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Selected Interventions in Nuclear Medicine: Gastrointestinal Motor Functions

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Abstract

Measurement of gastrointestinal functions by scintigraphy is established in clinical practice and research. The most commonly used test is the gastric emptying test. This is acknowledged as the gold standard and is conducted according to a consensus statement from the national nuclear medicine and motility societies. Other techniques are somewhat more esoteric (e.g. measurement of gastric accommodation with SPECT) or the scintigraphic approach is not the acknowledged gold standard (e.g. colonic transit, recto-anal angle and emptying, esophageal transit). The performance characteristics of many of the scintigraphic measurements have been published and the pros and cons established in the literature. Gastrointestinal scintigraphy is an integral and important component of the assessment of gastrointestinal function.

INTRODUCTION

Gastrointestinal (GI) diseases are a major cause of office visits and hospitalizations in the United States (1). Upper GI symptoms such as dyspepsia, bloating and gastroesophageal reflux account for a significant loss of work (2). Abdominal pain, nausea, vomiting are common GI complaints precipitating office visits and two of the top five selling drugs are GI medications (1). Patients with a variety of gastrointestinal complaints from dyspepsia to abdominal pain and bloating to constipation or diarrhea, can now be evaluated with gastrointestinal scintigraphy. Similar symptoms may result from different transit or motility abnormalities. For example, symptoms of accelerated gastric emptying may mimic delayed gastric emptying. Bloating, another common complaint, may be present in a condition affecting the colon or small bowel (3).

Measurement of gastrointestinal transit using nuclear medicine has increased in the last decade. New modalities have gained wider acceptance and availability, and have a direct impact on patient care. A recent consensus statement on the measurement of gastric emptying scintigraphy has gone a long way to add increased reliability and credibility to this test (4). Most scintigraphy tests are easy to perform, require only a modest amount of patient cooperation and have a low radiation burden. Whereas some of the studies that will be discussed are not generally available, the use of validated scintigraphic methods to measure diverse gastrointestinal functions is gaining wider acceptance. Limitations to scintigraphy still remain the lack of standardization of the technique and image processing (5). However, work is

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underway to establish standards for other gastrointestinal motility studies after consensus standards were developed for the leading indication [measurement of gastric emptying (6)].

ESOPHAGEAL TRANSIT

Scintigraphy Relative to Current Gold Standard

Dysphagia is a common esophageal complaint. Barium swallow, upper endoscopy and/or computed tomography (CT) are usually performed as first-line evaluations to exclude structural abnormalities. If no anatomical abnormality is identified, esophageal manometry is used next (7) and is considered the gold standard for evaluation of dysphagia (8) with defined criteria for achalasia, diffuse esophageal spasms and nutcracker esophagus. Esophageal manometry can also characterize the function of the lower esophageal sphincter which may be helpful in diseases such as scleroderma and to confirm normal peristaltic function prior to antireflux surgery (9). Limitations of esophageal manometry include its invasive nature and lack of widespread expertise in interpreting the results. High resolution manometry and multichannel intraluminal impedance are newer techniques with standardization, and criteria for diagnosis of common esophageal motility disorders (10–13), but it is not clear if they provide much more help in diagnosis (14). Combinations of these procedures (e.g. pH-impedance or manometry-impedance) provide more information on esophageal reflux of acid and non-acid contents and on bolus transit (15).

Esophageal transit scintigraphy was initially introduced as a way to qualitative evaluate the swallowing function of the esophagus, transit through the various segments of the esophagus and esophageal patency (16). The major current indications are to evaluate esophageal emptying and reflux in patients with esophageal dysmotility. It is fast, noninvasive, easy to perform and has minimal radiation exposure.. However, performance methods are not standardized and lack of standardization has limited its widespread use.

Indications for Esophageal Scintigraphy

- a. Patients who cannot tolerate manometry or who have equivocal manometry results (17).
- b. Repeat measurements after an intervention or therapy.
- c. Esophageal cancer after luminal patency is restored: Dysphagia is a common symptom in patients with esophageal cancer, which is increasing in prevalence in the western world (18). Upper gastrointestinal endoscopy, which carries its own risks, has been used to evaluate and treat malignancy-associated dysphagia. Many esophageal cancer patients have persistent dysphagia even after esophageal patency has been achieved with stenting. Esophageal scintigraphy provides a noninvasive way to assess for dysmotility and obstruction in one noninvasive test (19).
- d. Follow up of patients with scleroderma (systemic sclerosis): Scintigraphy should be considered to follow patients' symptoms, as it is only slightly less sensitive than manometry and also has the ability to detect esophageal involvement in asymptomatic patients (20). A study of scleroderma patients showed that scintigraphy correlated well with manometry and contrast radiology results in assessing dysmotility (21).

