

REVIEW

Measurement of Gastrointestinal and Colonic Motor Functions in Humans and Animals

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SUMMARY

Accurately measuring the complex motor behaviors of the gastrointestinal tract has tremendous value for the understanding, diagnosis, and treatment of digestive diseases. This review synthesizes the literature regarding current tests that are used in both human beings and animals. Further opportunity remains to enhance such tests, especially when such tests are able to provide value in both the preclinical and the clinical settings.

The ability to assess the complex motor functions of the gastrointestinal tract accurately has been of tremendous value to understanding and treating digestive diseases. Unlike other smooth or cardiac muscle organ systems with relatively more rhythmic and patterned motor behavior, the complexity of the diverse motor behaviors of the alimentary canal have made the development and use of clinical and preclinical tests of gastrointestinal motor function a great challenge. It is perhaps this complexity, as well as the importance of gastrointestinal function to overall health and well-being, that have fascinated early physiologists and continue to push modern physiologists and clinical diagnosticians to develop new and more accurate measurements of motility. It is also because of this complexity that the standardization of these measures presents hurdles to broad adoption and that the measurements of the more complex motility functions remain restricted mainly to tertiary referral centers. (*Cell Mol Gastroenterol Hepatol* 2016;2:412–428; <http://dx.doi.org/10.1016/j.jcmgh.2016.04.003>)

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Assessing motility in human beings has 3 obvious values. First, standardized clinical tests have diagnostic value in stratifying patients who present with a relatively limited repertoire of symptoms in the complex multifactorial digestive diseases into more manageable subsets and in the identification of underlying pathophysiology. Second, these clinical tests provide measures that can be used to objectively determine the efficacy of therapies for digestive diseases in the clinic and during drug and device development in clinical trials. Third, motility measurements in human beings have value in broadening

our understanding of the physiology and pathophysiology of the gastrointestinal tract to generate new hypotheses and new drug targets to understand and treat digestive diseases.

Motility tests in nonhuman animals also have value that parallels the value of tests for human beings. First, animals serving as companions, or in labor, sports, and food production industries, benefit from the diagnostic value of accurate motility tests in veterinary medicine. Second, motility tests provide the basis for objective measures to assess the efficacy and dosing guidelines of new therapies in preclinical drug and device development. Third, animal models provide the basis for understanding the physiology and pathophysiology of the gastrointestinal tract. This latter value historically has been greater in nonhuman animals because of the ability to conduct terminal or ex vivo experiments followed by anatomic or biochemical assessments that are not possible in human beings.

The purpose of this review is to critically assess the current state of motility tests (listed in [Table 1](#), and examples given in [Figure 1](#)), based on these values in both human beings and non-human beings. It is organized by region of the alimentary canal in an oral to anal direction, followed by measures of whole-gut transit. The hope is that such juxtaposition of human and nonhuman tests will enlighten both the benefit and deficiencies in each to aid in the de novo or cross-development of new motility tests.

In the interest of brevity, we will not describe tests of esophageal motility here. High-resolution manometry has become the diagnostic tool of choice, about which many recent reviews have been published.^{1–3}

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Abbreviations used in this paper: AC, ascending colon; CF6, filling the colon at 6 hours; CT, computed tomography; GEBT, gastric emptying breath test; HDAM, high-definition anorectal pressure manometry/topography; HRAM, high-resolution anorectal manometry; HT, hydroxytryptophan; IQR, interquartile range; MMC, migrating motor complex; MRI, magnetic resonance imaging; ^{99m}Tc, technetium-99m; SPECT, single-photon emission computed tomography; ¹³C, carbon-13; 3-D, 3-dimensional; WMC, wireless motility capsule.

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Table 1. Tests Currently Available for Measuring Gastrointestinal and Colonic Motility

Function	Tests available
Gastric capacity or accommodation	Barostat balloon measurements Nutrient drink test <i>SPECT</i> Ultrasonography MRI High-resolution intragastric manometry
Gastric emptying	<i>Scintigraphy</i> Wireless pH and motility capsule Stable isotope breath tests
Gastric transit in preclinical studies	Analysis of gastric contents <i>Stable isotope breath tests</i> Scintigraphy
Small-bowel transit	Breath hydrogen tests Stable isotope breath tests Scintigraphy Wireless pH and motility capsule
Whole-gut transit in preclinical studies	Nonabsorbable marker such as carmine red Scintigraphy using steel beads and barium in mice
Colonic transit	<i>Radiopaque markers</i> <i>Scintigraphy</i> Wireless pH and motility capsule
Gastrointestinal, colonic, and anorectal contractility	<i>Antropyloroduodenal manometry</i> Wireless pH and motility capsule <i>Colonic phasic contractility (including high-resolution manometry) and tone</i> <i>Anorectal manometry</i>
Colonic motility and transit in preclinical studies	Bead expulsion Colonic manometry (including high-resolution manometry) Scintigraphy
New MRI applications	All the earlier-described functions as well as anorectal and pelvic floor motion and anatomic integrity

NOTE. Tests with the strongest validation or most widely available and used are indicated in italics.

Tests to Evaluate Gastric Capacity and Accommodation

One of the principal functions of the proximal stomach is the storage of ingested food. The gastric fundus and body are able to accommodate large volume changes, while maintaining a relatively low intragastric pressure. Altered gastric tone and distensibility may occur in several disease states, including tumor infiltration, vagal dysfunction, and post-gastric surgery status, and in up to 40% of patients with functional dyspepsia.⁴

Barostat Balloon Measurements

The gold standard for the measurement of tone in hollow organs was the barostat,⁵ which estimates changes in tone by the change of volume of air in an infinitely (typically polyethylene) compliant balloon maintained at a constant pressure to maintain the balloon in apposition with the stomach lining. The barostat maintains the constant pressure by infusion or aspiration of air in response to relaxation or contraction of stomach tone. This method is not used extensively in clinical practice because it requires intubation and results in stress and discomfort during the tests, which may last 3 hours or longer.⁶

Development and validation studies of the barostat to measure compliance, tone, and postprandial accommodation in the dog were performed by Azpiroz and Malagelada.⁵ Since then, the barostat has been used extensively in animals including cats,⁷ rabbits,⁸ pigs,⁹ horses,¹⁰ rats,^{8,11} and mice.¹²

Satiation or Nutrient Drink Test

The nutrient drink test has been proposed as a surrogate method for estimating gastric volumes. In this test, a standardized liquid nutrient drink, such as Ensure (1 kcal/mL; Ross Products, Division of Abbott Laboratories, Columbus, OH), is ingested at a standard rate of 30 mL/min, and the volume to normal fullness and the maximum tolerated volume are recorded as measures of satiation. Postprandial symptoms of nausea, fullness, bloating, and pain are measured 30 minutes after the meal.¹³ Tack et al¹⁴ suggested that a high-caloric, slowly administered drinking test compared favorably with the barostat in predicting impaired gastric accommodation, especially in patients with a maximum tolerated volume less than 750 kcal. Because of the obvious limitations of feedback regarding sensory experiences, there are no reports of the use of nutrient drink tests in nonhuman animals.

