17 Electrogastrography, Breath Tests, Ultrasonography, Transit Tests, Wireless Motility Capsule, and Cine-MRI

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Electrogastrography

Electrogastrography (EGG) is a noninvasive test that records the gastric myoelectrical activity through cutaneous leads. The basis of the test is to identify the normal rhythmicity of the stomach of 3 cycles per minute (cpm), with a range of 2–4 cpm. This rhythm, which reliably corresponds to the slow waves generated by the gastric pacemaker region, has been confirmed in animal and human studies by simultaneous electrode recordings from the gastric mucosa, gastric serosa, and skin [1–3]. Values above and below this range are called tachygastria and bradygastria, respectively (Fig. 17.1). The variables evaluated by EGG include the dominant frequency, the dominant power (amplitude in decibels), the percentage of normal frequency, and the percentage of coupling. The rhythmicity from other organs (like heartbeat and respi-

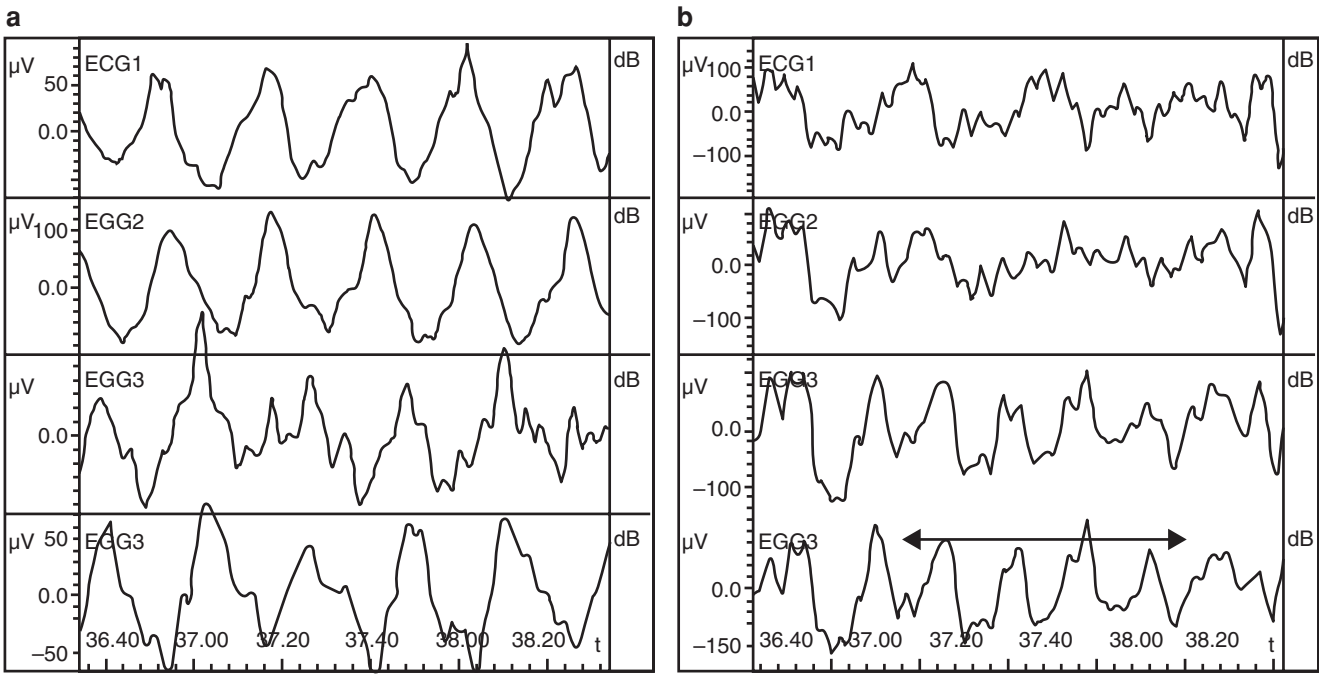

Fig. 17.1 Electrogastrogram tracing. (**a**) Shows normogastria or normal gastric rhythm of 3 cpm and (**b**) shows tachygastria with a rhythm of 5 cpm

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ration) is filtered out during the recording and motion artifact can be analyzed either visually or via a motion sensor and then manually excluded. The signal from all recordings is then selected and the EGG parameters are computed based on spectral analysis. This allows for an objective interpretation of the results. Since the first recording of an EGG in 1921 by Walter C. Alvarez [4], multiple improvements have been added to this technique.

In its early stages, most of the investigations with EGG were focused on its diagnostic role in peptic ulcer disease and gastric cancer and the physiological changes caused by gastric surgery. Over the last two decades, the focus has expanded to evaluate symptoms more than conditions. The first report of the use of EGG in children occurred in 1976, when Disembaeva et al. reported the normal EGG patterns in healthy children [5], followed by a report from Mirutko et al. describing its potential applicability in the evaluation and management of peptic ulcer disease [6]. The field of pediatric EGG exploded in the 1990s when the technique was evaluated in multiple disorders and symptoms.

Developmental Aspects

The gastric rhythm of 3 cpm seems to be irregular or absent at birth and matures over time [7, 8]. Although some have reported no difference between term and preterm infants [9], there seems to be agreement that the rhythmicity reaches adult characteristics in late childhood [7, 10].