Procedure

After at least a 3-hour to overnight fast, a radioactive bolus (usually liquid or viscous) is ingested, followed by repetitive swallows of the bolus (dry swallows may also be obtained), and images are obtained via a gamma camera while the patient is in a supine or upright position.

Analysis

Esophageal scintigraphy allows for quantitative measurements of esophageal transit times and esophageal retention/emptying at specified times. These measurements may be repeated serially to monitor efficacy of treatments in diseases such as achalasia or post-esophagectomy (22). The dynamics of swallowing can also be visualized. This can reveal abnormalities with gastroesophageal reflux, bolus retention in the oropharyngeal phase and aspiration (5).

Performance Characteristics

The reported sensitivity (95%) and specificity (96%) of esophageal scintigraphy to detect esophageal disorders vary widely depending on the technique used and esophageal disorder investigated (23,24). Early studies have shown that esophageal scintigraphy detects achalasia and scleroderma well but is less useful in detecting non-specific motility disorders [i.e., nutcracker esophagus, sensitivity 42–56% (23)]. However, the clinical importance of nonspecific esophageal motility disorders is currently under question. With use of multiple swallows, scintigraphy can diagnose the major esophageal motility disorders including achalasia, scleroderma or diffuse esophageal spasm (22).

GASTRIC EMPTYING

Scintigraphy Relative to Current Gold Standard

Scintigraphic measurement of gastric emptying is the gold standard. Patients with gastric dysmotility disorders may present with a wide array of symptoms from nausea and vomiting to early satiety and abdominal bloating of varying severity (25). Alterations in gastric emptying (accelerated or delayed-gastroparesis) and in accommodation or relaxation of the fundus can lead to similar symptoms and significant patient morbidity (26). Gastric motility disorders continue to pose a challenge to gastroenterologists; epidemiological studies show that diabetic gastroparesis persists during a decade of follow-up (27); these patients need continued care and repeat evaluations.

A variety of methods including scintigraphy, breath testing using stable isotopes, ultrasound, and magnetic resonance imaging (MRI) may be used to measure gastric emptying and function. Breath tests using ^{13}C bound to a meal are gaining more use and offer a noninvasive, office based method to measure gastric emptying. Breath tests are limited as the optimal method and analysis are still under investigation and there is no consensus method. Ultrasound is more reliable for liquid than for solid or dual phase emptying and is very dependent on operator and patient factors [e.g. obesity, cooperation (28,29)]. MRI is expensive, time consuming and has limited availability; however, the lack of radiation exposure and its ability to separately assess the emptying of fat and water, make it appealing. It may gain more use in the future for accessing gastric emptying, accommodation and wall motion in one session (30,31). Paracetamol (acetaminophen) absorption test measures emptying of liquids and provides limited information.

Indications for Scintigraphic Gastric Emptying

- a. Dyspepsia with a normal endoscopic exam;
- b. Suspected generalized motility disorders, post surgical nausea or vomiting;
- c. Recalcitrant gastroesophageal reflux;
- d. Diabetics with symptoms of gastroparesis or erratic glycemic control.

Procedure

In the past, there was a lack of standardization: different meals (liquid versus solid meal, high fat versus low fat), different frequencies or duration of images and different analysis software are used across centers. This has made the test results irreproducible and difficult to interpret. Recent consensus guideline from the Society of Nuclear Medicine (SNM) and the American Neurogastroenterology and Motility Society (ANMS) has provided a suggested protocol based on the current data available in the literature. It recommends a standardized low fat egg-white solid meal and images taken at 0, 1, 2 and 4 hours (4). The first recommendation for this approach was published by Mayo Clinic investigators (32). The consensus provides a protocol that meets the needs of the patients, clinicians and nuclear medicine technicians and radiologists. Liquid only gastric emptying and/or 2-hour examinations were the standard prior to the consensus. However, a large multi-center study by Tougas and colleagues established normal values for 4-hour testing (33). Four-hour testing is superior to 2-hour testing in that it detects more patients with delayed emptying and does not pose unnecessary burden on the imaging centers (32,34,35). Other studies have also shown that solid gastric emptying tests can detect delays earlier than liquid tests. Liquid emptying can remain preserved long after solid emptying is delayed (36,37).

