Diagnostic Assessment of Diabetic Gastroparesis

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Gastroparesis is characterized by a constellation of upper gastrointestinal (GI) symptoms in association with delayed gastric emptying (GE) in the absence of mechanical outlet obstruction from the stomach. Cardinal symptoms are nausea, vomiting, early satiety or postprandial fullness, bloating, and abdominal or epigastric pain (1). Gastric retention may be asymptomatic in some, possibly due to afferent dysfunction in the setting of vagal denervation (2,3), and delayed GE may be associated with recurrent hypoglycemia in patients without upper GI symptoms (4,5). In these individuals, the term "delayed GE" is preferred to gastroparesis (1), although others have used terms such as "gastric hypoglycemia" (6). Thus, clinical manifestations of impaired GE may include anorexia, weight loss, malnutrition, phytobezoar formation, poorer quality-of-life, or impaired glycemic control due to erratic delivery of nutrients to the small bowel for absorption, and these may occur independent of factors such as age, gender, alcohol consumption, tobacco use, and diabetes type (7–9).

Upper GI symptoms in diabetic patients may result from accelerated GE, often in association with vagal neuropathy and impaired proximal gastric accommodation (10). In addition, upper GI symptoms in diabetic patients were not significantly different in those with delayed compared with rapid GE, except possibly for postprandial distress (P = 0.076 on univariate analysis) (11). Hence, it is essential to measure GE in patients with upper GI symptoms if the right treatment is to be selected, such as choice of a prokinetic agent in those with delayed GE. Similarly, one cannot assume that patients with known vagal neuropathy and upper GI symptoms have gastroparesis, because the measured GE may be normal, fast, or slow in such patients. The magnitude of GE delay may also influence diagnosis; there is overlap in the clinical diagnosis of functional dyspepsia and gastroparesis in patients with mild GE delay and upper GI symptoms, whereas those with marked GE delay (greater than 35% retention at 4 h using a standard low-fat meal) should be diagnosed with gastroparesis (12,13).

The cumulative 10-year incidence of gastroparesis has been estimated at 5.2% in type 1 diabetes and 1% in type 2 diabetes among community patients with diabetes (14). However, the estimated incidence of gastroparesis is critically dependent on definition and previous higher estimates of diabetic gastroparesis on symptom surveys rather than the use of quantitative tests (14). Studies of the natural history of GE and upper GI symptoms in patients with diabetes suggest that delayed GE and symptoms are both relatively stable over 12 years or 25 years (15,16). Abnormalities, such as accelerated GE, visceral hypersensitivity, and impaired accommodation, may contribute to symptom generation in patients with diabetes (10,17). Mechanisms associated with abnormal gastric motor functions include impaired glycemic control (18), extrinsic (e.g., vagal) and intrinsic neuropathy, abnormalities of interstitial cells of Cajal (19–21), loss of nitric oxide synthase (22), and, possibly, myopathy (1,23).

The nonspecific nature of GI symptoms, multiple contributing pathophysiological mechanisms, diverse methods used to assess GE, varying degree of accuracy in assessment of GE of solids, and differences in patient selection across studies may all contribute to explaining the relatively weak association between symptoms and abnormal GE (3,24). Thus, careful evaluation of symptomatic patients through the use of validated techniques to document delayed GE is essential to diagnose and manage patients with suspected diabetic gastroparesis. GE assessment is also prognostically relevant, as it is associated with long-term morbidity due to diabetes (25).

The gold standard for the evaluation of GE is GE scintigraphy (GES), a noninvasive, physiologic, and quantitative assessment of GE (13). Alternative methods include stable-isotope GE breath testing (GEBT), a wireless motility capsule (WMC), and functional ultrasonography (Table 1). Additional data on gastric motor functions may also be obtained by tests such as antroduodenal manometry and electrogastrography, but these are regarded as secondary or research methods.

The aim of this review is to discuss available techniques for the diagnostic evaluation of diabetic gastroparesis and their relative advantages, limitations, and clinical and research applicabilities.