Normal Values

Multiple studies, unfortunately following different methodologies, have attempted to develop normal values in children. The largest study was done by Riezzo et al. in 114 healthy children aged 6–12 years, which reported a gastric rhythm in the 2–4 cpm range and a significant increase in postprandial dominant frequency and power [11]. Another study with 55 healthy volunteers age 6–18 years showed a mean dominant frequency of 2.9 ± 0.40 cpm preprandially and 3.1 ± 0.35 cpm postprandially, 80% ± 13% preprandial normogastria, and 85% ± 11% postprandial normogastria [12]. These normative values were independent from age, gender, body mass index, and position [11–13]. Another study demonstrated that the adult norms reported by the American Neurogastroenterology and Motility Society can be used in children and adolescents when the same methodology is applied [14]. Among the factors that could affect the test values are the meal content and position. Breast feeding compared to formula feeding for infants [15] and solid meals compared to liquid meals for adults [16] are associated with higher dominant frequency and power.

Clinical Applications

EGG has been considered as a substitute to other invasive tests, like gastric emptying scintigraphy and antroduodenal manometry, and for other noninvasive but associated with operator-dependent downsides, like ultrasonography. However, most studies have not used the same methodology in terms of number and position of electrodes, recording time, test meals, and analytical software, limiting the validity of the test. Multiple studies in healthy adults as well as adults with specific disorders have shown no significant correlation between the findings on EGG and gastric emptying scintigraphy. Small series in children have replicated those findings [17]. EGG is not useful to discriminate between the three phases of the migrating motor complex (MMC) in adults [18], but it is helpful in differentiating children with normal or abnormal antroduodenal manometry. However, there is significant overlap in EGG results related to artifact from movement leading to inability to interpret data in up to 12% of patients [19]. Also, EGG findings do not correlate with gastric emptying and motility measured by ultrasound [20]. Rather than a substitute for these studies, EGG should be seen more as a supplement for the evaluation of patients with functional and motility gastrointestinal disorders.

Functional Gastrointestinal Disorders

Although some have reported that EGG may not be helpful in differentiating functional abdominal pain from gastritis [21], others have reported significant EGG abnormalities in children with functional dyspepsia and functional abdominal pain [22–24] particularly in patients with severe pain [22]. Also, EGG does not seem to be a helpful tool when it comes to distinguishing functional abdominal pain from peptic disease since chronic gastritis does not seem to be associated with gastric dysrhythmias [21, 25]. A comprehensive systematic review and meta-analysis by Varghese et al. analyzed the clinical association of functional dyspepsia in adults with gastric dysrhythmia on EGG and found that patients spent less time in normogastria while fasted (both brady- and tachygastria) and postprandially when compared to controls. However, no significant differences were found on the power ratio and dominant frequency meal-response ratio, and there was no correlation between EGG metrics and symptom timing [26]. A systematic review and meta-analysis in pediatric patients with gastroduodenal disorders found that patients with functional dyspepsia spent significantly less time in normogastria during the pre- and postprandial period when compared to controls. Similarly symptom correlation with gastric electrophysiology was inconsistently reported [27].

Gastroesophageal Reflux

EGG has been extensively used to assess the potential role of gastric myoelectrical abnormalities in gastroesophageal reflux disease (GERD). In children, myoelectrical abnormalities associated with delayed gastric emptying seem to be associated with severe GERD [28]. However, in a systematic review and meta-analysis, electrophysiological abnormalities were inconsistently reported in pediatric patients with GERD [27].

Chronic Intestinal Pseudo-Obstruction

In children with chronic intestinal pseudo-obstruction (CIPO), EGG has been reported to be abnormal [29] showing a significant difference in the values of either preprandial dominant frequency with tachygastria or differences in the postprandial value of 3 cpm when compared to normal subjects [30].

Eating Disorders

Gastric myoelectrical abnormalities have been related to the symptom pathophysiology in patients with eating disorders. Studies have shown that these abnormalities are more common in bulimia than anorexia nervosa [31] and in patients with long-standing disease [32]. EEG has been shown to be normal in early stages of anorexia nervosa [33].

Effect of Medications on Gastric Myoelectrical Activity

Prokinetic agents domperidone [34] and cisapride [35], unlike erythromycin [36], were effective in normalizing gastric myoelectrical activity in children. General anesthesia has been associated with significant gastric dysrhythmias that return to baseline approximately an hour after anesthesia is stopped [37]. EGG has also been helpful to elucidate the potential mechanism of chemotherapy-induced emesis. Cytotoxic chemotherapy has minimal direct effect on gastric myoelectric activity in children who receive 5-HT3 antagonist prophylaxis. However, tachygastria was noticed during emesis episodes preceded by normal myoelectrical activity [38]. On the other hand, baseline abnormalities in gastric myoelectrical activity have been observed in patients who undergo high-dose chemotherapy and autologous stem cell transplantation despite normal gastric emptying scintigraphy and absence of symptoms [39].

Surgery

Nissen fundoplication may increase gastric myoelectrical abnormalities in neurologically impaired children. In part, this could explain the postoperative retching seen in some of these patients after fundoplication [40]. A study in children with neuromuscular scoliosis found that gastric myoelectrical power increased after surgical correction of spastic scoliosis, but the effect of surgery on gastric emptying, upper gastrointestinal symptoms, and nutritional status was minimal [41].

- *Strengths*: Noninvasive, easy to perform, can be accomplished at bedside, no radiation required, not operator dependent.
- *Limitations*: Nonstandardized methodology, significant motion artifact, need for significant amplification to detect signals with low amplitude.

