Practice guidelines on the use of esophageal manometry - A GISMAD-SIGE-AIGO medical position statement

Practice Guidelines on The Use of Esophageal Manometry – A GISMAD-SIGE-AIGO Medical Position Statement

Edoardo Savarino MD, PhD [1], Nicola de Bortoli MD, PhD [2], Massimo Bellini MD[2], Francesca Galeazzi MD[1], Mentore Ribolsi MD[3], Renato Salvador MD[4], Vincenzo Savarino MD, PhD[5], Roberto Penagini MD[6]

[1] Gastrointestinal Unit, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy

[2] Gastrointestinal Unit, Department of Gastroenterology, University of Pisa, Pisa, Italy

[3] Unit of Digestive Disease, Campus Bio Medico University, Rome, Italy

[4] Clinica Chirurgica III, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy

[5] Gastrointestinal Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy

[6] Gastroenterology and Endoscopy Unit - Department of Pathophysiology and Transplantation, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico - University of Milan, Milan, Italy

Keywords: GERD; PPI; high resolution manometry, Impedance-pH, pH

Financial support: none

Potential competing interests: ES has served as consultant for Medtronic

Guarantor of the article: Edoardo Savarino, MD, PhD

Electronic Word Count (excluding abstract, ref, tables, figures): 7497

Corresponding Author:

Edoardo Savarino, MD, PhD

Gastroenterology Unit, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy

Phone: +39 3498217749

Email: edoardo.savarino@unipd.it

Abstract

Patients with esophageal symptoms potentially associated to esophageal motor disorders such as dysphagia, chest pain, heartburn and regurgitation, represent one of the most frequent reasons for referral to gastroenterological evaluation. The utility of esophageal manometry in clinical practice is: (1) to accurately define esophageal motor function, (2) to identify abnormal motor function, and (3) to establish a treatment plan based on motor abnormalities. With this in mind, in the last decade, investigations and technical advances, with the introduction of high-resolution esophageal manometry, have enhanced our understanding and management of esophageal motility disorders. The following recommendations were developed to assist physicians in the appropriate use of esophageal manometry in modern patient care. They were discussed and approved after a comprehensive review of the medical literature pertaining to manometric techniques and their recent application. This position statement created under the auspices of the Gruppo Italiano di Studio per la Motilità dell'Apparato Digerente (GISMAD), Società Italiana di Gastroenterologia ed Endoscopia Digestiva (SIGE) and Associazione Italiana Gastroenterologi Ospedalieri (AIGO) is intended to help clinicians in applying manometric studies in the most fruitful manner within the context of their patients with esophageal symptoms.

Esophageal Physiology

The pharynx and esophagus act synergistically to transport food, saliva and secretions from the mouth into the stomach.

The esophagus starts at the cricoid cartilage and ends at the diaphragmatic level, with a length of 20-25 cm. The upper esophageal sphincter (UES) is the proximal border of the esophagus and acts as a valve [1, 2]. Indeed, its main functions are avoiding air entering into the esophagus during breathing and preventing refluxing of food and saliva from the esophagus to the airways. It is innervated by the glossopharyngeal nerve, and branches of the vagus and sympathetic nerves and is located behind the cricoid cartilage. It is made up mainly of cricopharyngeus and thyropharyngeus muscles and is manometrically identifiable as a 3-4 cm high pressure zone. UES pressure, mainly oriented toward the anterior-posterior direction, decreases during sleep and anesthesia and with ageing, whereas it increases during inspiration and phonation, psychological stress and anxiety. A swallow-induced UES relaxation takes 0.3-0.5 s, depending on the bolus volume [1]. The esophageal wall is made up of mucosa, submucosa and muscularis propria. The presence of skeletal muscle characterizes the upper portion, whereas the presence of smooth muscle is typical of the lower part, with a mixture of striated and smooth muscle in the middle portion ("transition zone"). Topographically, the esophagus can be divided into: a) Cervical: from UES to the suprasternal notch (4-5 cm long); b) Thoracic: from suprasternal notch to the diaphragmatic hiatus; c) Abdominal: from diaphragmatic hiatus to the cardia of the stomach (1 cm long). The lower esophageal sphincter (LES) is the distal border of the esophagus: it is made up of a thickened longitudinal and a circular muscle layer; the thickness increases or decreases with increase or decrease in LES pressure [3]. Clasp and sling fibers characterize the LES muscles: the former, mainly innervated by inhibitory neurons, maintain myogenic tone, whereas the sling fibers, mainly innervated by excitatory neurons, respond quickly to cholinergic agonists [1, 4]. The LES passes from the chest into the abdomen through the crural diaphragm (CD), thus allowing continuity with

the stomach. The CD, innervated by phrenic nerves, is made up of medial fibers located in a circumferential way and lateral fibers oriented in an oblique direction and it is strongly anchored to the LES by the phreno-esophageal ligament [5]. The intrinsic nervous system is made up of the myenteric plexus, with excitatory neurons containing acetylcholine (Ach) and substance P and inhibitory neurons containing nitric oxide (NO) synthase and vasointestinal active peptide (VIP), and Meissner's plexus. Interstitial cells of Cajal (ICCs) are also present and play a major role in neuromuscular transmission [1]. Extrinsic esophageal innervation is provided by both parasympathetic and sympathetic nerves**.** The vagus nerve, whose cell bodies are located in the dorsal motor nucleus (DMN) of the vagus and nucleus ambiguous in the brain stem, is the main motor nerve of the esophagus (muscles and secreto-motor innervation of the glands). Smooth muscle is provided by two different type of fibers originating from different types of DMN neurons: short latency fibers synapsing with myenteric inhibitory neurons and long latency fibers synapsing with myenteric cholinergic excitatory neurons. It also carries mechano-sensory (chemical, mechanical, thermal) information from the esophageal wall [6]. The sympathetic nerve supply comes from the intermedio-lateral cell columns of the T1-T10 spine and modulates contraction of blood vessels, esophageal sphincter tone, relaxation of the muscular wall and also glandular functions.

Swallow events are regulated and coordinated by the swallow pattern generators (SPG), neuronal networks localized in the brain stem (nucleus tractus solitaries, nucleus ambiguous and DMN of the vagus) which are also involved in controlling respiration and in cardiovascular reflexes. SPG are voluntarily activated (primary peristalsis), but they can also be involuntarily elicited in a reflex way (e.g. in secondary peristalsis) [7]. After food is mixed with saliva and reduced to a bolus, the contraction of the tongue against the palate pushes it toward the pharynx (oral phase), then the elevation of the soft palate closes the nasopharynx, preventing nasal regurgitation, and the contraction of the suprahyoid muscle closes the laryngeal inlet, providing a

further protective mechanism for the airways. In the meantime, the UES relaxes and pharyngeal peristalsis takes about one second to push the bolus toward the esophagus (pharyngeal phase) [1].

Esophageal peristalsis is regulated via the parasympathetic pathway by the vagus nerve and the intrinsic enteric nervous system. In particular, the UES and proximal striated esophageal muscle activity is modulated by a sequential excitation of lower motor neurons of the nucleus ambiguous, whereas peristalsis of smooth muscle is controlled by central and peripheral mechanisms. The central mechanisms imply the coordinated activity of both short- and long-latency vagal fibers. Indeed, swallow firstly activates the short latency nitrergic inhibitory fibers, which inhibit the esophagus motor activity. Subsequently, there is an activation of cholinergic excitatory neurons [8]. This mechanism prevents another peristaltic wave taking place if a second swallow starts within 10 seconds, enabling a coordinated and efficient motor activity [9, 10]. The direction, the amplitude and the speed of propagation are regulated by regional differences in the density of the inhibitory and excitatory neurons of the myenteric plexus. Indeed, inhibitory activity increases in the distal portion of the esophagus, thus delaying the onset of contraction and allowing propagation to move in a cranio-caudal direction [11-13]. Deglutitive inhibition is clearly shown by the "multiple rapid swallowing" test performed during manometry: esophageal body and LES remain relaxed and only after the last swallow can a peristaltic wave start [14]. Peristalsis is characterized by the coordinated contraction (behind the bolus) and relaxation (in front of the bolus) of the circular and longitudinal muscle layers: longitudinal muscle contraction foregoes the circular muscle contraction and lasts more than the circular contraction by 2-4 seconds. The contraction of circular muscle in a sequential manner causes bolus progression (primary peristalsis) whereas the contraction and the relaxation of longitudinal muscle provokes shortening and lengthening of the esophagus, respectively [15]. A normal peristaltic wave lasts from 6 to 10 seconds; wet swallows induce higher amplitude contractions with a lower speed of peristalsis than the dry ones, whereas a warm bolus increases and a cold one decreases the amplitude of contractions. Secondary peristalsis has been observed in the presence of a retained bolus in the esophagus or in case of distension. The latter is possibly

associated with gastroesophageal reflux, which induces a local reflex independent of the vagal input from the DMN: in these cases contraction waves begin immediately above the bolus (or the reflux content) and proceed toward the distal esophagus without any involvement of the proximal portion of the viscous [16].