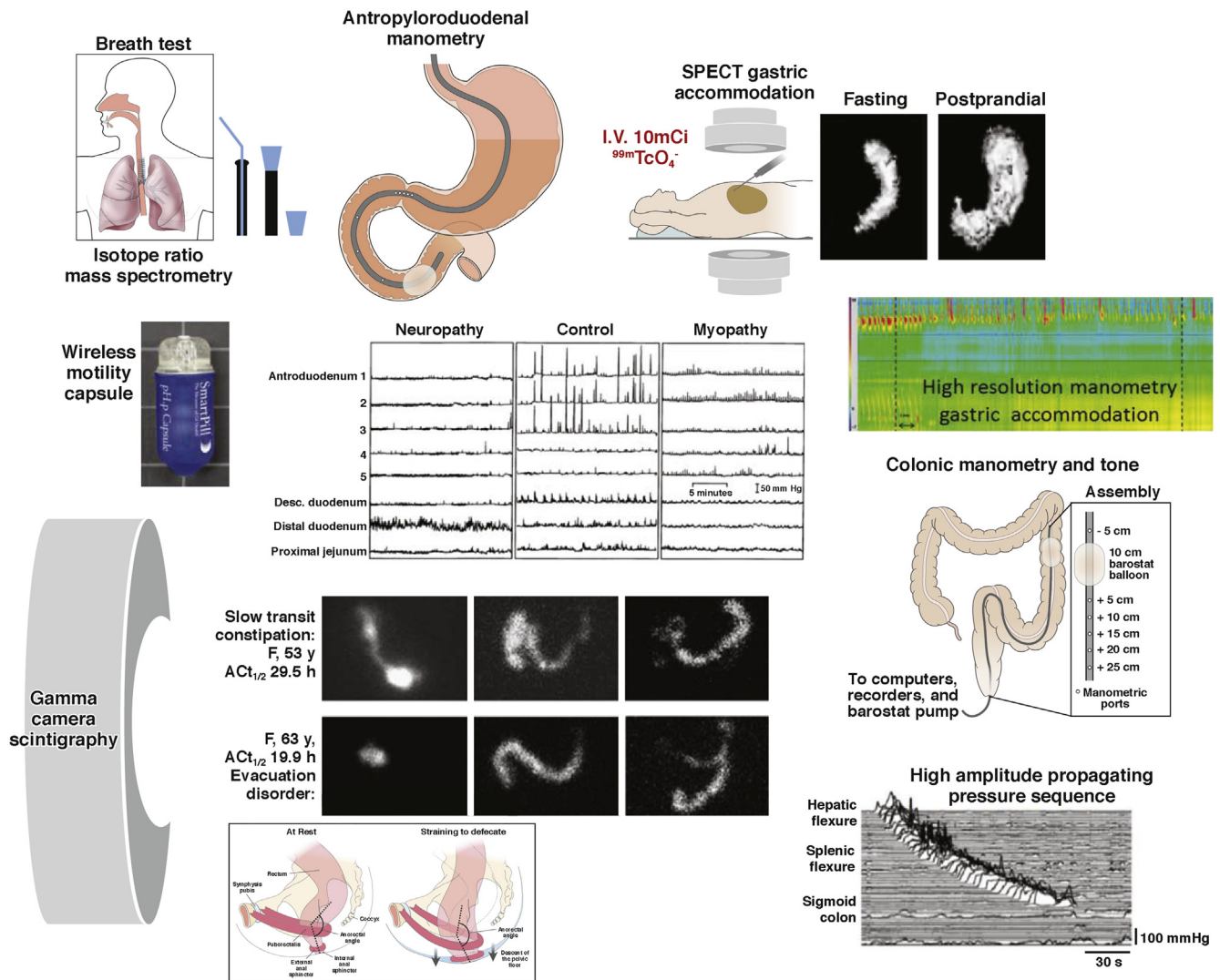


Figure 1. Examples of the wide range of motility measurements available for human studies: stable isotope breath test, scintigraphic transit, intraluminal manometry by perfused manometers or strain gauges on tubes or wireless capsules, and measurement of gastric capacity and accommodation by SPECT or high-resolution manometry.

Single-Photon Emission Computed Tomography

Single-photon emission computed tomography (SPECT) imaging has been validated extensively in vitro and in vivo for the measurement of gastric volumes during fasting and postprandially in human beings, including comparison with the barostat.^{15–17} After intravenous administration of 10 mCi technetium-99m (^{99m}Tc)-pertechnetate, a substrate for the sodium/iodide symporter that is accumulated and secreted into the lumen by parietal and mucin-secreting cells of the gastric mucosa, tomographic images of the stomach are acquired using a large field-of-view, dual-headed gamma camera, with the patient in a supine position. From the transaxial images of the stomach, 3-dimensional images are reconstructed using a commercially available software analysis program that is used for other 3-dimensional volume rendering with transaxial imaging (eg, computed tomography [CT], magnetic resonance imaging [MRI]) and total gastric volume is measured during fasting and during the

first 10 minutes after a standard liquid nutrient meal (300 mL Ensure). This allows reconstruction of the stomach based on the location of the mucosal layer, and the estimated volume serves as a surrogate for the internal volume of the stomach. SPECT shows the effects of disease on post-meal gastric accommodation and effects of medications such as nitrates, erythromycin, glucagon-like peptide-1, and octreotide^{18,19} in health and diseases such as diabetes, fundoplication, and functional dyspepsia.^{20,21}

Intraindividual and interindividual coefficients of variance in postprandial and accommodation volumes by SPECT were not significantly different and ranged from 16% to 22%.²² The effects of liquid and solid equaloric meals on gastric volumes have been described, and measurements of gastric volume with the same caloric liquid meal an average of 9 months apart showed a coefficient of variation of 10%.²³

It also is possible to measure gastric emptying and volume simultaneously.^{24,25} The noninvasive nature of the

method is attractive and is used extensively at the Mayo Clinic in research and practice, especially in suspected disorders of gastric accommodation such as dyspepsia. However, the test involves radiation exposure, and SPECT equipment and the 3-dimensional reconstruction and volume rendering are not widely available. Another potential pitfall is that the resolution of the imaging does not equal that of CT or MRI.

