker plots of healthy and gastroparetic subjects for (a) GES-2 h, (b) GES-4 h and (c) gastric emptying time (GET). The plots show the median (line) and 25–75% quartiles (box). For scintigraphic measurements, there were 87 healthy and 59 gastroparetic subjects, and for GET 77 healthy and 48 gastroparetic subjects. *Y*-axis is per cent retained for (a) and (b), and minutes to gastric emptying for (c). In each group plot, the times of healthy subjects were all statistically significantly different from the times of gastroparetic subjects ($P < 0.05$).

Table 2. Correlation of GES-2 h and GES-4 h gastric emptying time (GET) along with sensitivity and specificity values (n = 125)

Gastric emptying parameter	SP-GET correlation (95% CI)	Sensitivity	Specificity	*AUC* (95% CI)
GES-2 h	0.63 (0.50–0.75)	0.34	0.93	0.79 (0.71–0.88)
GES-4 h	0.73 (0.61–0.82)	0.44	0.93	0.82 (0.77–0.91)
GET	n/a*	0.65	0.87	0.83 (0.74–0.90)

* Not applicable.

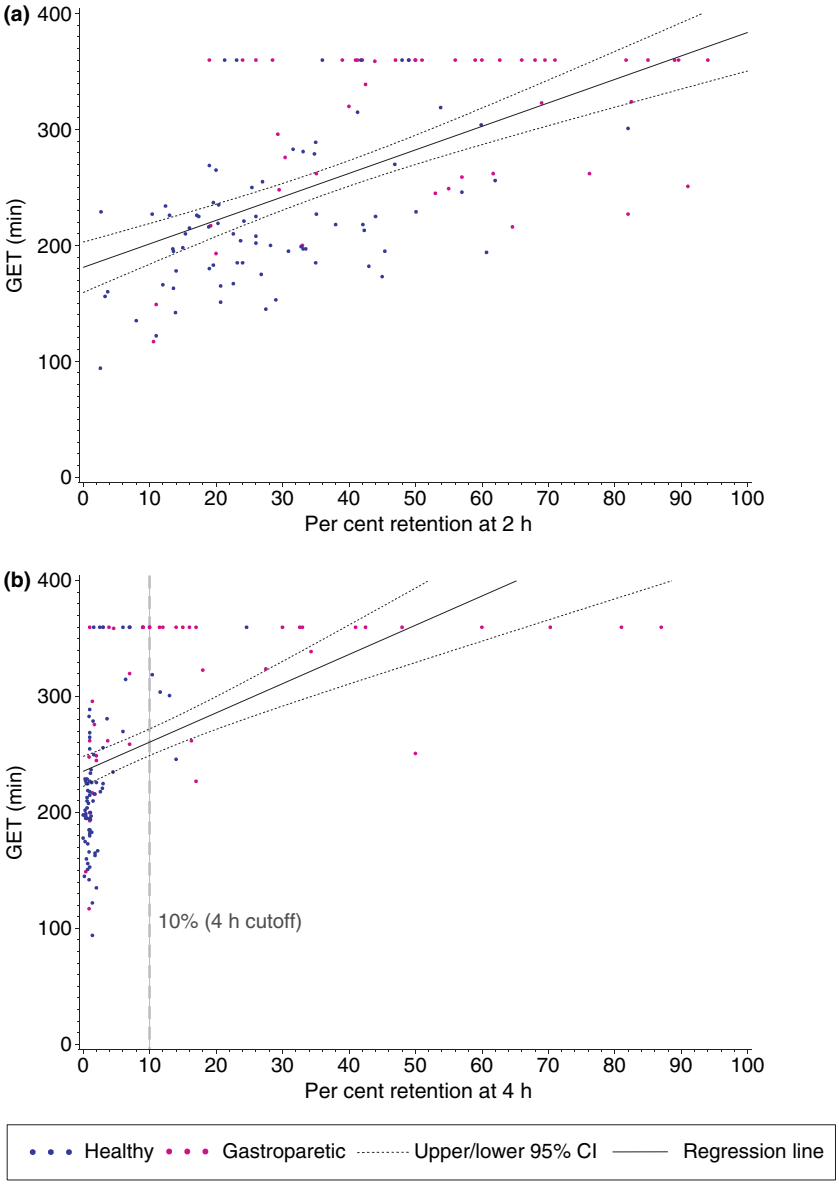


Figure 3. Correlations of gastric emptying time (GET) to (a) GES-2 h at r = 0.63, (b) GES-4 h at r = 0.73, with respective regression lines and 95% confidence interval bands. n = 125 for both scintigraphic and GET measurements. Times >360 min were capped at 360 because of the introduction of another meal. Vertical dashed lines in (b) represent the cut-offs used to determine abnormal gastric emptying by scintigraphy.