The esophagogastric junction (EGJ) is an antireflux barrier allowing the passage of esophageal contents into the stomach and is made up of the LES and crural diaphragm. The LES is controlled by autonomic nerves and the myenteric plexus and has its own myogenic tone regulated by hormonal, paracrine and neural factors. As a consequence, LES pressure is modulated by many hormones and paracrine substances (VIP, CCK, CGRP, dopamine, GIP, galanin, gastrin, serotonin, sexual hormones, substance P, glucagon, NO, etc.) [1, 7]. The crural diaphragm is a ventilator muscle, which has also a "sphincter–like" action. Indeed, separation of the LES from the crural diaphragm, as observed in hiatus hernia, can reduce the efficacy of antireflux barrier. Moreover, EGJ pressure increase during inspiration is due to crural diaphragm contraction and is related to the depth of inspiration. Abdominal compression, straight leg raise or Valsalva maneuver induce crural diaphragm contraction, which provides the necessary increase of EGJ pressure to avoid gastroesophageal reflux. The same happens with inspiration, during which there is an increase in negative intra-esophageal pressure and in gastric positive pressure [1, 5]. Normal resting LES pressure ranges from 10 to 30 mm Hg. Physiological LES relaxation starts immediately after the onset of swallow, lasting about 6 seconds, which is the time that a peristaltic wave takes to pass through the esophagus. After the peristaltic wave ends, the LES closes with a "rebound" pressure increase (pressure levels higher than basal levels) lasting 5-10 seconds [1]. During breathing and swallow-induced relaxation, the LES and crural diaphragm move together, but they can separate from each other during peristalsis and transient lower esophageal sphincter relaxation (TLESR) [1], which is a spontaneous relaxation of the esophagus. It was first observed in GERD and subsequently described also during belching, regurgitation, rumination and vomiting, even if it can also occur in normal subjects in coincidence with a "physiological reflux". TLESR is a vagal reflex

elicited by gastric distension and/or pharyngeal stimulation, but not by swallowing. It is accompanied by relaxation of the crural diaphragm together with an inhibition of the body of the esophagus. It generally lasts more than a normal swallow induced relaxation (>10 seconds) [5, 7, 17].

Manometric Assemblies, Standard Procedure, Adjunctive Tests and Classifications of Esophageal Motility Disorders

The esophageal motor function can be assessed by a variety of recording techniques including radiology, scintigraphy, manometry, and most recently intraluminal electrical impedance monitoring. Esophageal manometry is considered the "gold-standard" for the assessment of motor disorders and may be summarized in 3 domains: a) to accurately define esophageal motor function, b) to define abnormal motor function, and c) to delineate a treatment plan based on motor abnormalities.

MANOMETRIC ASSEMBLIES

Water perfused system. Water-perfused esophageal manometry catheters typically are configured with 3-8 pressure-sensing side-holes, which usually are spaced at 5 cm intervals on catheters with 3-4 sensors. The recorded pressure rises when the flow of water through the side-hole of a tube is impeded by circumferential contraction of the wall of the esophagus. A low- compliance pneumo-hydraulic pump is used to slowly perfuse the tubes with bubble-free water [18]. Upper and lower esophageal sphincters are detected with a manual pull-through technique unless a sleeve device is used (generally for the lower esophageal sphincter) enabling to keep the catheter in the same position for assessment of both esophageal body and sphincter motility [19]. The major disadvantage of the above systems is that the equipment is precarious and requires continuing maintenance. Further, it may be difficult to reliably record the motor function of the esophageal sphincters with manometric catheters using water-perfused side-holes as sensor-like points a few cm apart. By increasing the number of channels and having closely spaced side holes it is possible to perform water perfused high resolution manometry [20].

High-resolution solid-state manometry. An alternative to perfused manometric systems is an assembly incorporating miniature strain gauge sensors and solid-state electronic components.

The micro-transducers directly interface with the recorder, and the resultant system has a vastly expanded frequency response suitable for pharyngeal recording. Solid state is now considered as cheap as perfused systems, requires less maintenance and is generally used for esophageal high-resolution manometry (HRM) [21], although in emerging economies and in the Asian Pacific Region the majority of systems are still water perfused. This technique is characterized by an increased number of pressure sensors (up to 36 sensors) spaced closely. HRM has some advantages in clinical practice: in contrast to conventional manometry the pull-through for detecting sphincters is not required and shifts of position do not affect the reliability and reproducibility of pressure recordings. Moreover, in order to better visualize the data, it has been incorporated a process of interpolation between sensors to display the information in the form of seamless isobaric color regions on esophageal pressure topography plots (EPT) [21], which represent esophageal motility and sphincter functions on color-coded, pressure-space-time plots. The main disadvantage is that the equipment cannot be introduced and moved using an endoscopic-positioned wire in patients with diverticula or difficult EGJ (i.e. large hiatal hernia or spasm).

Impedance manometry. The combined measurement of impedance and pressure in the esophagus evaluates esophageal motility and bolus transport patterns. Impedance adds some aspects of bolus transport as clearing velocity, correlation between LES relaxation and bolus transit, esophageal bolus retention (when hypokinetic peristaltic defects are present). Using combined impedance–manometry additional data about esophageal motor function and associated bolus transport can be obtained during a single investigation without the use of radiation [22] Savarino et al showed a correlation between esophageal motor abnormalities and bolus transit defects in different subcategory of GERD patients [23]. Moreover, Pohl D et al proposed a bolus velocity cut-off in diagnosing patients with esophageal spasm and abnormal bolus transit [24].

STANDARD MANOMETRIC PROTOCOL AND ADJUNCTIVE TESTS DURING MANOMETRY

Before starting each study of esophageal manometry, the equipment should be checked and calibrated. Patients should fast for a minimum of six hours for solids and two hours for liquids prior to the procedure. Also, the use of drugs potentially influencing esophageal motility should be carefully evaluated and if possible discontinued since at least three days prior to testing (i.e. domperidon or erythromycin). Esophageal manometry should evaluate the upper and lower esophageal sphincter and the peristaltic contraction of esophageal body. A standardized protocol is internationally recognized for performing esophageal manometry (both standard and high resolution), as illustrated in **Table 1**.

Further, several authors have suggested that increasing esophageal workload (i.e. applying a 'physiologic challenge') in manometry protocols would increase the sensitivity of the investigation [25]. The use of multiple rapid swallows (MRS) represents the simplest provocative maneuver. Two different MRS tests have been proposed, a low volume one, consisting in the administration of five swallows (2 ml of water per swallow) in rapid sequence (less than 10 sec) and a high volume one (also named free drinking test), consisting in free rapid drinking of 200 ml of water. Indeed, when multiple swallows are rapidly administered, esophageal peristalsis is deeply inhibited, and pronounced LES relaxation ensues. After the last swallow of the series, a robust esophageal contraction is expected [26], the so-called "peristaltic reserve". Abnormal responses consist of incomplete inhibition (when contraction fragments are seen during the period of expected inhibition), or suboptimal contraction (when the post-MRS sequence fails to demonstrate augmentation of smooth muscle contraction) [26, 27]. Use of both low and high volume MRS in the same patient has shown that the former evaluates the peristaltic reserve, the latter is more valuable in identifying increased resistance to outflow, whereas both evaluate motor inhibition [28] The International High Resolution Manometry Working Group has acknowledged usefulness of low volume MRS in assessing peristaltic reserve in ineffective esophageal motility (IEM) [29].

Recently, Martinucci and co-workers showed an inverse correlation between low volume MRS response and acid exposure time in patients with negative endoscopy heartburn [30].

Other authors have proposed challenging esophageal function by introducing viscous solutions (e.g., apple sauce), solid bolus (e.g., marshmallow, cubed bread), or a test meal into the protocol [31-33]. For instance, Wang et al. [34] evaluated and standardized a high volume water test, multiple water swallow (MWS), performed with 200 mL of water and a solid test meal, which seemed to increase the diagnostic yield of HRM studies in patients with symptoms after fundoplication and to identify additional patients with outlet obstruction who may benefit from endoscopic dilatation. However, these tests need to be better standardized, because they seem to be more useful for provoking symptom events than detecting abnormal esophageal motor patterns.

To summarize, for the time being we suggest to incorporate both low volume and high volume MRS in all standard manometric studies unless a major motility disorder has been diagnosed using single water swallows

CLASSIFICATION OF ESOPHAGEAL MOTILITY DISODERS

Standard manometry. The first classification of esophageal motility abnormalities was suggested by Spechler and Castell in 2001 [35] and was based on abnormalities of the LES (both resting pressure and relaxation) and esophageal peristalsis, as shown in **Table 2**. The processes that affect the inhibitory innervation of the LES can cause inadequate sphincter relaxation. The abnormalities of esophageal wave propagation affecting the body of the esophagus were classified as uncoordinated contraction, hypercontraction and hypocontraction [35]. The basal LES pressure is considered normal in the range between 10-45 mmHg. The LES relaxation is considered normal when the LES residual pressure is lower than 8 mmHg. The distal wave amplitude is considered normal when the average value of 10 swallows (at two recording sites positioned 3 and 8 cm above the LES) ranges between 30 and 180 mmHg. In case of wave amplitude < 30 mmHg we have an ineffective peristalsis, whereas in case of wave amplitude >180 mmHg we have a nutcracker

esophagus. Further, in case of simultaneous contraction in more than 1 swallow we have a diffuse esophageal spasm. This classification is simple; however, even for experienced physiologists in tertiary centers, inter-observer agreement in the interpretation of manometric measurements is poor [36].

