Chapter

Gastrointestinal Physiopathological Testing for Upper GI Functional Disorders

Edda Battaglia, Maria Luisa Niola, Valentina Boano, Chiara M.C. Elia, Carlo Sguazzini and Mario Grassini

Abstract

Functional gastrointestinal disorders (FGIDs) are disorders of gut–brain interaction; it is a group of disorders classified by gastrointestinal (GI) symptoms related to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, altered central nervous system processing. In general, investigations on intestinal motility should be reserved for patients with symptoms correlated to motor alterations that greatly influence the quality of life, nutrition and productivity, as they are justified only if a result can be expected that influences the clinical management of the patient. Esophageal High-resolution manometry (HRM) today permits greater understanding of the function of the esophagogastric junction and the esophageal motility. In the more frequent clinical manifestation, like as Gastroesophageal reflux disease (GERD), despite endoscopy, the pH-impedance is considered the most accurate and detailed method to assess acid/weakly acid or non acid gastroesophageal reflux, to identify the specific phenotypes of reflux disease spectrum. To investigate gastric motor function, the scintigraphic gastric emptying test is the gold standard, but it still has poor uniformity of the protocols, that undermine the quality and usefulness of the test. The current and increasingly widespread alternative to scintigraphic emptying is the breath-test with octanoic acid (OBT) or Spirulina labeled with C13, a test that has the favor of not using radioactive substances and that has shown a high concordance with the scintigraphic test. The intraluminal capsule test is a recent promising tool, that records intraluminal pH, pressure, temperature and post-prandial gastric contractions, and transmits wireless data to a receiver. EGG is a non-invasive technique that measures gastric myoelectric activity- and consequently its function- using skin electrodes placed in the upper abdomen. Gastro-jejunal manometry with multiple pressure sensor catheters located in the antrum, pylorus, duodenum and jejunum is the only clinically available test that allows detailed evaluation of coordinated gastro-duodenum-jejunal contraction models. The functional ultrasound, the barostat, the SPECT and resonance methods have provided preliminary data on their application in the study of gastrointestinal motility, but the data are still missing and the methods are not validated.

Keywords: functional gastrointestinal disorders, functional tests, manometry, pH-impedance

1. Introduction

Functional gastrointestinal disorders (FGIDs) are disorders of gut–brain interaction; it is a group of disorders classified by gastrointestinal (GI) symptoms related to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, altered central nervous system processing [1].

2. Esophageal function

The evaluation of the esophageal function is not clearly defined because its dysfunction is mainly due to neuromuscular disorders, so its pathophysiology is complex.

However, esophageal manometry and 24-hour pH-impedance monitoring are two useful tests to classify the organ's disorders [2].

2.1 Manometry

Manometry is considered as the gold standard [3] to diagnose motor alterations of the esophagus. Conventional examination uses mostly water-perfused probes, with recording points placed every 5 cm along the length of the esophageal catheter, in order to measure internal contraction and pressure. However, high-resolution manometry (HRM) is nowadays the most accurate and available tool. HRM is equipped with high-resolution solid-state catheters that transmit data on the internal condition of the esophagus, which are then converted into graphs (topography plots, EPTs). The probes are placed every 1 cm, for a total of 32–36 transducers all along the organ [4].

In the standard procedure the patient is placed in a supine position in order to eliminate the gravitational effect, and a basal recording is made for 30 seconds, followed by at least 10 consecutive swallowings, during which various parameters of esophageal peristalsis are detected and recorded, the main ones being DCI (Distal Contractile Integral) and DL (Distal Latency).

The DCI represents the contractile vigor of the esophagus, i.e., amplitude x duration x length of contraction of the distal esophagus with an isobaric contour of 20 mmHg.

The DL (measured in seconds) is the interval between relaxation of the UES and the point of deflection along the 30 mmHg isobaric contour where the propulsion velocity slows (contractile deceleration point, CDP): it represents an indirect measure of post-deglutitive inhibition and thus normal peristalsis [3].

It has to be mentioned the IRP (Integrated Relaxation Pressure, in mmHg), which is defined as the mean pressure of the EGJ measured for 4 contiguous or not-relaxation seconds, during the ten seconds following deglutive relaxation of the UES [5].

The first step of the data analysis is focalized on the evaluation of the esophagogastric junction (EGJ): basal pressure of the lower esophageal sphincter (LES), IRP and crural diaphragm (CD) are evaluated, and junction subtypes are defined.