Other Mojavarian[7–9] studies provide evidence of reproducibility. He reported a mean GRT of 3.5 ± 0.60 in healthy male subjects and a mean GRT 8 days later of 3.5 ± 0.63. Although the capsule used by Mojavarian was smaller in diameter than the capsule used in our study, the dynamics of emptying for both capsules are the same. In addition, Mojavarian concluded that the nondigestible capsule empties by migrating motor

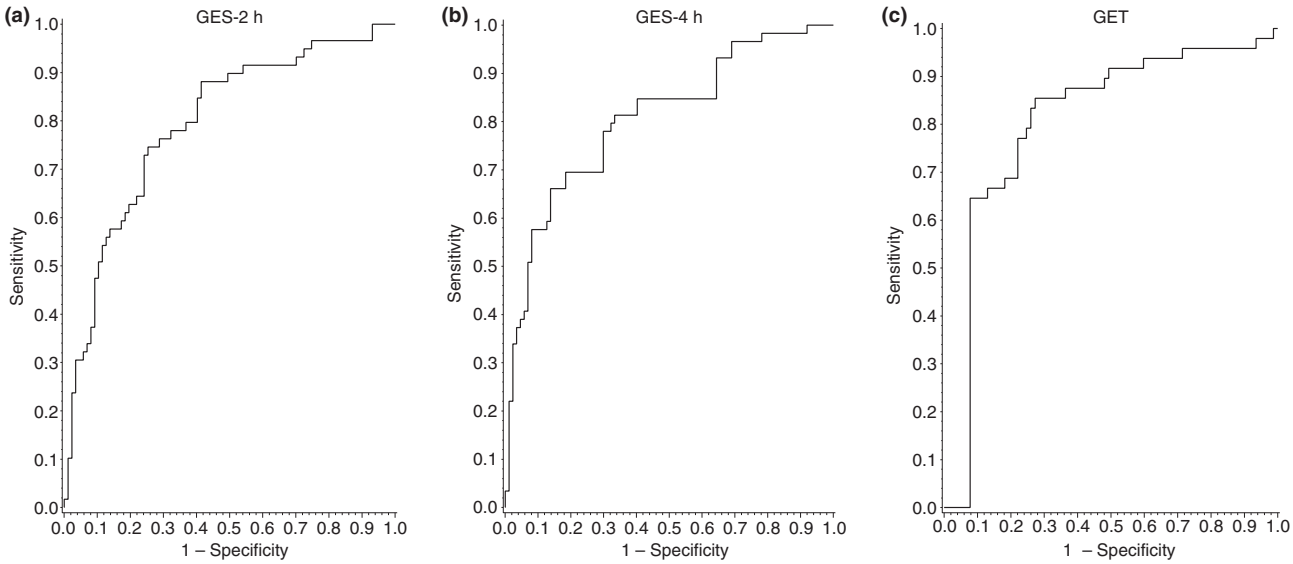


Figure 4. Receiver operating characteristics curves for the ability of the gastric emptying measures to diagnose subjects with a history of gastroparesis. For scintigraphy, n = 146 (87 healthy, 59 gastroparetic) and for gastric emptying time (GET) n = 125 (77 healthy, 48 gastroparetic). (a) GES-2 h AUC = 0.79, (b) GES-4 h AUC = 0.82 and (c) GET AUC = 0.83.

Table 3. Adverse events

		AE relationship to the study device		
		Not related (n)	Probably not related (n)	Definitely related (n)
Body system	Reported term			
Cardiovascular	Dizziness upon standing	1	0	0
Gastrointestinal	Bloating	0	1	0
	Capsule retention	0	0	1
	Nausea	1	0	0
	Vomiting	1	1	0
	Stomach pain	1	0	0
	Abdominal pain	1	0	0
Nervous	Taste bitter	1	0	0
Nonspecific skin	Burn local	0	1	0
Total number of AE subjects		6	3	1

complexes in studies where GRT was measured simultaneously with gastroduodenal manometry.[17] Reproducibility studies for the SP capsule technology are in the planning stages.

The GET end point is derived in part from the detection of the abrupt rise in pH as the capsule leaves the acidic stomach and enters the more alkaline duodenum. Previous studies utilized this physiological landmark to measure gastric emptying and documented the presence of an abrupt pH rise.[7–10] Detection of the rise may be compromised in conditions where normal gastric or duodenum pH is altered such as atrophic gastritis and PPI therapy. We evaluated the subjects who were taking acid suppression medications before enrolling in the study and found that all had a >3 pH unit rise between the stomach and duodenum after stopping medication for a week before evaluation.

