New Directions in the Assessment of Gastric Function: Clinical Applications of Physiologic Measurements

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Key Words

Gastric function testing · Scintigraphy · Stable isotope breath tests · Water and nutrient drink tests · Electrogastrography · Ultrasound · Antroduodenal manometry · Magnetic resonance imaging · Single photon emission computed tomography

Abstract

A variety of methods exist to assess gastric motor and sensory function. Specific techniques allow for the measurement of emptying, contractility, accommodation and sensation. Several of these techniques are suitable for in-office use rather than in a hospital or gastroenterology laboratory. While gastric function tests continue to proliferate and become more clinically accessible, their relevance to specific digestive symptoms or syndromes remains poorly studied. Additionally, the ability of gastric function testing to guide therapy or predict responses to interventions also remains poorly studied. Gastric function testing should be employed cautiously in clinical practice with an awareness that test results represent observations rather than diagnosis.

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Introduction

The stomach is responsible for storage, mixing, trituration and emptying. It also provides important sensory feedback regarding fullness and satiation. Normal function allows the successful and generally pleasant ingestion of a variety of substances. Deranged gastric function can result in a wide range of unpleasant sensations and alter both the ability to pleasantly and successfully ingest. As gastric function is multifaceted and complex, a variety of tests are available to assess gastric function. This paper reviews currently available tests of gastric function.

When interpreting results of digestive function testing, it is essential to remember that digestive function is strongly influenced by both intrinsic and extrinsic factors. The central nervous system acting primarily through the autonomic nervous system and hypothalamic-pituitary-adrenal axis can greatly modify visceral function and sensation [1]. Additionally, disturbances in function of one digestive organ can, via enteric reflexes, result in alterations in function in other digestive structures [2, 3]. As such, an abnormal test of gastric function in the clinical arena should never be regarded as a diagnosis. Results of gastric function testing simply provide information that may inform the clinician of diagnostic possibilities.

Scintigraphy

Scintigraphy remains the most widely studied and available method for measuring gastric emptying rates [4, 5]. The most commonly reported measurements from scintigraphic studies of gastric emptying are the percentage of gastric retention at specific time points after ingestion and the time required for half-emptying of the test meal ($T_{1/2}$ or T_{50}). Also frequently reported is the time required for transfer of solid food from the fundus to the antrum and for the antrum to triturate the meal into a particle size (<2 mm) that can be emptied (T_{lag}). These parameters are variously calculated depending upon methods of image acquisition and the mathematical modeling assumptions used to estimate emptying [5].

Scintigraphy can also evaluation regional gastric function and antral motor activity. Dynamic antral scintigraphy can estimate both the frequency and magnitude of antral contractions. The magnitude of antral contractions has been shown to be increased in patients with functional dyspepsia and decreased in patients with diabetes [6, 7].

Scintigraphy has a number of pitfalls. There is radiation exposure. The test is time consuming for patients and medical staff. The radioisotope may separate from the test meal, migrate with the liquid phase of a meal producing falsely increased rates of gastric emptying. Clinically, the test is poorly standardized and this variability limits interpretation of results. Scanning times are also highly variable. Most centers scan continually for 90 min, although a preferred method is to obtain static images at various time points. This approach is less labor intensive, more cost effective and provides results comparable to dynamic acquisition [8, 9]. Gastric retention $>10\%$ at 4 h has been shown to be highly predictive of gastric stasis [9]. Even when consistently performed, the coefficient of variation (the ratio of the standard deviation to the mean) is a substantial 15% [10].

Stable Isotope Breath Tests

Stable isotope breath tests use nonemitting isotopes to measure gastric emptying. The nonradioactive isotope, ^{13}C , is usually bound to a medium chain triglyceride (octanoic acid) or proteinaceous algae (*Spirulina*), which is incorporated into a standardized test meal. The ^{13}C -labeled substrate is ingested, emptied by the stomach and then absorbed in the proximal small intestine. Absorbed ^{13}C is metabolized in the liver to $^{13}\text{CO}_2$ and expired through the lungs. The test assumes that the rate-limiting