Application in animal studies. Although NanoSPECT-CT (Mediso Medical Imaging Systems, Budapest, Hungary) of gavaged technetium-labeled activated charcoal diethylene triaminepentaacetic acid has been used to assess gastrointestinal transit in mice,²⁶ to our knowledge SPECT imaging has not been used to assess gastric accommodation specifically in nonhuman animals. Given the rapidly advancing use of ^{99m}Tc-pertechnetate and other sodium/iodide symporter substrates in numerous animal models^{27,28} as well as descriptions of methods to circumvent the high stomach signal that confounds such studies,²⁹ it is reasonable to assume that this well-validated approach to assess gastric accommodation in human beings can be reverse-translated easily for use in preclinical studies.

Ultrasonography

Imaging-based methods to measure gastric volume include 3-dimensional reconstruction of images acquired by ordinary ultrasonography assisted by magnetic scan-head tracking.^{30,31} Thus, an outline of the total stomach volume visualized after ingestion of a liquid meal (that serves as a contrast medium)³² has been applied in adolescents and compared with simultaneously measured gastric volumes by SPECT.³³

Magnetic Resonance Imaging

The first application of MRI using a spin-echo T1-weighted imaging sequence addressed the volume of the stomach during fasting, but not in the postprandial period.³⁴ Volumes measured with MRI and barostat differ significantly because the barostat measures only the proximal stomach, whereas MRI records the entire stomach volume; however, there was a statistically significant correlation between the 2 methods, and MRI also was able to show volume effects induced by glucagon (increase) and erythromycin (decrease).

MRI, using 3-dimensional gradient-echo and 2-dimensional half-Fourier acquisition single-shot turbo spin echo sequences,³⁵ has been used to measure postprandial gastric volume change, which exceeded the ingested meal volume by 106 ± 12 mL (SEM). The advantage of MRI over SPECT is the ability to distinguish air from fluid under fasting and postprandial conditions, respectively. MRI also has shown that the postprandial volume excess mainly comprised air (61 ± 5 mL), which was not significantly different when the volume ingested was ingested in 30- or 150-mL aliquots. Fasting and postprandial gastric volumes measured by MRI generally were reproducible within subjects. Gastric volumes measured by SPECT were higher than MRI, reflecting the fact that SPECT reconstruction includes the volume occupied by the imaged gastric wall. Although

MRI has many advantages, including a lack of radiation exposure, it is not widely used to measure gastric accommodation in clinical practice or research.

High-Resolution Intra-gastric Manometry

By using a high-resolution manometry catheter, which typically is used for esophageal motility measurements, Janssen et al³⁶ showed that, during nutrient drink ingestion, there is a reduction in intraluminal pressure that provides a less-invasive alternative to the barostat for the assessment of gastric accommodation. The method also has been used to show pharmacologic effects, such as with peppermint oil³⁷ and liraglutide.³⁸

Gastrointestinal and Colonic Transit

Gastric Emptying

Scintigraphy. Gamma camera scintigraphy is the most widely used test for the assessment of gastric motility; it provides a direct, noninvasive quantification of gastric emptying.³⁹ A simplified protocol with imaging at 1, 2, and 4 hours with a standard meal was first proposed at the Mayo Clinic,⁴⁰ and a variation subsequently was validated in a large multinational study in 123 subjects⁴¹ and was adopted by the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine.⁴² A standard, 2% fat meal consisted of 4 ounces of Eggbeaters (Conagra Foods, Omaha, NE) or equivalent egg white substitute, 2 slices of bread, strawberry jam (30 g), and 120 mL water (total 240 kcal) and was radiolabeled with 0.5–1 mCi ^{99m}Tc-sulfur colloid. This is a relatively small meal, which may not reliably induce symptoms in patients with functional dyspepsia, although it is useful for diagnosing gastroparesis.

The Mayo Clinic method uses 2 natural eggs and contains 30% of the calories as fat (total, 320 kcal). The test meal determines the rate of emptying,⁴³ and normal values are essential for interpretation of the test when performed clinically; thus, Mayo Clinic published data from 319 healthy controls.⁴⁴ There is significant intraindividual variation in gastric emptying rates of 12%–15%, even in healthy individuals.^{44,45} The performance characteristics of the 30% fat, 320-kcal meal have been documented.⁴⁴

The main indications for use of this test are the investigation of unexplained nausea, vomiting, and dyspeptic symptoms; screening for impaired gastric emptying in diabetic patients being considered for incretin treatment to enhance glycemic control (eg, pramlintide and GLP-1 agonists); and assessment of patients with suspected diffuse gastrointestinal motility disorder in combination with small-bowel and colonic transit.

In human research, the gastric emptying test is used to understand the pathophysiology of symptoms or in the development of pharmacologic agents. There is a vast amount of literature on the use of radioscintigraphy to measure gastric emptying in large animals. The first application documented the effects of vagotomy and carbachol on gastric emptying in dogs.⁴⁶

Wireless pH and motility capsule. These nondigestible wireless capsules can measure pH, pressure, and

temperature throughout the gastrointestinal tract. The abrupt change in pH from the gastric acidic milieu to the almost alkaline duodenum usually is associated with antral phasic contractions of the migrating motor complex (MMC), and it signals that the capsule has left the stomach.⁴⁷ When taken with a meal, the capsule generally empties from the stomach after liquids and triturable solids have emptied, usually with phase III of the MMC or, in approximately one third of cases, with high-amplitude antral contractions.⁴⁸

Patients ingest the capsule with a standard meal and, from 6 hours after capsule ingestion, patients can engage in normal daily activity, including ad libitum feeding. The wireless capsule acquires data continuously for up to 5 days, and this permits calculation of gastric, small-bowel, colon, and whole-gut transit. These wireless capsules also measure intraluminal pressure. In validation studies conducted with simultaneous gastric emptying by scintigraphy in healthy subjects and patients with gastroparesis,⁴⁹ the gastric emptying time for the capsule and the scintigraphic gastric emptying time at 4 hours were correlated significantly ($r = 0.73$), and the capsule discriminated between normal or delayed gastric emptying with a sensitivity of 0.87 at a specificity of 0.92.⁴⁹ The advantages of the motility capsule are that the study can be conducted anywhere, there is a lack of radioactivity, and it has an ability to determine small-bowel, colon, and whole-gut transit times, as well as contractility.⁵⁰⁻⁵² The wireless motility capsule also is capable of identifying the effects of pharmacologic agents on gastric contractility.⁵³

Stable isotope breath tests. These tests evaluate gastric emptying noninvasively and without radiation hazard. The carbon-13 (¹³C) isotope can be incorporated into components of a solid meal (eg, the medium-chain fatty acid, octanoic acid, or the blue-green algae, *Spirulina platensis*) or in a liquid meal (¹³C-acetate) to assess gastric emptying of liquids. After ingestion, the solid meal is triturated and emptied by the stomach, digested, and absorbed in the proximal small intestine, metabolized by the liver, and ¹³CO₂ is excreted by the lungs, resulting in an increase in expired ¹³CO₂ over baseline. The test and breath sample collection can occur at the point of care. The rate-limiting step in ¹³CO₂ excretion is gastric emptying of the meal.