To reduce the likelihood of hypoglycaemia that could result from prolonged fasting amongst our

diabetic patients, we introduced a second meal of Ensure at 6 h. Ensure disrupts any further accurate measure of capsule emptying based on the emptying of the original test meal only because the subject has returned to the gastric fed state, effectively ending the test. Consequently, we capped all GET values that exceeded 6 h at 6 h. Capping restricts the quantitative assessment of the severity of the delay, but does not alter the ability to assess whether the patient does or does not have delayed emptying. A similar limitation in assessing severity can be suggested for scintigraphy when, as seen in clinical practice, the test is ended after 90 min or 2 h and emptying end points are estimated with extrapolation techniques. In clinical practice, a doctor is most interested in assessing whether a patient does or does not have delayed emptying, and such a qualitative assessment is provided by SP within the 6 h following meal ingestion.

Eligibility criteria for gastroparetics included both a history of GI symptoms and a documented delayed scintigraphy test within the past 2 years. Despite this, only 44% of the symptomatic subjects were delayed by GES (Tougas 4 h cut-off; >90% emptied at 4 h)[11] on the day of study. In comparison, 65% of symptomatic subjects were delayed by GET using the optimal 5 h cut-off. The lower than expected yield of confirmed gastroparesis subjects from the symptomatic population is a limitation of our study design and basing entry criteria strictly on a standardized, current scintigraphy test could have made the analysis of results more straightforward. It is possible that some subjects had resolution of their delayed gastric emptying in the time between the index study and our study date; however, all were reporting symptoms of gastroparesis during the time of our study. The index scintigraphy studies were performed mainly by institutions outside the study centres with widely varying techniques (meal types and lengths of monitoring) and thresholds of normal and abnormal cut-offs. In addition, 6% of healthy subjects were delayed based on having a GES-4 h ≥10% of the meal retained at 4 h. However, these results were not unanticipated based on the results of the Tougas study where the scintigraphic characteristics of per cent meal remaining at 4 h are quite similar between the two studies with regard to median (1% and 1%), 25–75 quartiles and the 95th percentile (10% and 12%)[11] suggesting that the normal populations are quite similar to previous trials.

To assess the diagnostic performance of GET further, only symptomatic subjects with abnormal day of study scintigraphy results were classified as gastroparetic, and only healthy subjects with normal day of study scintigraphy results were classified as healthy. The reclassification improved the estimates of sensitivity and specificity for GET to 0.86 and 0.92, respectively. The accuracy for sensitivity is diminished because of the smaller sample size. Thus, within the limitations of the study, the wireless capsule is at least comparable to scintigraphy for discriminating gastroparetic patients. The study was powered for evaluating correlation between GES and GET as the primary end point. The correlation is unaffected by reclassification.

There was a mismatch in gender between healthy and symptomatic subjects. The mismatch reflects clinical reality where predominantly females present with gastroparesis. We observed no statistically significant difference in the GET between healthy males (mean GET = 218 min) and females (mean GET = 221 min) ($P = 0.64$).

Sixteen of 146 (11%) subjects had a technical capsule failure resulting in the inability to acquire GET data. The reliability issues have been addressed in design improvements to software, printed circuit board design and power supply during the study. Changes do not involve or effect data sensing, measurement or integrity but rather are improvements in the reliability of the device. To adjust for data loss, we increased enrolment beyond the original power calculation of 130 subjects.

In the study, subjects ingested the capsule before ingesting the test meal, and in five subjects the capsule emptied with MMCs prior to conversion to the fed state. In a subsequent study, a revised protocol requiring meal ingestion before capsule ingestion eliminated early emptying of the capsule.[18]

An abdominal X-ray was ordered for subjects (46%) who did not return the capsule because we believed that confirming capsule elimination was wise and prudent for safety. There were no capsule retentions in the study. Capsule exit is ascertained from: (i) assessing whether data are still being received from the capsule (indicating that the capsule has not been eliminated) and (ii) inspecting the test results (the MOTILIGI graph) for specific temperature, pH and pressure patterns that indicate capsule passage. From the clinical experience and the available markers for signifying exit, capsule exit without a KUB can be adequately determined. A KUB to confirm passage is not routinely

recommend unless capsule elimination cannot be confirmed by these methods or if the patient is experiencing symptoms that indicate bowel obstruction.

This study demonstrates a clinically significant correlation between capsule GET and scintigraphy for the evaluation of gastric function (>0.7). The emptying of the nondigestible capsule occurs after a digestible meal empties, assessing a unique aspect of gastric emptying that is related to meal emptying. The sensitivity and specificity characteristics of the wireless capsule method were comparable to scintigraphy. Thus, GET of the capsule distinguishes healthy subjects from subjects with gastroparesis, is well tolerated and safe, and represents a novel technique to assess upper GI symptoms of nausea, vomiting, bloating, abdominal pain and early satiety potentially caused by gastroparesis. This novel wireless pH and motility capsule offers an office-based alternative to scintigraphy.

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