GES

GES is considered the gold standard test for measurement of GE (26) and the diagnosis of gastroparesis. A consensus statement from the Society of Nuclear Medicine and Molecular Imaging and the American Neurogastroenterology and Motility Society recommends a single standardized GES protocol, with a universally acceptable test meal, and provides details on technical procedures intended for uniform adoption (13). A standard low-fat meal (27) is used to perform solid-phase GES to document delayed GE. Dual-isotope labeling of solid and liquid phases may also be performed. The physiology of liquid emptying differs from that of solids; thus, liquid GE may not become abnormal until gastroparesis is very severe (28). When delayed liquid GE occurs with normal solid GE (29–31), it may increase sensitivity of detecting gastroparesis by 25–36% among symptomatic patients when using non-nutrient

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TABLE 1
Comparison of easily available measurement of GE for diagnosis of gastroparesis

	GES	Stable-isotope GEBT	Pressure and pH WMC	Ultrasonography	Paracetamol testing	Radiopaque markers
Indication/ function measured	GE	GE	Emptying and pressure amplitude	GE	GE	GE
Device/ assembly/ special requirements	External γ camera; isotope-labeled meal	Breath collection vials; stable isotope-labeled meal	Intraluminal capsule with miniaturized strain gauge and pH measurement	2D or 3D ultrasound equipment	Blood collection tubes and liquid drink containing acetaminophen	Radiopaque markers, standard meal, X-ray equipment
Placement of device	—	—	Capsule swallowed	On abdomen repeatedly	—	—
Performance/ versatility/ interpretation	Excellent; standardized meals, data acquisition and interpretation	Becoming standardized; performance related to mathematical analysis	Standard acquisition; delayed emptying fairly valid; pressures of unclear significance	Becoming standardized; performance related to technical expertise; best for liquid emptying	Validated for liquid emptying only	High specificity, low sensitivity; indicates return of phase III MMC
Duration of study (h)	Typically 4 h, could be added to small bowel and colon transit	3–4 h	6 h, could be added to small bowel and colon transit	Typically 2 h	2–8 h	6 h
Availability/ potential use	+	+++	+	+	+++	+++
Cost	++	+	++	++	+	+

Adapted from Szarka LA, Camilleri M. Methods for measurement of gastric motility. Am J Physiol Gastrointest Liver Physiol 2009;296:G461–G475. The "+" signs signify the lowest (+) to the highest (+++) availability or potential use. 2D, two dimensional; 3D, three dimensional.

liquids such as water. However, there is evidence to suggest that the relationship between GE of solids and of nutrient-containing liquids is relatively weak among patients with diabetes (32). The clinical significance of these observations needs further investigation.

Indications. Measurement of GE with GES may be indicated in patients with diabetes with upper GI symptoms (other than isolated heartburn or dysphagia), patients with poor glycemic control, and those being considered for or who are taking treatment with hypoglycemic medications that may slow GE, including amylin analogs and glucagon-like peptide (GLP-1), and severe reflux symptoms unresponsive to standard therapy (33,34).

Preparation and procedure. GES should be performed after exclusion of mechanical or structural causes of abnormal GE. As with all tests of GI motility, patients should discontinue all motility-altering medications for at least 2–3 days before testing, including prokinetics, opiates, and anticholinergics. GLP-1 agonists may also delay GE, and it may be reasonable to consider alternative therapies that do not delay GE (e.g., dipeptidyl peptidase IV inhibitors [35]). Patients should refrain from smoking and consuming alcohol on the test day as both may slow GE (36). Significant hyperglycemia delays GE, and fasting blood glucose should be <275 mg/dL on the day of testing based on expert consensus (26). Although researchers have shown that changes in blood glucose within the normal postprandial range delay GE by 20–30% in healthy subjects and type 1 patients with diabetes without GI symptoms, the magnitude of delay was significantly greater in healthy subjects (37).

In addition, acute or short-term improvements in glucose control among type 2 patients with diabetes have not been shown to significantly affect GE (38). The available evidence more clearly establishes effects of significant hyperglycemia at levels >275 mg/dL (39), including a recent study by Laway et al. (40) showing normalization of delayed GE in type 2 diabetic women with significant hyperglycemia (14 mmol/L) after achieving euglycemia (5–6 mmol/L). Accelerated GE has also been shown with insulin-induced hypoglycemia. However, it is unclear whether this effect is entirely attributable to vagal stimulation, because Russo et al. (41) showed no significant difference in the magnitude of change in GE of solids or liquids in patients with autonomic or vagal neuropathy during euglycemia and hypoglycemia.