The Lyon Consensus [6] proposes to study EGJ in two different ways, from an anatomic and morphologic point of view and then from his contractility.

Morphologically, three types of junctions are described, where type 3 is associated with decreased LES pressure due to anatomical separation >3 cm between LES and CD. By the second measurement the EGJ-CI (EGJ Contractile Integral) is calculated, which measures the level of barrier provided by the junction.

The second step is about evaluating the peristalsis of the esophageal body, based on various parameters including the DCI and the interruptions of the isobaric

contour of 20 mmHg, although with the latest Chicago classification (CC v3.0) it has been proposed to eliminate this last parameter from the assessment of esophageal contractile force, and to consider it as a descriptor of the contractile pattern [7]. So, contractile vigor can be described as absent (DCI <100 mmHg·s·cm), weak (DCI >100 but <450), inefficient (absent or weak), or hypercontractile (DCI ≥8000); contractile pattern instead can be premature (DL >4.5 sec), fragmented (interruptions >5 cm on the isobaric contour with DCI >450) or normal [3, 5].

Basing on the results obtained from the manometry, the patient is included in one of the four groups describing esophageal motility, as defined in CC v3.0 [8]:

- incomplete relaxation of the LES, such as achalasia subtypes I and III or EGJ outflow obstruction;
- major peristalsis disorders, such as distal esophageal spasm, esophageal 'jackhammer' hypercontractility, or absent contractility;
- minor motor disorders, such as fragmented peristalsis or ineffective esophageal motility (IEM);
- normal esophageal motility (**Figure 1**).