Breath Tests

The most common indications for breath testing (BT) include assessment for lactose intolerance and small bowel bacterial overgrowth. The first is assessed by measuring breath hydrogen levels in response to lactose ingestion and the second by measuring breath hydrogen levels after an oral challenge with glucose or lactulose.

Recently, BT has been used as a noninvasive and nonradioactive alternative to the gold standard test for gastric emptying with scintigraphy. For this purpose, ^{13}Carbon (^{13}C) isotope is used to label the substrate used for the oral challenge. The test is based on measuring the ratios of ^{12}C and ^{13}C. Both isotopes naturally exist in normal breath, 99% as ^{12}C and 1% as ^{13}C. This ratio is changed by the test meal enriched with ^{13}C resulting in expired $^{13}CO_2$. The exhalation of $^{13}CO_2$ in the patients' breath over time reflects the emptying of the substrate from the stomach. The substrates used for the evaluation of gastric emptying are ^{13}C-octanoic acid for solids and ^{13}C-sodium acetate for liquids. Recently, the ^{13}C-*Spirulina platensis* breath test has been validated and was compared to scintigraphy for gastric emptying in healthy volunteers [42–44].

BT has also been evaluated as an alternative to measuring whole gut transit (WGT). Lactulose has been classically used for this purpose. However, due to concerns of inherent transit acceleration by increasing the osmolality of the gut contents, other substrates have been used, including lactose (^{13}C-ureide breath test) and, more recently, inulin has been found to be the most reliable substrate since it does not seem to affect gastric emptying [45, 46]. ^{13}C is typically measured in breath by continuous flow isotope ratio mass spectrometry, although some have also suggested the use of nondispersive infrared spectrometry (IRMS) as a feasible method [47, 48]. The test relies on normal small intestine absorption, liver metabolism, and pulmonary function to validate the results. An important concern is the high inter- and intrasubject variability [49, 50]. There is also significant inconsis-

tency associated with the meal caloric content in healthy adult volunteers [51], although some have reported very little intrasubject variability in critically ill subjects [52], making the test particularly attractive for this patient population.

^{13}C-octanoic acid has been reported as feasible [53], reliable, and reproducible in preterm [54, 55] and term infants [56] and results seem to be relatively independent from milk amount in preterm newborns during the first hours of life [55]. In healthy children, BT has performed poorly when assessing gastric emptying of both liquids [57] and solids [58] and a high day-to-day variability has been reported in the evaluation of WGT [59]. In preterm infants, gastric emptying measured by ^{13}C-octanoic acid BT does not seem to be affected by feeding osmolality, volume, or energy density; however, reducing osmolality and increasing feeding volume increase gastric emptying [60]. It is important to take into account the meal utilized for the study in children, as human milk [56] and hydrolyzed formulas [61] empty faster than partially and nonhydrolyzed formula. Another significant concern is the potential overestimation of gastric emptying by ^{13}C-octanoic BT due to gastric processing of the substrate. A correction factor of approximately 60 min has been classically added and validated in infants [62], while others have suggested the use of the Wagner-Nelson method [63]. BT with ^{13}C-sodium acetate for liquids and semisolids [64] and ^{13}C-octanoic acid for solid meals [65] have been validated for gastric emptying compared to scintigraphy. In adults, both the ^{13}C-sodium acetate [66] and ^{13}C-octanoic acid [67] do not seem to be affected by age, gender, or body mass index (BMI). In a recent study, normal values for gastric emptying of a standardized test milk-drink in healthy children were determined using the ^{13}C-acetate BT and concluded that the technique is reliable and well accepted by the patients [68].

Clinical Applications

Gastric Emptying

Functional Gastrointestinal Disorders

BT does not correlate with scintigraphy in functional dyspepsia [69] and could not discriminate between healthy volunteers and subjects with dyspeptic symptoms [70].

Gastroparesis

In children with gastroparesis, the ½ emptying time of ^{13}C-sodium acetate correlates with the time to empty half of radioisotope [71, 72] and also discriminates between healthy volunteers and children with symptoms due to gastroparesis [71]. BT has been reported as feasible in neurologically impaired children with GER [73]. BT can be done at bedside, which makes it useful under certain circumstances like in mechanically ventilated patients in the intensive care unit [74]. In a study of adult patients with diabetic gastroparesis, ^{13}C-octanoic acid BT was useful in discriminating between subjects with normal or delayed gastric emptying measured by scintigraphy [75].

Whole Gastrointestinal Transit

BT has demonstrated a constant WGT after the first month of age when a weight adapted dose of lactulose is given [76]. The lactose-[^{13}C]-ureide breath test has been reported useful to evaluate WGT in children older than 8 months [77]. Results in healthy volunteers using lactulose BT have been reproducible [78] and this method has also been useful in the evaluation of small bowel transit (SBT) in patients with anorexia nervosa [79].

- *Strengths*: Noninvasive, low cost, safe, office based, not operator dependent, no radiation required, useful in particular situations (pregnancy, intensive care setting and infants).
- *Limitations*: Requires normal intestinal, liver, and pulmonary function, poorly reproducible in children and adults, equipment may be expensive (IRMS).