After an overnight fast, the patient consumes a standardized test meal within 10 min. The most commonly used meal is a 255 kcal low-fat test meal consisting of Egg Beaters (120 g) labeled with 0.5 mCi technetium-99m–S colloid radioisotope, two slices of bread, strawberry jam (30 g), and water (120 mL) (27). The stability of the radiolabel binding of this meal, important in ensuring that the isotope does not separate from the solid meal and empty with the liquid phase, has been validated in vitro under gastric conditions (27). Standard imaging of the gastric area with the patient standing is performed at baseline (after meal ingestion) and at 1, 2, and 4 h after meal ingestion. Changes in body position may have marked effects on GE of radiolabeled liquids (42) but only a minor effect on the intragastric meal distribution and lag-time or postlag emptying rate for solid and liquid meals

(43). Anterior and posterior images are obtained sequentially with a single-headed camera or simultaneously with a dual-headed camera (34).

Precautions. Imaging should be completed over 4 h to produce a reliable estimate of half-life time ($T_{1/2}$). Shorter imaging protocols with mathematical extrapolation of $T_{1/2}$ may complicate interpretation, and data to support the use of abbreviated protocols are insufficient (13,26). The study meal should also be consumed within 10 min, and the time required for consumption should be recorded by the nuclear medicine technician because prolonged times for meal ingestion may affect measurement of GE. With the typical caloric loads involved in GE measurements, the increase in blood glucose to >275 mg/dL is unlikely given that the fasting level is <275 mg/dL to start and the patients are administered their usual antidiabetic medications. Patients should, however, be monitored for signs of hypoglycemia and blood glucose measured as clinically indicated.

Pitfalls. Factors that may affect interpretation of GES include the use of a nonstandard test meal with a lack of validated normal ranges, patient positioning, and frequency of imaging. Meal composition may need to be appropriately altered in select cases due to the patient's symptoms, specific food allergies, or known food intolerance (13).

A pitfall in interpretation is the significant association between sex and solid GE rates; female subjects are on average 15% slower than male subjects (44). The reasons for this difference are unclear and some have hypothesized hormonal effects (45), but a clear association between sex hormones and GE rates has not been shown (46). The cumulative evidence, including data from the largest study of GE to date showing female subjects being on average 15% slower than male subjects (44), mandates the need for separate reference values for each sex, which are not available at most centers (13). Studies have also shown an inconsistent association of BMI with GE (44,47).

Calculation and interpretation. Quantification of GE is performed using computerized software; a region of interest is drawn around the stomach on both anterior and posterior images at each time point. Geometric means of anterior and posterior counts are calculated and corrected for tissue attenuation and isotope decay. Results are expressed as the percentage of radioactivity retained in the stomach at each time point, normalized to the baseline value (Fig. 1). GE is considered delayed if there is greater than 60% retention at 2 h or 10% retention at 4 h (13,27). Estimated $T_{1/2}$ may be calculated with the traditional power exponential curve (48) or by linear interpolation due to the relatively linear emptying of solids in the postlag phase (49).

Merits. GES is considered the gold standard for diagnosis of gastroparesis because it is noninvasive, quantitative, and provides direct assessment of GE using a physiological meal. GES is unique in its ability to characterize the complex physiology of GE of solids and liquids as well as the intragastric distribution of antral and fundal contents (13).

Limitations. Major limitations to widespread use of GES include lack of adherence to a standardized protocol across institutions, limited access to γ-camera facilities, and radiation exposure precluding its use in pregnant women or children. Owing to the inconsistent correlation between symptoms and GE, the degree of delay by GES should not be used to grade the severity of disease without considering clinical parameters such as symptom severity, nutritional status, glycemic control, and need for hospitalizations or emergency department visits (33,34). There