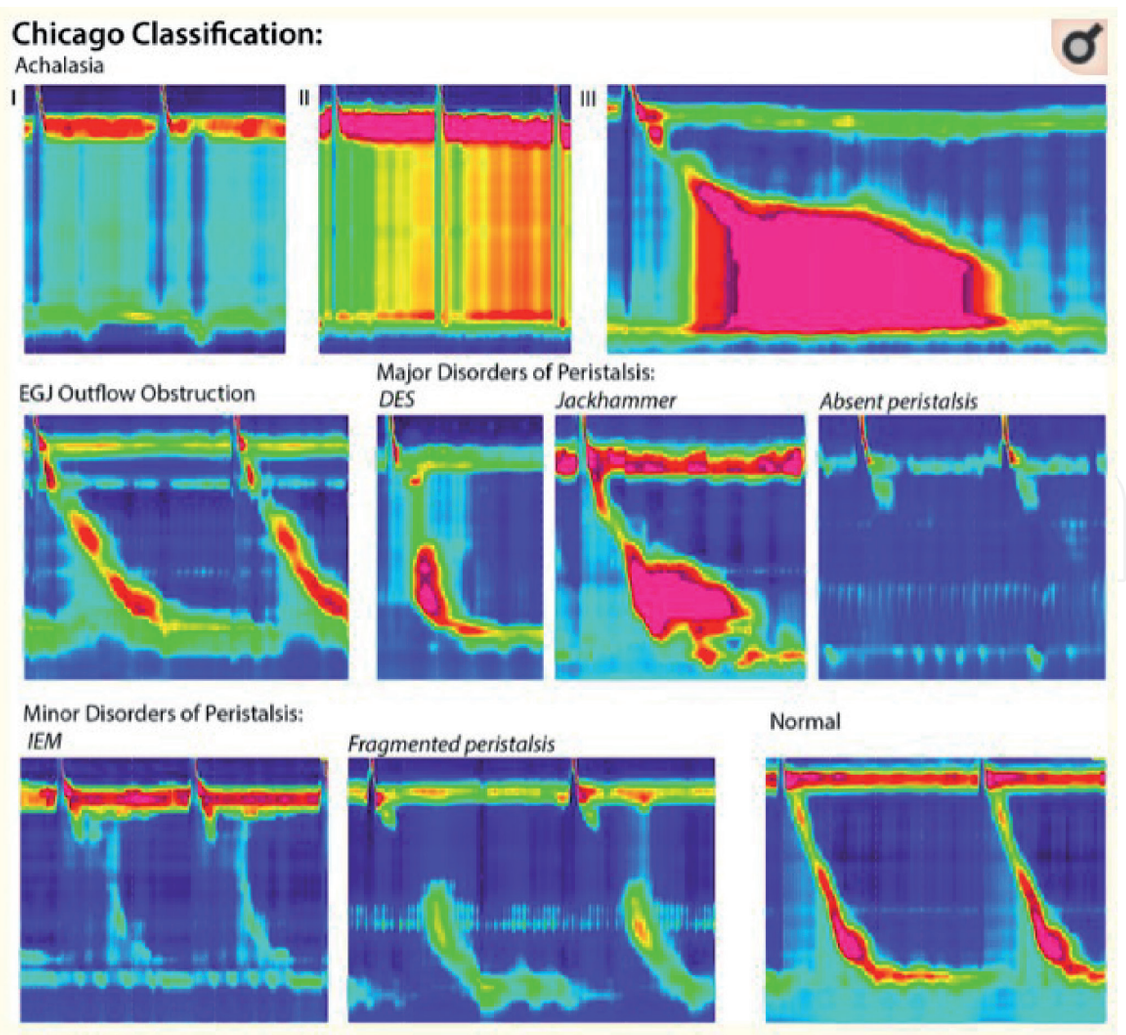

Figure 1.
Chicago classification on HRM [8].

2.2 24-hour pH-impedance monitoring

24-hour pH-impedance monitoring is today the most useful and sensitive test to study every type of reflux episode, its composition, proximal extension, duration and clearance. It is based on the simultaneous measurement of pH and endoluminal electrical impedance: a pair of electrodes correspond to an impedance segment that provides a measure of impedance (resistance): it is inversely proportional to conductivity, increasing if air is passing through the esophagus and decreasing if water/swallowed material or reflux is passing through it [9].

By combining the two measurement, the chemical nature and the physical nature of the reflux episode can be defined as acid, weakly acidic, weakly alkaline and liquid, gaseous or mixed.

Changes in pH occurred simultaneously with impedance drops of at least 50% are classified as follows:

- Acid reflux: a drop in pH <4 from a pre-event pH >4, lasting >5 seconds;
- Superimposed acid reflux: liquid reflux monitored by impedance electrodes while the esophageal pH is still <4, i.e., the pH in the distal esophagus has not returned to >4 after an episode of acid reflux;
- Weakly acid reflux: the pH nadir is ≥4 but <7 during reflux;
- Weakly alkaline reflux: no acid is present as the intra-esophageal pH increases to ≥7 or remains ≥7 during reflux (**Figure 2**).

Furthermore, a liquid episode is defined as a retrograde flux (to the proximal esophagus) capable of changing the basal impedance value by at least 50% in two consecutive channels; a gaseous episode, on the other hand, corresponds to a simultaneous increase in impedance >3000 Ω in two consecutive channels, with a channel having an absolute value >7000 Ω. Finally, a mixed episode is a gaseous reflux that occurs during or immediately after a liquid one [10].

By measuring the impedance on different levels of the esophagus the extension of reflux can be determined; it is relevant if the pH is altered at 15 cm cranially from the LES [11]. Moreover, the Acid Exposure Time (AET) can be calculated: a total exposure of less than 4% is judged normal while a value >6% is surely pathologic, and the total number of refluxes is considered normal if <54 [12]. The temporal

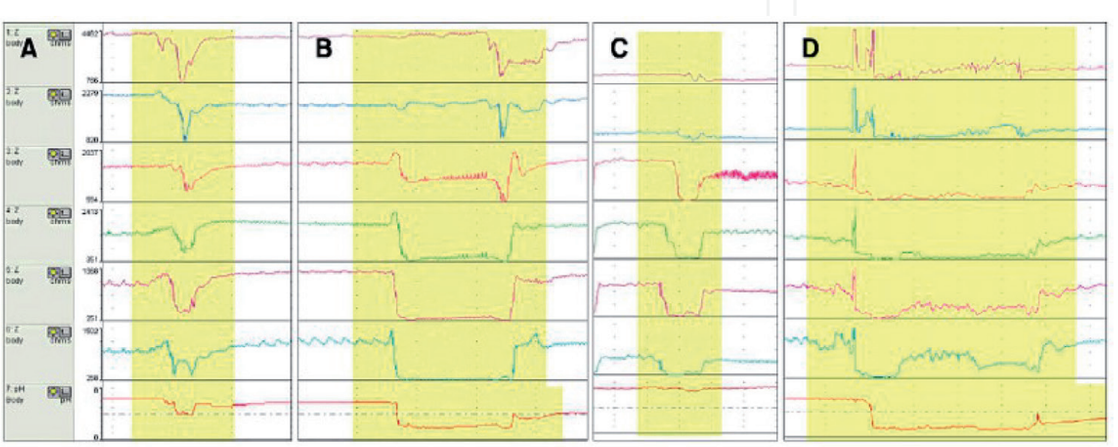

Figure 2.
(A) Weakly acidic reflux episode, (B) acidic episode, (C) weakly alkaline episode, (D) superimposed episode [9].

