

Esophageal testing: What we have so far

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Abstract

Gastroesophageal reflux disease (GERD) is a common disorder of the gastrointestinal tract. In the last few decades, new technologies have evolved and have been applied to the functional study of the esophagus, allowing for the improvement of our knowledge of the pathophysiology of GERD. High-resolution manometry (HRM) permits greater understanding of the function of the esophagogastric junction and the risks associated with hiatal hernia. Moreover, HRM has been found to be more reproducible and sensitive than conventional water-perfused manometry to detect the presence of transient lower esophageal sphincter relaxation. Esophageal 24-h pH-metry with or without combined impedance is usually performed in patients with negative endoscopy and reflux symptoms who have a poor response to anti-reflux medical therapy to assess esophageal acid exposure and symptom-reflux correlations. In particular, esophageal 24-h impedance and pH monitoring can detect acid and non-acid reflux events. EndoFLIP is a recent technique poorly applied in clinical practice, although it provides a large amount of information about the esophagogastric junction. In the coming years, laryngopharyngeal symptoms could be evaluated with up and coming non-invasive or minimally invasive techniques, such as pepsin detection in saliva or pharyngeal pH-metry. Future studies are required of these techniques to evaluate their diagnostic

accuracy and usefulness, although the available data are promising.

Key words: Gastroesophageal reflux disease; High resolution manometry; Multichannel impedance and pH; BRAVO; EndoFLIP; PEP-test; Restech

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Core tip: In the last few decades, new technologies have evolved and have been applied to the functional study of the esophagus, allowing for the improvement of our knowledge of the pathophysiology of gastroesophageal reflux disease. High-resolution manometry permits a greater understanding of the function of the esophago-gastric junction and the risks associated with hiatal hernia. The Chicago Classification V3.0 could define a hierarchic classification that accurately defines the major and minor disorders of esophageal motility. Esophageal 24-h pH-metry, especially when it is combined with impedance, is usually performed in patients with negative endoscopy and reflux symptoms who have a poor response to anti-reflux medical therapy to assess esophageal acid exposure and symptom-reflux correlations. In particular, esophageal 24-h impedance and pH monitoring are able to detect acid and non-acid reflux events. EndoFLIP is a recent technique poorly applied in clinical practice, although it provides a large amount of information about the esophago-gastric junction. Recently, up and coming non-invasive or minimally invasive techniques, such as pepsin detection in saliva or pharyngeal pH-metry, have been suggested to detect laryngopharyngeal reflux disease. Future studies are required for these techniques to evaluate their accuracy and usefulness, although the available data are promising.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a highly prevalent disease in Western countries, affecting up to 20% of the general population, with important impacts on health care costs and the quality of life of patients^[1]. According to the Montreal Definition, GERD develops when the reflux of gastric contents causes troublesome symptoms and/or complications^[2,3].

In the past decade, it was realized that, in addition to the presence of esophageal mucosal lesions (*i.e.*, erosions, intestinal metaplasia), the majority of GERD patients (approximately 70%) have typical reflux

symptoms (*i.e.*, heartburn, regurgitation) without any esophageal mucosal breaks on upper endoscopy; thus, they are considered to have non-erosive reflux disease (NERD)^[2,4]. In keeping with this definition, a GERD diagnosis can be based on the presence of typical symptoms only. In contrast, several recent studies have emphasized that NERD represents a heterogeneous group of patients with several pathophysiological and clinical differences, and it should be better classified using appropriate techniques able to characterize gastro-esophageal refluxate because the management and therapeutic response can change on the basis of the main mechanisms of symptom generation^[5-7]. Conventional pH monitoring was first considered a useful tool to identify GERD patients, by evaluating distal esophageal acid exposure time (AET), number of acid reflux episodes and the association between symptoms and acid reflux^[8,9]. However, the growing acknowledgment that factors/stimuli different from acid were involved in symptom generation in GERD has paved the way toward the search for innovative diagnostic and therapeutic approaches to GERD^[10]. Moreover, the more frequent request to evaluate patients refractory to therapy with proton pump inhibitors (PPIs) has provided further impetus in this direction^[11-13]. Finally, it is relevant to bear in mind the increasing referral to our outpatient clinics of subjects with extra-esophageal symptoms suggestive of GERD, such as laryngeal and pulmonary symptoms, representing a true challenge in our clinical practice due to the difficulties in evaluating the potential relationship of their symptoms and GERD with appropriate management^[14,15]. In this context, the advent of novel esophageal function testing, such as impedance-pH monitoring (MII-pH) and high resolution manometry (HRM), has allowed for relevant progress in the understanding of the pathophysiological mechanisms contributing to the development of GERD and, thereafter, its diagnosis and management. Moreover, the role of new technology to detect laryngopharyngeal reflux (LPR)^[16-18], as well as the presence of pepsin in clinical samples^[19], deserves careful consideration. The aim of the present review article is to report on the current literature about recent advances in diagnosing GERD.

HIGH RESOLUTION MANOMETRY

GERD is primarily a motility disorder in which impairment of the esophago-gastric junction (EGJ) and ineffective esophageal motility (IEM) play an important roles^[20-26].

Esophageal manometry, which assesses intraluminal esophageal pressures, peristalsis and bolus transit, is currently considered the gold standard to detect the esophageal motility abnormalities. Conventional manometry techniques record esophageal peristalsis using a catheter with 5 to 8 water-perfused channels, with or without a sleeve sensor to measure continuously the maximum lower esophageal sphincter (LES) pressure.