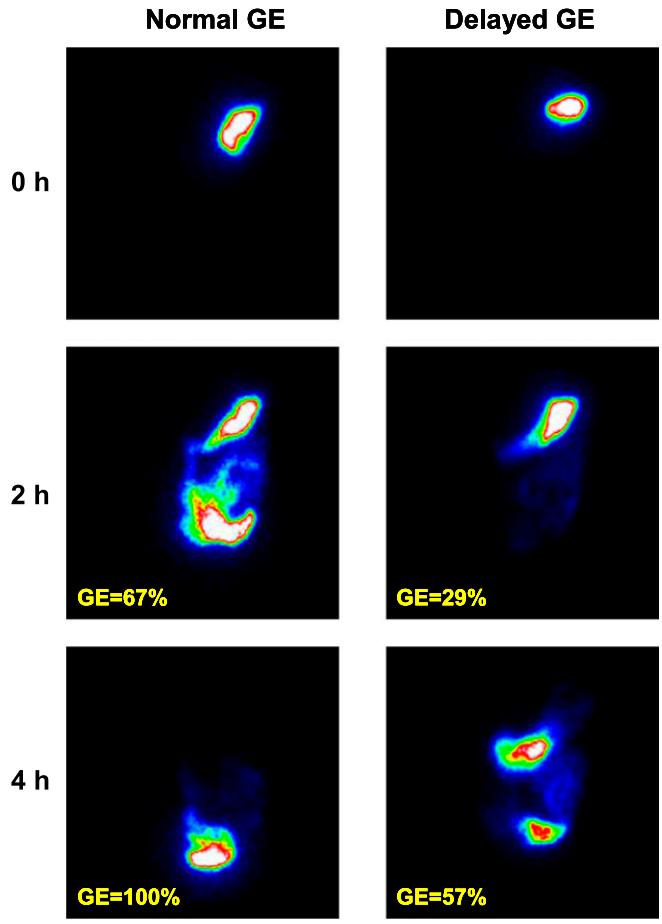

FIG. 1. GES displays normal and delayed GE in a patient with type 1 diabetes.

is also a significant within-individual coefficient of variation in GE rates by GES of up to 24% in healthy individuals (44). This degree of variation is similar to that observed with stable-isotope GEBT in head-to-head comparisons, suggesting it may be secondary to true within-individual variation rather than the technique itself (44,50,51).

Finally, GES with the standardized protocol uses a low-fat, low-fiber meal, which may empty normally in a patient in whom symptoms and gastric retention occur with the consumption of a normal meal in their diet (23); hence, centers with large databases and established 4-h tests of GE with meals with higher fat content and ~320 kcal have elected to retain their established method (44) while adhering to all other guidelines from the national societies (13). The latter strategy may be considered in patients with impaired glycemic control in whom it is suspected that there is a mismatch in timing between subcutaneous insulin administration and delivery of the meal from the stomach. A meal that empties more slowly may be expected to increase the likelihood of demonstrating such a mismatch between food delivery and subcutaneous administration of insulin; such a meal would be would be one of higher fat or caloric content.

STABLE-ISOTOPE GEBT

GEBT using ^{13}C-labeled substrates, typically ^{13}C-octanoic acid or ^{13}C-*Spirulina platensis* (blue-green algae), have been proposed and validated as promising alternatives to

GES (52). This noninvasive method is easy to perform and does not involve radiation exposure. In GEBT, the rate of GE of the ^{13}C substrate incorporated in a solid meal is reflected by breath excretion of $^{13}CO_2$ (52).

Indications. Indications for GEBT are the same as those for GES. It may specifically be indicated in patients in whom GES is not feasible, such as pregnant women. GEBT has been used extensively in research (24,53); however, use in clinical diagnosis has been limited (54), possibly because the commercial test with ^{13}C-octanoate provides results that have questionable validity (see Calculation and Interpretation below), and the better validated test based on ^{13}C-*S. platensis* is not yet approved for marketing.

Preparation and procedure. GEBT begins in the same manner as for GES: discontinuing gastric motility-altering medications for at least 2–3 days, refraining from consuming alcohol and smoking on test days, and testing after an overnight fast. The patient consumes a standardized test meal containing a ^{13}C substrate, either ^{13}C-octanoic acid or ^{13}C-*S. platensis*, both of which have been shown to provide acceptable solid GE assessment (51,52,55,56). Octanoic acid is a medium-chain fatty acid found in dietary fats that is firmly retained in the solid phase of the test meal (52,57). During preparation of the test meal, ^{13}C-octanoic acid substrate is mixed into egg yolk and baked. The patient ingests the meal, and the ^{13}C-octanoic acid is rapidly absorbed in the duodenum only after the solid contents of the meal have been triturated and liquefied to chyme (52,57,58). It is then transported to the liver via the portal circulation and oxidized to $^{13}CO_2$, which is released in the end-tidal breath samples collected in a Vacutainer. These samples are analyzed by isotope ratio mass spectrometry to determine the GE rate (50,54,57,58). Although there have been various recommendations on sufficient duration of sampling, some have advocated at least a 6-h sampling scheme for accurate prediction of GE (51) because an overestimation of $T_{1/2}$ by 4-h breath testing has been shown when the formula proposed by Ghoos et al. (52) is used. This can be corrected by 6-h sampling (51).

