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Gastrointestinal Transit Assessment: Role of Scintigraphy: Where Are We Now? Where Are We Going?

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Opinion statement

The diagnostic imaging evaluation of patients with suspected esophagogastrointestinal transit disorders is changing. Anatomical methods, e.g., barium studies, endoscopy, manometry, radiopaque markers, have long been the techniques available and used for diagnosis. The one exception has been gastric emptying, where radionuclide scintigraphy has been the standard for decades. Esophageal transit scintigraphy is an old and reliable methodology but probably underutilized. The diagnostic use of small and large intestinal transit scintigraphy is increasing, in part, because of the limitations of the other methods but, most importantly, because it is truly physiologic, i.e., the transit of radiolabeled food can be imaged and quantified from the mouth to rectum. Limitations to its wider use have been the lack of standardization, general availability, and reimbursement issues. Radionuclide methods are increasingly being used to evaluate esophagogastrointestinal transit in a single study, from top to bottom.

Introduction

The symptoms of esophagogastrointestinal transit disorders are common and include dysphagia, post-prandial nausea, abdominal pain, early satiety, diarrhea, and constipation. Evaluation of these patients can be challenging. The underlying causes are numerous and not always fully understood; thus, the entities are often labeled as functional [1]. Scintigraphy is increasingly being used to confirm or exclude a gastrointestinal transit disorder which, in turn, can lead to more appropriate therapy.

Radionuclide gastric emptying studies have been the gold standard for evaluating gastric transit for decades. However, for evaluation of transit in other gastrointestinal organs, endoscopy, barium studies, breath tests, manometry, and radio-opaque markers have been the primary diagnostic tools. However, these tests are either invasive, not always reliable, result in unnecessarily high radiation to the patient, and most important, they are not physiologic, i.e., they are handled by the gastrointestinal tract in a manner different than food. Scintigraphy is by its nature physiologic. A nuclear medicine gamma camera can acquire timed images of the transit of the ingested radiolabeled food. The exam is non-invasive, results in a relatively low radiation dose to the patient, while providing valuable qualitative and quantitative transit information.

This review will discuss the transit studies, first, each individual esophagogastrointestinal organ, e.g., the esophagus, stomach, and small and large intestines. Increasingly both anatomic and scintigraphic diagnostic motility/transit studies are combining these tests into a single sequential exam, e.g., the wireless motility capsule and "whole gut" or "comprehensive gastrointestinal transit" scintigraphy. The reasons are that symptoms of the upper and lower gastrointestinal tracts may overlap, patients may have more than one organ with a transit abnormality, and the entire gastrointestinal tract can be assessed in one exam.

Esophageal transit

The radiographic barium swallow study and/or manometry is often the first diagnostic test used to investigate dysphagia. They provide anatomic and pressure information but, to a lesser extent, transit. Esophageal transit scintigraphy was first introduced in 1972 [2]. The sensitivity and specificity of the test are high when directly compared to manometry [3, 4]. Achalasia and scleroderma can readily be detected and often differentiated with esophageal scintigraphy. Diffuse esophageal spasm and non-specific esophageal motor disorders can also be detected, with somewhat lower sensitivity.

Advances in esophageal transit scintigraphy over the years have enhanced its diagnostic utility, including frequent image acquisition which improves temporal resolution, division of the esophagus into proximal, middle, and distal esophageal regions to assess bolus progression, cinematic display, and quantification.

There are situations where transit scintigraphy is underutilized, e.g., in patients unable to complete manometry or when anatomic and manometric studies provide conflicting or indeterminant results and for patients with symptoms of dysphagia who have normal results on initial studies, where scintigraphy can confirm that there is indeed normal transit [5]. Quantification is routine with esophageal scintigraphy and thus can be valuable for assessing a patient's response to therapy [6, 7].

Gastric emptying

The use of a radionuclide to measure gastric transit was first published in the Lancet over 50 years ago, in 1966 [8]. Gastric emptying studies are routinely ordered to confirm or exclude gastroparesis in patients presenting with postprandial symptoms of nausea, vomiting, abdominal pain, and early satiety. Gastric emptying scintigraphy can also provide important information in patients with esophageal reflux unresponsive to therapy, and in diabetics with poor glycemic control, to confirm or exclude delayed gastric emptying as a contributing factor in a patient's poor response to therapy.