Ultrasonography

Ultrasonography (US) is a noninvasive technique that can be used to evaluate gastric emptying, receptive accommodation, antral contractility, transpyloric flow, and gastric anatomical changes (volume and wall width) during meal and therapy challenges. US has been useful to demonstrate trituration of solids to small size particles, retention of larger particles with linear emptying of liquids [80], and antral motility coordination with pylorus flow during normal conditions [81]. Antral waves noticed on US correlate with peristaltic waves seen in antroduodenal manometry, with 99% propagating aborally and 68% becoming lumen occlusive at the site of the ultrasound marker [82]. US has been used in the evaluation of duodenogastric reflux in healthy volunteers [83] as well as in subjects with gastric ulcers [84]. The reproducibility in the assessment of gastric emptying is controversial with some studies reporting significant intra- and interobserver variability [85, 86], while others report differing findings [87, 88], but there is a common agreement on the significant day-to-day variability [87]. More recently, 3D US has been used to assess gastric emptying and has shown good correlation with scintigraphy in healthy subjects [89], but more studies are needed to validate the test.

Developmental Aspects

US has been invaluable in the evaluation of fetal gastrointestinal physiology demonstrating evidence of gastric emptying by 12–13 weeks [90], gastric filling and emptying by 20 weeks, and an important change in gastric volume by 25 weeks [91]. The frequency of these emptying cycles reaches a periodicity of 35–55 min by about 35 weeks [92] and demonstrates a clear normalization along pregnancy with cycles of longer duration and stronger power along the third trimester [93]. Gastric accommodation also seems to develop over time with preterm infants showing delayed gastric distention with feeds at 26 weeks, followed by a subsequent improvement by the time full feeds are tolerated and, almost immediate gastric distention with feeds by 32 weeks [94].

Clinical Applications

Gastric Emptying

The most common technique requires measurements by the same observer after fasting and at regular 30-min intervals postprandially. The emptying time is the time at which the antral area or volume returns to a baseline value [95], although others have also reported the half emptying time. US has shown a strong correlation with scintigraphy in assessing gastric emptying of liquids in healthy adult volunteers at rest [96, 97] and after exercise [98] as well as in subjects with diabetic gastroparesis [99]. In children, US has shown good correlation with scintigraphy; however, discordances associated with overlapping of duodenum and stomach during scintigraphy and shadowing of the gastric antrum by air during US have been reported [100]. Establishing a safe preoperative fasting time has been another use of US in children after ingesting liquids [101] and in adults before undergoing anesthesia [102] and endoscopy [103]. US is reliable in assessing gastric emptying in preterm infants with a good correlation with intragastric volume [104] and particularly in very low birth weight infants with nasal continuous positive airway pressure [105]. US is also useful during pregnancy when radiation should be avoided. Another advantage is that it allows for simultaneous assessment of gallbladder emptying [106]. US reliably assesses changes in gastric emptying in response to use of prokinetic agents like domperidone [107–109], metoclopramide [110], cisapride [111], mosapride [112], and erythromycin [113].

Gastric Receptive Accommodation

US has emerged as an attractive alternative to the more invasive barostat to assess gastric accommodation. The test demonstrates no significant intra- and interobserver variability but moderate day-to-day variability in healthy adult volunteers [114]. It has been reported as a reliable tool to assess gastric accommodation in subjects with functional dyspepsia [115, 116], children with recurrent abdominal pain [114], and the effect of therapy with prokinetic agents like mosapride [117] and other medications like sumatriptan [118].

Antral Motility

A novel use of US is to characterize antroduodenal motility associated with transpyloric fluid movement in healthy volunteers [119] and in subjects with GER symptoms [120]. Some have suggested an advantage of US by allowing a simultaneous observation of antral contractions and gastric emptying and have also reported a good correlation between antral hypomotility and delayed gastric emptying in patients with dyspepsia [121].

- *Strengths*: Noninvasive, no radiation required, readily available, inexpensive.
- *Limitations*: Reliable for the assessment of liquids only, dissimilar, and nonstandardized methodologies, requires certain expertise, operator dependent, obesity and presence of air impair study interpretation (gaseous distention is common in gastrointestinal motility disorders).

Transit Studies

Several tests have been developed to assess gastrointestinal transit as an alternative to other more invasive and expensive tests associated with radiation, like scintigraphy transit studies. Here, we describe tests to assess transit in different segments of the gastrointestinal tract.

Gastric Emptying

Paracetamol Absorption Test

The rate of paracetamol absorption measured by serial serum levels after oral ingestion has been used in multiple research studies as an indirect and noninvasive test to assess gastric emptying of liquids. The test has low interindividual variability [122] with good correlation with scintigraphy [123, 124], although recent studies have questioned this correlation [125]. It is not widely used in clinical practice due to the technical requirements of frequent blood draws, the cost of the assays, and lack of sensitivity to assess gastric emptying in certain clinical situations [126, 127]. Its use has been relegated mostly to pharmacokinetic studies [128] and in special situations where radiation, mobilization, or meal intake is a limitation, like patients in the intensive care units [127] and during pregnancy [129].

Epigastric Impedance

This is a noninvasive method used for the assessment of gastric emptying/transit by measuring electrical impedance through skin electrodes. Results are comparable to scintigraphy [130]. The method has been revised and improved by adding applied potential tomography to generate tissue electrical impedance images and estimate gastric emptying and/or transit [131, 132]. Despite being an attractive noninvasive alternative, it is not widely used or recommended because of its low reproducibility due to significant motion artifact [133, 134]. In addition, the relationship between phasic contractions and phasic variations in impedance does not appear consistent enough to allow clinical application of the technique [135].

Radiopaque Markers

Radiopaque markers (ROM) have been extensively used in the evaluation of gastrointestinal transit due to their low cost, minimal radiation exposure, and uncomplicated performance and interpretation. Despite good correlation between gastric transit of ROM and gastric emptying measured by US [136], the test is not widely used due to the lack of standardization and the availability of other more reliable tests.