correlation between reflux episodes and symptoms is analyzed by measuring three parameters: the Symptom Index (SI), the Symptom Association Probability (SAP) and the Symptom Sensitivity Index (SSI). Additionally, two more parameters have been recently introduced, namely the Post reflux Swallow- induced Peristaltic Wave (PSPW) index, and the Mean Nocturnal Baseline Impedance (MNBI). The former refers to a vagal reflex that is activated after reflux and consists of swallowing that raises esophageal pH. The latter reflects the permeability of the esophageal mucosa and low values are related to alterations in tight junctions[1]. Thus, calculation of MNBI and PSPW together is useful in general to improve the yield of pH-impedance testing [13], and is particularly advantageous when the diagnosis of gastroesophageal reflux disease is doubtful (e.g., with normal AET and discordant SAP and SI) to distinguish patients with hypersensitive esophagus from patients with functional heartburn [14].

In conclusion, 24-hour pH-impedance monitoring is a test which is not so specific for functional disorders, but it allows to analyze multiple parameters. It allows therefore to make a diagnosis of gastroesophageal reflux disease, or to exclude it when there are doubts, as well as to distinguish the typical forms of reflux from those belonging to functional disorders (for example functional heartburn or reflux hypersensitivity).

3. Gastric function

The main tests to study the stomach function are gastric barostat, scintigraphy, tests using an intraluminal capsule, breath test, electrogastrography (EGG) and Water Load Test (WLT).

3.1 Barostat

Gastric barostat studies are the best-established methods of measuring gastric accommodation, and they are considered as the gold standard.

The barostat is a computerized air pump device that measures fundic relaxation in response to a meal, by monitoring the volume of air within an intragastric bag (a polyethylene balloon [15]) that is clamped at a constant pressure level [16]. The system maintains a constant pressure by fixing it and changes the bag's volume reflecting gastric relaxation or contraction (**Figure 3**). In this way, gastric accommodation response to various interventions is recorded.

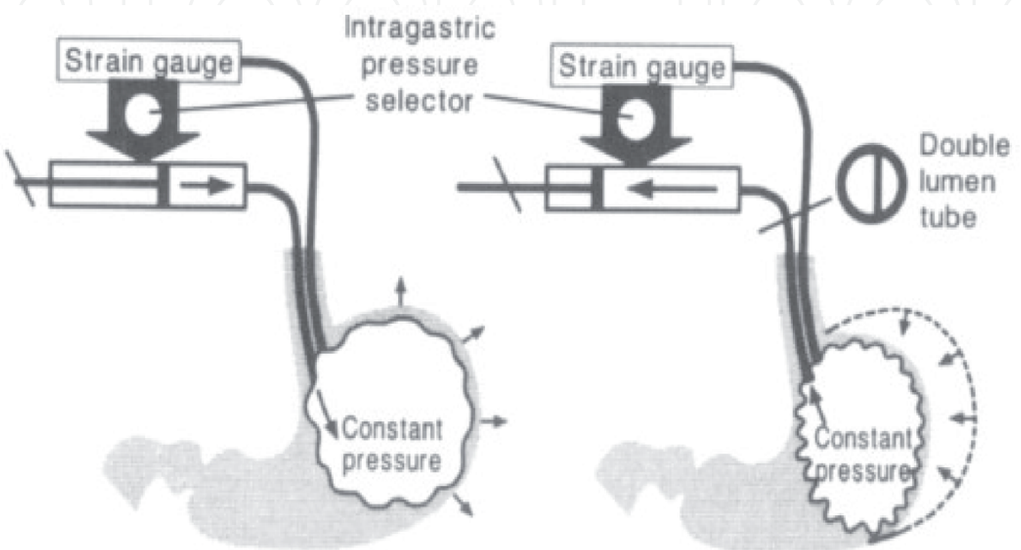

Figure 3.
Working mechanism of a barostat balloon [16].

The problem is that the barostat is an invasive test [17]: although it is a valuable technique, it is not practical in daily clinical assessment for patients nor for research studies. This is the reason why today non-invasive methods are preferred, and they will be later described in this chapter. Moreover, the barostat balloon can't perfectly measure post-prandial accommodation of the entire stomach, and it is possible that it interferes with the intra-gastric management of the meal [18] (**Figure 3**).