Analysis

The three parameters that are most frequently reported are:

- i. Lag time (time to 50 or 10 % emptying) and post-lag gastric emptying slope, from which the $T_{1/2}$ can be calculated (38,39);
- ii. β and κ from the power exponential analysis, from which the $T_{1/2}$ can be calculated (40);
- iii. Proportion emptied at 1, 2 or 4 hours (4,32).

Performance Characteristics

The intra-individual coefficient of variation for $T_{1/2}$ is 12% and between-subject 25% (41), and for gastric residual at 4 hours 4% (42).

Pitfalls, Limitations and Precautions

While scintigraphy is the accepted gold standard for diagnosis of gastroparesis (25), it has limited validation for detection of rapid gastric emptying which has been observed in functional dyspepsia, cyclical vomiting, post-gastric surgery symptoms, and diabetics with early stages of autonomic dysfunction. These patients cannot be distinguished from gastroparetics by symptoms alone. Larger studies are needed to validate scintigraphy for rapid gastric emptying (43,44).

Patients should be off prokinetic or anti-kinetic medications for at least 48 hours before testing, and fasting blood glucose should be $<180\text{mg/dL}$ on the day of testing. One limitation is that there is limited concordance between gastric emptying abnormality and symptoms. Similarly, patients may respond to prokinetic agents without a significant change in their gastric emptying (45).

Adaptations of Gastric Scintigraphy to Measure Antral Motility

Dynamic antral scintigraphy during the postprandial period has also been used to characterize gastric antral contractions in diseases like gastroparesis and dyspepsia (46). This sophisticated method has been used in research but has had little uptake in clinical practice.

GASTRIC ACCOMMODATION

Scintigraphy Relative to Current Gold Standard

Impaired relaxation (accommodation) to a meal has been proposed as a mechanism to explain postprandial symptoms in 40% of dyspeptic patients (47). Physiologically, accommodation allows the stomach to increase volume without an increase in pressure. Gastric barostat studies have been used classically in research settings to evaluate accommodation, and the barostat is regarded as the gold standard. Barostat measurements are limited by their invasive nature (48) and the potential artifact induced by the low grade intra-balloon pressure which is not physiological (49). Other imaging approaches to measure gastric volumes are MR imaging (50–52) and 3D-ultrasonography (53,54), which have the advantage of giving no radiation exposure to patients. However, they are not as fully validated or applied as single photon emission computed tomography (SPECT) imaging.

Procedure

SPECT allows measurement of the whole stomach volume during fasting and postprandially and, unlike the barostat, it is noninvasive. Intravenous ^{99m}Tc -pertechnetate is injected and accumulated by the gastric mucosa. SPECT images are taken pre- and postprandially, and the volume change is measured as a surrogate for accommodation in health and disease (48,55). Bouras and colleagues validated SPECT measurement compared to simultaneous measurement, and established normative values for the postprandial volume change in males and females (56,57).

Analysis

The analysis is not standardized; the Mayo group uses a customized program based on a proprietary ANALYZE™ program; the Temple group used an open source program that is available from the National Institutes of Health (<http://rsb.info.nih.gov/ij/index.html>).

Performance Characteristics

The SPECT measurement of gastric volumes in response to a nutrient liquid meal is reproducible: inter- and intra-individual coefficients of variation were 13 and 13.8% (58).

Pitfalls and Limitations

The proprietary analysis program that is used in the vast majority of studies in the literature has compromised the general use of SPECT to measure accommodation. One group has suggested that SPECT measures only the volume of the meal in the stomach (59). This appears to be contradicted by the experience of the Mayo and Temple groups and by the observation with other techniques such as MRI that the postprandial volume is greater than the fasting volume plus the volume of the meal ingested (52).

Simultaneous measurement of gastric emptying and gastric accommodation by SPECT has been reported by two centers and has the potential to provide comprehensive assessment of gastric motor functions (60,61).

SMALL BOWEL TRANSIT

There are two approaches to measure small bowel transit: a substrate-breath hydrogen test and scintigraphy. Small bowel transit is difficult to quantify and, thus far, scintigraphy has yielded the most reliable results (62). Transit through the small bowel can be impeded by slow colonic transit. Symptoms attributable to disorders of the small bowel may mimic those of derangements in gastric emptying, which may make it difficult to know when to check for

small bowel transit. Small bowel transit by scintigraphy has been described as colonic filling at 6 hours or orocecal transit time (3). However, orocecal transit also includes the time taken for gastric emptying, and scintigraphy allows for this collection, but breath H₂ test does not.