Intestinal Transit

Carmine dye, pellets, and ROM have been used in the evaluation of intestinal transit. Unfortunately, the correlation between these methods and scintigraphy is poor. Small intestinal transit is best assessed by scintigraphy, which is considered the gold standard, and wireless motility capsule. If these are not available, ROM should be considered.

Colon Transit

ROM studies have been used to evaluate colonic transit (CT) and several protocols exist for this purpose. The main drawback for ROM studies is the lack of standardization between the multiple methods and the centers performing the studies. The simplified protocol assesses normal versus abnormal colonic transit. It requires the ingestion of a single ROM capsule (24 markers) on the first day followed by an abdominal film on the fifth day. Retention of >5 rings is considered abnormal. The Metcalf protocol (Fig. 17.2) is used for the same purpose with the added information on segmental transit, providing a broader extent of information. In this method, three sets of distinctive ROM capsules (24 markers per capsule) are ingested on 3 consecutive days followed by an abdominal film on the fourth day. Retention of >50 markers indicate delayed colonic transit. This protocol has shown good correlation with transit values obtained with other methods that require multiple films. The normal values for the test are total colonic transit 35.0 ± 2.1 h, right colon 11.3 ± 1.1 h, left colon 11.4 ± 1.4 h, and rectosigmoid colon 12.4 ± 1.1 h with overall shorter transit in men and no effect by age [137]. In children, norms by the Metcalf protocol have been established: total colonic transit time 37.8 ± 6.2 h, 10.8 ± 3.5 h for the right colon, 12.2 ± 2.7 h for the left, and 14.7 ± 2.1 h for the rectosigmoid [138]. The Metcalf protocol has been used to discriminate between constipated and nonconstipated adolescents showing a statistically significant difference in total colonic, right and left colon transit times [139].

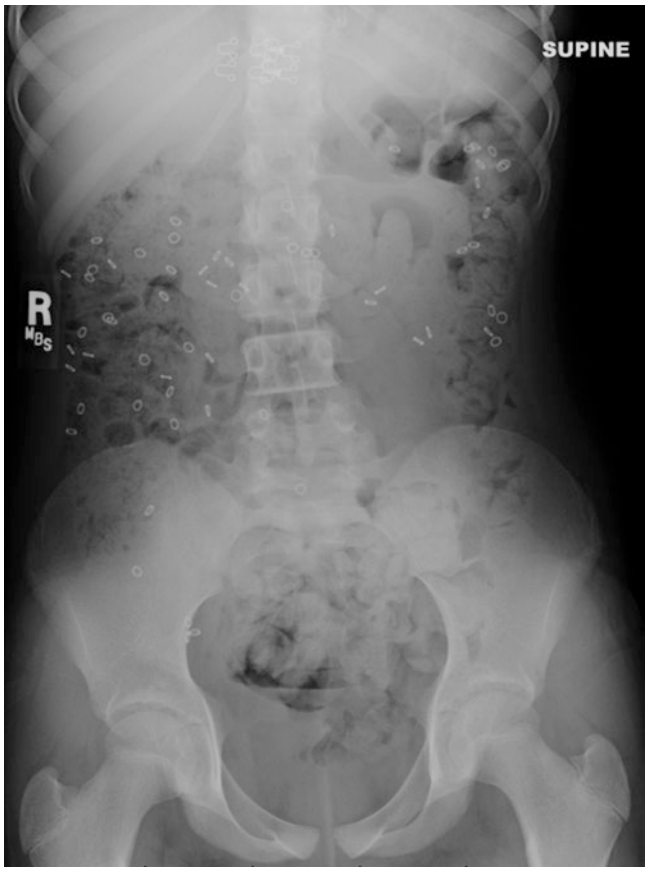

Fig. 17.2 Radiopaque marker study. This abdominal film was obtained on day 4 after ingesting three daily capsules with 24 markers each. Note the retention of all markers

Transit measured by ROM seems to be faster than colonic transit measured by scintigraphy [140]. Overall, mean colon transit time does not differ significantly between young adults and children [140]. However, there are regional differences within the colon in relation to age, with children having faster transit times in the right and left colon, and stagnation in the rectosigmoid [141]. In regard to clinical applications in children, ROM transit studies have been helpful to define pediatric slow transit constipation [142] and to demonstrate correlation between colonic transit and severity of symptoms [143], slower colonic transit in constipated children without soiling compared to those with soiling [144], rectosigmoid transit delay in low variety and global delay in high variety anorectal malfor-

mations [145], constipation in neurologically impaired children associated with slow colonic transit rather than fecal retention [146] and response to therapy for constipation [147]. Similarly, the whole colon and segmental (right colon) transit times measured by ROM and the Metcalf protocol is significantly higher in children with cystic fibrosis (CF) and associated constipation when compared to those without constipation [148].

- *Strengths*: Readily available, minimal radiation, noninvasive, easy to interpret, inexpensive.
- *Limitations*: Multiple nonstandardized methodologies.