Fig. 1. Association between half-emptying times ($t_{1/2}$) for scintigraphy values compared with estimates from a generalized linear regression model based on ^{13}C -*Spirulina* breath test values from the first 3 h of data (A) and for two time points from the first 3 h of sampling (B). The correlation between the methods is highly significant. The variation in differences between estimates by the two methods is expressed as SD (range). Adapted from Lee et al. [11].

step for excretion of $^{13}\text{CO}_2$ is gastric emptying [11]. Breath samples are collected at specific intervals for periods of up to 3–6 h. Enrichment of breath samples with $^{13}\text{CO}_2$ is determined by either isotope ratio mass spectrometry or laser infrared spectroscopy and this allows estimation of gastric emptying rates. Results from ^{13}C breath tests using labeled *Spirulina*, octanoate and acetate have all correlated well with simultaneously performed scintigraphic measures (fig. 1) [11–13].

Fig. 2. Volumes required to produce satiety in healthy subjects and patients with functional dyspepsia using WL5. Male and female dyspeptics ingested significantly less water than healthy subjects. # $p < 0.0001$ vs. controls; * $p < 0.005$ vs. controls of the same sex; ** $p < 0.0013$ vs. functionally dyspeptic males. Adapted from Jones et al. [14].

Stable isotope breath tests offer office-based, nonradioactive, standardized measures that potentially overcome the procedural variability seen with scintigraphy. Presently, breath samples are most often analyzed at a central facility, but office-based infrared spectroscopy units are increasingly available. Test results may be altered in patients with liver, pancreatic and pulmonary diseases as well as any condition altering intestinal absorption. Further validation studies are needed in patients with conditions known to accelerate or delay gastric emptying as most studies to date were performed in healthy subjects. If accuracy comparable to scintigraphy is confirmed in these conditions, stable isotope breath tests will offer a useful diagnostic alternative to scintigraphy.

Water and Nutrient Drink Tests

Drink tests developed as a noninvasive alternative to more invasive methods assessing sensory responses to gastric distension such as the barostat. A variety of methods have been proposed using either water or a variety of nutrient drinks consumed at either fixed rates or over ad libitum over a given interval [14–16]. No method has been proven superior, although the majority of investigators appear to favor nutrient-based drinks at present. Both water and nutrient drink tests are reproducible and

consistently demonstrate that patients with functional dyspepsia report fullness at lower volumes than healthy subjects (fig. 2) [14]. Volumes to fullness with nutrient drink tests are not well correlated with volumes to fullness for water load tests [14].

The advantage of drink tests is that they are inexpensive and noninvasive. The disadvantage of drink tests is that no one is certain what exactly the drink test measures. Drink test volumes correlate poorly with SPECT and barostat-derived measures of gastric accommodation [15, 17]. Drink test volumes and dyspeptic symptoms also poorly correlate, although an inverse correlation with nausea has been noted [15, 18, 19]. Presently, the drink test cannot be advocated as having value in the clinical arena and its investigational utility requires clarification.

Electrogastrography

The gastric pacemaker generates slow wave potentials at a frequency of 3 cpm. These slow waves lead to varying degrees of smooth muscle depolarization and potentially contraction. Abnormal pacemaker activity and neuromuscular function may result in changes in slow wave frequency with resultant alterations in gastric contractility. Electrogastrography (EGG) is a noninvasive method of recording gastric myoelectrical activity using cutaneous recording electrodes. These cutaneous recordings

have been shown to correlate well with recordings made from serosal electrodes [20, 21]. Abnormal gastric myoelectrical activity studied with EGG is reported in a variety of conditions including functional dyspepsia, motion sickness, a variety of disorders with nausea as a dominant symptom, gastroparesis of varying etiologies and mesenteric ischemia [22].

Equipment to perform EGG is commercially available. Recording and interpretation requires a certain degree of skill. Recordings are extremely susceptible to motion artifact so prolonged recordings or studies performed during other interventions are difficult to perform. Finally, as the American Motility Society has stated, 'the value of any diagnostic test is determined by its roles in directing therapy or providing prognostic information. To date, very few investigations have been performed to demonstrate a critical role for EGG in patient management' [22]. The technique will continue to be employed in an investigational setting, but until studies demonstrate the utility of EGG in improving treatment outcomes, there is little to recommend its clinical use.