In studies comparing the ¹³C gastric emptying breath test (GEBT) performed simultaneously with scintigraphy, the GEBT provided accurate assessment of the gastric emptying of solids with a coefficient of variation comparable with scintigraphy.⁴⁵ In addition, the ¹³C-spirulina GEBT documented accelerated or delayed gastric emptying induced with erythromycin or atropine, respectively.⁵⁴ The ¹³C-spirulina GEBT was approved by the Food and Drug Administration in 2015⁵⁵ based on a clinical study using data from 115 participants who typically would have undergone a gastric emptying test, showing that the GEBT results agreed with the scintigraphy results 73%–97% of the time when measured at various time points during the test.⁵⁶ Pitfalls included a potential loss of accuracy in patients with diseases involving the intestinal mucosa, pancreas, liver, and respiratory system.

Gastric Emptying Studies in Nonhuman Animals
Acute gastric emptying study by analysis of gastric contents. The long history and vast number of physiological and preclinical drug development studies using timed end point analysis of gastric contents after gavage or ingestion of a labeled or visually detectable and quantifiable meal to study gastric emptying are too numerous to reproduce in this short review. The approach is precise and inexpensive because, rather than relying on indirect measurements, the percentage of the meal remaining in the stomach can be calculated directly. Therefore, the approach remains the standard by which preclinical validation studies of novel tests of gastric emptying are compared. Relatively recent advancements in this approach have been the development of new tracers to increase the sensitivity of labeled meal detection as well as the detection of the labeled meal throughout the gastrointestinal tract to assess overall transit as measured by the geometric center,^{57,58} rather than the percentage emptied or leading edge. These new tests that define the geometric center and segment distribution also can be used to study whole-gut transit.

Longitudinal gastric emptying studies. The advent of longitudinal studies in mice that required repeated measures of gastric emptying during disease development or therapy has led to the use of gastric emptying tests developed for human beings in preclinical models. In these studies, the need for noninvasive repeatable measures outweighs the relatively low interindividual variability and cost of end point studies. These tests include scintigraphy^{59,60} and the ¹³C-octanoic acid GEBT.^{61,62} The ¹³C-octanoic acid GEBT also has been validated for measurement of gastric emptying in horses,^{63,64} cattle,⁶⁵ dogs,^{66,67} and rats.⁶⁸ In addition, in nonobese diabetic mice, a model of type 1 diabetes, the expected effects of bethanechol and atropine were shown.⁶² These gastric emptying tests developed in human beings and now used routinely in preclinical studies, which can be translated directly into clinical trials, are the clearest example of the benefit of the bedside-to-bench-to-bedside approach, and should serve as a model for other motility tests that are presented in this review.

Gamma camera scintigraphy has been validated for use in small animals; thus, awake mice were accustomed to light restraint and to eating cooked egg white (0 g fat), whole egg (0.10 g fat/g), or egg yolk (0.31 g fat/g). Gastric emptying of each diet was measured by labeling the test meals with ^{99m}Tc-mebrofenin and using a conventional gamma camera equipped with a high-resolution, parallel-hole collimator. This method has been used to document the effects of devazepide (a cholecystokinin-A-receptor antagonist)⁶⁰ botulinum toxin injection into the antral wall in knockout animals and in pharmacologic modulation,^{69,70} and the role of inflammation and novel therapies for postoperative ileus in animal models.^{71,72}

Recent advances in ultrasound research in nonhuman animals have suggested that clinical tests using this noninvasive approach soon may be in development.^{73,74}

Orocecal or Small-Bowel Transit

Breath Hydrogen Tests

The breath test is based on the presumption that the hydrogen excreted in the breath is the product of colonic bacterial fermentation of unabsorbed carbohydrates ingested orally. Lactulose is the most widely used carbohydrate substrate for orocecal transit time determination because the time lag between ingestion of lactulose and the increase in breath hydrogen is at least 3, 5, or 10 parts per million above baseline. There is a high degree of correlation with simultaneous liquid transit by scintigraphy,^{75–78} and the test documents pharmacologic effects on gut motility.^{79–83} Unfortunately, lactulose itself markedly accelerates transit, presumably owing to its osmotic activity. In addition, these tests usually are conducted during fasting, and this may not accurately reflect postprandial small-bowel transit, and, usually, symptoms occur postprandially.

Stable Isotope Breath Test

A stable isotope (lactose ¹³C-ureide) was proposed with a very small dose of the substrate (0.5–1.2 g), which cannot be cleaved at the human intestinal brush border and requires the colonic bacterial flora to free ¹³C-ureide, which subsequently undergoes hydrolysis with release of ¹³CO₂ and excretion by the lungs. The ratio of breath ¹³CO₂/¹²CO₂ is determined by isotope ratio mass spectrometry, and the first increase in breath at 2.5 SDs greater than the running average indicates the orocecal transit time.⁸⁴ The lactose ¹³C-ureide test has been validated by comparison with scintigraphy⁸⁴ and has been used to evaluate the effects of pharmacologic agents.^{85–87}

Small-Intestine Scintigraphy

Small-bowel scintigraphy is not used commonly outside of research as part of whole-gut transit tests.⁸⁸ Small-bowel transit time can be calculated as the time for 10% or 50% of the radiolabel to arrive at the terminal ileum or cecum, after correcting for gastric emptying by subtracting the time for the equivalent proportion emptied from the stomach.⁸⁹ A valid surrogate for the 10% scintigraphic small-bowel transit time is the percentage of the meal filling the colon at 6 hours (CF6), which reflects orocecal transit.⁴⁰ Because the radiolabel is ingested with the meal, the result is impacted significantly by the rate of gastric emptying. The range of normal values for colonic filling at 6 hours is 11%–70% with radiolabeled nondigestible particles,^{90,91} or 43%–95% for radiolabeled digestible solids.⁹² However, more recent studies conducted in more than 200 healthy controls have shown that variation in CF6 in healthy subjects is 0%–100% and, therefore, it is not possible to definitely diagnose abnormal small-bowel motility using CF6 (Camilleri, unpublished data). In clinical practice, a low value (eg, <20%) of CF6 often is associated with slow colonic transit, particularly in the right colon, and it is unclear whether this is a reflection of significant pathology in the small intestine or is simply a consequence of failed ascending colon emptying preventing the flow of the ileal content into the colon.