Wireless Motility Capsule

This novel device offers the ability to simultaneously measure contractility and transit. The wireless motility capsule (WMC, SmartPill™), measures 26.8 × 11.7 mm and has three different sensors that detect pressure (to measure contractility), pH (to measure transit from stomach to small bowel and from small bowel to colon), and temperature (to assess capsule exiting the body). The capsule is ingested orally with a standard meal, then the patient is discharged and wears a recording device for 3–5 days. The most important use of this device is to record pressures and simultaneously measure transit throughout the different segments of the gastrointestinal tract. In this regard, WMC has been used to evaluate gastric residence time (GRT), small bowel transit (SBT), colonic transit (CT), and whole gut transit (WGT) (Fig. 17.3). Perhaps the most significant contribution of the WMC in gastrointestinal physiology is the reaffirmation of the concept that nondigestible solids empty from the stomach primarily with the return of the phase III of the MMC when the fed state is over and the pylorus is completely open. No less important is the novel finding of gastric emptying of nondigestible solids in some subjects in association with high-amplitude antral contractions and not with the phase III of the MMC [149]. Since the WMC is an equivalent to a nondigestible solid, in healthy volunteers the gastric residence time moderately correlates with the gastric emptying of digestible solids measured by scintigraphy and, it is not surprising that there is a stronger correlation with emptying at 4 h than at 2 h [150, 151]. The WMC has been also useful

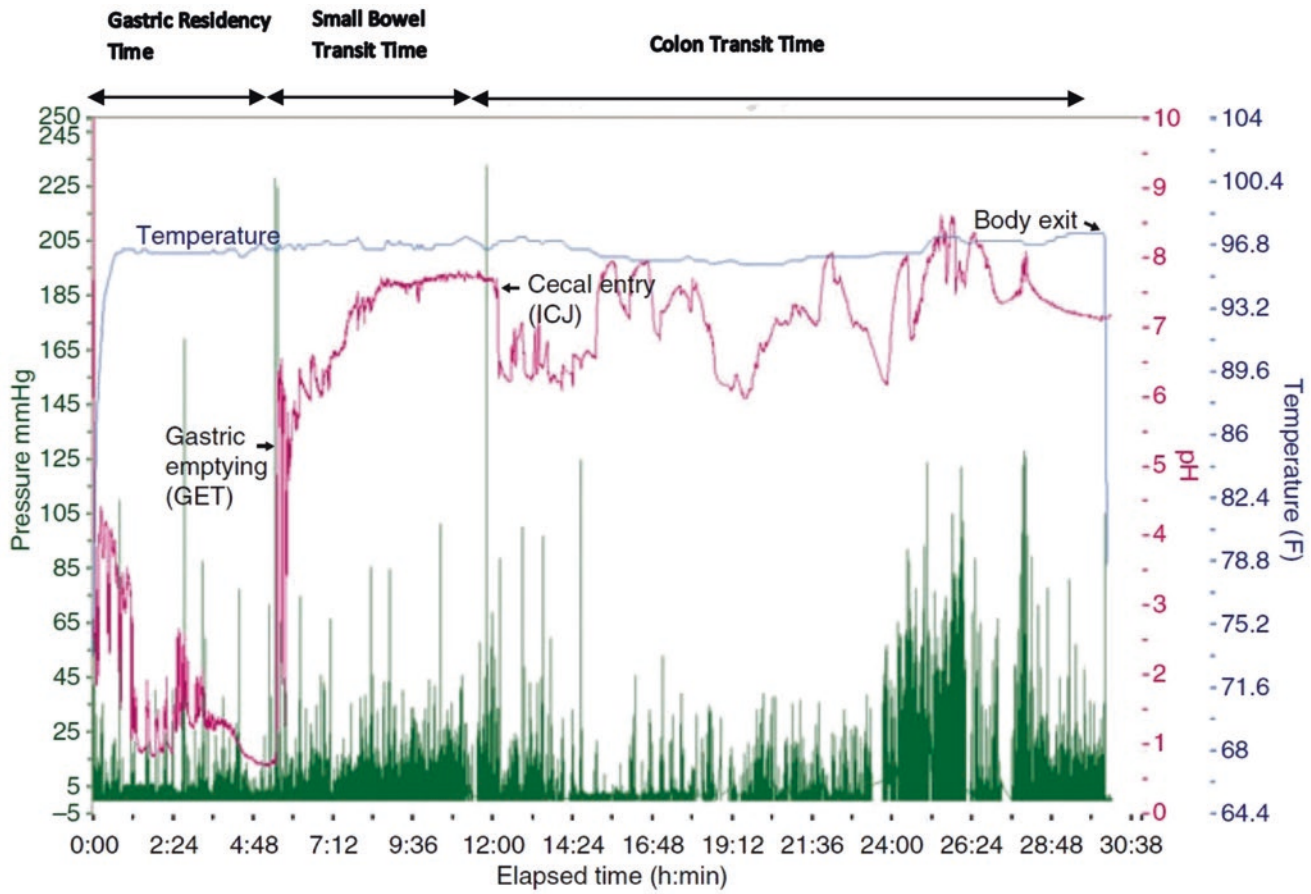

Fig. 17.3 SmartPill tracing. Notice the prolonged gastric residency time as well as significantly prolonged colonic transit. (Courtesy of Dr. Braden Kuo and Dr. Margarita Brun)

to demonstrate the lack of effect of proton pump inhibitors on antral and small bowel motility and transit [152]. A great concern with transit studies with scintigraphy is the significant daily variability, which also potentially applies to the WMC. This has not been addressed in humans, but animal studies have shown a significant variability of GRT by WMC and gastric emptying by scintigraphy with important intraindividual variability [153] and an inverse relationship between GRT and body weight [154].