Ultrasound

Ultrasonography has been used to evaluate gastric emptying, antral wall motion, transpyloric flow, and proximal stomach volumes [23–25]. Measurements are made relative to anatomic landmarks. Interobserver correlations are high [26]. Correlation with scintigraphic and stable isotope measures of gastric emptying is good [27, 28].

Ultrasound has the advantage of being widely available. As with any sonographic technique, body habitus and bowel gas may limit the study. Additionally, ultrasound does not lend itself well to prolonged studies. Presently, the technique is used in a few specialized centers. Studies demonstrating reproducibility and validity in more diverse practice settings are needed before the technique can fully endorsed.

Antroduodenal Manometry

Intraluminal pressure recordings from the antrum, pylorus and duodenum can be obtained using either water-perfused or solid-state catheters. Recording may be either stationary (typically several hours duration) or ambulatory. Antroduodenal manometry (ADM) assesses interdigestive and fed motor patterns. Ambulatory techniques

allow for longer periods of recording and are best suited for assessment of interdigestive motility patterns, symptom-associated motility events and sleep-related motility changes [4]. Stationary studies are preferred when assessing antral responses to meals and antropyloroduodenal coupling.

ADM involves intestinal intubation and requires fluoroscopy for accurate catheter placement. While sedation can improve procedure tolerance of the procedure, commonly used medications may alter motility patterns. Use of reversal agents has been suggested but not studied [4].

ADM is most valuable when the study is normal. This excludes dysmotility as a symptom etiology. Other scenarios in which ADM may be helpful include suspected small bowel obstruction and detection of visceral myopathy. For gastric motility, ADM is rarely needed but can detect abnormalities associated with post-vagotomy syndromes, mechanical obstruction or rumination [29–31]. In children, the absence of migrating motor complexes has been shown to predict poor responses to enteral feeding and prokinetic therapy [32, 33]. Such data are lacking in adults.

Overall, ADM is a technically challenging study requiring specialized equipment and expertise in performance and interpretation of studies. The procedure should be performed in centers with interest and experience in this technique.

Magnetic Resonance Imaging

Gastric emptying of both solids and liquids can be measured using MRI and the results correlate well with simultaneously performed scintigraphy [34, 35]. Preliminary data also support MRI in the measurement of gastric accommodation [36]. Gastric motility can also be evaluated using a real-time fast imaging sequence (fig. 3) [37]. MRI has also been used to evaluate intragastric distribution of drug models as well as to evaluate the motility responses of the stomach to various motility-modifying agents and meals [38–41].

One obvious advantage of MRI is the absence of radiation exposure. The technique also allows for repeated or prolonged observations, although procedure time currently restricts the migration of this technique from the research setting to the clinical realm. Additionally, studies must be performed supine which influences the mechanics of gastric emptying. Finally, confinement in the scanner can be unpleasant and the ability to breath-hold is required during image acquisition.

Fig. 3. Two-dimensional real-time imaging in a healthy volunteer demonstrates motion of a peristaltic wave towards the pylorus (arrow). **A–C** Images are sequential. Adapted from Ajaj et al. [37].

Single Photon Emission Computed Tomography

Single photon emission computed tomography (SPECT) is currently a research tool used to evaluate gastric accommodation. SPECT utilizes ^{99m}Tc -pertechnetate which is taken up by the gastric mucosa (parietal and mucin-secreting cells). Tomographic images of the stomach are acquired with the patient in a supine position. SPECT has been shown to possess excellent intra- and interobserver agreement [42]. It is superior to balloon-based measures of accommodation since intubation is not required. However, a comparison of SPECT with barostat measurements showed poor correlation between the two techniques with respect to meal-induced accommodation (fig. 4) [43]. Barostat was also superior in assessing changes in gastric tone. Finally, barostat but not SPECT allows assessment of gastric sensory responses. While SPECT appears to be a robust and noninvasive method to measure gastric accommodation, further study is required to define its utility in research and clinical applications. If impaired accommodation can be shown to be a relevant pathophysiologic factor in functional dyspepsia, SPECT will no doubt assume an important role in the evaluation of that disorder.