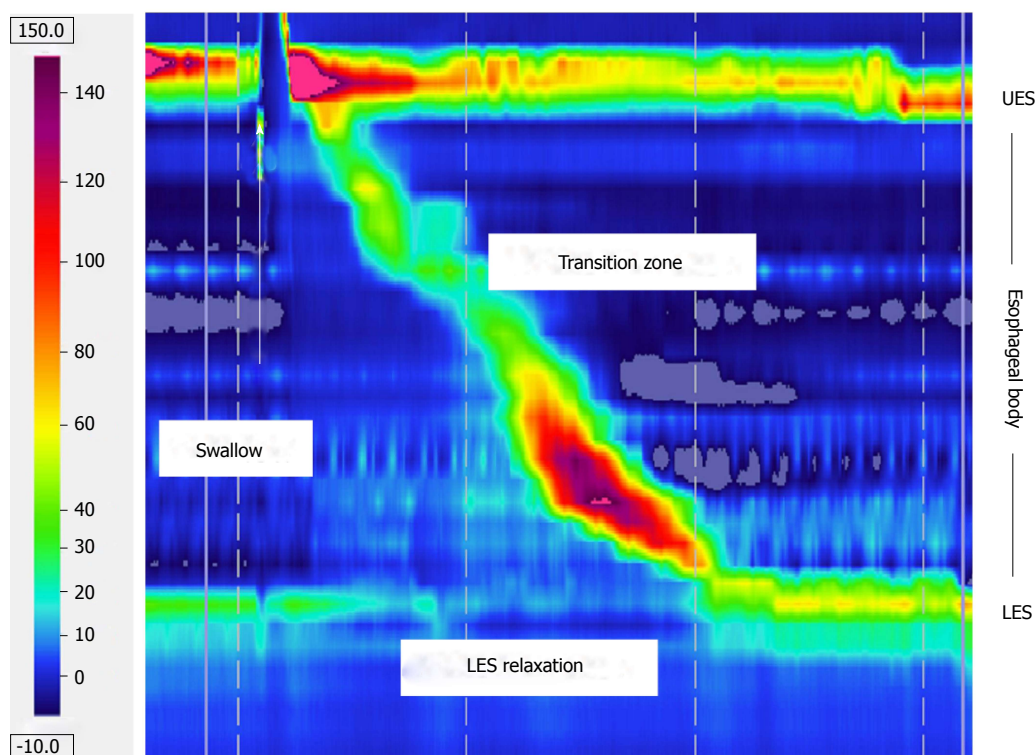


Figure 1 High resolution pressure topography of a peristaltic wave. In the picture, both the upper and lower esophageal sphincters and swallowing-induced relaxation of the lower esophageal sphincter are well represented. UES: Upper esophageal sphincter; LES: Lower esophageal sphincter.

HRM was described for the first time in 1991, introducing an increased number of pressure sensors along the catheter and the use of spatio-temporal plots^[27,28], leading to the subsequent development of the Chicago Classification for primary esophageal motility disorders^[29,30]. In HRM systems, multiple sensors (up to 36) are distributed longitudinally and radially, closely spaced along the length of the manometric catheter. Two main types of manometric catheters are currently available, solid state and water perfused, each with different physical and performance characteristics and specific advantages and disadvantages concerning costs, preparation, the location of transducers, autoclave possibility and the rate of pressure increase. Nevertheless, HRM allows for simultaneous pressure readings within both the sphincters and the esophageal body, providing detailed esophageal pressure topography (EPT) (Figure 1). With HRM, pull-through techniques became unnecessary and several problems, such as artifacts attributable to swallow-induced sphincter movement^[31] or EGJ conformational changes that can spontaneously occur, were overcome^[32-34]. HRM provides a dynamic representation of the pressure within and across the EGJ, and it also creates opportunities to quantify more precise measurement of EGJ relaxation and morphology^[25,26,31], providing the opportunity to detect expiratory LES pressure and crural diaphragm (CD) contraction^[35-39]. On this basis, the EGJ was recently reviewed and classified into three types: Type I (no LES-CD separation); type II (the LES and

CD are spatially separated such that there is a double-peaked pressure profile, but the nadir pressure between LES and CD does not decrease to gastric pressure); an type III (the separation between peaks is > 2 cm, and the nadir pressure between LES-CD is equal to or less than the gastric pressure; in type III a, the pressure inversion point is located at the CD, while in type III b, it is placed at the LES level^[30,36]).

Pandolfino *et al.*^[36] compared the EPT attributes of the EGJ between 156 GERD patients and 75 asymptomatic controls. Although both lower LES pressure and greater LES-CD separation were associated with GERD, impaired CD function was most strongly associated factor and the only independent predictor of GERD. A study designed to analyze the relationship between obesity and the morphology of the EGJ pressure segment showed that obese subjects were more likely to have a spatial separation between the diaphragm and LES (Figure 2) and an augmented gastroesophageal pressure gradient^[37]. These findings might partially explain why gastro-esophageal reflux is more frequent in obese subjects, as also evidenced in patients with NERD^[40]. Bredenoord *et al.*^[32] showed that, in cases of small hiatal hernias in which intermittent reduction of the hernia frequently occurs, spatial separation of the CD and LES in the non-reduced state resulted in a 2-fold increase in acid and weakly acidic reflux.