Clinical Applications

Delayed Gastric Emptying and Constipation

GRT measured by the WMC correlates with the gastric emptying measured by scintigraphy with higher sensitivity at 4 h than at 2 h [151]. WMC also has been useful to discriminate between healthy subjects and patients with diabetic gastroparesis [151] and to measure contractility assessed by number of contractions and motility index in antrum and small bowel [155]. WMC has proven to be useful in classifying and diagnosing regional and generalized motility disorders with good agreement with other conventional motility studies [156]. A recent study by Green et al. compared the WMC with gastric emptying by scintigraphy and antroduodenal manometry in children with upper gastrointestinal symptoms. They reported a sensitivity and specificity of 100% and 50%, respectively, for the detection of gastroparesis by the WMC compared with the 2-h gastric emptying study. Both WMC and antroduodenal manometry were equal in detecting the presence of the MMC but the WMC was more sensitive in detecting motor abnormalities [157].

Colon contractility is poorly characterized in adult patients with constipation and irritable bowel syndrome-constipation subtype. The WMC has been proven useful to measure contractility pressures in different segments of the gastrointestinal tract in these patients. A study by Hasler et al. that evaluated colon contractility and transit in healthy adult patients demonstrated greater pressures in the distal colon when compared to the proximal colon. In the same study, constipated patients with normal or moderately delayed transit showed increased motor activity that was partly explained by IBS. The findings in this study emphasize the differential effects on transit and motility in different constipation subtypes [158].

The WMC has been validated for measurement of the CTT and WGT by the simplified and Metcalf protocol. For the Metcalf protocol, a recent large multicenter study demonstrated that although the measured transit time was significantly different between the WMC and ROM, the agreement for delayed transit was 80% and 91% for normal transit with an overall device agreement of 87% [159]. The WMC with the simplified method showed slower GRT, SBT, CTT and WGT in subjects with constipation compared to controls. Interestingly, the CTT was slower in women than in men and, more importantly, showed upper gastrointestinal transit delay in subjects with constipation [160]. In addition, the WMC has demonstrated that stool form predicts delayed versus normal CTT in adults in contrast to stool frequency [161] and, has reiterated the concept of a generalized gastrointestinal dysmotility beyond the stomach in patients with gastroparesis by evidencing delayed CTT [162]. WMC has been also validated with scintigraphy for the evaluation of gastric emptying, colonic and whole gut transit (WGT) in healthy subjects as well as patients with constipation [163]. In regard to therapy outcomes, the only available study has demonstrated a possible positive effect on CTT and WGT by increasing dietary fiber [164].

In one of the largest studies in pediatrics, Rodriguez et al. [165] prospectively evaluated the diagnostic and clinical utility of the WMC in children with functional GI symptoms by measuring the WMC transit and motility and comparing them with gastric emptying times measured by scintigraphy and colonic ROM (Metcalf protocol), respectively. The authors found fair interpretation agreement between WMC and scintigraphy and moderate interpretation agreement between WMC and colonic ROM in a good proportion of patients with upper and lower GI symptoms, respectively. Interestingly, they found a significant detection rate of abnormal and severe gastric retention with WMC when compared to scintigraphy (>35% radiotracer retention at 4-h). Also, they found a significant correlation between the colon transit time measured by both methods and although the median transit time measured by colonic ROM was higher when compared to WMC, it was not statistically significant. However, they found no association between WMC study interpretation, motility and transit parameters, and GI symptoms. Capsule retention was associated with prolonged colon transit times and not related to symptoms, age, or gender. The authors concluded that WMC is well tolerated in children as young as 8 years of age and provides additional transit information not detected by the other modalities.

Cystic Fibrosis

Patients with pancreatic insufficiency secondary to CF require optimal proximal intestinal neutralization of gastric acid for timely release of pancreatic enzyme replacement therapy. As mentioned above, the WMC has the ability to measure pH and transit in different regions of the gastrointestinal tract. A recent study by Gelfond et al. demonstrated delayed SBT and, more importantly, deficient proximal intestinal buffering capacity measured by WMC in adult pancreatic insufficient CF patients when compared to controls. This study also adds that measurement of gastrointestinal pH using the WMC may

be a method to aid in the development of pharmacological interventions for patients with CF and potentially assess individualized interventions [166].

- *Strengths*: Allows evaluation of transit of the whole GI tract and pressure measurements simultaneously, not operator dependent, ambulatory.
- *Limitations*: Cost, availability, requires expertise in interpretation, risk of capsule retention causing obstruction, capsule size limits use in children, no studies have been done in children.

Cine-MRI

Magnetic resonance imaging (MRI) is a well-known radiologic modality that utilizes strong magnetic fields, radio waves, and magnetic field gradients to generate detailed images of visceral organs, thus providing comprehensive physio- and pathophysiological information. MRI offers the advantage that it does not involve ionizing radiation, it is widely available, and is useful to monitor disease progression. MRI of GI tract function, known as dynamic or cine-MRI, was first described by Stehling et al. in 1989 in four healthy volunteers using a high-speed echo-planar imaging technique and demonstrated a detailed quantitative measurement of the peristaltic patterns in the antrum and proximal small intestine during fasting, after a feed and pharmacologic stimulation [167]. Consequently, cine-MRI became an attractive technique that continues to evolve, currently being applied to study and define GI physiology parameters including GI volumes, motility, transit, and also disease. There are, however, important limitations to its use, particularly the optimization of quantitative imaging analysis. Different quantification methods have been described, including the visual assessment, diameter measurements, displacement mapping, and GI tagging [168]. Other limitations include issues related to imaging acquisition and duration of scans; breath-hold and free-breathing protocols are being explored as potential solutions to address those problems.