HRM and the Chicago Classification. The enhanced pressure resolution and the objective metrics of esophageal function are immediately available with HRM/EPT and can be applied to classify individual swallows and generate an esophageal motility diagnosis.

Esophagogastric junction (EGJ). Two different constituents compose the EGJ: the lower esophageal sphincter (LES) and the crural diaphragm (CD) [37]. The EGJ morphology is simply classified into three types: *type I*, there is a complete overlap of CD and LES with no spatial separation evident on the Clouse plot; *type II*, LES and CD are partially separated (double-peaked spatial pressure variation plot), but the nadir pressure between the two peaks does not decline to gastric pressure; *type III*, in which LES and CD are clearly separated as shown by a double peaked spatial pressure variation plot and the nadir pressure between the peaks equal to or less than gastric pressure [29]. Different EGJ characteristics (type, resting pressure, contractile integral) were recently correlated with GERD [38-40]. During swallowing, EGJ relaxation is evaluated using the integrated relaxation pressure (IRP). This is defined as the mean of the 4s (contiguous or non-contiguous) of maximal deglutitive relaxation in the 10s window beginning at deglutitive UES relaxation. The 4-s IRP using a cutoff of 15 mmHg performs optimally with 98% sensitivity and 96% specificity in the detection of achalasia [41].

EPT metrics to score individual swallows. The main HRM deglutitive peristaltic metrics used to evaluate esophageal contractile function are the distal contractile integral (DCI) and the distal latency (DL). The DCI represents the contractile vigor of the esophageal contraction. It was introduced with the Chicago Classification (CC) and represents the amplitude x duration x length (mmHg-s-cm) of the distal esophagus contraction with an isobaric contour of 20 mmHg from proximal to distal pressure troughs. The DL represents the interval between UES relaxation and the

inflection point along the 30 mmHg isobaric contour where propagation velocity slows demarcating the tubular esophagus from the frenic ampulla (contractile deceleration point, CDP). The DL represents an indirect measurement of deglutitive inhibition and thus of normal peristalsis and a value lower than 4.5 s defines a premature contraction. The characteristics of peristaltic wave (contraction vigor and contraction pattern) are reported in **Table 3**.

A classification scheme was initially proposed based on the analysis of clinical studies performed at Northwestern University and subsequently named the Chicago Classification of esophageal motility disorders [29].

Disorders with EGJ outflow obstruction. Disorders of the EGJ outflow are subdivided into achalasia subtypes and EGJ outflow obstruction. Three clinically relevant subtypes of achalasia have been defined in the CC [29, 42]: *type I achalasia* is characterized by 100% failed contractions and no esophageal pressurization*; type II achalasia* is defined as 100% failed contraction and panesophageal pressurization for at least 20% of swallows; and *type III achalasia* is defined as the presence of preserved fragments of distal peristalsis or premature contractions for at least 20% of the swallows [29] The CC improves our ability to diagnose and treat patients with achalasia. The CC (v 3.0) suggests to evaluate EGJ relaxation by means of the median instead of the mean value of IRP assessed with 10 swallows in order to minimize the effect of occasional outliers [43]. A different condition characterized by an impaired EGJ relaxation is defined EGJ outflow obstruction (EGJ-OO). The EGJ-OO exhibits not only an IRP greater than 15 mmHg, but also a preserved peristalsis and elevated intra-bolus pressure above the EGJ during peristalsis [44].

Major motility disorders. Major motility disorders are defined as patterns of motor function that are not encountered in controls in the context of normal EGJ relaxation. *Aperistalsis*: (absent peristalsis) is defined by the combination of a normal IRP and 100% failed contractions (DCI <100 mmHg-s-cm) [35]. Type I achalasia should be considered in cases of borderline IRP [44]. *Distal esophageal spasm (DES)*: it should be considered when 20% or more esophageal contractions result to be premature with a DL value lower than 4.5s in a context of normal EGJ relaxation [45].

Hypercontractile disorders (Jackhammer esophagus): it is defined as the occurrence of >20% of swallows with a DCI >8000 mmHg-s-cm and normal latency. When the hypercontractility can involve the LES or even might be restricted to the LES, it is necessary to expand the DCI measurement to the EGJ [29, 46].

Minor motility disorders. The clinical significance of minor motility disorders continues to be debated. *Ineffective esophageal motility (IEM)*: it is defined as ≥ 50% ineffective swallows based on a DCI < 450 mmHg-s-cm. No distinction needs to be made between failed swallows and weak swallows. *Fragmented peristalsis*: it is defined as ≥ 50% fragmented contractions (large breaks >5 cm in the 20-mmHg isobaric contour) with the added stipulation of not meeting IEM criteria [29, 47].

Different Equipment-based Normal Values. Currently, several different HRM systems are commercially available and in addition new types of catheters are being developed as the clinical importance of esophageal manometry grows. HRM is actually worldwide diffuse, and whereas in the United States and Europe an almost exclusive use of the 36-channel solid-state catheter exists, in emerging economies and the Asian Pacific region the majority of systems are water perfused.

Normative thresholds have been collected in different studies by means of the available HRM systems. These different thresholds seem to be influenced by demographic factors, catheter diameter, body position during testing, consistency of bolus swallows, and esophageal length. Thus it would be ideal to have different sets of normal values for each of these factors, yet at the moment the amount of normative data is limited. In **Table 4** the most important studies and the different thresholds for each HRM system are reported [31, 48-57].

Finally, a recent European multicenter study reported the normal values of esophageal motility after anti-reflux surgery in patients who did not develop dysphagia [58]. HRM metrics after Toupet fundoplication were found similar to normal values derived from healthy subjects used for CC. However, after Nissen fundoplication a higher EGJ resting pressure and higher IRP were

observed in asymptomatic subjects suggesting that this could be considered normal in the postoperative setting [58]. The results from this study are reported in **Table 5**.

Clinical Indications for Esophageal Manometry

Manometry is an excellent tool to define the integrity of peristalsis and EGJ function. In fact, it permits to detect functional abnormalities potentially related to esophageal symptoms: absent or weak peristalsis, hypercontractile peristalsis, abnormalities of EGJ pressure (i.e. defective or hypercontractile LES), and impaired EGJ relaxation (i.e. achalasia, outflow obstruction). However, it must be stressed that, at present, the relationship between these abnormalities and esophageal symptoms is unclear, so that it will remain the object of research in the next years, particularly with the wide application of HRM with or without impedance. In **Table 6**, the recommendations for the clinical indications for the use of esophageal manometry have been summarized.

GASTRO-ESOPHAGEAL REFLUX DISEASE AND RUMINATION SYNDROME

Diagnosis of GERD. GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications [59]. Esophageal manometry is of limited value in the primary diagnosis of GERD. Several investigations carried out with conventional manometry have demonstrated that a decreased basal LES pressure, low contraction wave amplitude and a hiatal hernia were more prevalent in patients with GERD than in controls [60, 61]. Further, these findings well correlated with the increasing severity of esophageal mucosal injuries, being high-grade esophagitis or long-segment Barrett's esophagus the conditions with the lowest values of both basal LES pressure and wave amplitude and the highest frequency of HH [62-66]. However, these features had shown limited sensitivity and specificity [67] Similar findings were observed with HRM, which offers the advantage of clearly defining the two components of the EGJ, the LES and the CD, and better characterizing the esophageal body peristalsis [38, 39, 68, 69]. Decreased values of EGJ pressure, increased frequency of HH (clear separation between LES and CD) and higher prevalence of peristalsis breaks were more common in patients with GERD

compared to healthy volunteers and subjects with functional heartburn [23, 40, 60, 70-73], but again the predictive value of these findings is low, and therefore manometry, either conventional or HRM, cannot be used to make a diagnosis of GERD [47, 67]. The reason for this limited diagnostic value is likely due to the presence of other potential mechanisms involved in GERD pathophysiology, including hypersensitivity of esophageal mucosa and TLESRs [74-78]. With regard to TLESRs, HRM has shown an increased capability in detecting them, but confirmed that it is not the absolute number of TLESRs but, rather, the proportion of TLESRs associated with both acid and non-acid reflux that differentiates patients with GERD from controls, further highlighting the limited diagnostic value of manometric features for GERD [74, 79, 80].

Manometry should be used to aid the placement of transnasal pH or pH-impedance probes for reflux testing. Conventionally, catheters for performing reflux monitoring should be positioned 5 cm above the proximal margin of the LES. Different methodologies have been proposed, including pH electrode withdrawal (detection of pH increase as a measure of passage from the stomach to the esophagus), endoscopy, fluoroscopy, calculation according to subject height, or manometry. Of these methods, the manometric definition of LES borders remains the most accurate one [81, 82], except in the very young pediatric population, in which antropometric measure well correlated with esophageal length [83].