Transient LES relaxations (TLESRs) are the most common mechanism of reflux. They occur independently from swallowing and are not accompanied by peristalsis,

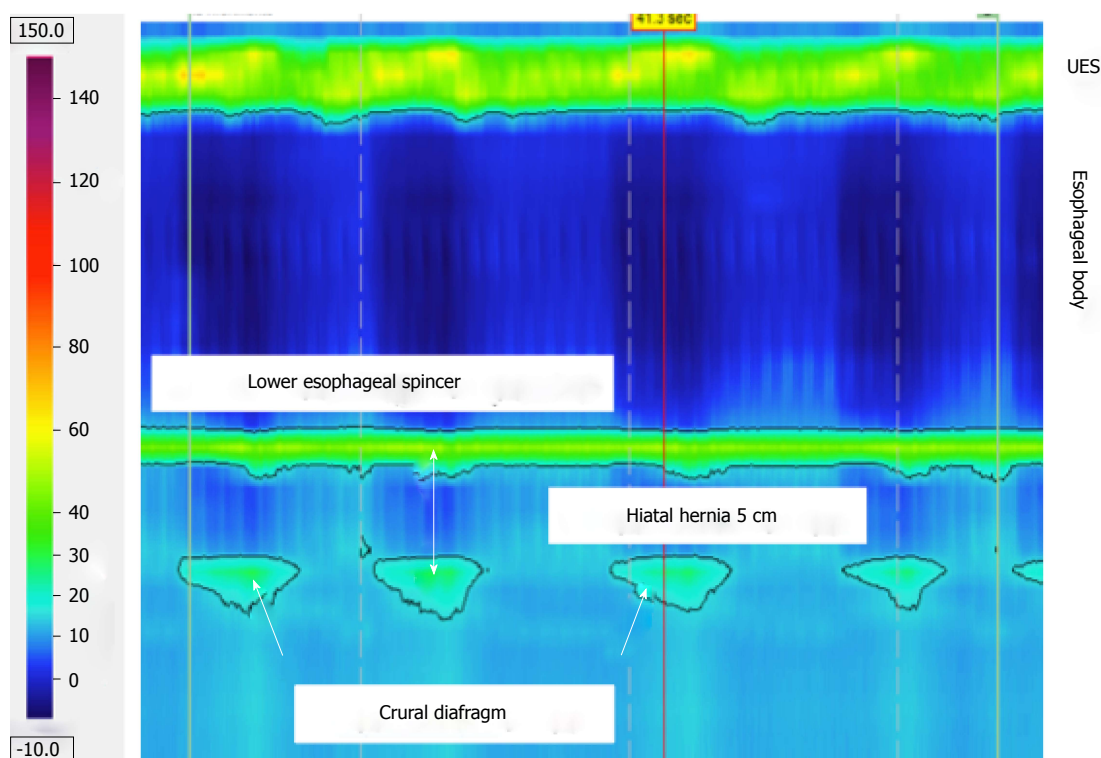


Figure 2 High resolution pressure topography at 30 s resting pressure calculation. In the picture, both the upper and lower esophageal sphincters and the crural diaphragm are well represented. This picture represents a large hiatal hernia (5 cm). UES: Upper esophageal sphincter.

but they are accompanied by diaphragmatic inhibition, and they persist for longer periods than swallow-induced LES relaxations (> 10 s)^[41,42]. In a recent study, Roman *et al*^[43] demonstrated that HRM is reproducible and more sensitive than perfused-sleeve manometry to detect TLESRs, providing better inter-observer agreement. Notably, in GERD patients, there is not an increased frequency of TLESR compared with controls but only a greater frequency of acid reflux during TLESRs^[44]. Bredenoord *et al*^[45] investigated the factors associated with reflux during TLESRs but no differences were observed in TLESR duration, trans-sphincteric pressure gradient, the prevalence, duration and amplitude of esophageal pre-contractions or sphincteric post-contractions. Pandolfino *et al*^[35] studied the largest number of TLESRs in the postprandial period. They observed that the key events associated with EGJ opening were CD inhibition, LES relaxation, distal esophageal muscular contraction and a positive gradient between the stomach and the esophagus, but in only a few cases was manometric signature of EGJ opening associated with evidence of reflux on pH-metry.

It has been shown that 21%-38% of patients with GERD present with severely impaired esophageal peristalsis (Figure 3), resulting in more severe reflux, slower acid clearance, worse mucosal injury, and more frequent respiratory symptoms^[46]. The Chicago Classification V3.0 approved the term "IEM", which is frequently used in conventional manometry^[30]. In this recent Chicago Classification version, IEM was defined

as 5 or more ineffective swallows of 10 with a DCI threshold of 450 mmHg-s-cm. No distinction need be made between failed swallows (DCI < 100 mmHg-s-cm) and weak swallows (450 mmHg-s-cm)^[30].

Multiple rapid swallowing (MRS) as a provocative test has been suggested to diagnose IEM (in borderline conditions). MRS consists of administering 2 mL of water five times, for a total amount of 15 mL of water, in less than 10 s. MRS inhibits the esophageal body and LES during the first four swallows, and it is normally followed by an esophageal contraction of increased amplitude. It was suggested that many patients with suspected IEM had normalized esophageal contraction amplitude after MRS^[47].

Manometric studies have described decreased pressure between striated and smooth esophageal muscle^[48]. Pohl *et al*^[49] correlated the size of the esophageal low-pressure zone and its possible relationship with esophageal symptoms (dysphagia, chest pain, and heartburn/regurgitation).