Various non-radionuclide methodologies have been published that measure gastric emptying, including electrogastrography, antroduodenal manometry, magnetic resonance imaging, and ultrasonography. However, they are rarely used in today's practice. Recently, the wireless motility capsule and the stable C-13 breath test have become commercially available; both of which can be initiated in the physician's office. However, the wireless motility capsule is not physiologic, requires swallowing a large capsule, wearing a receiver for 5 days, and is relatively expensive [9]. The C-13 breath test has been preliminarily validated but has had limited clinical use to date, and there are various known interpretative pitfalls [10].

The radionuclide gastric emptying study has been the standard clinical and research methodology for the diagnosis and evaluation of functional gastric motility disorders for decades because it is physiologic and accurate. It utilizes radiolabeled food and a gamma camera to measure gastric transit and emptying. The amount of radiolabeled food ingested is directly proportional to its volume, and therefore, gastric emptying can be simply and accurately quantitated to determine whether transit is normal, rapid, or delayed. To rule out mechanical obstruction, endoscopy or radiographic barium studies are required. Gastroesophageal reflux can also be detected, although sensitivity for detection improves with more rapid image acquisition than the standard methodology for gastric emptying.

In the recent past, different radionuclide gastric emptying methodologies have been used at different imaging clinics, e.g., different meals and different acquisition, processing, and quantification methods, and as a result, they often had different normal values. Normal values are dependent on the specific meal ingested as well as the methodology used. This was of concern to gastroenterologists because study results from different imaging clinics were difficult to directly compare. So in 2007, gastroenterologists and nuclear medicine physicians met to discuss and decide on consensus recommendations for gastric emptying scintigraphy. These recommendations were published both in the gastroenterology and nuclear medicine literature in 2008 [11, 12].

The consensus report recommended that all imaging centers use the same specific protocol, one that was published in 2000 by Tougas et al. [13]. This is a simplified methodology that can be performed at any imaging center. The publication had reported that frequent image acquisition, e.g., every 5–10 min, as had been done in many clinics was unnecessary and that imaging at only four time points allowed for accurate quantification, i.e., immediately after meal ingestion and at 1, 2, and 4 h. The standardized meal consists of an egg-white sandwich, jam, and water. Normal values were established in 123 healthy subjects. The 4-h study length was longer than that used at most institutions, where 2 hours had been the norm. However, it was shown that the longer study improved sensitivity, thus increasing the number of patients diagnosed with gastroparesis, by approximately a third [14–16].

Standard teaching in textbooks and review articles has been that solid empting is more sensitive than liquid emptying for detection of gastroparesis, that liquid emptying is preserved until the disorder is advanced, and that solid-phase studies reveal delayed emptying before liquids [17, 18]. However, this was not based on scientific published investigations but was merely an impression put forth by institutions doing dual-isotope dual-phase gastric emptying studies. Recent investigations have proven this to be wrong.

In a study of diabetics in 1991, investigators reported delayed liquid but normal solid emptying in 24 % of their patients, using simultaneous ingestion of the solid and liquid meal [21]. In 2009, two published prospective investigations at Johns Hopkins, including 40 and 101 consecutive patients referred clinically with symptoms suggestive of gastroparesis, found delayed liquid emptying in 32 % of patients who had normal solid emptying. The liquid and solid meal were ingested sequentially, first a 30-min liquid-only (water) study and then the standardized solid meal. Surprisingly, these two studies also found that the liquid-only study detected more delayed gastric emptying than the solid study (33 vs. 23 %) [19, 20]. In a retrospective study published in 2011 by an institution that had been using simultaneous dual-phase solid and liquid emptying for years, 26 % of patients with normal solid emptying were reported to have delayed liquid emptying [22].

The physiology of liquid and solid gastric emptying is different. Liquids without nutrients empty rapidly from the stomach in a mono-exponential pattern (t1/2 < 23 min) [20]. Normal solid emptying has a delay before emptying begins (lag phase) lasting 5–25 min but then usually proceeds to empty in a relatively linear pattern.

Physiologically, the fundus or proximal portion of the stomach is responsible for liquid emptying, which is the result of tonic contraction that produces a pressure gradient from the proximal stomach to the pylorus. The antrum is responsible for solid emptying, with phasic contractions that grind up food into small enough size to pass through the pylorus (1–2 mm), thus the explanation for the lag phase. When liquids are simultaneously ingested with solids, liquid emptying has a multi-exponential emptying pattern and is slower than that seen with clear liquids only, which empty mono-exponentially. The liquid component in the combined study is very much influenced by the solid meal. In our experience, most patients who have delayed liquid-only studies do not have delayed combined solid-liquid studies, and vice versa, suggesting different pathophysiologies.