Breath hydrogen may reflect bacterial contamination of the small bowel, and cautious interpretation is required in conditions that may be associated with bacterial overgrowth. In the orocecal transit time, measurements are taken every 10 minutes and defined as the time it took 10% of small bowel counts to accumulate into colon (63). This is a very laborious and costly. Therefore, small bowel scintigraphy is not commonly used outside of research, but an assessment of orocecal transit in the form of colonic filling at 6 hours is gaining increased use in conjunction with gastric emptying or whole gut transit tests. There is a wide range of normal values for colonic filling at 6 hours, depending on the isotope used (11–70% with radiolabeled, nondigestible particles (64,65) or 43–95% for digestible solids (66). The inter-subject coefficient of variation is 30% and intra-subject 19%.

COLON TRANSIT

Scintigraphy Relative to Current Gold Standard

Constipation is a common complaint in gastroenterology and primary care visits. Office visits for constipation have increased in the last decade, and the cumulative incidence of constipation is up to 17.6% (67,68). Differentiating between the types of constipation (IBS, slow transit, rectal outlet obstruction) is important in management. Transit studies using radiopaque markers and serial abdominal radiographs are used most commonly in clinical practice (69,70). They require serial radiation exposure and multiples visits over the course of the test to ensure the passage of the markers and do not give sufficient information on rapid transit; however, recent studies including earlier radiographs demonstrate utility of the method even for accelerated transit (71).

Colon transit scintigraphy, a safe and noninvasive method, has been shown to correlate with radiopaque markers. Colon transit scintigraphy provides information on regional and overall colon transit (72).

Indications

- i. Unexplained constipation;
- ii. Unexplained diarrhea;
- iii. Constipated patients with upper GI symptoms or evaluation of patients in whom surgery is considered for slow transit constipation. Whole gut dysmotility is a relative contraindication for colectomy in such patients.

Procedure

A methacrylate-coated capsule containing ¹¹¹Indium-labeled activated charcoal particles is ingested. The coated capsule dissolves in the alkaline pH of the distal ileum and releases into the colon (65,73). External markers are placed over the iliac crests to localize the position of the capsule in the small bowel. At the same time, a ^{99m}Techetium-labeled egg meal is used to assess gastric and small bowel transit. Other centers (e.g. Temple University, Johns Hopkins) radiolabel the solid and liquid phase of the meal of ^{99m}Tc egg sandwich with ¹¹¹In DTPA in water. The transit of the radiolabeled water is used to assess small bowel and colonic transit (74).

Analysis

Anterior and posterior images are obtained at specified times (e.g., 4, 24, and 48 hours) while the patient stands erect and an area of interest is drawn around the colon. The geometric center (GC), a weighted average of the radioactivity over regions of the bowel, is identified. In the Mayo Clinic method, the colon is divided into geometric centers as follows: 0 ileocecal, 1 ascending colon, 2 transverse colon, 3 descending colon, 4 rectosigmoid, and 5 expelled stool (65,66). Average time at 24 hours is $2.7 \pm \text{SD } 1.05$. Patients with a GC <1.7 are considered slow and those with a GC of >4.0 are considered accelerated. Scintigraphy can identify regional patterns of delays in colon transit which could suggest slow transit constipation, or colon inertia, or accelerated transit [e.g. in carcinoid diarrhea (75) or IBS with diarrhea (76)]. About 35% of patients with IBS have abnormal overall colonic transit, including 48% of those with IBS-D.

In other centers, the geometric center is based on 6 colonic regions (4 main regions plus hepatic and splenic flexures) and stool (74).

Performance Characteristics

The inter-individual coefficients of variation for colonic transit at 24 hours and 48 hours are 37% and 24%, and intra-individual coefficients of variation are 24% and 14% respectively.

Limitations and Pitfalls

The lack of standardization in procedure and analysis has compromised the use of the method across centers. Nevertheless, the colonic transit of liquid isotope probably reflects the transit of solids in the distal bowel; a head to head comparison of the two methods is needed.

Slow colonic transit can be the result of an evacuation disorder and is not specific for slow transit constipation.