In conclusion, HRM is faster and easier to perform than conventional water-perfused manometry. Moreover, HRM does not require time-consuming pull-through maneuvers, and it allows for accurate evaluation of the intrinsic and extrinsic components of EGJ, thus improving the identification of TLESRs. However, the clinical application of this technique in GERD remains very limited; TLESRs cannot be used in the diagnosis of GERD because their prevalence is similar between GERD patients and normal subjects. Furthermore, minor

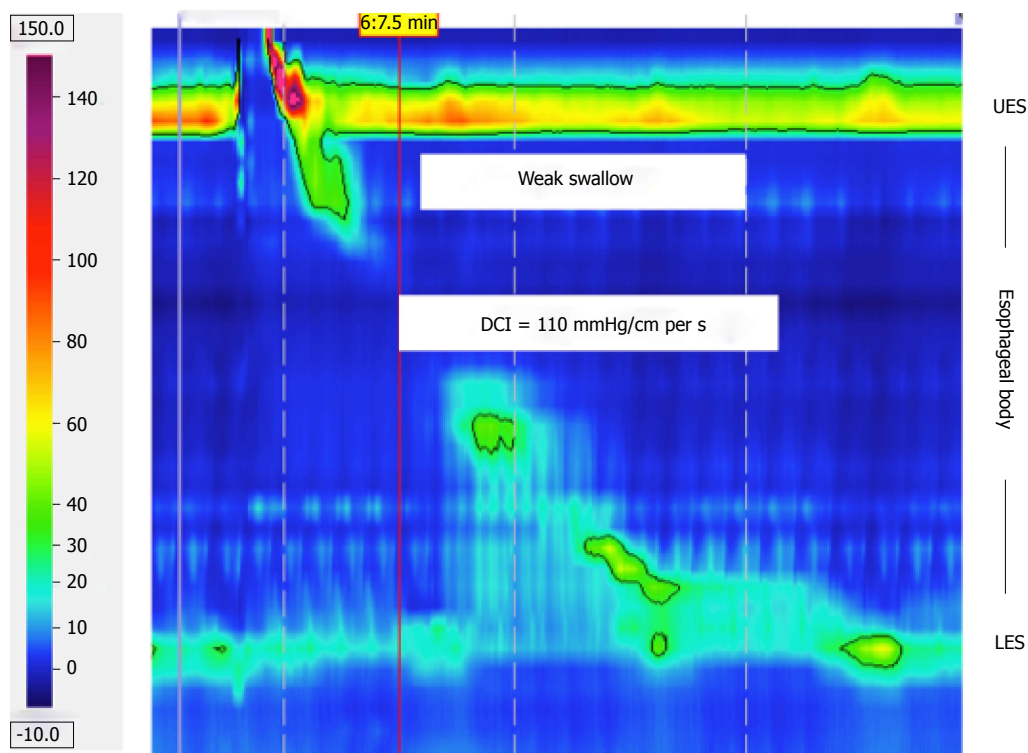


Figure 3 High resolution pressure topography of a weak peristaltic wave (distal contractile integral 110 mmHg-s-cm). UES: Upper esophageal sphincter; LES: Lower esophageal sphincter; DCI: Distal contractile integral.

esophageal motility abnormalities, observed in GERD patients, are not specific and can either be primarily or secondarily related to GERD^[50]. However, HRM represents an important advance in the assessment of esophageal motor function and a promising technique for the evaluation of the mechanical abnormalities involved in GERD. Further studies are needed to evaluate additional possible benefits of this technique in clinical practice.

MULTICHANNEL INTRALUMINAL IMPEDANCE AND PH

Multichannel intraluminal impedance (MII) has been promoted to detect the movement of fluid, solid, and air in the esophagus regardless of its pH^[51].

This new device, which combines MII-pH analysis, provides a sophisticated characterization of reflux episodes over a 24-h period. The most common catheter allows for 6 channels for intraluminal impedance (at 3, 5, 7, 9, 15, and 17 cm) and a pH sensor (at 5 cm above the upper border of the LES)^[52].

MII-pH is an innovative technique that provides a detailed characterization of each reflux event including chemical (acid and non-acid reflux) and physical properties (liquid, mixed, gas) (Figure 4)^[53]. To date, non-acid reflux represents the majority of reflux episodes in patients with GERD on PPI therapy^[54,55]. Indeed, the total number of reflux episodes is not affected by acid suppressive therapy, and weakly acidic reflux accounts

for approximately 90% of all reflux episodes in patients on PPIs, thus representing a potential mechanism underlying the failure of PPI treatment in patients with reflux-related symptoms^[56,57]. Moreover, MII-pH monitoring, as well as pH-metry alone, provides the opportunity to assess the temporal relationship between the occurrence of refluxes and the onset of symptoms^[58,59]. The relationship between symptoms and reflux events can be evaluated with the symptom index (SI) and symptom association probability (SAP), which are the most commonly used symptom indices^[59].

Based on esophageal pH monitoring, NERD patients with physiological esophageal AET and a close temporal relationship between symptoms and reflux events have been defined as hypersensitive to acid stimuli. In contrast, in agreement with the Rome III criteria, patients with heartburn, normal upper endoscopy, physiological AET, and negative correspondence between symptoms and reflux and who fail to respond to PPIs are defined as having functional heartburn (FH)^[8,9,60]. In this regard, the advent of MII-pH monitoring has improved the diagnostic yield of GERD patients, mainly by identifying a positive SAP or SI with weakly acidic or non-acid reflux^[61-68]. In particular, if pH-metry and the patient's response to PPI therapy are compared with MII-pH, we can observe an underestimation of GERD patients^[69,70].