Anti-Reflux Surgery. Manometry is recommended before antireflux surgery in patients with typical GERD symptoms, primarily to rule out achalasia, severe hypomotility (scleroderma-like esophagus), non-reflux induced esophageal spasm or hypercontractile esophagus, conditions that would be contraindications to surgical fundoplication, but not to tailor the operation [84-87]. Indeed, some experts consider impaired peristalsis as a relative contraindication for anti-reflux surgery or for considering Toupet 270° instead of Nissen 360° fundoplication, because the former one has been associated with a lower risk of dysphagia after surgery [88]. However, to date, definite data on this controversial issue have not been published [67]. Ongoing research with the more sensitive techniques to assess bolus flow (impedance associated with either conventional or HRM)

and mechanical/functional defects (HRM) suggests that equally important considerations should be reserved to EGJ function, in terms of basal pressure and relaxation, and esophageal peristalsis [23].

Recently, the technique of using low volume MRS has been suggested as a useful and simple test to assess the presence of an adequate peristaltic reserve of the esophageal smooth muscle and therefore to predict dysphagia after surgery. In particular, Shaker et al. [89] showed that the strength of smooth muscle contraction augments almost twofold with MRS in normal controls and that lack of strong contraction is significantly more prevalent in GERD patients, who develop postoperative dysphagia [27]. This is a promising test for the surgeon in order to tailor his fundoplication in patients at risk for developing dysphagia. It has also been suggested that a free drinking test and especially a solid test meal in patients with post-fundoplication dysphagia help to identify symptomatic outlet obstruction in order to offer endoscopic dilatation to these patients [34]. However, further controlled data are needed before inclusion of these tests in clinical practice is recommended. On the other hand, there is no controversy on the fact that postoperative manometry combined with upper endoscopy or barium esophagogram is of value for the assessment of postoperative dysphagia, particularly when it persists for 4 weeks after surgery [67]. Indeed, they may reveal a migration or disruption of the wrap or abnormalities in terms of peristaltic function, LES pressure, and LES relaxation (i.e. wrap too tight).

Hiatal Hernia and Rumination Syndrome. Recent published data underlined the role of manometry, and in particular HRM, in the identification and sizing of HH and combined manometry-impedance for the diagnosis of Rumination Syndrome (RS) in patients with typical GERD symptoms who do not respond to PPI therapy. Thanks to the ability of HRM to assess LES and crural diaphragm position, it has been shown that a better definition of HH can be formulated, in comparison with endoscopy and barium esophagogram [38-40, 90]. Whether this improved HH detection will be useful for the clinical and surgical management of GERD patients will be evaluated in future studies, but certainly we have now a more efficient and sensitive method to define HH and to understand its role in GERD.

Rumination is a phenomenon characterized by retrograde flow of gastric contents into the mouth, otherwise known as regurgitation, due to an intragastric pressure increase [91]. Repetitive excessive occurrence of rumination is considered abnormal and is known as rumination syndrome. It occurs through 3 distinct mechanisms, thus classifying the syndrome into primary, secondary, and supragastric belch-associated rumination [91]. As symptoms of postprandial regurgitation are often mistaken for GERD or vomiting, the rumination syndrome is an underappreciated condition. Combined manometry-impedance can distinguish rumination from GERD. Moreover, treatment of the rumination syndrome consists of a thorough explanation of the mechanisms underlying the rumination episodes and behavioral therapy. Therefore, its clear identification and graphical representation is fundamental for its management.

DYSPHAGIA

Dysphagia is defined as a sensation of difficult bolus transit, and could be further subdivided into oropharyngeal dysphagia (difficulty in initiating a swallow) and esophageal dysphagia (sensation of bolus impaction along the esophagus). In case of dysphagia, an accurate medical history as well as the use of esophageal function testing are crucial. In the assessment of a patient with dysphagia, the priority is to exclude obstructive, organic causes, such as peptic or caustic strictures, infectious diseases and neoplastic lesions. To this purpose, the first step is usually upper endoscopy or barium esophagogram [67]. Furthermore, during upper endoscopy, esophageal biopsies should be performed in order to exclude eosinophilic esophagitis (EoE) [92]. A recent report described the occurrence of EoE in a patient with an achalasia pattern at manometry who well responded to steroids treatment both in terms of EoE and achalasia outcome [93]. [93]. Once organic causes of dysphagia have been excluded, esophageal manometry is the subsequent step to assess motility disorders that can be present in patients with dysphagia, although the relationship between these motor disorders and esophageal symptoms is in some cases not completely elucidated (i.e. DES and EGJ-OO) [94].

Achalasia. Of the esophageal motility disorders, achalasia is actually the most well-established disorder, causing dysphagia due to the poor or absent bolus transit at EGJ level as shown by fluoroscopy or scintigraphy. Pathologically, achalasia is attributable to destruction of the inhibitory ganglionic neurons in the smooth muscle esophagus and this leads to incomplete or absent LES relaxation and aperistalsis [42]. Indeed, according to conventional manometry, achalasia is based on the presence of incomplete relaxation of the LES (defined as a mean resting LES pressure > 8 mmHg above gastric pressure) and aperistalsis of the esophageal body (presence of simultaneous esophageal contractions or no esophageal contractions [35]. HRM allowed to refining the definition of both these criteria, greatly improving the accuracy in its diagnosis and inter-observer reproducibility [29, 42, 95] HRM is able to precisely evaluate LES residual pressure, CD contraction, or intrabolus pressure through the EGJ. The HRM parameter that encompasses

these features is IRP, which is measured within the deglutitive window of the LES, starting from the initiation of the swallow until the arrival of the peristaltic contraction, and represents the 4s period of lowest EGJ pressure during this time-window [41]. In addition to the presence of impaired LES relaxation, HRM allowed to identify three subtypes of achalasia [29]. Consequently, achalasia has been defined in presence of elevated median IRP (>15 mmHg) with 100% failed peristalsis (Type I, classic achalasia) or with 100% failed peristalsis and panesophageal pressurization with ≥20% of swallows (Type II, achalasia with esophageal compression) or with no normal peristalsis, premature contractions with ≥20% of swallows (Type III, spastic achalasia) [29]. An important consideration is that the cutoff for the upper limit of normal is technology-specific, ranging from a low value of 15 mmHg for the Sierra design transducers to as high as 28 mmHg for the Unisensor design [20]. A second caveat is that achalasia may be present also in case of an IRP or LES residual pressure within the normal values [43], emphasizing that the diagnosis of achalasia always requires a detailed anamnesis and a multi-diagnostic meaningful approach, including manometry, upper endoscopy and radiology. As to the clinical usefulness of identifying different manometric subtypes, it has been demonstrated that type II achalasia were significantly more likely to respond to any therapy, followed by type I and type III [95]. Recently, it has been reported that a higher percentage of patients with type II achalasia are treated successfully with pneumatic dilation or laparoscopic Heller myotomy than patients with types I and III achalasia. Success rates in type II are high for both treatments, but significantly higher in the pneumatic dilation group, whilst patients with type III can probably be best treated by laparoscopic Heller myotomy or peroral endoscopic myotomy (POEM) [96]. Recently, short-term outcome data after POEM have been published [97]. POEM is a recently developed achalasia treatment method, which combines the efficacy of surgical myotomy with the benefits of endoscopic procedures [98]. The first report of over 100 cases of patients with achalasia treated with POEM were extremely good and independent of age, type of achalasia, and previous treatment method [97]. Further, data from prospective single or multicenter studies have been published confirming the potential positive outcome of this

endoscopic approach in all types of manometry-detected achalasia [99, 100]. However, randomized clinical trials are mandatory before suggesting this approach outside the research setting. Finally, pseudoachalasia accounting for up to 5% of cases, should be always considered, particularly in patients older than 50 years [101].

EGJ outflow obstruction. EGJ-OO encompasses the group of dysphagia patients with impaired EGJ relaxation, but not meeting the criteria for achalasia because they demonstrate intact peristalsis [29]. Besides IRP value > 15mmHg and intact peristalsis, patients with EGJ outflow obstruction have often increased intra-bolus pressure above the EGJ, being the consequence of the impaired relaxation. The outflow obstruction could be sustained by a premature or incomplete expression of achalasia or by undetected mechanical causes, such as hiatus hernia or organic stenosis. Consequently, these patients should be handled carefully with further imaging studies, in order to exclude inflammatory or malignant etiologies. Once EGJ-OO has been confirmed, patients might reasonably benefit from the same approach of achalasia patients, but limited outcome data are available [102].

Distal esophageal spasm. DES represents a motility disorder often associated with dysphagia, whose diagnostic criteria have been changed from conventional manometry to HRM era. According to CC, DES is defined by normal median IRP with ≥ 20% premature contractions (distal latency < 4.5 seconds) [29]. The presence of relaxed LES is crucial to distinguish DES from type III achalasia. In case of dysphagia with manometric evidence of DES, treatment is recommended. Nitrates and calcium channel antagonists could be useful [103]. Sildenafil seems to be effective, as confirmed by improved manometric findings. Endoscopic treatment, like botulin injection or POEM, need to be further evaluated, given the paucity of available data [104, 105].