In research, these measurements of small-bowel transit time have shown the effects of treatment, such as cisapride in gastroparesis and chronic intestinal dysmotility,^{93,94} tegaserod in irritable bowel syndrome with constipation,⁹⁵ or prucalopride and YKP10811 in functional constipation.^{96,97}

First CT enterography and now MR enterography have become routine diagnostic tools for inflammatory bowel disease,^{98,99} and it is of great interest that these tests include dynamic image sets to assess motility in affected bowel segments.¹⁰⁰ Perhaps the routine collection of large data sets can be used to develop better automated image analyses and more robust small-bowel imaging for motility disorders independent of organic disease. Indeed, a very recent study used the automated motility assessment of MR enterography developed for patients with Crohn's disease to assess small-bowel motility in patients with chronic intestinal pseudo-obstruction,¹⁰¹ showing the potential of such an approach.

Use of Wireless pH and Motility Capsule to Measure Small-Bowel Transit

Small-bowel transit time also can be measured with a wireless motility capsule (WMC).⁴⁹ The transit of large indigestible solids depends on the phase II and phase III activity of the interdigestive motor complex,¹⁰² as well as fed intestinal motility, but the evidence is limited. The procedure is similar to that for WMC measurement of gastric emptying. The WMC small-bowel transit time is defined as the interval between this increase in pH and the time when the pH suddenly decreases by more than 1 U for at least 5 minutes as the WMC enters the cecum.

In separate studies in 9 healthy subjects, the median WMC small-bowel transit time was 350 minutes (interquartile range [IQR], 169–676 min),¹⁰³ 276 minutes (IQR, 240–354 min),¹⁰⁴ and 234 minutes (IQR, 201–293 min).¹⁰⁵ A practical disadvantage of the test is occasional difficulty in identifying the 1-U pH decrease signifying passage into the cecum, especially in patients with postsurgical changes (eg, right hemicolectomy) or incompetent ileocecal valve resulting in bacterial colonization of the distal ileum. The nondigestible, 26 × 13 mm WMC may become impacted in the gastrointestinal tract; therefore, contraindications include suspected mechanical obstruction, recent gastrointestinal surgery (within 3 months), and Crohn's disease.

Whole-Gut Transit in Preclinical Models

Whole-gut transit in mice typically is studied by the oral administration of a nonabsorbable marker such as carmine red and subsequent monitoring for the first appearance of the marker in stool.^{106,107} Obviously, this test is an assay of the leading edge of the content within the digestive tract that may simplify or misrepresent the overall motility of the gastrointestinal tract. Terminal experiments, in which the orally administered tracers are assayed in numerous segments of the gastrointestinal tract to assess overall transit as measured by the geometric center,^{57,58} improve the limitations of leading edge experiments such as carmine red,

but re-introduce the requirement for terminal, rather than repeatable, tests of whole-gut transit.

A recent study described scintigraphy using steel beads and barium in mice to measure intestinal transit in a nonterminal manner.¹⁰⁸ This is an intriguing development that may lead to better noninvasive preclinical studies; however, the relatively poor accuracy of clinical scintigraphy for intestinal transit, as presented earlier, may limit the translational potential of the method.

WMC for use in whole-gut transit was validated using dogs¹⁰⁹ and has been used in several studies in dogs,^{110–112} pigs,¹¹³ rabbits,¹¹⁴ and horses.¹¹⁵ To our knowledge, validated technologies have not been developed for use in small animals.

Evaluation of Colon Transit

Radiopaque Markers

Radiopaque markers can be used to evaluate total and segmental colonic transit times. Several different methods to measure colonic transit with radiopaque markers have been described.^{116–120} The minimum number of markers to be ingested daily should be at least 10–12 for reporting colonic transit time in days or hours.¹²¹

Localization of retained markers in the rectosigmoid area suggests functional outlet obstruction, whereas diffuse distribution of the retained markers is suggestive of slow-transit constipation. However, this is not diagnostic because delayed rectosigmoid transit resulting from pelvic floor dyssynergia may inhibit proximal colonic transit and result in widespread distribution of markers.

Segmental transit times are measured in the right colon to the right of the vertebral spinous processes and above a line from the fifth lumbar vertebra to the pelvic outlet. The left colon is the area to the left of the vertebral spinous processes and the line above the fifth lumbar vertebra and the left anterior superior iliac crest. The rectosigmoid is the area under the line from the pelvic brim on the right to the superior iliac crest on the left. The advantages of the radiopaque marker method are the well-established normal values and standardization of methods, it also readily is available and is reasonably inexpensive. Sadik et al¹²⁰ have quantitated rapid colonic transit using radiopaque markers. Radiopaque markers are the reference standard for colon transit evaluation in clinical practice.¹²²

Colonic Scintigraphy

Measurement of colonic transit by scintigraphy is safe, noninvasive, correlates with radiopaque markers, and provides information on ascending colon (AC) emptying and overall colon transit.¹²³ In the most widely published method, subjects ingest a pH-sensitive methacrylate-coated capsule containing indium-111-labeled activated charcoal particles after fasting overnight, the coated capsule dissolves in the neutral pH in the terminal ileum, releasing the radioisotope into the lumen.⁹¹ The alternative method follows the transit of radiolabeled liquid in a whole-gut transit test for a solid-liquid meal including colonic transit.¹²⁴ Repeated anterior and posterior abdominal scans of 2

minutes' duration acquired with a gamma camera at 4, 6, 8, 24, and 48 hours after ingestion to appraise colonic transit¹²⁵ were summarized as a geometric center (weighted average) of radioactivity based on 5¹²⁵ or 7 regions.¹²⁴ The times of greatest interest for overall colonic transit are at 24, 48, and 72 hours. The delayed-release capsule facilitates the measurement of AC emptying as the time for emptying half of the radioactivity from the AC, which is calculated by linear interpolation of values on the AC emptying curve.¹²⁶ Thus, by delivering radiolabeled charcoal particles to the ileocolonic region upon capsule dissolution, the particles empty from the ileum into the colon by bolus movements.¹²⁷

Normal values, performance characteristics, coefficients of variation, application in patients with diarrhea or constipation, differences in transit profile between slow colonic transit constipation and defecation disorders, and relationship between colonic transit summaries at 24 and 48 hours and bowel function symptoms have been documented extensively.^{126,128–130}

The intraindividual coefficients of variation were 31% at 24 hours and 27% at 48 hours over a period of less than 3 weeks, and 38% at 24 hours and 30% at 48 hours over a median interval of 2 years.¹²⁶ The degree of variation is similar across different mean values of colonic transit, and the vast majority of individuals have replicate values within 1 geometric center unit of measurement. This variation reflects the physiological, natural variation in stool frequency and consistency.