In contrast, all of the available diagnostic tests for GERD have some limitations. The drawbacks of MII-pH are mainly due to the day-to-day variability of the test^[71-73]. Additionally, the reflux-symptom correlation in patients with GERD who do not respond to PPI therapy

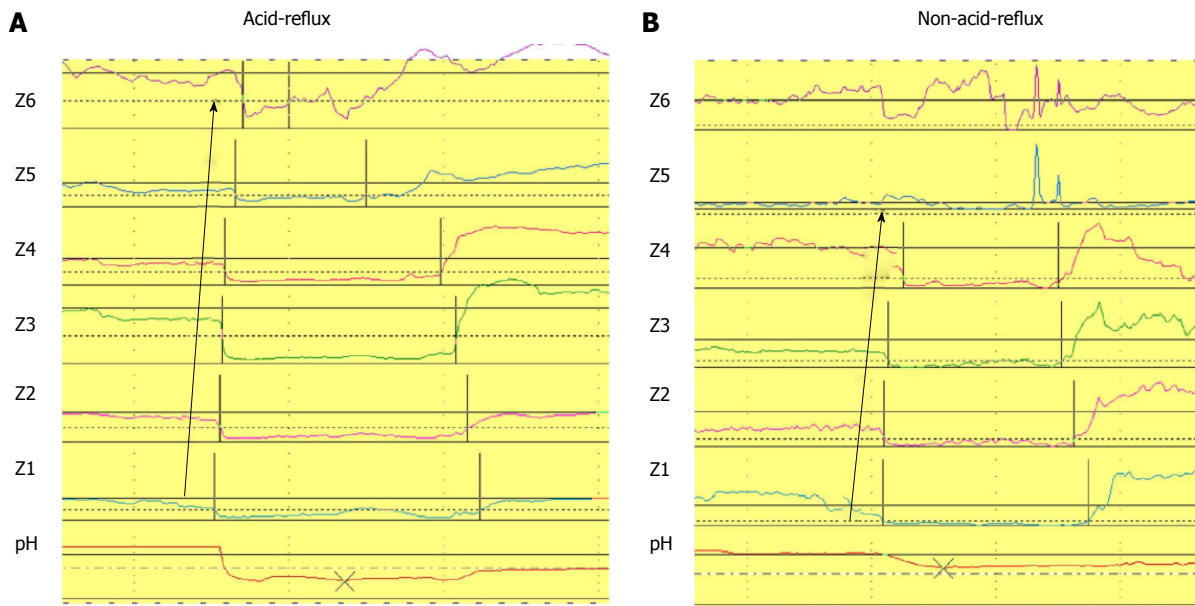


Figure 4 Graphic representation of MII-pH reflux events: (A) acid-proximal reflux; (B) non-acid distal reflux. Z1-Z6: Impedance channel; pH: Channel for pH recording.

is actually also calculated by the SI or SAP if its validity is still uncertain^[74,75]. Recently Zerbib *et al.*^[76] reported that MII-pH findings were not always able to predict the response to PPIs in patients with typical reflux-related symptoms when the test is performed off PPI therapy.

Regarding the clinical utility of pathophysiological investigations in patients with heartburn, we described a group of patients (more than 19% of the whole population enrolled) with heartburn who completely responded to PPI, in whom GERD was not diagnosed with the MII-pH test^[5]. Thus, our data suggested that PPI response alone should not be always considered a good predictor of a GERD diagnosis^[5]. Overall, it is notable that NERD patients vary greatly from a pathophysiological point of view and should be accurately studied by means of MII-pH to undertake the best therapeutic approach^[6]. Indeed, a meta-analysis found that the once defined low response rate in NERD was likely the result of the inclusion of patients with heartburn who did not have reflux disease^[77].

Recently, the ability to perform MII-pH testing to understand GERD pathophysiology better has improved through the introduction of up and coming parameters, such as the post-reflux swallow-induced peristaltic wave (PSPW) index, which indicates the efficacy of esophageal clearance^[78], and baseline impedance values, which indicate the presence of a lack of integrity in the esophageal mucosa^[79]. Constant changes in esophageal chemical clearance could represent a specific mechanism involved in GERD pathophysiology. PSPW has been shown to be lower in patients with abnormal AET, compared to healthy volunteers (HVs) or FH patients. Moreover, this parameter was not altered after medical or surgical therapy^[78]. Further, Kessing *et al.*^[80] described lower values of baseline impedance levels in the distal

esophagus of patients with abnormal esophageal AET, compared to HVs. The authors described a negative correlation between baseline impedance levels and esophageal AET^[80]. We recently described a large group of patients with typical GERD symptoms, negative endoscopy and any pathophysiological characteristics of GERD (normal AET, number of refluxes and negative SI and SAP). We observed that patients with good symptom relief after PPI therapy had lower baseline impedance values than FH patients (non-responders). FH patients showed similar baseline values to HVs. Moreover, we observed almost the same results when analyzing the PSPW index, which was lower in responders than in non-responders and HV groups. A direct linear correlation between PSPW and baseline impedance values has been described. Overall, these data suggest that baseline impedance values and PSPW could be considered up-and-coming parameters that could be helpful in better investigating patients with GERD-related symptoms, particularly when symptom-reflux association indexes fail to do so^[81].

MII-pH testing showed that acid reflux events and their clearance were determinant factors that provoked esophageal mucosal breaks. Non-acid reflux does not appear to be directly related to the development of esophageal mucosa lesions; however, it is definitely involved in the genesis of symptoms in both NERD and erosive esophagitis (EE) patients. Ambulatory MII-pH studies have suggested that patients with moderate or severe esophagitis have rates of weakly acidic reflux similar to or slightly greater than healthy controls^[69]. In this regard, it is important to emphasize that weakly acidic reflux is not synonymous with bile reflux. A simultaneous Bilitech and MII-pH study showed no relationship between the percentage of time for bilirubin

absorbance and weakly acidic or weakly alkaline reflux. Indeed, this study showed that the greatest number of bile refluxes occurred concomitantly with acid refluxes^[82].