3.2 Scintigraphy

Gastric Emptying Scintigraphy (GES) is a non-invasive test that uses 99mTc-Nanocolloidal as the radioactive substance. The patient is usually given a solid and radiolabeled meal, then data are acquired, and the emptying time is analyzed. A liquid meal with water labeled with indium-111 diethylenetriaminopentacetic acid may also be used. The procedure should be repeated after 1 hour, 2 hours and 4 hours: in fact, delayed gastric emptying is detected with greater sensitivity at 4 hours, and images detect gastroparesis with 30% greater frequency. Imaging at 0,1,2 and 4 hours allows identification of both rapid and delayed gastric emptying, which is important because patients are treated in a different way, even though their symptoms are similar. Moreover, images at 60 minutes have a specificity and sensitivity of 90% for rapid gastric emptying, whereas images at 240 minutes show a specificity of 70% and sensitivity of 100% for delayed one [19]. Delayed emptying is considered to be gastric retention of more than 90% at 1 hour, more than 60% at 2 hours, and more than 10% at 4 hours [20].

3.3 Intraluminal capsule

The capsule test is performed by ingesting a capsule with the meal: this records intraluminal pH, pressure, temperature and post-prandial gastric contractions, and transmits wireless data to a receiver. In healthy people it is detected in the duodenum after about 5 hours. The test has a concordance of 90% with scintigraphic tests and has excellent sensitivity and specificity especially in detecting gastroparesis [21]. This technique offers a non-radioactive, ambulatory alternative to scintigraphy [22].

3.4 Breath test

A functional test for the study of gastric emptying (GE) is the breath test (GEBT) [23]. It is a non-invasive method, feasible also in pregnancy and children, that does not use any radiation, it is easily repeatable, and it is based on the measurement of the 13CO2/12CO2 ratio in the exhaled breath after the administration of a standard meal, labeled with 13C-Spirulina or 13C-Acetate or 13C-Octanoic Acid. The procedure is repeated at 45, 90, 120, 150, 180, and even 240 minutes after the end of the meal. By measuring the change in this ratio over time from the pre-meal value, the rate of 13CO2 excretion can be calculated and the individual's rate of gastric emptying determined.

When compared with scintigraphy, it showed similar values: good agreement was found between the two tests, thus validating the breath test as an alternative method for studying gastric emptying. Based on the study of normal values, the 10th and 90th percentiles of t 1/2 calculated with scintigraphy were used to classify patients as follows: subjects with delayed (t1/2 > 86 min), accelerated (t1/2 < 52 min), or normal (t1/2 52–86 min) [24] gastric emptying.

3.5 Electrogastrography (EGG)

EGG is a non-invasive technique that measures gastric myoelectric activity- and consequently its function- using skin electrodes placed in the upper abdomen. Normal activity consists of slow waves ad potential spikes (which would correspond to contractions), and the normal frequency is approximately 3 wpm [25].

The correlation between EGG and gastric emptying has been reported in several studies: in patients with functional dyspepsia, 40% of patients showed abnormal EGG [26]. The presence of EGG abnormalities in patients with dyspepsia or delayed gastric emptying, and the presence of motor abnormalities in many patients with GERD, leads to the conclusion that EGG abnormalities can be detected in some patients with gastroesophageal reflux disease, too.

3.6 Water Load Test

The Water Load Test is an economic, non-invasive and easy to perform test, that can be reproduced in healthy subjects as well as in patients with reflux disease or functional dyspepsia [27]. It is useful to assess visceral hypersensitivity, that has been identified as an important pathophysiologic mechanism in patients with functional disorders of the upper gastrointestinal tract [28].

The test consists of having the patient drink as much water as possible, consecutively for 5 minutes (WL5), or until a feeling of satiety is reached. The patients have to complete a visual analogue scale (VAS) in order to objectivate their symptoms before and after the test, and they have to assign a value for each of them, scaled from 0 (absent) to 10 (severe). Then, water is consumed from an unmasked flask that is refilled after each drink, but the patients are blinded as to the actual volume of water consumed. Finally, the total volume of water ingested, and the perceived symptoms are registered and analyzed [29].

There is also evidence that some GERD patients, more often with non-erosive disease, may improve dyspeptic symptoms after acid-suppression therapy [25]; however, large cohort studies suggest that that the reflux patients and dyspeptic patients represent two distinct populations [26]: GERD patients with mild erosive oesophagitis and with non-erosive reflux disease have the WLT abnormal, similar but not identical to that reported in patients with functional dyspepsia [29]. The WLT does not allow a precise determination of visceral hypersensitivity; however, it is worth noting that these findings appear somewhat similar to those described in other studies by means of the barostat technique in dyspeptic patients, although a correlation between these two methods is still not available. Although there is literature evidence suggesting abnormalities of gastric motor and sensory function in GERD patients [30, 31].