Hypercontractile esophagus. According to conventional manometry, the presence of nutcracker esophagus was defined by the presence of distal esophageal wave amplitude > 180mmHg with preserved LES function [35]. However, the clinical relevance of nutcracker esophagus has been challenged, since its presence may or may not be associated with dysphagia. It

has been reported that up to 97% of patients with nutcracker esophagus have normal bolus transit, assessed by multichannel impedance [106]. As to HRM, the latest version of CC has identified the hypercontractile esophagus (jackhammer) by the presence of at least two swallows with DCI > 8000 mmHg/s/cm with normal LES relaxation. The cut-off of 8000 mmHg/s/cm is a value never observed in normal subjects and is highly associated with dysphagia. The clinical value of this modified manometric entity has to be fully elucidated as well as its management, although preliminary data on the use of botulin toxin injection during upper endoscopy in patients with hypercontractile esophagus and dysphagia seem to corroborate the relationship between this manometric abnormality and esophageal symptoms, and thus to suggest its treatment [104]. If patients with hypercontractile esophagus or DES have predominant chest pain, an empirical PPI trial should be done, because GERD may be associated and responsible for chest pain independently of motor abnormalities and no convincing effects of PPIs on esophageal motility have been shown [107, 108].

Hypomotility disorders. The definition of IEM has been used with conventional manometry to describe an esophageal motility pattern similar to that observed in scleroderma patients, and characterized by at least 30% of swallows with distal esophageal peristaltic amplitude < 30mmHg or failed/absent peristalsis. This definition, however, encompasses a large group of individuals with or without dysphagia [35]. HRM allows us to better assess the peristaltic vigor and integrity, leading to (perhaps) a better comprehension of esophageal hypomotility and its relationship with esophageal symptoms. Based on HRM studies, IEM is defined by ≥ 50% ineffective swallows (failed or weak swallows, i.e. DCI < 450 mmHg/s/cm), whereas fragmented peristalsis is defined by presence of ≥ 50% fragmented contractions [29]. The main dilemma of esophageal hypomotility is that not all patients with weak peristalsis display incomplete bolus transit and/or dysphagia. Furthermore, a major limitation in identifying this kind of minor motility abnormalities is the lack of an effective medical treatment to adopt. Indeed, treatment options as prokinetics, erythromycin or metoclopramide have been used, but their benefit is not definitely

established. A possible reason for the lack of effect of prokinetics is that esophageal peristalsis does not improve in part of the patients after their administration. Selection of patients with a peristaltic reserve using low volume MRS may improve outcome of prokinetic treatment, but this hypothesis needs to be tested. The future concomitant evaluation of motor activity (i.e. pressure) and bolus transit (i.e. impedance) with the use of HRM combined with impedance will be likely of help to clarify the relationship between hypomotility, bolus transit and dysphagia.

~~Gastro-Esophageal~~ Esophago-gastric Surgery. Manometry should be used to evaluate patients with a suboptimal response to achalasia treatment, either surgical or endoscopic, and should be always performed in association with a timed barium swallow to demonstrate poor esophageal emptying [42]. Indeed, surgical or pneumatic dilation or POEM failure may be due to an incomplete myotomy or inadequate disruption of the LES, scarring, functional obstruction by Dor fundoplication in case of surgery, para-esophageal hernia, or profound esophageal dilatation [109, 110]. Recent data also emphasize the need for a more complete diagnostic approach in patients who undergo bariatric surgery with restrictive operations, like gastric or mini-gastric bypass, because of the potential development of esophageal symptoms due to under-recognized or silent motility abnormalities [111-113].

NON CARDIAC CHEST-PAIN

Non cardiac chest pain (NCCP) is a troublesome condition of difficult diagnosis, with potentially underlying musculoskeletal, neuropathic, pulmonary, vascular and esophageal causes [114]. Chest pain of esophageal origin may be caused by GERD, motor abnormalities like achalasia or DES, or altered sensitivity. Among them, GERD is by far considered the most common cause of chest pain and chest pain is commonly reported among patients with typical reflux symptoms (37%) [115], NCCP patients frequently complain of heartburn and regurgitation (53-58%) [116] and a large proportion of them respond to PPI test [117, 118]. Thus, the role of esophageal manometry in the evaluation of NCCP is particularly challenging and has been matter of debate in the last 20 years.

Studies with conventional manometry have shown esophageal motor abnormalities in 30-70% of cases, probably depending on patient selection and hospital interest. In a center dedicated to motility disorders only 30% of patients showed motor disorders, the most common finding being nutcracker esophagus, observed in 14.4%, and non-specific esophageal disorders were described in 10.8% [119]. In a non-dedicated hospital the most common finding was hypotensive lower sphincter, probably reflecting the inclusion of GERD as a cause of chest pain [120]. Achalasia, DES, hypertensive LES were uncommon findings and this leaded to underscore the role of manometry in the diagnostic algorithm of NCCP.

Presence of heartburn/regurgitation or dysphagia may guide the physician toward the suspicion of GERD or major motility disorders, such ad achalasia or hypercontractile conditions. In contrast, when chest pain is an isolated symptom with episodic appearance, the causal relationship between symptom and manometric findings is difficult to demonstrate. Furthermore, the non-specific and often heterogeneous motor alterations found in patients with chest pain may only represent an epiphenomenon rather than the underlying mechanisms. The prolonged measurement

with 24-h esophageal manometry did not significantly improve the sensitivity in NCCP, being the correlation between symptom and motor abnormalities found only in 23-24% of patients [121].

The introduction of HRM with a topographic assessment of esophageal pressure leading to development of new parameters and the new classification of motor disorders with definition of specific entities - such as distal esophageal spasm and jackhammer esophagus [29] - may also allow to better investigate segmental abnormalities potentially related to acid exposure [122]. Furthermore, provocative tests, such as balloon distension, may still help in defining a condition of hypersensitivity in patients with functional chest pain [123].

In conclusion, in the absence of symptoms suggesting major motor disorders, the diagnostic yield of esophageal manometry is limited in NCCP. HRM defines new pathological entities, however data on the prevalence of these new entities in the NCCP population are still incomplete. Thus, HRM should ideally be performed in all patients with NCCP pain within large multicentric studies with uniform instruments and reference parameters.

However, keeping an eye on cost-effectiveness, data borrowed from conventional manometry in clinical practice suggest the following indications: a) if chest pain is suspected to be due to GERD and prolonged pH-monitoring is indicated, manometry is mandatory for establishing placement of intraluminal device; b) if chest pain is accompanied by dysphagia, manometry is strongly indicated after organic obstructions are ruled out; c) if chest pain is an isolated symptom, a trial with PPI can be performed prior to manometric study; d) manometry can be considered as first line procedure in the setting of large clinical and research studies.

SYSTEMIC DISEASES

Several systemic conditions affecting neuromuscular function are associated with altered gastro-intestinal motility, such as scleroderma and collagen diseases, diabetes, generalized motility disorders. One of the most characteristic manometric alterations is found in scleroderma patients with esophageal involvement [124, 125]. In these patients, reduced LES pressure with a severely impaired or absent contractile activity in the 2 distal thirds of the esophagus and preserved motility of the upper esophagus is typically found [126, 127]. Clinically, this often results in dysphagia and GERD along with its complications. More recent studies have demonstrated that patients with SSc and interstitial lung disease have reduced LES pressure and distal esophageal peristaltic activity and these manometric features have been associated with more severe reflux disease, potentially contributing to the pulmonary condition [128]. In localized scleroderma (i.e. systemic sclerosis and morphea), despite the presence of symptoms, conventional manometry did not show esophageal motility alterations in adults [129], while in a pediatric population of juvenile localized scleroderma, non-specific esophageal motor abnormalities were found in 1/3 of patients with antinuclear antibodies (ANA) positivity, even in absence of specific symptoms [130]. Esophageal motor alterations in SSc have been recently further characterized using HRM, confirming high prevalence of esophageal body dysmotility (67.3%), hypotensive EGJ in 55.1% of patients, with reduced amplitude contractions in middle esophagus; esophageal involvement was associated with Scl70 and absence of anticentromere anitbodies (ACA), esophageal symptoms were highly prevalent (87.5%), but not predictive of esophageal dismotility [131].

In Sjogren syndrome, dysphagia has been attributed not only to reduced salivary flow, but also to possible presence of dismotility: studies with conventional manometry have shown the presence of non-specific peristaltic alterations, reduced velocity as well as altered LES pressure. Furthermore, association with nutcracker esophagus and achalasia has also been reported [132].

Altered gastro-intestinal motility in diabetes is well known, involving particularly gastric motility with delayed emptying, especially in long lasting disease and in presence of complications.

In these patients esophageal motor alterations have also been observed, and recent studies using HRM have found impaired contractile inhibition during multiple swallowing and increased intra-bolus pressure, as possible consequence of gastroparesis or expression of neuropathy [133].