S. platensis is an edible blue-green algae consisting of 50–60% protein, 30% starch, and 10% lipid (59). The most validated test meal involves ^{13}C-*S. platensis* administered as an egg meal, which may be available as a 27-g freeze-dried egg mix, 6 saltine crackers, and 180 mL water. This meal provides the added convenience of a long shelf life and stability at room temperature (60). The ^{13}C-*S. platensis* is incorporated into the egg mix to allow for assessment of solid GE. The contents of the algae cells are not freely diffusable (55), and ^{13}C is released only after the meal has been digested, emptied from the stomach, and the ^{13}C substrates absorbed. As with ^{13}C-octanoic acid breath testing, end-tidal breath samples are collected to assess GE. Measurements of $^{13}CO_2$ enrichment are taken at baseline and at 45, 90, 120, 150, 180, and 240 min, although a strategy using only the 45, 150, and 180 min time points has been shown to be valid (60).

Pitfalls and precautions. Reliability of $^{13}CO_2$ excretion may be influenced by changes in endogenous CO_2 excretion caused by physical activity. Activities of moderate intensity, such as walking, may double energy expenditure and affect CO_2 excretion. This effect can easily be prevented by asking patients to avoid physical activity.

Calculation and interpretation. CO_2 breath excretion is used to estimate GE $T_{1/2}$ derived by mathematical analysis. Several mathematical models have been developed; the most widely used method is the nonlinear regression method proposed by Ghoos et al. (52). However, observations of significantly different results using this method compared with simultaneous GES (61) raised uncertainty regarding its accuracy (50,62). Practicality has also been questioned due to the need for 6-h sampling (54,55). Thus, an alternative approach using a generalized linear model was developed based on a minimal number (typically 5) of breath samples (56,63) (Fig. 2). Subsequent methods for mathematical analysis have included the Wagner-Nelson method (64) and the linear regression method (60). In a comparison of these methods and cumulative breath $^{13}CO_2$ excretion, all methods, except for the Wagner-Nelson