3.7 Other tests

Although these tests were not created exclusively to study gastric function, they are becoming a useful help in order to assess its accommodation in a non-invasive way: ultrasonography, magnetic resonance (MRI) and Single-proton Emission Computed Tomography (SPECT) are some examples.

Ultrasound imaging is a widely available method but offers only an indirect measure of gastric accommodation through antral diameter [17]. On the other hand, MRI is able to provide information about gastric meal emptying, the total volume of gastric contents and also three-dimensional images of the stomach [32].

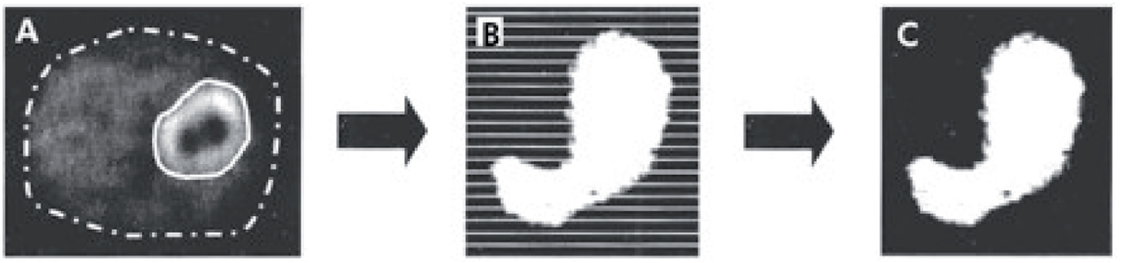

Figure 4.
(A) Multiple SPECT images are reconstructed with the help of a software system (B) into a three-dimensional image of the stomach (C) for the measurements of gastric volumes [35].

SPECT is an emerging test that uses intravenous injection of ^{99m}Tc-pertechnetate with tomographic imaging (three-dimensional reconstruction) of gastric mucosa. The evaluation of gastric accommodation is completed by measuring gastric volumes in fasting and post-prandial state [33] and by analyzing them with a commercially available software. Mean volumes detected by SPECT are comparable to that of barostat; moreover, it permits simultaneous assessment of gastric emptying and accommodation [34] (**Figure 4**).

4. Clinical usefulness

In what clinical conditions is it correct to perform these tests?

For standard esophageal manometry or HR esophageal manometry and reflux monitoring recent guidelines have given clear and shared indications [3, 4]. The utility of esophageal manometry in clinical practice is to accurately define esophageal motor function, to identify abnormal motor function, and to establish a treatment plan based on motor abnormalities, in patients with dysphagia, chest pain or in GERD patients before surgery.

Reflux testing has generally no indication in the majority of patients with typical GERD symptoms (i.e., heartburn and/or regurgitation) who have adequate symptom relief with medical therapy. The role of reflux monitoring is more important in patients with reflux symptoms and without endoscopic mucosal breaks, in whom an objective diagnostic test to define their disease is more likely to be needed. The prolonged reflux monitoring with pH-impedance catheter actually represents the most sensitive tool to document the role of reflux in patients with GERD symptoms. A further indication for reflux testing is represented by belching disorders and one of the most common use of reflux monitoring is the evaluation of patients with persistent typical GERD symptoms despite medical therapy, when refractory heartburn can be defined as the presence of heartburn that does not respond to at least 8-weeks of double-dose acid suppressing medications [4]. Furthermore it's recommended the evaluation of patients with esophageal symptoms suggestive for GERD before surgery, to confirm the reflux and the evaluation of children with symptoms suggestive for GERD (particularly in case of neurological symptoms and low growth).

As regards gastro-jejunal functional tests, there are no guidelines or consensus, but, extrapolating the data from the literature, we can consider these data useful in:

- Severe functional dyspepsia and related syndromes.
- Rumination symptoms.
- Atypical/estraesophagel forms of reflux.

- Pseudo-obstruction symptoms.
- Diabetes mellitus with functional symptoms and/or difficult metabolic compensation.
- Suspected gastroparesis (including post-surgery).
- Functional pre-intervention evaluation (plastic antireflux, colectomies for constipation, implantation of gastric pacemakers).
- Identification of specific feeding site enteral or for the administration of drugs enterally (Parkinson's).