Stomach

Measurement of gastric volumes by MRI is feasible, and has been utilized in studies assessing gastric emptying of Gd-DOTA (gadolinium tetra-azacyclododecane tetra-acetic acid) labeled liquid and solid meals in healthy adults with good agreement with scintigraphy [169, 170]. Similarly, this technique has allowed to simultaneously measure the diameters and the contractions per minute of both the proximal and distal stomach before and after a meal [171]. The study is reproducible (assessing the postprandial gastric volumes and gastric emptying within and in between healthy controls and adults with functional dyspepsia) [172] and has a good correlation with antral motility evaluated by water-prefusion manometry during fasting and postprandially (water intake) [173]. Cine-MRI has also been used to study the effects of prokinetic medications, like cisapride, on gastric motor function in diabetic gastroparesis [174] and, to simultaneously measure gastric accommodation, emptying and motility in patients with Ehlers-Danlos syndrome hypermobility type with dyspepsia [175].

Small Bowel

Volume assessment of small bowel by MRI continues to be challenging due to the tortuosity, length, and uneven filling of the lumen. Nevertheless, significant progress has been made in cine-MRI and small bowel motility, both in health and disease. In general, most methods require luminal distension with contrast (enteroclysis, enterography) and evaluation of both fasting and postprandial motility and volumes [168]. Breath-hold protocols that minimize motion artifacts and respiratory displacement are typically used, but may limit the amount of information obtained from the study [176]. Khalaf et al. developed a method using cine-MRI to assess pan-intestinal motility during fasting and the postprandial state during a single session [177]. In this study, healthy adult volunteers underwent baseline and postprandial MRI scans and measured gastric volume, gallbladder volume, small bowel water content, small bowel motility, and whole gut transit. In addition, serum GI peptides (glucagon-like peptide-1, polypeptide YY, and cholecystokinin) were measured and information regarding symptoms (fullness, bloating, distension, abdominal pain, nausea) were collected from the subjects following a 204 kcal liquid meal. Based on their findings, the authors established a method that assesses postprandial small bowel motility by cine-MRI and were able to correlate their measurements with known physiologic peptide response and symptoms.

The utility of cine-MRI has also been evaluated in GI disease. A prospective study using cine-MRI measured and compared the luminal diameter, contraction ratio, and contraction cycle in healthy subjects, patients with irritable bowel syndrome and chronic intestinal pseudo-obstruction (CIPO) and demonstrated that in patients with CIPO the small bowel luminal diameter was significantly higher and contraction ratio was significantly lower when compared to IBS patients and controls, with no differences in contraction cycle [178]. A retrospective study later found that luminal and motor abnormalities detected by cine-MRI are useful in predicting disease severity and outcomes in CIPO when

compared to controls [179]. Another study utilized the pan-intestinal motility technique based on motion capture MRI and compared their findings between CIPO patients and controls. Unsurprisingly, the authors found that the baseline global bowel motility index was significantly lower in CIPO. Subjects were later randomized to undergo repeat MRI and receive intravenous neostigmine or normal saline and were able to detect an increased motility in the both groups receiving neostigmine but noticed a reduced response in CIPO secondary to scleroderma, highlighting the potential utility of cine-MRI to determine treatment response [180].

Colon

The application of cine-MRI in the assessment of colon motility is very limited, mostly assessing response to medications or the simultaneous use of manometry. One study aimed to assess colon motility in healthy volunteers after stimulation with senna tea and erythromycin. Colon motility was measured according to changes in the luminal diameter at five different locations in the ascending, transverse, and descending colon and found significant changes in all segments, highest after senna tea [181]. However, the main limitation of this study was the inability to assess the sigmoid colon. A different study used cine-MRI to measure small bowel content, ascending colon motility index, and regional colonic volumes after the ingestion of a single dose (2 L on day of study) or split dose (1 L evening before and 1 L on day of study) of polyethylene glycol (PEG). The authors found a fourfold increase in small bowel water content after both single- and split-dose PEG ingestion and a significant increase in colon volumes after single-dose PEG. Most importantly, the ascending colon motility index was twofold higher after single-dose PEG [182].

Colon manometry is considered the gold standard method to assess colonic motility, but it is invasive, time consuming, requires a bowel clean out and colonoscopy. A feasibility study by Kirchhoff et al. stimulated high-amplitude propagated contractions (HAPCs) with bisacodyl and aim to measure them in the descending colon of healthy volunteers by manometry and cine-MRI. HAPCs were detected by manometry in all subjects and cine-MRI simultaneously detected colon luminal changes corresponding to these contractions [183]. Recently, a feasibility study by Vriesman et al. also assessed the simultaneous assessment of colon motility in children with functional constipation by manometry and cine-MRI. Unlike the adult study, not all HAPC recorded by manometry was noticed during cine-MRI. However, cine-MRI detected colon activity not seen in patients with absent HAPC's on manometry [184]. Both studies demonstrated that the simultaneous acquisition of colon motor activity by manometry and cine-MRI is feasible making the latter an attractive and noninvasive alternative to colon manometry.

- *Strengths*: Allows evaluation of volume, luminal diameter, motility and transit of the whole GI tract, no radiation involved, not operator dependent, ambulatory.
- *Limitations*: Cost, requires expertise in interpretation, no standardized methodology available, movement or use of sedation limits use in children, limited information available in pediatrics.

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