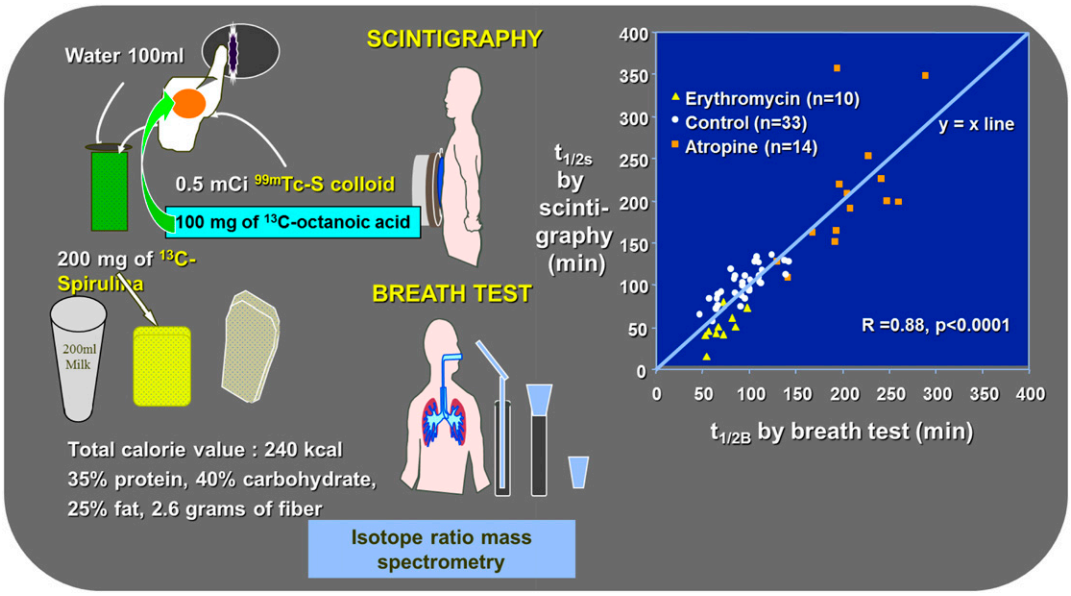

FIG. 2. Methods for GE assessment by breath test ($T_{1/2}$B) and scintigraphy ($T_{1/2}$S), and corresponding correlation of $T_{1/2}$ in erythromycin (n = 10), control (n = 33), and atropine (n = 14) groups showing a significant correlation between estimates (r = 0.88, P < 0.0001) based on the multiple linear regression model. Reproduced with permission from Viramontes et al. (63).

method, resulted in a mean GE $T_{1/2}$ that approximated the $T_{1/2}$ obtained with scintigraphy; in addition, the generalized linear regression and linear regression appear to provide most accurate assessment of $^{13}CO_2$ excretion (62).

Merits. GEBT is safer than scintigraphy because it does not require radiation exposure and may be used in pregnant women, women who are breast-feeding, and children. It is also less expensive and easier to perform than GES. Collected samples may be sent to a central laboratory for analysis, and testing may be performed almost anywhere, including in community and office-based practices.

Limitations. GEBT is an indirect measure of GE, and the effect of variation in postgastric metabolism between individuals is still unclear. There is potential for loss of accuracy in patients with malabsorption, pancreatic exocrine insufficiency, and significant lung or liver disease (65). In addition, despite evidence supporting the use of linear regression and generalized linear regression methods as optimal methods of analysis (62), there still remains a lack of standardization of mathematical analysis, study duration, and sampling frequency (54,57). High reproducibility, comparable to that of scintigraphy, has been shown in healthy volunteers, but reproducibility has not been specifically studied in patients with delayed GE (60).

THE WMC

The WMC using the SmartPill (SP) has been approved by the U.S. Food and Drug Administration for the evaluation of GE, colonic transit time in patients with suspected slow transit constipation, and for measurement of pH, temperature, and pressure throughout the GI tract (66); it is a safe and practical alternative to GES (67). It consists of a small (<2-cm long) wireless transmitting capsule that has the ability to record and transmit data on pH, pressure, and temperature to a portable receiver that may be worn around the patient's neck. Data can be acquired continuously for up to 5 days, and significant events (e.g., meal ingestion, sleep, or GI symptoms) can be recorded with the use of an "event button" (23). GE is reflected by an abrupt change in pH as the capsule moves from the acidic environment of the stomach to the alkaline environment of the duodenum. This typically occurs with return of the fasting state and phase III migrating motor complex (MMC) after emptying of liquids and triturable solids (68,69).

Indication. WMC testing is used in the evaluation of GE and whole-gut transit in patients with suspected gastroparesis.

Preparation and procedure. The procedure should begin in the morning after an overnight fast. Before testing, medications suppressing gastric acid production should be stopped (ideally proton-pump inhibitors for 1 week and histamine H_2 receptor antagonists for 3 days) because they may interfere with the pH-dependent measurement of GE. Similarly, medications that may affect GI motility are stopped 2–3 days before the test. However, there is evidence to show that capsule GE time may still be assessed in the setting of proton-pump inhibitors use by an easily recognized increase in pH (69). The patient consumes a standardized nutrient meal on the morning of the test, followed by ingestion of the WMC with 50 mL water. The patient fasts for the next 6 h (70).

Pitfalls and precautions. WMC emptying may not correspond to physiologic emptying of food (71). Cassilly et al. (68) showed capsule residence time was correlated strongly with time to the first phase III MMC (r = 0.813), which is the fasting repertoire of motor activity that is resumed only after solid meal emptying is complete or nearly complete; in about one-third of subjects, emptying of the capsule occurred with postprandial high-amplitude isolated antral contractions and not with the phase III MMC. Whereas capsule GE time showed moderate correlation (r = 0.606) with GE of the solid meal, capsule GE time does not specifically measure the GE of a meal (68), and the significance of the measurement is unclear. Similar to direct assessment of GE, acute hyperglycemia may also decrease gastric motility and inhibit phase III activity, which may potentially affect results of the test (72,73).