Whole colonic scintigraphic transit and AC emptying have been reported to be abnormal in several diseases of colonic motility, including idiopathic constipation, functional diarrhea, carcinoid diarrhea,¹³¹ and different subtypes of irritable bowel syndrome¹³² and bile acid diarrhea. It therefore is plausible that colonic transit measurement may serve as a biological marker of colonic function in disease and as a surrogate end point in the evaluation of drug therapy.¹³³ For example, scintigraphic colonic transit correctly has predicted clinical efficacy with medications targeting different mechanisms, including prokinetics such as 5-HT₄ agonists, bisacodyl, and neurotrophin-3; medications retarding transit such as 5-hydroxytryptophan₃ antagonists and cholecystokinin-1 antagonist; and secretagogues such as linaclotide and lubiprostone. Equally important, colonic transit measurement correctly has predicted a lack of efficacy of medications to alter bowel dysfunction in irritable bowel syndrome in clinical trials when there were no significant effects of the drug on colonic transit, such as pexacerfont (corticotropin-releasing factor-1 antagonist) and solabegron (β_3 adrenergic agonist).

Use of Wireless pH and Motility Capsule to Measure Colonic Transit

The passage of the WMC into the cecum is determined by the sudden decrease of pH by more than 1 U, which lasts for at least 5 minutes; colonic transit time is the time from entry into the cecum to the time the WMC passes out of the colon with the sudden decrease in temperature and loss of

pressure recordings. Colonic transit time in 78 constipated and 87 healthy subjects showed a median value of 21.7 hours (IQR, 15.5–37.3 h; 95th percentile, 59 h) in healthy subjects and 46.7 hours (IQR, 24.0–91.9 h) in constipated patients.¹³⁴ The correlation of the WMC to the percentage of radiopaque markers retained on day 5 was significant ($r = 0.69$) in constipated patients studied simultaneously with both methods.¹³⁴

In a large multicenter study of 158 patients with constipation, there was overall agreement of 87% for classifying subjects as having slow or normal colonic transit.¹⁰⁵ The WMC also has been used to characterize pressure activity in colons of healthy controls and in constipated patients.⁵²

The advantages of the WMC assessment of colonic transit are performance in the patients' usual surroundings, appraisal of whole gut and regional transit, and no radiation exposure. Sometimes, discerning the 1-U decrease in pH (entry into the cecum) may be difficult. The method is more expensive than other methods (radiopaque markers, scintigraphy) to measure colonic or whole-gut transit.

Tests to Evaluate Gastrointestinal, Colonic, and Anorectal Contractility

Antropyloroduodenal Manometry

The distal stomach, pylorus, and duodenum, with their relatively small diameters and ability to generate high-amplitude pressure activity, are suitable for manometric recordings (Figure 2). Antroduodenal manometry is available mainly at a few tertiary referral centers; the test is invasive, typically requiring tube placement with the aid of upper gastrointestinal endoscopy, time consuming, and requires skilled technical support. An alternative, a wireless motility capsule, detects the frequency and amplitude of phasic contractions during the process of capsule emptying from the stomach and its passage through the small intestine (and colon, see later).

The main indications for antroduodenal manometry are as follows: evaluation of the cause of documented gastric or small-bowel transit (neuropathy or myopathy) and clarification of whether there is a generalized or localized dysmotility in patients with suspected colonic inertia. The method typically uses water-perfused manometric catheters or solid-state sensors mounted on motility catheters. The tube is positioned with the aid of fluoroscopy. The intragastric sensors should be 1 cm apart or less, to ensure optimal measurements of distal antral contractile activity proximal to the pylorus, which can be identified manometrically by a combination of distal antral and duodenal peaks and the presence of a high-pressure zone (tone). A solid-liquid meal is ingested during the test, which predominantly appraises the amplitude of contractions and the physiological responses in the fasting and postprandial periods. Thus, normal gastroduodenal motility consists of at least 1 MMC per 24 hours, conversion to the fed pattern with ingestion of a meal without return of the MMC for at least 2 hours after a meal of more than 400 kcal, and consistent distal postprandial antral (>40 mm Hg, with

an average frequency of 1 contraction/min during the first postprandial hour) and small intestinal contractions (>20 mm Hg).¹³⁵

Myopathic disorders (eg, scleroderma, amyloidosis, hollow visceral myopathy) are characterized by low-amplitude contractions (consistently <20 mm Hg in the small bowel and <40 mm Hg in the distal antrum).¹³⁶ In neuropathic disorders, there is increased frequency (eg, 3 during 3 hours) of fasting MMCs in the duodenum while awake, postprandial antral hypomotility (average frequency of contractions in distal antrum <1/min during the first postprandial hour), and a return of phase III MMC-like activity within 2 hours of the ingestion of a meal of more than 400 kcal.¹³⁷

Correlations of findings on manometry with histopathology are poor, but they are based on a few detailed reports¹³⁸ of cases of pseudo-obstruction. Manometry has to be interpreted with caution because abnormal motor patterns do not necessarily imply causation of the patient's symptoms. Stress related to the intubation and procedure may delay gastric emptying, impair antral contractility, suppress MMC cycling, and induce intestinal irregularity.

The greatest use of gastroduodenal manometry in research is in drug development, that is, in showing prokinetic effects of novel medications in addition to effects on gastric emptying, such as with the 5-HT₄-receptor agonist, cisapride,⁹³ and the ghrelin-receptor pentapeptide agonist, relamorelin.¹³⁹

Colonic Phasic Contractility and Tone

Tone is measured by the barostat, phasic contractions can be measured by manometry or wireless pressure capsule. Stationary laboratory-based studies to assess motility usually are conducted for 6 hours, during which colonic compliance, fasting, and 2-hour postprandial recordings of contractions and tone are conducted. Ambulatory studies usually are conducted over 24 hours and involve measurement of phasic contractions.¹⁴⁰ There is evidence that an increased number of solid-state sensors on the colonic tube or a fiberoptic manometry catheter, pioneered by thorough and systematic research conducted predominantly by Australian groups,¹⁴¹ results in high-resolution measurements of antegrade and retrograde contractions, as well as definition of the locus of origination of high-amplitude propagated contractions.