In patients with Barrett's esophagus (BE), MII-pH testing showed overall more severe reflux disease with a greater number of acid and weakly acidic reflux events and higher proximal extension^[71]. By means of MII-pH, Savarino *et al.*^[71] showed that patients with BE and EE had greater numbers of acid and weakly acidic reflux episodes, higher percentages of proximal migration of the refluxate and higher total acid and volume clearance. Notably, it has been emphasized that a significantly increased amount of total reflux occurs in both the long and short segments of BE, compared with EE. In BE patients, the MII-pH tracks are not easy to analyze, especially in the long segment of BE. Inflammation and histologic modifications are supposed to reduce baseline impedance values thus impairing the ability to detect the real number of reflux episodes. This phenomenon has led some investigators to be more accurate during the manual analysis of MII-pH in patients with BE^[62]. However, some authors have shown the viability of MII-pH even in BE patients^[71,83]. In clinical practice, BE patients should be evaluated with MII-pH "on" PPI therapy to evaluate the effectiveness of acid suppression.

The presence of EE, which represents clear endoscopic evidence of esophageal mucosal injury (30% of all endoscopic series in patients with GERD-related symptoms), can obviously be responsible for symptoms provoked by the refluxate. In contrast, the absence of macroscopic damage makes it difficult to clarify the occurrence of the same symptoms in patients with NERD, and it is reasonable to hypothesize that microscopic damage is responsible for the GERD-related symptoms in them^[84]. According to this assumption, recent investigations have focused their attention on the evaluation of the presence of dilated intercellular spaces, considered the most important microscopic alteration involved in symptom perception in patients with GERD^[85]. Recently Savarino *et al.*^[86] showed that the frequency of microscopic esophagitis did not differ between patients with FH and control subjects and was significantly lower in FH patients than in the EE and well-defined NERD patients evaluated with MII-pH.

The overall MII-pH assessment "on" or "off" PPI therapy is actually a matter of discussion. In a recent seminar, Bredenoord *et al.*^[52] affirmed that combined MII-pH is better performed off PPIs when the diagnosis of GERD has not yet been established and on-PPIs when the diagnosis has been already made (*i.e.*, positive endoscopy for EE, MII-pH off-therapy already performed, BE surveillance). In particular, MII-pH off PPIs is useful to investigate the causes of ineffective PPI treatment. To confirm the presence of GERD, Hemmink *et al.*^[87] reported that PPI-resistant patients should preferably be evaluated with MII-pH monitoring after cessation of PPI treatment. This approach could increase the likelihood of observing a positive relationship

between symptoms and reflux.

GERD is considered an important cause of laryngeal inflammation. Laryngoscopic examinations are very important to exclude abnormalities in the laryngeal mucosa or vocal cords (nodules or neoplastic lesions), but it is not sufficiently specific/sensitive to detect LPR^[88]. We recently described that MII-pH analysis detected GERD at least in 40% of patients who were diagnosed with LPRD. In particular, MII-pH analysis was able to identify patients with NERD, those with HE and those without GERD, whereas laryngeal symptoms and laryngoscopic findings were not able to do so^[89].

Finally, some interesting studies, performed by means of MII-pH analysis, evaluated the effectiveness of raft-forming gel formulation in "add-on" treatment for GERD symptoms. These studies have clearly demonstrated the efficacy of raft-forming gel preparation in reducing the total number of refluxes and their proximal migration^[90-92].

To conclude, MII-pH is able to improve the ability to detect GERD compared with pH-metry alone in patients with GERD-related symptoms. MII-pH is able to provide more information and to exclude GERD diagnosis definitively in PPI non-responder patients (FH). The outcomes studies are unmet clinical needs for determining whether MII-pH truly leads to a change in management.

Combined multichannel intraluminal impedance and manometry has been considered a very helpful device because it provides information about esophageal contraction and bolus transit simultaneously. Tutuian *et al.*^[93] described results from a large cohort of patients (350), showing a very strong correlation between dysphagia and incomplete bolus transit. Moreover, the largest defects of bolus transit were correlated with diagnoses of achalasia, scleroderma, distal esophageal spasm and IEM. Outcome studies are needed to clarify better the role of this technique in clinical diagnosis.

WIRELESS PH CAPSULE (BRAVO)

The wireless pH capsule (BRAVO) is a novel technology able to assess esophageal exposure to acid. This device is placed transorally 6 cm above the EGJ during an upper endoscopy, usually under sedation, or 5 cm above the LES, previously detected by means of esophageal manometry^[94]. The capsule transmits recording data via telemetry to an external receiver. This method is usually performed after the failure of a PPI test, alternatively at MII-pH or during an upper endoscopy before the PPI test. Capsule detachment occurs spontaneously in most cases between 2-3 d and 2 wk^[95]. Adverse events or complications (severe or persistent chest pain) are very rare (1% to 2%)^[94]. The technique is usually well tolerated, and the principal side effect reported is mild to moderate chest pain. The recording time of the wireless capsule is usually 48 h, showing overall good reproducibility between the 2 d of recording^[96]. However, several studies have shown a relevant day-

to-day variability responsible for discrepancies in AET between the first and the second days of recording^[97,98]. The reasons for these findings remain controversial and are the subject of debate.

A great day-to-day variability in AET might be frequent during 24-h pH-metry testing. pH monitoring prolonged to 48 h is routinely performed with the BRAVO technique, and it should provide a better overview of esophageal acid exposure and symptom-reflux correlation.