5. Conclusions

The gastrointestinal functional tests represent the study modalities of esophageal-gastric motility and intestine, useful for the diagnostic definition and therapeutic management of functional gastric and intestinal disorders. These diseases affect a large proportion of the world population, compromise the quality of life and cause significant health care costs. It is important to underline that functional tests must always be preceded by a careful clinical evaluation that excludes other etiologies. In general, investigations on intestinal motility should be reserved for patients with symptoms correlated to motor alterations that greatly influence the quality of life, nutrition and productivity, as they are justified only if a result can be expected that influences the clinical management of the patient [36].

Author details

Edda Battaglia*, Maria Luisa Niola, Valentina Boano, Chiara M.C. Elia, Carlo Sguazzini and Mario Grassini
Physiopathology and Manometry Section, Gastroenterology and Endoscopy Unit, Cardinal Massaia Hospital, ASL AT, Asti, Italy

*Address all correspondence to: edda.battaglia@gmail.com

References

[1] Drossman DA. Functional gastrointestinal Disorders: History, Pathophysiology, Clinical Features, and Rome IV. Gastroenterology. 2016; 150:1262-79.

[2] Ang D, Fock KM, Law NM, Ang TL. Current status of functional gastrointestinal evaluation in clinical practice. Singapore Med J. 2015 Feb; 56(2):69-79; quiz 80. doi: 10.11622/smedj.2015021. Erratum in: Singapore Med J. 2015 Mar; 56(3):179.

[3] Savarino E, de Bortoli N, Bellini M, Galeazzi F, Ribolsi M, Salvador R et al. Practice guidelines on the use of esophageal manometry – A GISMAD-SIGE-AIGO medical position statement. Dig Liver Dis. 2016; 48(10):1124-35.

[4] Baldwin D, Puckett Y. Esophageal Manometry. [Updated 2020 Jun 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559237/

[5] Yadlapati R. High-resolution esophageal manometry: interpretation in clinical practice. Curr Opin Gastroenterol. 2017; 33(4):301-9.

[6] Gyawali CP, Kahrilas PJ, Savarino E, Zerbib F, Mion F, Smout A et al. Modern diagnosis of GERD: the Lyon Consensus. Gut. 2018; 67:1351-62.

[7] Kahrilas PJ, Bredenoord AJ, Fox M, Gyawali CP, Roman S, Smout AJ et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil. 2015; 27(2):160-74.

[8] Rohof WO, Bredenoord AJ. Chicago Classification of Esophageal Motility Disorders: Lessons Learned. Curr Gastroenterol Rep. 2017; 19(8):37.

[9] Cho YK. How to Interpret Esophageal Impedance pH Monitoring. J Neurogastroenterol Motil. 2010; 16(3):327-30.

[10] Savarino E, Frazzoni M, Marabotto E, Zentilin P, Iovino P, Costantini M et al. A SIGE- SINGEM-AIGO technical review on the clinical use of esophageal reflux monitoring. Dig Liver Dis. 2020; 52(9):966-80.

[11] Gyawali CP, Kahrilas PJ, Savarino E, Zerbib F, Mion F, Smout A et al. Modern diagnosis of GERD: the Lyon Consensus. Gut. 2018; 67:1351-62.

[12] Zentilin P, Iiritano E, Dulbecco P, Bilardi C, Savarino E, De Conca S et al. Normal values of 24-h ambulatory intraluminal impedance combined with pH-metry in subjects eating a Mediterranean diet. Dig Liver Dis. 2006; 38(4):226-32.

[13] Frazzoni M, Savarino E, de Bortoli N, Martinucci I, Furnari M, Frazzoni L et al. Analyses of the Post-reflux Swallow-induced Peristaltic Wave Index and Nocturnal Baseline Impedance Parameters Increase the Diagnostic Yield of Impedance-pH Monitoring of Patients with Reflux Disease. Clin Gastroenterol Hepatol. 2016; 14(1):40-46.

[14] Frazzoni M, de Bortoli N, Frazzoni L, Furnari M, Martinucci I, Tolone S et al. Impairment of chemical clearance and mucosal integrity distinguishes hypersensitive esophagus from functional heartburn. J Gastroenterol. 2017; 52(4):444-51.

[15] Amiriani T, Javadi H, Raiatnavaz T, Pashazadeh AM, Semnani S, Tabib SM, Assadi M. Assessment of Gastric Accommodation in Patients with Functional Dyspepsia by 99mTc-Pertechtenate Single Photon Emission Computed Tomography Imaging: Practical but not Widely Accepted. Mol Imaging Radionucl Ther. 2015 Oct 5;24(3):105-9.