In clinical practice, the main indications for colonic manometry (usually with barostat assessment of compliance and tone) are as follows: severe constipation with slow colonic transit and no evidence of an evacuation disorder in patients who are unresponsive to medical therapy,¹⁴² and confirmation of chronic megacolon or megarectum (Figure 3) when viscus diameters exceed 10 and 15 cm, respectively.¹⁴³ The most useful measurements in research and clinical practice are compliance^{142,143} and high-amplitude propagated contractions,¹⁴⁴ and the responses to intravenous neostigmine.¹⁴⁵ The reproducibility and performance characteristics of compliance and tone measurements have been documented in the literature.¹⁴⁶

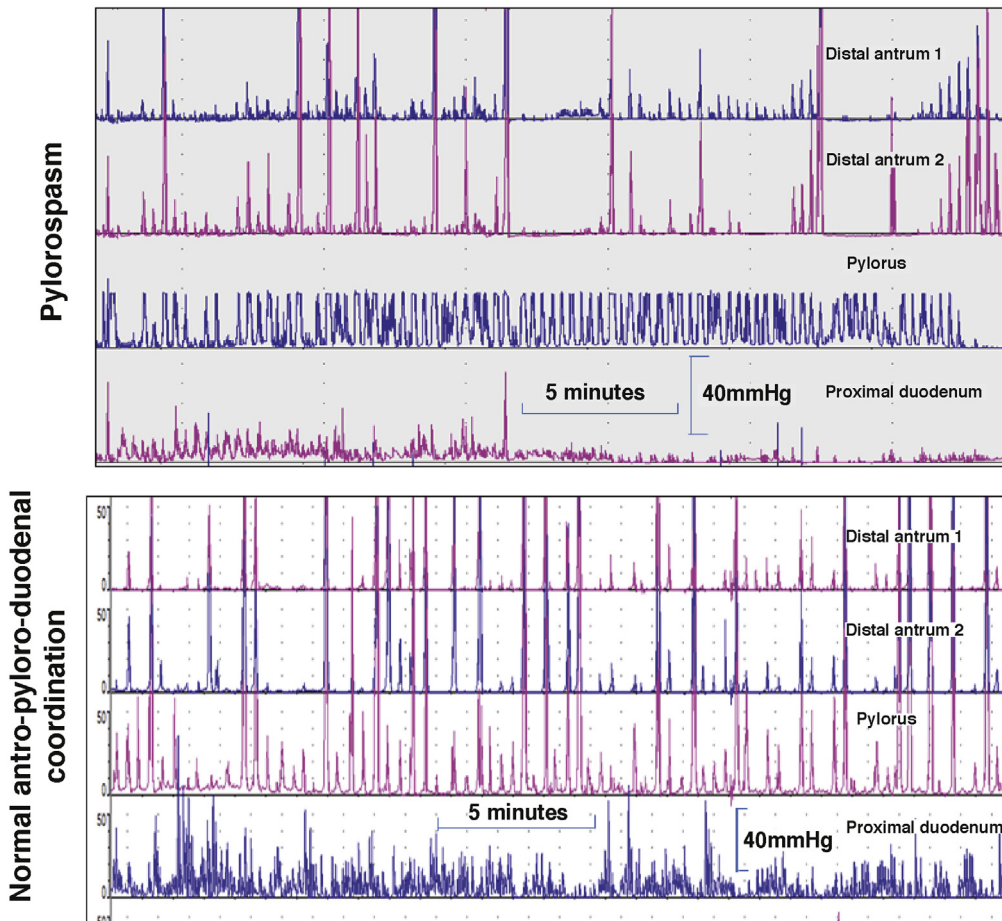


Figure 2. Antroduodenal motility tracings in the postprandial period with sensors 1-cm apart. Note in the upper example the consistent phasic and tonic contractions at the pylorus with intermittent loss of distal antral contractions 1 and 2 cm proximal to the pylorus. In contrast, note the consistent antropyoric coordination in the normal example in the lower tracings. Reproduced with permission from Camilleri.¹⁸⁵

Colonic motility and tone or compliance have been used to show the effects of biological agents (eg, bile acids),¹⁴⁷ pharmacologic agents (eg, cholinergic modulation as with neostigmine),¹⁴⁸ adrenergic agents,¹⁴⁹ cannabinoid-receptor agonist,¹⁵⁰ ghrelin-receptor agonist,¹⁵¹ and 5-HT₄-receptor agonist.¹⁵²

Colonic measurement of contractions has been used in several preclinical models recorded by surgically implanted strain-gauge transducers. For example, Briejer et al¹⁵³ showed induction of giant migrating contractions by prucalopride in the dog, and Sarna et al¹⁵⁴ examined several neurotransmitter substances that modulate contractile activity of the rat colon. High-resolution manometry has advanced rapidly and may become a preclinical model of choice.¹⁵⁵

Similarly, measurement of colonic tone, compliance and reflexes, and responses to meals and pharmacologic agents have been measured in the canine colon, into which a barostat device was inserted, typically through a cecal cannula.^{156–158} More recently, barostat studies of the colon have been performed in the horse¹⁵⁹ and pig.¹⁶⁰

Anorectal Manometry

Anorectal manometry is essential for the evaluation of patients with constipation (to exclude evacuation disorders)

or fecal incontinence.¹⁵⁵ Two technologies that currently dominate in practice and research^{161–163} are as follows. First, high-resolution anorectal manometry (HRAM) with flexible catheters, typically with 8–12 longitudinal sensors spaced approximately 0.6- to 1-cm apart, and the most proximal 1 or 2 sensors within a balloon attached to the uppermost part of the catheter for rectal distension/sensory testing, and the most distal sensor, left outside of the anal canal, recording atmospheric pressure. Other configurations use 12–36 circumferential sensors or 4 radially arranged sensors at each level, from which pressures can be averaged to provide a mean pressure. Second, 3-dimensional high-definition anorectal pressure manometry/topography (3-D HDAM), which uses a rigid probe (100-mm length and 10.75-mm diameter) housing 256 pressure sensors arranged in 16 rows spaced 4-mm apart, each containing 16 circumferentially oriented sensors 2.1-mm apart). The area of measurement is 6.4-cm long and provides detailed anal morphology by linear interpolation through dedicated software to provide 2-dimensional or 3-D cylindrical topography of the anal canal, which can be viewed from all sides.