In the past, it has been reported that 20–40 % of patients with dyspeptic symptoms have abnormal gastric emptying studies [23]. Today, these numbers have very likely increased. By extending the study from 2 to 4 h as suggested by the consensus recommendations, an additional 1/3 of patients are diagnosed with gastroparesis [16]. And in patients with normal solid gastric emptying, liquid gastric emptying will be abnormal in another third of patients [20]. Appropriate therapy may be different for liquid and solid emptying.

Intestinal transit

Small bowel symptoms may overlap with upper gastrointestinal symptoms, and patients with large intestinal dysmotility may also have upper gastrointestinal symptoms. This suggests that intestinal transit scintigraphy might further increase the number of patients diagnosed who have dyspeptic symptoms, as well as clarifying lower gastrointestinal symptoms of diarrhea and constipation. In the past years, non-scintigraphic studies have primarily been used to investigate intestinal motility, e.g., the lactulose breath test, radiopaque markers, and the wireless motility capsule. Although useful, they have limitations, which include reliability, radiation dose, cost, and most important, they are not physiological, i.e., they are not handled by the intestinal tract in a manner similar to ingested food.

The first radionuclide intestinal transit study publication was in 1976 [24]. A recent PubMed review by this author revealed over 60 publications describing radionuclide tests of the small and large intestinal transit [25–29]. The methodologies varied, e.g., easily over a dozen of different foods and radiotracers were described. Still, to date, few imaging clinics, even at most academic centers, routinely perform intestinal transit studies. But this is changing.

Two centers in the USA have had considerable experience with scintigraphic intestinal transit studies, the Mayo Clinic and Temple University. Both perform what they call "whole gut transit". The Mayo Clinic uses an interesting radiopharmaceutical, a pH-sensitive methacrylate-coated capsule that dissolves in the distal ileum at a pH of 7.2, releasing In-111-activated charcoal particles [30]. A standardized gastric emptying study can be combined with the intestinal transit study. However, the radiolabeled charcoal particles are not FDA approved, thus not available for clinical use at other centers, and charcoal is not really physiological, i.e., it is handled differently than food in the gastrointestinal tract.

For many years, Temple University has been routinely performing dual-isotope dual-phase (simultaneous solid and liquid) gastric emptying studies. In-111 diethylenetriaminepentaacetic acid (DTPA) is mixed in the liquid (water) phase and Tc-99m sulfur colloid is bound to the solid-phase meal. The liquid component is quantified at 1 h and solid components are quantified according to the standardized test for solid gastric emptying (0, 1, 2, and 4 h). To quantify small intestinal transit, the test is extended to 6 h, and the percent of In-111 radiotracer arriving at the ileocecal valve is used as a measure of small bowel transit. For large intestinal transit, images are obtained at 24, 48, and 72 h [31]. In-111 DTPA has a long half-life (2.8 days), and thus, quantification of large bowel transit can be performed at these later time points.

Both the Mayo Clinic and Temple University use a somewhat complicated quantification method for colonic transit. They draw 5–7 regions of interest for the large intestine (cecum, ascending colon, hepatic flexure, etc.), use increasing weighting factors from proximal to distal colonic regions, and then calculate a geometric center of activity to give an indication of the extent and rapidity of its transit.

At Johns Hopkins University, we initiated a study more than 3 years ago which we call Comprehensive Gastrointestinal Transit Scintigraphy [32•]. We use a methodology in some ways similar to the Temple whole gut transit study, i.e., using In-111 DTPA in water to follow liquid phase gastric and intestinal transit. However, our protocol differs in several ways. First, we begin the study by doing an esophageal swallow transit exam, followed by a liquid-only (water) study, then a simultaneous solid-liquid study. We do the two liquid studies because of our experience and theory that they likely represent different pathophysiology. We then extend the imaging out to 6 h to calculate small intestinal transit. Finally, single images at 24, 48, and 72 h are acquired to calculate large intestinal transit and rectal emptying.