RECTOANAL ANGLE AND EMPTYING

Scintigraphy Relative to Current Gold Standard

The gold standard for assessing pelvic floor and rectoanal dynamics during defecation in patients with rectal evacuation problems or anal incontinence is probably barium defecography. However, it has been significantly challenged by MR defecography. Dynamic imaging and the use of open magnets that allow for studies in the seated position provide detailed information about structure and integration with function. For example, MRI helps to identify different phenotypes of obstructed defecation (77), abnormal structure and function of the pelvic floor and anal sphincters in people with incontinence (78,79), and physiological alterations associated with aging (77).

Scintigraphic measurements of the change in rectoanal angle and the proportion of semisolid radiolabeled content from the rectum during defecation was popularized over two decades ago and it is performed at a few centers (80,81). The normal change in angle with simulated defecation is ≥ 15 degrees, and 55–75% of radiolabeled Veegum is emptied from the rectum during normal defecation. Thus, although rectal scintigraphy has potential advantages as a diagnostic test in terms of quantitation and decreased radiation exposure, one expert center reported the inability of the test to distinguish patients with slow transit constipation from those with defecatory complaints, raising questions about the potential utility of the test in clinical and investigative settings (82). The test may be helpful to confirm descending perineum syndrome (83). Given the controversy in the literature, the reader is referred to the original articles for details on procedure, analysis and pitfalls. There are no descriptions of the performance characteristics of the test in the literature.

DRUG PHARMACODYNAMICS INVESTIGATED BY SCINTIGRAPHY OF THE GI TRACT

Scintigraphy of the GI tract has wide clinical application and has helped in demonstrating the efficacy of treatments or medications. Gastrointestinal (GI) and colonic transit provide the most robust and consistent results for effect of medications that affect GI transit time, such as in patients with IBS. These include alosetron (84,85); tegaserod (86); renzapride (87,88); the guanylate cyclase-C agonist, linaclotide (89); and the probiotic combination, VSL#3 (90). Regional or total colonic transit is correlated significantly with stool number or stool form with a number of drugs including the prokinetics, prucalopride (91), tegaserod (86), and renzapride (87); the guanylate cyclase-C agonist, linaclotide (89); and the chloride channel activator, lubiprostone (92). Colonic transit studies also correctly predicted the demonstration of clinical efficacy of treatments in phase IIB or phase III studies in IBS with alosetron, tegaserod, prucalopride, renzapride, linaclotide, and lubiprostone.

CONCLUSION

The use of scintigraphy to measure gastrointestinal transit is an important tool for the clinician in the diagnosis and treatment of common gastrointestinal diseases. Studies such as colonic transit and SPECT for measuring gastric accommodation are gaining wider acceptance and availability; however, others such as recto-anal angle and emptying and esophageal scintigraphy are not widely available or lack standardization of the techniques and/or interpretation of the results. Small bowel scintigraphy is the best available approach to measure small bowel transit, although it has some limitations. Gastric emptying scintigraphy still remains the most widely used test and has been established as the gold standard for measuring gastric emptying. Scintigraphy studies are well tolerated and easy to perform.

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Figure 1.

Gastric emptying, colonic filling and colonic transit in a patient with gastrointestinal symptoms. Regions of interest are drawn over the stomach and different regions of the colon in which isotope is identified. Note the delay in gastric emptying at 2 and 4 h, and the reduced colonic filling at 6 h (reflecting orocecal transit). At 6 h, note that the isotope is partly in the small bowel and partly in the colon. In the presence of delayed gastric emptying, reduced percent colonic filling should be interpreted with caution and may be normal. Colonic transit is within normal range. GC = geometric center, the weighted average of counts in the 4 colonic regions and stool.

Figure 2. Method using SPECT imaging to measure gastric volume during fasting and postprandially. After i.v. injection of ^{99m}Tc pertechnetate, transaxial images are obtained and subsequently 3-dimensional reconstructions of all transaxial images provides an estimate of gastric volumes.

Figure 3.

Scintigraphic measurement of rectal emptying, perineal descent and recto-anal angle during simulated defecation. The instillation of radioisotope into the rectum allows measurement of the recto-anal angle with a lateral view image. Normally, at least 65% of the radiolabeled Veegum® should be excreted from the rectum; the degree of perineal descent relative to the pubococcygeal line is 5.8 cm (normal >1cm or <4.0 cm), and the rectoanal angle opening is <15°, suggesting abnormal emptying dynamics secondary to descending perineum syndrome. R-A=recto-anal angle