However, the above-mentioned motility abnormalities are neither sensitive nor specific for collagen vascular diseases and can be found in GERD patients without them. For this reason, a previous American Gastroenterological Association position statement omitted specific guidelines for the study of patients with collagen disease, limiting the use of esophageal manometry in symptomatic patients [134].

REGFERENCES

(1) Mittal R. Motor function of the pharynx, esophagus, and its sphincters. Granger DN and Granger JP. Morgan & Claypool Publishers Life Sciences 2011.

(2) Yazaki E, Sifrim D. Anatomy and physiology of the esophageal body. Dis Esophagus 2012;25:292-8.

(3) Liu J, Parashar VK, Mittal RK. Asymmetry of lower esophageal sphincter pressure: is it related to the muscle thickness or its shape? Am J Physiol 1997;272:G1509-17.

(4) Yuan S, Costa M, Brookes SJ. Neuronal pathways and transmission to the lower esophageal sphincter of the guinea Pig. Gastroenterology 1998;115:661-71.

(5) Fox M, Kahrilas P, Pandolfino JE, et al. Manual of high resolution esophageal manometry. 1st edition. UNI-MED, Bremen 2014.2014.

(6) M.J. B, D.C.E. B, W J, et al. Extrinsic sensory afferent nerves innervating the gastrointestinal tract. In: Elsevier AP-, editor. Physiology of the Gastrointestinal Tract - Fourth Edition2006.

(7) Goyal RK, Chaudhury A. Physiology of normal esophageal motility. J Clin Gastroenterol 2008;42:610-9.

(8) Gidda JS, Goyal RK. Regional gradient of initial inhibition and refractoriness in esophageal smooth muscle. Gastroenterology 1985;89:843-51.

(9) Vanek AW, Diamant NE. Responses of the human esophagus to paired swallows. Gastroenterology 1987;92:643-50.

(10) Ask P, Tibbling L. Effect of time interval between swallows on esophageal peristalsis. Am J Physiol 1980;238:G485-90.

(11) Lecea B, Gallego D, Farre R, et al. Origin and modulation of circular smooth muscle layer contractions in the porcine esophagus. Neurogastroenterol motil 2012;24:779-89, e355.

(12) Broad J, Hughes F, Chin-Aleong J, et al. Regionally dependent neuromuscular functions of motilin and 5-HT(4) receptors in human isolated esophageal body and gastric fundus. Neurogastroenterol motil 2014;26:1311-22.

(13) Muinuddin A, Xue S, Diamant NE. Regional differences in the response of feline esophageal smooth muscle to stretch and cholinergic stimulation. American J Physiol Gastrointest Liv Physiol 2001;281:G1460-7.

(14) Sifrim D, Janssens J, Vantrappen G. A wave of inhibition precedes primary peristaltic contractions in the human esophagus. Gastroenterology 1992;103:876-82.

(15) Mittal RK, Hong SJ, Bhargava V. Longitudinal muscle dysfunction in achalasia esophagus and its relevance. J Neurogastroenterol Motil 2013;19:126-36.

(16) Bardan E, Xie P, Aslam M, et al. Disruption of primary and secondary esophageal peristalsis by afferent stimulation. Am J Physiol Gastrointest Liv Physiol 2000;279:G255-61.

(17) Holloway RH, Boeckxstaens GE, Penagini R, et al. Objective definition and detection of transient lower esophageal sphincter relaxation revisited: is there room for improvement? Neurogastroenterol Motil 2012;24:54-60.

(18) Arndorfer RC, Stef JJ, Dodds WJ, et al. Improved infusion system for intraluminal esophageal manometry. Gastroenterology 1977;73:23-7.

(19) Dent J. A new technique for continuous sphincter pressure measurement. Gastroenterology 1976;71:263-7.

(20) Herregods TV, Roman S, Kahrilas PJ, et al. Normative values in esophageal high-resolution manometry. Neurogastroenterol Motil 2015;27:175-87.

(21) Clouse RE, Staiano A, Alrakawi A, et al. Application of topographical methods to clinical esophageal manometry. Am J Gastroenterol 2000;95:2720-30.

(22) Savarino E, Tutuian R. Combined multichannel intraluminal impedance and manometry testing. Dig Liv Dis 2008;40:167-73.

(23) Savarino E, Gemignani L, Pohl D, et al. Oesophageal motility and bolus transit abnormalities increase in parallel with the severity of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2011;34:476-86.

(24) Pohl D, Ciolino J, Roberts J, et al. Functional aspects of distal oesophageal spasm: the role of onset velocity and contraction amplitude on bolus transit. Dig Liv Dis 2012;44:569-75.

(25) Fox MR, Bredenoord AJ. Oesophageal high-resolution manometry: moving from research into clinical practice. Gut 2008;57:405-23.

(26) Fornari F, Bravi I, Penagini R, et al. Multiple rapid swallowing: a complementary test during standard oesophageal manometry. Neurogastroenterol Motil 2009;21:718-e41.

(27) Stoikes N, Drapekin J, Kushnir V, et al. The value of multiple rapid swallows during preoperative esophageal manometry before laparoscopic antireflux surgery. Surg Endosc 2012;26:3401-7.

(28) Elvevi A, Mauro A, Pugliese D, et al. Usefulness of low- and high-volume multiple rapid swallowing during high-resolution manometry. Dig Liv Dis 2015;47:103-7.

(29) Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil 2015;27:160-74.

(30) Martinucci I, Savarino EV, Pandolfino JE, et al. Vigor of peristalsis during multiple rapid swallows is inversely correlated with acid exposure time in patients with NERD. Neurogastroenterol Motil 2016;28:243-50.

(31) Sweis R, Anggiansah A, Wong T, et al. Normative values and inter-observer agreement for liquid and solid bolus swallows in upright and supine positions as assessed by esophageal high-resolution manometry. Neurogastroenterol Motil 2011;23:509-e198.

(32) Sweis R, Anggiansah A, Wong T, et al. Assessment of esophageal dysfunction and symptoms during and after a standardized test meal: development and clinical validation of a new methodology utilizing high-resolution manometry. Neurogastroenterol Motil 2014;26:215-28.

(33) Daum C, Sweis R, Kaufman E, et al. Failure to respond to physiologic challenge characterizes esophageal motility in erosive gastro-esophageal reflux disease. Neurogastroenterol Motil 2011;23:517-e200.

(34) Wang YT, Tai LF, Yazaki E, et al. Investigation of Dysphagia After Antireflux Surgery by High-resolution Manometry: Impact of Multiple Water Swallows and a Solid Test Meal on Diagnosis, Management, and Clinical Outcome. Clin Gastroenterol Hepatol 2015;13:1575-83.

(35) Spechler SJ, Castell DO. Classification of oesophageal motility abnormalities. Gut 2001;49:145-51.

(36) Nayar DS, Khandwala F, Achkar E, et al. Esophageal manometry: assessment of interpreter consistency. Clin Gastroenterol Hepatol 2005;3:218-24.

(37) Pandolfino JE, Kim H, Ghosh SK, et al. High-resolution manometry of the EGJ: an analysis of crural diaphragm function in GERD. Am J Gastroenterol 2007;102:1056-63.

(38) Tolone S, De Bortoli N, Marabotto E, et al. Esophagogastric junction contractility for clinical assessment in patients with GERD: a real added value? Neurogastroenterol Motil 2015; 27(10):1423-31.

(39) Tolone S, de Cassan C, de Bortoli N, et al. Esophagogastric junction morphology is associated with a positive impedance-pH monitoring in patients with GERD. Neurogastroenterol Motil 2015;27:1175-82.

(40) Bredenoord AJ, Weusten BL, Timmer R, et al. Intermittent spatial separation of diaphragm and lower esophageal sphincter favors acidic and weakly acidic reflux. Gastroenterology 2006;130:334-40.

(41) Ghosh SK, Pandolfino JE, Rice J, et al. Impaired deglutitive EGJ relaxation in clinical esophageal manometry: a quantitative analysis of 400 patients and 75 controls. Am J Physiol Gastrointest Liver Physiol 2007;293:G878-85.

(42) Pandolfino JE, Gawron AJ. Achalasia: a systematic review. JAMA 2015;313:1841-52.

(43) Salvador R, Savarino E, Pesenti E, et al. The Impact of Heller Myotomy on Integrated Relaxation Pressure in Esophageal Achalasia. J Gastrointest Surg 2016;20:125-31.

(44) Lin Z, Kahrilas PJ, Roman S, et al. Refining the criterion for an abnormal Integrated Relaxation Pressure in esophageal pressure topography based on the pattern of esophageal contractility using a classification and regression tree model. Neurogastroenterol Motil 2012;24:e356-63.

(45) Pandolfino JE, Roman S, Carlson D, et al. Distal esophageal spasm in high-resolution esophageal pressure topography: defining clinical phenotypes. Gastroenterology 2011;141:469-75.

(46) Fox MR, Pandolfino JE, Sweis R, et al. Inter-observer agreement for diagnostic classification of esophageal motility disorders defined in high-resolution manometry. Dis Esophagus 2015;28:711-9.

(47) Kahrilas PJ, Pandolfino JE. Ineffective esophageal motility does not equate to GERD. Am J Gastroenterol 2003;98:715-7.