We have simplified the large intestinal transit quantifications by calculating the percent colonic emptying (similar to gastric emptying) at each of the time points, at 24, 48, and 72 h, rather than calculating a geometric center of activity. We have reported that the two methods strongly correlate and this has much simplified the quantification [32•]. In addition to quantifying the amount of colonic transit at each time interval, we report the visual transit of radioactivity, i.e., whether we see normal uniform colonic transit, diffuse colonic delay, or a regional delay. We have established and published our own normal reference values in healthy subjects, which differ somewhat from the above two institutions, and have now studied over 250 patients in the past 2 years [32•] (Fig. 1).

In the first 103 patients referred to us with symptoms suggestive of an intestinal transit disorder, our study results showed abnormal transit in the following regions: esophageal transit, 16 %; liquid-only gastric emptying, 14 %; liquid gastric emptying simultaneous with ingestion of the solid meal, 7 %; solid gastric emptying, 12 %; small intestinal transit, 27 %; and large intestinal transit, 44 %. An abnormality was diagnosed in more than one gastrointestinal organ in 21 % of patients. Most of the patients with the delayed liquid-only study did not have delayed liquid ingested simultaneously with the solid and vice versa. In the first 18 patients, our study changed clinical management in 62 % of patients [32•]. We are presently evaluating the overall clinical utility of the study in our first 220 patients.

The radiation dose to the patient from our Comprehensive Gastrointestinal Transit Scintigraphy study is approximately 130 mRems effective dose. The