[16] Azpiroz F, Malagelada JR. Gastric tone measured by an electronic barostat in health and postsurgical gastroparesis. Gastroenterology. 1987; 92:934-43.

[17] Schwizer W, Steingötter A, Fox M, et al. Non-invasive measurement of gastric accommodation in humans. Gut 2002;51: i59-i62.

[18] Kim DY, Camilleri M. Noninvasive measurement of gastric accommodation by SPECT. Korean J Intern Med. 2002 Mar; 17(1):1-6.

[19] Farrell MB. Gastric Emptying Scintigraphy. J Nucl Med Technol. 2019; 47(2):111-19;

[20] Abell TL, Camilleri M, Donohoe K, Hasler WL, Lin HC, Maurer AH et al. American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. Am J Gastroenterol. 2008 Mar;103(3):753-63.

[21] Kuo B, McCallum RW, Koch KL, Sitrin MD, Wo JM, Chey WD et al. Comparison of gastric emptying of a nondigestible capsule to a radio-labelled meal in healthy and gastroparetic subjects. Aliment Pharmacol Ther. 2008;27(2):186-96.

[22] Saps M, Di Lorenzo C. 29 - Gastric Motility Disorders, In: Wyllie R, Hyams JS (editors). Pediatric Gastrointestinal and Liver Disease (Fourth Edition). WB Saunders. 2011; p. 309-318.e4.

[23] Bharucha AE, Camilleri M, Veil E, Burton D, Zinsmeister AR. Comprehensive assessment of gastric emptying with a stable isotope breath test. Neurogastroenterol Motil. 2013; 25(1): e60-e69.

[24] Szarka LA, Camilleri M, Vella A, Burton D, Baxter K, Simonson J et al. A stable isotope breath test with a standard meal for abnormal gastric emptying of solids in the clinic and in research. Clin Gastroenterol Hepatol. 2008; 6(6):635-43.e1.

[25] Yin J, Chen JD. Electrogastrography: methodology, validation and applications. J Neurogastroenterol Motil. 2013; 19(1):5-17.

[26] Chen CL, Hu CT, Lin HH, Yi CH. Clinical utility of electrogastrography and the water load test in patients with upper gastrointestinal symptoms. J Smooth Muscle Res. 2006; 42(5):149-57.

[27] Battaglia E, Grassini M, Navino M, Niola P, Verna C et al. Water load test before and after PPI therapy in patients with gastro-oesophageal reflux disease. Dig Liver Dis. 2007; 39(12):1052-56.

[28] Sarnelli G, Vandenberghe J, Tack J. Visceral hypersensitivity in functional disorders of the upper gastrointestinal tract. Dig Liver Dis. 2004; 36:371-6.

[29] Chen CL, Lin HH, Chen MC, Huang LC. Dyspeptic symptoms and water load test in patients with functional dyspepsia and reflux disease. Scand J Gastroenterol. 2005; 40(1):28-32.

[30] Parkman HP, Fisher RS. Contributing role of motility abnormalities in the pathogenesis of gastroesophageal reflux disease. Dig Dis 1997;15(Suppl. 1):40-52.

[31] Zerbib F, des Varannes SB, Ropert A, Lamouliatte H, Quinton A, Galmiche JP. Proximal gastric tone in gastro-oesophageal reflux disease. Eur J Gastroenterol Hepatol 1999;11:511-5.

[32] Schwizer W, Maecke H, Fried M. Measurement of gastric emptying by magnetic resonance imaging in humans. Gastroenterology. 1992;103(2):369-76.

[33] Kim DY, Camilleri M. Noninvasive measurement of gastric accommodation

by SPECT. Korean J Intern Med. 2002 Mar;17(1):1-6.

[34] Hong SP. Assessment of Gastric Accommodation by SPECT. J Neurogastroenterol Motil. 2010 Oct;16(4):347-9. Epub 2010 Oct 30.

[35] Bouras EP, Delgado-Aros S, Camilleri M et al. SPECT imaging of the stomach: comparison with barostat, and effects of sex, age, body mass index, and fundoplication. Gut 2002; 51:781-6.

[36] Battaglia E, Boano V, Sguazzini CE, Elia CM, Grassini M. Gastrointestinal physiopatological testing: what's new? Minerva Gastroenterol Dietol. 2020;6(1):1-3