The prolonged pH-monitoring period increases the likelihood of detecting reflux events (12.5% increase), potentially improving symptom association (5.2% increase)^[99]. These data were confirmed in patients on anti-reflux therapy^[99], in patients with endoscopy negative heartburn^[100] and in patients with non-cardiac chest pain^[101].

Overall, BRAVO is a good method for reflux monitoring, especially in patients with less frequent symptoms (*i.e.*, non-cardiac chest pain) and in those who refuse catheter-based techniques, but it has some limitations, including higher cost than MII-pH and the possible risk of misplacement; more importantly, non-acid reflux events cannot be detected.

ENDOFLIP

An important property of the reflux barrier that is not assessed by manometry is distensibility (*i.e.*, the ease with which the EGJ is opened)^[102]. If pressure and radius can be measured simultaneously in the LES, the circumferential tension in the wall can be estimated, as it has been firstly demonstrated by McMahon *et al.*^[103].

The EndoFLIP (Endo Functional Luminal Imaging Probe system; Crospon Ltd., Galway, Ireland) consists of a polyurethane balloon (maximum volume of 60 mL) mounted on the distal 14 cm of a probe (length 240 cm, diameter 25 mm) attached to the EndoFLIP unit. This balloon assumes a 10-cm long cylindrical shape with maximum diameter of 2.5 cm when filled. Along a 7.5-cm segment within the balloon, 17 ring electrodes are spaced 5 mm apart to obtain 16 CSA measurements using an impedance planimetry technique. The probe also contains a solid-state pressure transducer to measure intra-balloon pressure.

The EndoFLIP system provides real-time and dynamic information on EGJ distention that is visualized as cylinders of different diameters, based on instantaneous CSA measurements (included instant pressure measurements).

Using this technique, Kwiatek *et al.*^[104] compared GERD patients with healthy controls, with the following major findings: (1) the EGJ was 2 to 3 times more distensible in GERD patients than controls; (2) 20- to 30-mL distention volumes provided, in patients with GERD, a two- to three-fold increased EGJ distensibility, compared with controls; and (3) the endoscopic estimation of the flap valve grade seemed poorly correlated with EndoFLIP measurements.

Recently, Regan *et al.*^[105] used the EndoFLIP system to measure upper esophageal sphincter (UES) distensibility. EndoFLIP provided definitive information regarding UES compliance without the need for fluoroscopy. The results regarding the anatomic parameters and physiology of UES were directly matched with current knowledge. Few data are yet available, but EndoFLIP could be able to provide determinant information about UES in patients with dysphagia before and after surgery or rehabilitation.

DX-PH (RESTECH)

As mentioned above, the diagnosis and treatment of GERD are particularly difficult in cases of LPR^[106].

Some authors have described LPR by means of dual-channel impedance and pH monitoring^[107,108]. These studies have described the frequency, location, and direction of any gas or liquid refluxate along the esophagus, as well as in the hypopharynx^[107]. Despite initial enthusiasm^[108,109], outcome studies with impedance monitoring have been lacking, and their clinical significance with regard to medically recalcitrant LPR patients remains unclear^[110].

The Dx-pH measurement system, called Restech (Respiratory Technology Corp., San Diego, CA, United States), was designed to detect aerosolized acid, thus identifying patients whose symptoms are due to acidic mist or liquid refluxing into the pharynx. Because the distal part containing the pH sensor does not traverse the UES, it is more comfortable than a conventional pH catheter, and it does not require esophageal manometry^[17].

Restech has a higher frequency of measurement than older catheter-based pH probes and wireless pH probes, with a pH measurement obtained every 0.5 s (sampling rate, 2 Hz), compared with traditional catheter-based pH probes, which sample every 4 s to 5 s (at a rate of 0.2-0.25 Hz), and wireless pH probes, with a pH measurement every 6 s (0.17 Hz). This increased sampling rate theoretically allows Restech to detect more reflux events, which is a characteristic that could prove useful in patients with LPR^[111].

Recently, Worrell *et al.*^[112] demonstrated, that in patients with extraesophageal reflux symptoms who underwent antireflux surgery, esophageal pH monitoring in the proximal esophagus failed to recognize 50% of the patients who recorded good outcomes post-antireflux surgery. Vailati *et al.*^[113] showed the high specificity and reasonable sensitivity of the Restech technique, which could be considered an interesting tool that can be used before therapy in patients with pharyngoesophageal reflux. In contrast, Ummarino *et al.*^[114] did not show any correlation, although chronic coughing was the only symptom reported by patients, and when they compared MII-pH and Restech, the superiority of the first technique seemed clear. Similarly, Becker *et al.*^[115] evaluated, in a prospective, single-center trial, the differences between MII-pH and Dx-pH. They demonstrated that acid pharyngeal pH levels detected with Dx-pH were not correlated with GERD, and acid

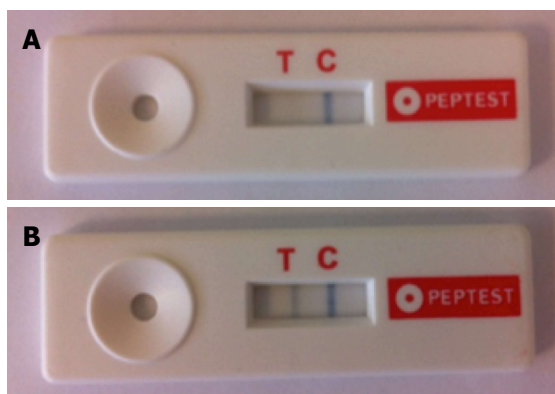


Figure 5 The picture shows the lateral flow device test to detect the presence of pepsin in saliva (PEP-test; RDBiomed, Hull, United Kingdom). A: A negative test indicates that no pepsin was detected in clinical sample (only C line is colored); B: A positive test, it indicates that pepsin is present in the sample (saliva/sputum). In the both T and C line are colored.

esophageal reflux episodes did not result in pharyngeal pH alterations. Mazzoleni *et al.*^[116], observed a very poor correlation between Dx-pH probe oropharyngeal monitoring and MII-pH in a group of 68 patients.