(48) Niebisch S, Wilshire CL, Peters JH. Systematic analysis of esophageal pressure topography in high-resolution manometry of 68 normal volunteers. Dis Esophagus 2013;26:651-60.

(49) Weijenborg PW, Kessing BF, Smout AJ, et al. Normal values for solid-state esophageal high-resolution manometry in a European population; an overview of all current metrics. Neurogastroenterol Motil 2014;26:654-9.

(50) Xiao Y, Read A, Nicodeme F, et al. The effect of a sitting vs supine posture on normative esophageal pressure topography metrics and Chicago Classification diagnosis of esophageal motility disorders. Neurogastroenterol Motil 2012;24:e509-16.

(51) Kuribayashi S, Iwakiri K, Kawada A, et al. Variant parameter values-as defined by the Chicago Criteria-produced by ManoScan and a new system with Unisensor catheter. Neurogastroenterol Motil 2015;27:188-94.

(52) Capovilla G., Savarino E., Costantini M., et al. Inter-Rater and Inter-Device Agreement For The Diagnosis of Primary Esophageal Motility Disorders based on Chicago Classification Between Solid-State and Water-Perfused HRM System A Prospective, Randomized, Double Blind, Crossover Study. Digestive Disease Week 2014. Chicago 2014.

(53) Bogte A, Bredenoord AJ, Oors J, et al. Normal values for esophageal high-resolution manometry. Neurogastroenterol Motil 2013;25:762-e579.

(54) Kessing BF, Weijenborg PW, Smout AJ, et al. Water-perfused esophageal high-resolution manometry: normal values and validation. Am J Physiol Gastrointest Liv Physiol 2014;306:G491-5.

(55) Shi Y, Xiao Y, Peng S, et al. Normative data of high-resolution impedance manometry in the Chinese population. J Gastroenterol Hepatol 2013;28:1611-5.

(56) Gao F, Gao Y, Hobson AR, et al. Normal esophageal high-resolution manometry and impedance values in the supine and sitting positions in the population of Northern China. Dis Esophagus 2014 [Epub ahead of print].

(57) do Carmo GC, Jafari J, Sifrim D, et al. Normal esophageal pressure topography metrics for data derived from the Sandhill-Unisensor high-resolution manometry assembly in supine and sitting positions. Neurogastroenterol Motil 2015;27:285-92.

(58) Weijenborg PW, Savarino E, Kessing BF, et al. Normal values of esophageal motility after antireflux surgery; a study using high-resolution manometry. Neurogastroenterol Motil 2015;27:929-35.

(59) Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006;101:1900-20; quiz 43.

(60) Savarino E, Giacchino M, Savarino V. Dysmotility and reflux disease. Cur Opin Otolaryngol Head Neck Surg 2013;21:548-56.

(61) DeVault K, McMahon BP, Celebi A, et al. Defining esophageal landmarks, gastroesophageal reflux disease, and Barrett's esophagus. Ann N Y Acad Sci 2013;1300:278-95.

(62) Savarino E, Zentilin P, Frazzoni M, et al. Characteristics of gastro-esophageal reflux episodes in Barrett's esophagus, erosive esophagitis and healthy volunteers. Neurogastroenterol Motil 2010;22:1061-e280.

(63) Frazzoni M, Savarino E, Manno M, et al. Reflux patterns in patients with short-segment Barrett's oesophagus: a study using impedance-pH monitoring off and on proton pump inhibitor therapy. Aliment Pharmacol Ther 2009;30:508-15.

(64) Loughney T, Maydonovitch CL, Wong RK. Esophageal manometry and ambulatory 24-hour pH monitoring in patients with short and long segment Barrett's esophagus. Am J Gastroenterol 1998;93:916-9.

(65) Savarino E, Tutuian R, Zentilin P, et al. Characteristics of reflux episodes and symptom association in patients with erosive esophagitis and nonerosive reflux disease: study using combined impedance-pH off therapy. Am J Gastroenterol 2010;105:1053-61.

(66) Savarino E, Zentilin P, Savarino V. NERD: an umbrella term including heterogeneous subpopulations. Nat Rev Gastroenterol Hepatol 2013;10:371-80.

(67) Pandolfino JE, Kahrilas PJ, American Gastroenterological A. AGA technical review on the clinical use of esophageal manometry. Gastroenterology 2005;128:209-24.

(68) Nicodeme F, Pipa-Muniz M, Khanna K, et al. Quantifying esophagogastric junction contractility with a novel HRM topographic metric, the EGJ-Contractile Integral: normative values and preliminary evaluation in PPI non-responders. Neurogastroenterol Motil 2014;26:353-60.

(69) Kahrilas PJ, Dodds WJ, Hogan WJ, et al. Esophageal peristaltic dysfunction in peptic esophagitis. Gastroenterology 1986;91:897-904.

(70) Pohl D, Ribolsi M, Savarino E, et al. Characteristics of the esophageal low-pressure zone in healthy volunteers and patients with esophageal symptoms: assessment by high-resolution manometry. Am J Gastroenterol 2008;103:2544-9.

(71) Bogte A, Bredenoord AJ, Oors J, et al. Relationship between esophageal contraction patterns and clearance of swallowed liquid and solid boluses in healthy controls and patients with dysphagia. Neurogastroenterol Motil 2012;24:e364-72.

(72) Savarino E, Pohl D, Zentilin P, et al. Functional heartburn has more in common with functional dyspepsia than with non-erosive reflux disease. Gut 2009;58:1185-91.

(73) Savarino E, Zentilin P, Tutuian R, et al. The role of nonacid reflux in NERD: lessons learned from impedance-pH monitoring in 150 patients off therapy. Am J Gastroenterol 2008;103:2685-93.

(74) Martinucci I, de Bortoli N, Giacchino M, et al. Esophageal motility abnormalities in gastroesophageal reflux disease. World J Gastrointest Pharmacol Ther 2014;5:86-96.

(75) de Bortoli N, Martinucci I, Bertani L, et al. Esophageal testing: What we have so far. World J Gastrointest Pathophysiol 2016;7:72-85.

(76) Weijenborg PW, Bredenoord AJ. How reflux causes symptoms: reflux perception in gastroesophageal reflux disease. Best Pract Res Clinical Gastroenterol 2013;27:353-64.

(77) Savarino E, Zentilin P, Tutuian R, et al. Impedance-pH reflux patterns can differentiate non-erosive reflux disease from functional heartburn patients. J Gastroenterol 2012;47:159-68.

(78) Savarino V, Savarino E, Parodi A, et al. Functional heartburn and non-erosive reflux disease. Dig Dis 2007;25:172-4.

(79) Savarino E, Marabotto E, Zentilin P, et al. The added value of impedance-pH monitoring to Rome III criteria in distinguishing functional heartburn from non-erosive reflux disease. Dig Liv Dis 2011;43:542-7.

(80) Sifrim D, Holloway R. Transient lower esophageal sphincter relaxations: how many or how harmful? Am J Gastroenterol 2001;96:2529-32.

(81) Mattox HE, 3rd, Richter JE. Manometry vs. pH step-up. Am J Gastroenterol 1991;86:1280-2.

(82) Klauser AG, Schindlbeck NE, Muller-Lissner SA. Esophageal 24-h pH monitoring: is prior manometry necessary for correct positioning of the electrode? Am J Gastroenterol 1990;85:1463-7.

(83) Staiano A, Clouse RE. Value of subject height in predicting lower esophageal sphincter location. Am J Dis Child 1991;145:1424-7.

(84) Fibbe C, Layer P, Keller J, et al. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. Gastroenterology 2001;121:5-14.

(85) Mughal MM, Bancewicz J, Marples M. Oesophageal manometry and pH recording does not predict the bad results of Nissen fundoplication. Brit J Surg 1990;77:43-5.

(86) Fuchs KH, Babic B, Breithaupt W, et al. EAES recommendations for the management of gastroesophageal reflux disease. Surg Endosc 2014;28:1753-73.

(87) Jobe BA, Richter JE, Hoppo T, et al. Preoperative diagnostic workup before antireflux surgery: an evidence and experience-based consensus of the Esophageal Diagnostic Advisory Panel. J Am Coll Surg 2013;217:586-97.

(88) Lund RJ, Wetcher GJ, Raiser F, et al. Laparoscopic Toupet fundoplication for gastroesophageal reflux disease with poor esophageal body motility. J Gastrointest Surg 1997;1:301-8; discussion 8.

(89) Shaker A, Stoikes N, Drapekin J, et al. Multiple rapid swallow responses during esophageal high-resolution manometry reflect esophageal body peristaltic reserve. Am J Gastroenterol 2013;108:1706-12.

(90) Saleh CM, Smout AJ, Bredenoord AJ. The diagnosis of gastro-esophageal reflux disease cannot be made with barium esophagograms. Neurogastroenterol Motil 2015;27:195-200.

(91) Kessing BF, Smout AJ, Bredenoord AJ. Current diagnosis and management of the rumination syndrome. J Clin Gastroenterol 2014;48:478-83.

(92) Roman S, Savarino E, Savarino V, et al. Eosinophilic oesophagitis: from physiopathology to treatment. Dig Liv Dis 2013;45:871-8.