Calculation and Interpretation. Sensed data are transmitted by the single-use capsule to the receiver worn by the patient, and pH values from 0.5 to 9.0 units, pressure activity, and temperature are recorded. GE time is defined as the time from capsule ingestion to a rise in pH from gastric baseline to >4.0 pH units, marking the passage of the capsule from the antrum to the duodenum. Normal emptying of the capsule should occur within 5 h of ingestion. If it does not occur within 6 h, a maximum GE time value of 6 h is assigned (74) (Fig. 3).

Merits. WMC testing has been proposed as a safe nonradiological alternative to GES. Its advantages include point-of-care use in ambulatory settings and avoidance of pitfalls of GES, such as radiation exposure, need of a γ camera, and lack of standardized practices across centers (74). Utility of WMC testing has been enhanced with data (75) showing that pressure profile measurements recorded by the capsule can differentiate patients with diabetic gastroparesis from healthy individuals by the significantly lower numbers of contractions and motility indices.

Limitations. Healthy subjects and (more likely) patients with gastroparesis may not have a phase III MMC contraction within 6 h when the next meal is given, and capsule emptying may be inhibited by induction of the fed repertoire of contractions with suspension of the MMC for about 1 h for each 200 kcal ingested (76). Diabetic patients

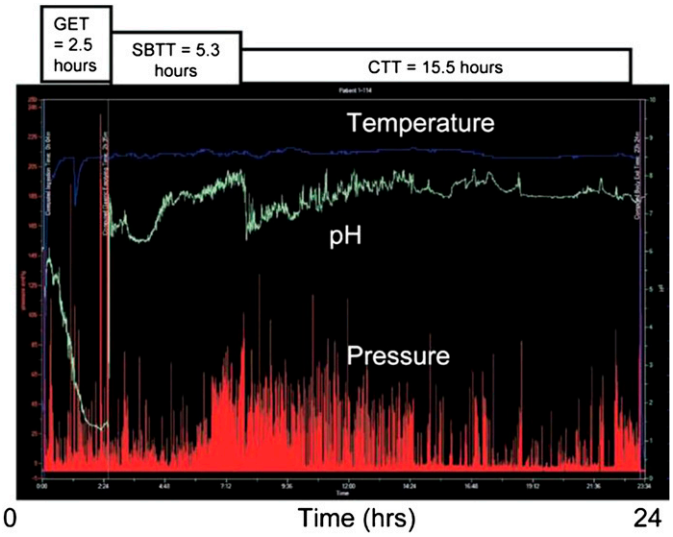

FIG. 3. Normal GI motility tracing using the WMC shows GE, small bowel transit, and colonic transit are normal. The GE time is indicated by the abrupt rise in pH. The capsule also records phasic pressure and body temperature. Whole-gut transit time is indicated by the drop in temperature from body to environmental temperature. Reproduced with permission from Rao SS, Kuo B, McCallum RW, et al. Investigation of colonic and whole-gut transit with wireless motility capsule and radiopaque markers in constipation. Clin Gastroenterol Hepatol 2009;7:537-544. CTT, colonic transit time; GET, gastric emptying time; SBTT, small bowel transit time.

undergoing evaluation for gastroparesis receive a second meal at 6 h as part of the standard method and to avoid hypoglycemia in those receiving medium-duration insulin preparations (77).

Other limitations are possible difficulty with capsule ingestion and the potential for capsule retention or obstruction. Use of the capsule is contraindicated in children and patients with a known history of esophageal stricture. However, serious complications are rare, and there have been no reported cases of prolonged capsule retention or luminal obstruction not amenable to endoscopic retrieval or administration of a prokinetic (70,77).

ADDITIONAL TECHNIQUES

Functional ultrasonography, magnetic resonance imaging, and other approaches are detailed in the Supplementary Data.

CONCLUSIONS

GES remains the gold standard of assessment for delayed GE among patients with suspected gastroparesis due to its well-established validity, reproducibility, ease of quantification, and ability to provide direct characterization of gastric physiology. Alternative methods, such as GEBT and the WMC, have emerged as reasonable approaches in settings where scintigraphy may not be feasible. Techniques such as functional ultrasonography and magnetic resonance imaging may provide a more comprehensive assessment of GI pathophysiology when available. Consideration of patient-specific factors, such as age, sex, comorbid diseases, patient preference, and availability of testing procedures, should be made when determining the test of choice.

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