Until now, the use of Dx-pH recordings could not be recommended in clinical practice, given the discrepancies between traditional MII-pH monitoring and the current technologies used to measure oro-pharyngeal pH events.

PEP-TEST

Recent studies have shown that patients with LPR do not reap great benefit from PPI therapy because, at this level, the damage is not mediated by acid but rather by pepsin^[117]. For this reason, it was recently decided to search for pepsin as a marker of reflux because the enzyme is secreted only by gastric main cells^[118]; therefore, its presence above UES is a certain sign of GERD.

The pepsin lateral flow device (LFD), also called the PEP-Test (RDBiomed, Hull, United Kingdom), is a rapid, non-invasive test to detect salivary pepsin as a surrogate marker for GERD. The PEP-Test is an immunological *in-vitro* diagnostic medical device that contains two pepsin monoclonal antibodies; this test is able to detect pepsin in a clinical sample of saliva/sputum quickly and easily; the limit of detection is 16 ng/mL of pepsin. The patient must collect 30 mL of saliva, and this sample is centrifuged at 4000 rpm for 5 min; then, 80 μ L from the surface layer are drawn up and mixed with a buffer solution using a vortex mixer. The sample obtained is applied in the circular well of the PEP-Test device, and after a few minutes, it is possible to check for the presence of pepsin: If it occurs on antigen-antibody binding, two blue lines appear on the display, while if pepsin is not present, it will be possible to see only the control line. The blue lines are visible on the display because the monoclonal antibody is directly labelled with blue latex beads, which detach at the time

of Ag-Ab binding. Saritas Yuksel *et al.*^[119] evaluated the PEP-Test (defined as ELISA LFD) in 47 patients using pH-metry as a reference standard. The results were compared with a control population, which underwent only the PEP-Test, which has sensitivity and a specificity of 87% (Figure 5).

More recently Hayat *et al.*^[119] compared the PEP-test with MII-pH and showed a higher prevalence and concentration of salivary pepsin in patients with GERD or HE, compared with patients with FH and healthy controls. The authors suggested that salivary pepsin might complement questionnaires in the office-based diagnosis of patients with GERD-related symptoms.

The most important advantages of the PEP-Test are its low cost, its non-invasiveness, and, not to be underestimated, its feasibility while the patient is undergoing PPI therapy. However, given the very limited data available in the medical literature, further studies are needed to understand and assess the clinical utility of this test.

CONCLUSION

The reflux of gastric contents into the esophagus results in a broad and varied GERD spectrum. Thus, advances in the diagnosis of GERD represent the necessary progress in clinical investigation and therapeutic management as well as progress for more-in-depth assessment of the underlying pathophysiological mechanisms.

The pathogenesis of GERD is multifactorial, including esophageal motility abnormalities of which the most important are TLESRs and hypotensive LES and IEM. Recently, the role of esophageal dysmotility has gained relevant interest, showing an increased prevalence with increasing severity of GERD, from NERD to EE and BE^[120]. To date, HRM is the gold standard for characterizing esophageal motility disorders. Indeed, HRM improves characterization of LES zones and esophageal body motility, increasing diagnostic yield and accuracy^[121]. Moreover, HRM must be regarded as the new gold standard for detecting TLESRs^[43]. However, the value of HRM in clinical practice has yet to be established fully. Exclusion of severe esophageal motility disorders (*i.e.*, achalasia) is important because such diseases can present with heartburn and regurgitation, which could lead to an erroneous diagnosis of GERD^[122].

Ambulatory MII-pH has become the gold standard for investigating GERD, owing mainly to its ability to detect both acid and non-acid reflux^[68,123]. Of particular importance, MII-pH has enabled the subdivision of patients with NERD into different subsets, including patients with an excess of acid and those with symptomatic non-acid reflux, and MII-pH has the ability to identify patients with FH whose symptoms are not GERD related and who must be excluded from the realm of GERD^[6,56,109].

Moreover, diagnosing patients with HE to non-acid reflux, MII-pH has contributed to narrowing down the population of patients with FH^[70]. Recently, it has been

demonstrated that a more-in-depth pathophysiological evaluation of MII-pH tracings, including baseline impedance levels and PSPW index evaluation, could be helpful in better investigating patients with heartburn and appropriately identifying those with reflux disease and particularly those with HE, when symptom-reflux association analysis fails to do so^[5,78,81].

According to the Montreal Classification, extra-esophageal symptoms of GERD can occur, such as hoarseness, coughing, and asthma^[2]. However, establishing that extra-esophageal symptoms caused by GERD can be difficult, and in this context, the advent of new technologies deserves careful consideration. The Dx-pH measurement system is a sensitive and minimally invasive device for detecting acidic refluxate in the oropharynx. The PEP-Test is a sensitive and specific *in vitro* diagnostic test that allows for the rapid detection of pepsin, a marker of reflux, in a clinical sample. Overall, further studies are warranted to substantiate the clinical roles of these new technologies in diagnosing GERD.

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