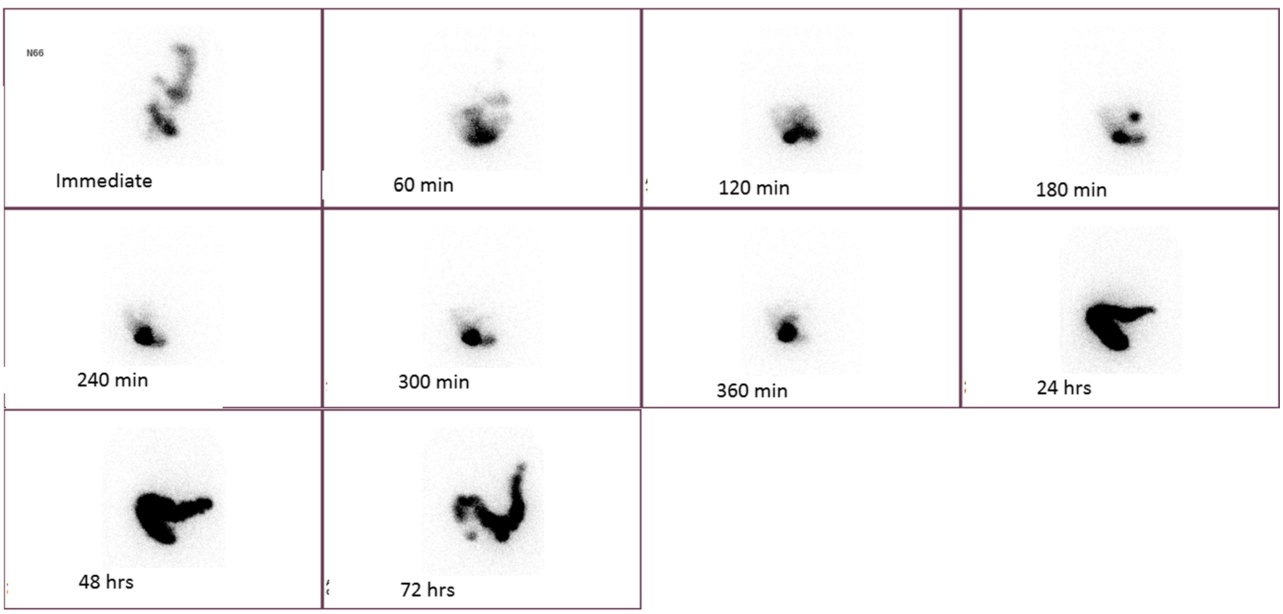

Fig. 1. Comprehensive gastrointestinal transit scintigraphy—delayed colonic transit. The In-111 liquid-phase images are shown, starting after the esophageal swallow and liquid-only study. The first image (*left*, *first row*) is acquired immediately after ingestion of the simultaneous liquid-solid gastric emptying meal. Then subsequent images at 60, 120, 180, and 240 min. The liquid phase empties rapidly from the stomach, with rapid transit into the proximal and distal small bowel. Small bowel phase transit is calculated at 360 min which shows accumulation in the region of the ileo-cecal valve. The small intestinal transit was normal. Images at 24, 48, and 72 h show delayed colonic transit. At 24 h, activity is in the ascending colon and the proximal portion of the transverse colon. Normally, most of the activity will be in the transverse colon at this time point. At 48 h, very little transit is seen. Normally activity is predominantly in the descending colon at this time point. At 72 h, the activity has gotten to the splenic flexure but no further. Normally, there is only a small amount of residual activity remaining in the distal colon and rectum at this time point. Thus, there is diffusely delayed colonic transit, confirmed by the quantitative values of less than 10 % colonic emptying (normal >14 % at 24 h, 41 % at 48 h, and 67 % at 72 h).

radiation dose from X-ray imaging of radiopaque markers is approximately 350 mRems, depending on the methodology.

Where do we go from here?

The standardized scintigraphic gastric emptying study was initiated so that it could be performed in any imaging clinic and the results would be similar between clinics. Eight years after the publication of the consensus recommendations, many imaging clinics have adopted this methodology. However, surprisingly, there are still imaging centers that do not use the standardized gastric emptying protocol [33]. Practice patterns change slowly. The best incentive for clinics to change is for the referring physicians to request/demand that their clinics follow the consensus recommendations.

Each of the three centers in the USA described above doing intestinal transit studies has developed a home-grown in-house methodology, including the acquisition and processing methods, and they have different normal values. A limiting factor to the spread of intestinal scintigraphy to other imaging clinics is this lack of standardization. Another factor is the unavailability of intestinal transit software on many nuclear medicine workstations that would permit routine acquisition and quantification. Camera and workstation manufacturers are just beginning to respond to this need. On the other hand, it may be best in the near future to expand these studies mainly to motility referral centers, where there is sufficient volume to establish and maintain high-quality results. Ultimately, it is likely that the methodology will spread to other imaging centers and a standardized method will evolve with more experience.

Until recently, intestinal transit scintigraphy did not have an ICD-10 code, making insurance reimbursement unlikely. Recently codes have been assigned. However, CMS, who determines Medicare and Medicaid reimbursement, has not given this approval, and thus, this continues to be a disincentive to performing these studies. We added the esophageal transit study because of our large scleroderma population who often has esophageal as well as other gastrointestinal transit disorders. Reimbursement for the esophageal study as well as the liquid and solid studies also made it more palatable to our administrators to offer intestinal transit.

Some patients have post-prandial symptoms due to the lack of normal fundal gastric accommodation. When one ingests a meal, the proximal stomach relaxes to accommodate the meal. Without that accommodation reflex, the patient will have symptoms of post-prandial nausea, pain and discomfort, and early satiety. Evaluation of gastric accommodation has been limited to water-swallowing stress tests (water loading) and gastric balloon barometric exams. The barostatic balloon test is considered the gold standard but is invasive and very poorly accepted by patients. Ultrasonography and MR methods to diagnose gastric accommodation have been published; however, they need further validation [34, 35].

The best standardized and validated method to date is the use of nuclear medicine SPECT/CT using Tc-99m pertechnetate, a radiopharmaceutical extracted by gastric mucosa and long used for diagnosis of Meckel's diverticulum. The volume of the stomach is measured on computer workstations, both fasting and again after eating a standard meal to determine if there is normal post-prandial gastric fundal relaxation or not. The Mayo Clinic has pioneered this methodology, established normal values based on their methodology, and uses it as a routine diagnostic test [36•, 37]. Other centers have reported on similar methodology for evaluating gastric accommodation [38, 39]. We are in the process of establishing our own methodology and normal values at Johns Hopkins and hope to provide this as a routine clinical study in the very near future.

Summary and conclusion

Scintigraphy is playing an increasingly important role in the diagnosis of transit abnormalities of the esophagus, stomach, and small and large intestines. A major advantage of scintigraphy is that it is physiologic. Consensus recommendations have been published for gastric emptying methods and normal values. Methods for intestinal transit scintigraphy vary somewhat from center to center, but it is increasingly available at motility referral centers and will likely become available at other imaging centers in the not too distant future. Methodologies are now available that permit evaluation of transit from the esophagus to the rectum in one radionuclide study.

Compliance with ethical standards

Conflict of interest
Harvey A. Ziessman declares that he has no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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