Normal values that are influenced by age, sex, and body mass index have been published. In general, there is reasonable concordance between studies of average values reported for anal resting tone, although resting tone and

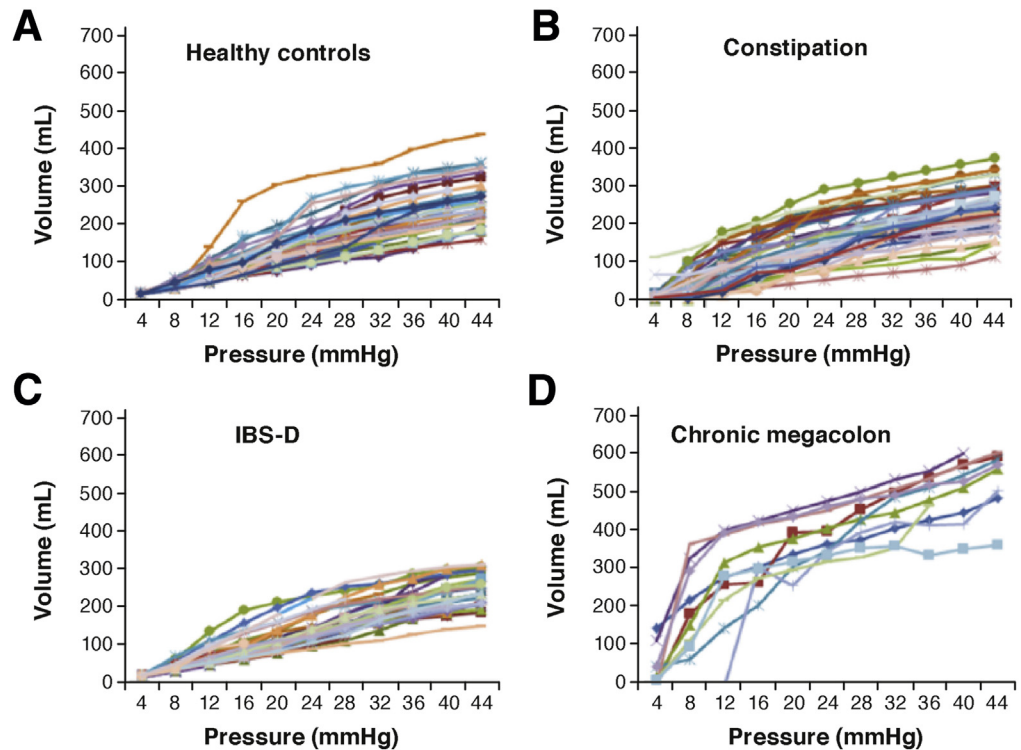


Figure 3. Colonic compliance in (A) healthy, (B) functional constipation/constipation-predominant irritable bowel syndrome, (C) diarrhea-predominant irritable bowel syndrome (IBS-D) groups; and (D) patients with chronic megacolon. Note the markedly increased volume of the intracolonic balloon (10-cm long) in patients with megacolon compared with controls. Reprinted with permission from O'Dwyer et al.¹⁴³

squeeze pressures generally are higher when measured with HRAM/3-D HDAM techniques, possibly owing to reduced fidelity of traditional water-perfused systems. Further studies are required to validate the utility of HRAM/3-D HDAM techniques for evaluating and diagnosing dys-synergia in patients with defecatory disorders and fecal incontinence.^{155,164}

Anorectal manometry studies are applied less often in research studies other than for the assessment of different methods for normalizing functions in defecatory disorders or fecal incontinence.¹⁶⁵

Colonic Motility and Transit in Preclinical Studies

Bead expulsion assays in mice have become the pre-clinical model of choice to understand effects on colonic motility.^{166,167} The assay involves the intrarectal insertion of a 2- to 3-cm glass bead within the colon in awake mice and measurement of the time it takes for the bead to leave the anus. There is tremendous variability in the assay both between and within individual animals. This variability likely is owing to stress-induced defecation in mice in which 5–6 fecal pellets, the entire content of the mouse colon, are expelled at once.

Colonic motor activity in mice also has been assessed using water-based¹⁶⁸ and solid-state manometers.¹⁶⁹ Although these measures of pressure improve the ability to assess colonic motility beyond the limits of bead expulsion assays, they remain isolated measures of contractility. The development of dual-sensor manometric probes¹⁷⁰ to

assess propulsive and retropropulsive contractions in mouse colon provides hope that more advanced technologies for mouse colonic motility are forthcoming.

Scintigraphy and manometry have been used to study colonic motility in rats.^{170–174} In addition, the defecation reflex has been well characterized in rats, making this animal model suitable to replace dogs for preclinical testing.¹⁷⁵ Fluoroscopic analysis of colonic motility has been studied extensively in the pig.¹⁷⁶ Although pigs typically are not used in drug discovery, the pig has been developed as a preclinical model of electrical stimulation for evacuation dysfunction and manometry to assess contractility.¹⁷⁷ Colonic motility in the rabbit also has been characterized radiographically,¹⁷⁸ and recent advances in high-resolution colonic manometry are being validated using rabbit colon,¹⁷⁹ which may make rabbits a preclinical animal of choice in the near future.

New MRI Parameters of Gastrointestinal Function

MRI applications have been proposed to measure several gastrointestinal functions: gastric volumes and emptying; small-bowel water content; colonic volumes; bowel gas volumes; esophageal, gastric, small-bowel, and colonic motility; anorectal and pelvic floor motion and anatomic integrity; and whole-gut transit measured using MRI capsule markers filled with watery gel pellets or water labeled with an MRI contrast agent. These methods have been reviewed in detail elsewhere.¹⁸⁰ It is interesting to note that software-quantified bowel motility using cine MRI

has potential as a future tool to investigate enteric dysmotility, using a validated motility assessment technique based on motion-capture MRI.¹⁰¹ Another application of MRI to measure colonic motility involves challenge with a laxative preparation (polyethylene glycol 3350 electrolyte solution) and use of MRI marker pills.¹⁸¹

Conclusions

There have been numerous recent advances in measurement of gastrointestinal motility in both human and preclinical models. Imaging technologies especially have advanced rapidly, and it is encouraging to recognize that digestive disease researchers appear to be keeping pace with these advances. It is instructive to understand that, just as the invention of the Roentgen tube in 1895 was adapted rapidly by Cannon^{182,183} to make the first seminal observations of modern gastrointestinal motility and formed the basis for the modern scintigraphic tests presented here,¹⁸⁴ modern neurogastroenterologists rapidly are adapting other medical imaging technologies and high-resolution or fiberoptic measurements of intraluminal pressures into novel clinical tests. It also is important to recognize the value of reverse translating new clinical tests for use in preclinical studies. Nowhere is this idea better shown than the reverse translation of gastric emptying tests for use in mice. It is our sincere hope that the juxtaposition of state-of-the-art motility tests for both human beings and animals will inform researchers of the great potential of this bedside-to-bench-to-bedside approach for the future of neurogastroenterology.

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