Other Tests of Interest

Gastric Emptying and Radiopaque Markers

Several studies over the past decade have attempted to quantitate gastric emptying using various types of radiopaque markers (ROM) [44–48]. Emptying of indigestible ROM depends upon the successful initiation of a phase III contraction at the end of the fed period. In general, emptying of ROM correlates with gastric emptying measured either scintigraphically or sonographically [47, 48]. While appealing, this method is not standardized and poorly studied. The sensitivity and specificity of the

Fig. 4. Correlation plot between meal-induced accommodation assessed by single photon emission computed tomography (SPECT) scanning and barostat. Note that SPECT volumes are not significantly different from 200 ml ($p = 0.1$), which equals the volume of the ingested meal. Adapted from van den Elzen et al. [43].

method needs to be determined. Finally, ROM methods require radiation exposure. Stable isotope breath tests will offer superior performance characteristics without radiation.

Multichannel Intraluminal Impedance

Multichannel intraluminal impedance has been studied extensively in the esophagus. The technique has also been successfully applied in assessing small intestinal transit [49]. At present, there are no published data evaluating this technique with respect to gastric motility beyond esophagogastric junction function. Multichannel

Table 1. Clinical applicability of currently available gastric function tests

Test	Measured parameter	Radiation exposure	Performance location	Clinical utility
Scintigraphic gastric emptying	Gastric emptying	Yes	Radiology	Usefulness of gastric emptying data in guiding therapy and predicting outcomes is uncertain
Stable isotope breath tests	Gastric emptying	No	GI lab or office	Usefulness of gastric emptying data in guiding therapy and predicting outcomes is uncertain
Ultrasound	1. Gastric emptying 2. Accommodation 3. Transpyloric flow	No	Radiology	Currently investigational
Drink tests	Unknown	No	GI lab or office	No demonstrated clinical utility at present time
Electrogastrogram	Myoelectrical activity	No	GI lab or office	Utility in managing patients unproven and understudied
Antroduodenal manometry	1. Gastric and intestinal contractions 2. Antropyloroduodenal coupling	Yes	GI lab	Utility in adults unstudied but may be of value when normal or obstruction suggested. May help predict responses to enteral feeding and prokinetic therapy in children
Magnetic resonance imaging	1. Emptying 2. Antral contractions 3. Accommodation	No	Radiology	Currently investigational
Single photon emission computed tomography (SPECT)	Accommodation	Yes	Radiology	Currently investigational

intraluminal impedance may be of value in assessing transpyloric flow and duodenal-gastric reflux.

Recommendations for the Use of Gastric Function Testing in Clinical Practice

Reviewed diagnostic modalities are summarized in table 1. While a wide variety of techniques are available to assess gastric motility and sensation, their relevance in clinical practice largely remains unproven. This statement is supported by three lines of evidence.

First, the association abnormal of gastric function with specific digestive symptoms or symptom complexes has not been conclusively demonstrated. Several investigators have reported an increased prevalence of gastric motor disturbances in patients with functional dyspepsia who have nonpainful symptoms such as nausea, bloating or early satiation [50, 51]. Most of these reported asso-

ciations are modest and a far larger body of evidence has failed to demonstrate consistent associations of gastric function testing with either specific symptoms or symptom subgroups of patients with functional dyspepsia [15, 19, 52, 53].

Second, abnormalities seen during gastric function testing may represent epiphenomenon rather than pathophysiologic determinants of symptoms. Examples of this include delayed gastric emptying in patients with anorexia nervosa [54], suppressed anger [55] and motion sickness [40]. This further emphasizes that the results of motility assessment represent an observation rather than a diagnosis.

Finally, the utility of currently available tests of gastric function to guide therapy or predict outcomes has not been conclusively established. While several studies have suggested that abnormal gastric emptying or EGG predicts a clinical response to cisapride [56–58], a recent systematic review has shown that there is a poor correlation between

changes in rates of gastric emptying and symptom relief [59]. This is an area that demands further rigorous study.

In summary, a variety of techniques exist to assess various parameters of gastric motor and sensory function. While these techniques often provide accurate physiologic

assessment, the relevance of these measurements with respect to symptoms or guiding therapy remains largely unproven and understudied. Clinicians should employ these tests cautiously and be equally cautious in interpreting the results.

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