(93) Savarino E, Gemignani L, Zentilin P, et al. Achalasia with dense eosinophilic infiltrate responds to steroid therapy. Clin Gastroenterol Hepatol 2011;9:1104-6.

(94) Roman S, Huot L, Zerbib F, et al. High-Resolution Manometry Improves the Diagnosis of Esophageal Motility Disorders in Patients With Dysphagia: A Randomized Multicenter Study. Am J Gastroenterol 2016;111:372-80.

(95) Pandolfino JE, Kwiatek MA, Nealis T, et al. Achalasia: a new clinically relevant classification by high-resolution manometry. Gastroenterology 2008;135:1526-33.

(96) Rohof WO, Salvador R, Annese V, et al. Outcomes of treatment for achalasia depend on manometric subtype. Gastroenterology 2013;144:718-25; quiz e13-4.

(97) Shiwaku H, Inoue H, Yamashita K, et al. Peroral endoscopic myotomy for esophageal achalasia: outcomes of the first over 100 patients with short-term follow-up. Surg Endosc 2016 [Epub ahead of print].

(98) Inoue H, Minami H, Kobayashi Y, et al. Peroral endoscopic myotomy (POEM) for esophageal achalasia. Endoscopy 2010;42:265-71.

(99) Werner YB, Costamagna G, Swanstrom LL, et al. Clinical response to peroral endoscopic myotomy in patients with idiopathic achalasia at a minimum follow-up of 2 years. Gut 2015.

(100) Bechara R, Ikeda H, Inoue H. Peroral endoscopic myotomy: an evolving treatment for achalasia. Nat Rev Gastroenterol Hepatol 2015;12:410-26.

(101) Kahrilas PJ, Kishk SM, Helm JF, et al. Comparison of pseudoachalasia and achalasia. Am J Med 1987;82:439-46.

(102) van Hoeij FB, Smout AJ, Bredenoord AJ. Characterization of idiopathic esophagogastric junction outflow obstruction. Neurogastroenterol Motil 2015;27:1310-6.

(103) Swamy N. Esophageal spasm: clinical and manometric response to nitroglycerine and long acting nitrites. Gastroenterology 1977;72:23-7.

(104) Vanuytsel T, Bisschops R, Farre R, et al. Botulinum toxin reduces Dysphagia in patients with nonachalasia primary esophageal motility disorders. Clin Gastroenterol Hepatol 2013;11:1115-21 e2.

(105) Khashab MA, Messallam AA, Onimaru M, et al. International multicenter experience with peroral endoscopic myotomy for the treatment of spastic esophageal disorders refractory to medical therapy (with video). Gastrointest Endosc 2015;81:1170-7.

(106) Tutuian R, Castell DO. Combined multichannel intraluminal impedance and manometry clarifies esophageal function abnormalities: study in 350 patients. Am J Gastroenterol 2004;99:1011-9.

(107) Borjesson M, Rolny P, Mannheimer C, et al. Nutcracker oesophagus: a double-blind, placebo-controlled, cross-over study of the effects of lansoprazole. Aliment Pharmacol Ther 2003;18:1129-35.

(108) Almansa C, Heckman MG, DeVault KR, et al. Esophageal spasm: demographic, clinical, radiographic, and manometric features in 108 patients. Dis Esophagus 2012;25:214-21.

(109) Zaninotto G, Costantini M, Rizzetto C, et al. Four hundred laparoscopic myotomies for esophageal achalasia: a single centre experience. Ann Surg 2008;248:986-93.

(110) Eckardt VF, Hoischen T, Bernhard G. Life expectancy, complications, and causes of death in patients with achalasia: results of a 33-year follow-up investigation. Eur J Gastroenterol Hepatol 2008;20:956-60.

(111) Tolone S, Savarino E, de Bortoli N, et al. Esophagogastric junction morphology assessment by high resolution manometry in obese patients candidate to bariatric surgery. Int J Surgery 2015 [Epub ahead of print]

(112) Mion F, Tolone S, Garros A, et al. High-resolution Impedance Manometry after Sleeve Gastrectomy: Increased Intragastric Pressure and Reflux are Frequent Events. Obes Surg 2016 [Epub ahead of print].

(113) Tolone S, Cristiano S, Savarino E, et al. Effects of omega-loop bypass on esophagogastric junction function. Surg Obes Relat Dis 2016;12:62-9.

(114) Fass R, Achem SR. Noncardiac chest pain: epidemiology, natural course and pathogenesis. J Neurogastroenterol Motil 2011;17:110-23.

(115) Locke GR, 3rd, Talley NJ, Fett SL, et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997;112:1448-56.

(116) Eslick GD, Jones MP, Talley NJ. Non-cardiac chest pain: prevalence, risk factors, impact and consulting--a population-based study. Aliment Pharmacol Ther 2003;17:1115-24.

(117) Fass R, Fennerty MB, Ofman JJ, et al. The clinical and economic value of a short course of omeprazole in patients with noncardiac chest pain. Gastroenterology 1998;115:42-9.

(118) Dickman R, Emmons S, Cui H, et al. The effect of a therapeutic trial of high-dose rabeprazole on symptom response of patients with non-cardiac chest pain: a randomized, double-blind, placebo-controlled, crossover trial. Aliment Pharmacol Ther 2005;22:547-55.

(119) Katz PO, Dalton CB, Richter JE, et al. Esophageal testing of patients with noncardiac chest pain or dysphagia. Results of three years' experience with 1161 patients. Ann Int Med 1987;106:593-7.

(120) Dekel R, Pearson T, Wendel C, et al. Assessment of oesophageal motor function in patients with dysphagia or chest pain - the Clinical Outcomes Research Initiative experience. Aliment Pharmacol Ther 2003;18:1083-9.

(121) Breumelhof R, Nadorp JH, Akkermans LM, et al. Analysis of 24-hour esophageal pressure and pH data in unselected patients with noncardiac chest pain. Gastroenterology 1990;99:1257-64.

(122) Kushnir VM, Prakash Gyawali C. High resolution manometry patterns distinguish acid sensitivity in non-cardiac chest pain. Neurogastroenterol Motil 2011;23:1066-72.

(123) Farmer AD, Coen SJ, Kano M, et al. Psychophysiological responses to visceral and somatic pain in functional chest pain identify clinically relevant pain clusters. Neurogastroenterol Motil 2014;26:139-48.

(124) Gemignani L, Savarino V, Ghio M, et al. Lactulose breath test to assess oro-cecal transit delay and estimate esophageal dysmotility in scleroderma patients. Semin Arthritis Rheum 2013;42:522-9.

(125) Savarino E, Furnari M, de Bortoli N, et al. Gastrointestinal involvement in systemic sclerosis. Press Med 2014;43:e279-91.

(126) Carlson DA, Crowell MD, Kimmel JN, et al. Loss of Peristaltic Reserve, Determined by Multiple Rapid Swallows is the Most Frequent Esophageal Motility Abnormality in Patients with Systemic Sclerosis. Clin Gastroenterol Hepatol 2016 [Epub ahead of print].

(127) Savarino E, Mei F, Parodi A, et al. Gastrointestinal motility disorder assessment in systemic sclerosis. Rheumatol 2013;52:1095-100.

(128) Savarino E, Bazzica M, Zentilin P, et al. Gastroesophageal reflux and pulmonary fibrosis in scleroderma: a study using pH-impedance monitoring. Am J Respir Crit Care Med 2009;179:408-13.

(129) Arif T, Masood Q, Singh J, et al. Assessment of esophageal involvement in systemic sclerosis and morphea (localized scleroderma) by clinical, endoscopic, manometric and pH metric features: a prospective comparative hospital based study. BMC Gastroenterol 2015;15:24.

(130) Guariso G, Conte S, Galeazzi F, et al. Esophageal involvement in juvenile localized scleroderma: a pilot study. Clin Exp Rheumatol 2007;25:786-9.

(131) Roman S, Hot A, Fabien N, et al. Esophageal dysmotility associated with systemic sclerosis: a high-resolution manometry study. Dis Esophagus 2011;24:299-304.

(132) Turk T, Pirildar T, Tunc E, et al. Manometric assessment of esophageal motility in patients with primary Sjogren's syndrome. Rheumatol Int 2005;25:246-9.

(133) Roman S, Marjoux S, Thivolet C, et al. Oesophageal function assessed by high-resolution manometry in patients with diabetes and inadequate glycaemic control. Diabet Med 2014;31:1452-9.

(134) Pandolfino JE, Kahrilas PJ, American Gastroenterological A. American Gastroenterological Association medical position statement: Clinical use of esophageal manometry. Gastroenterology 2005;128:207-8.

(135) Roman S, Kahrilas PJ, Boris L, et al. High-resolution manometry studies are frequently imperfect but usually still interpretable. Clin Gastroenterol Hepatol 2011;9:1050-5.

(136) Salvador R, Watson TJ, Herbella F, et al. The preoperative manometric pattern predicts the outcome of surgical treatment for esophageal achalasia. J Gastrointest Surg. 2010;14(11):1635-45.