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INVITED REVIEW

Novel Diagnostic Techniques in the Evaluation of Gastroesophageal Reflux Disease (GERD)

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Abstract

In our present clinical paradigm, patient symptoms and presentation in the setting of traditional findings from endoscopy (erosive esophagitis, Barrett's esophagus, reflux-mediated stenosis), esophageal high-resolution manometry, and/or ambulatory reflux monitoring (distal esophageal acid exposure time, numbers of reflux events, reflux-symptom association) guide the care of patients with suspected GERD. However, novel metrics and techniques acquired from or performed at endoscopy, manometry, or pH-impedance monitoring, beyond conventional evaluation, are of great interest to the gastroenterology community given the frequent (and sometimes challenging) presentation of suspected GERD. These novel and evolving diagnostic approaches have the potential to enhance the evaluation of these patients and optimize their management. In this invited review, we discuss the present evidence and potential clinical utility of selected GERD metrics and techniques of interest at endoscopy (dilated intercellular spaces, mucosal impedance), manometry (contractile integral, impedance analysis, straight leg raise, multiple rapid swallow maneuvers), and reflux monitoring (mean nocturnal baseline impedance, post-reflux swallow-induced peristaltic wave indices), and how these tools may be most optimally adopted and utilized for clinical care (Fig. 1).

Keywords Ambulatory reflux monitoring · pH-impedance testing · Mucosal integrity · Contractile segment impedance · Mean nocturnal baseline impedance · Post-reflux swallow-induced peristaltic wave index

Abbreviations

AET	Acid exposure time
AUROC	Area under receiver operating characteristic curve
BI	Baseline impedance
CD	Crural diaphragm
CSI	Contractile segment impedance
DIS	Dilated intercellular spaces
EGJ	Esophagogastric junction
EGJ-CI	Esophagogastric junction-contractile integral
EOE	Eosinophilic esophagitis
FH	Functional heartburn
GERD	Gastroesophageal reflux disease
HRM	High-resolution manometry
IAP	Intra-abdominal pressure
IEM	Ineffective esophageal motility
IEP	Intra-esophageal pressure
ISD	Intercellular space diameter
LES	Lower esophageal sphincter
MI	Mucosal impedance
MNBI	Mean nocturnal baseline impedance
MRS	Multiple rapid swallows
NERD	Non-erosive reflux disease
PPI	Proton pump inhibitor
PSPW	Post-reflux swallow-induced peristaltic wave
SLR	Straight leg raise
TEM	Transmission electron microscopy

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Introduction

Symptoms potentially attributable to gastroesophageal reflux disease (GERD) are among the most common indications for referral to and evaluation by gastroenterology providers [1]. Although a proton pump inhibitor (PPI) trial is reasonable for typical GERD symptoms of heartburn and/

or regurgitation in the absence of alarm features, clinical guidance recommends further evaluation in the setting of symptoms not adequately responsive to PPI therapy, for atypical symptoms, and/or when invasive intervention is under consideration [2–4]. In clinical practice, this work-up typically begins with upper endoscopy, where advanced erosive esophagitis (Los Angeles Grades C or greater), long-segment Barrett's esophagus, and/or peptic esophageal stenosis represent conclusive or confirmatory evidence for GERD [3–5].

If endoscopy is unrevealing, without confirmatory evidence for GERD or alternate explanations for symptoms, esophageal function testing is appropriate for further evaluation [2]. Esophageal high-resolution manometry (HRM) can play important roles in suspected GERD beyond guiding placement for catheter-based reflux testing, such as ruling out confounding diagnoses (including achalasia spectrum disorders), assessing for behavioral disorders (rumination syndrome or supragastric belching), and informing optimal tailoring of invasive antireflux interventions through evaluation of esophageal contractile reserve [6–9].

Ambulatory reflux monitoring, wireless or catheter-based, represents the primary means of objective evaluation for GERD when endoscopy is unrevealing. While reflux-symptom association and elevated total numbers of reflux events may represent adjunctive or supportive evidence, distal esophageal acid exposure time (AET) > 6% represents confirmatory evidence for GERD [5, 10]. In contrast, AET < 4% across all days of reflux monitoring with normal endoscopy essentially rules out GERD [4, 5].

While combinations of these conventional findings from upper endoscopy, HRM, and/or ambulatory reflux monitoring can help facilitate a thoughtful, individualized approach to patients with suspected GERD [4], novel techniques and metrics at these diagnostic modalities show tremendous promise to enhance our care of patients with suspected GERD by optimizing diagnostic yield, providing adjunctive evidence, and/or streamlining diagnostic work-up with potential ramifications for patient experiences and costs (Fig. 1). In this review, we highlight the present evidence and potential utility of these selected techniques and metrics at upper endoscopy (dilated intercellular spaces (DIS), mucosal impedance), HRM (esophagogastric junction (EGJ) contractile integral, straight leg raise, baseline impedance, contractile segment impedance, multiple rapid swallow responses), and reflux monitoring (mean nocturnal baseline impedance (MNBI), post-reflux swallow-induced peristaltic wave indices (PSPWI) (Table 1).

Upper Endoscopy

At upper endoscopy, findings of advanced erosive esophagitis, long-segment Barrett's esophagus, or peptic esophageal stenosis may be considered conclusive evidence for GERD [3, 5]. In their absence, dilated intercellular spaces and mucosal impedance show promise for GERD diagnosis.

Dilated Intercellular Spaces (DIS)

While conventional esophageal biopsy histopathology has limited value for GERD diagnosis [11], the presence of DIS on lower esophageal mucosal biopsies (3–5 cm above the EGJ) reflects impaired esophageal mucosal integrity, and

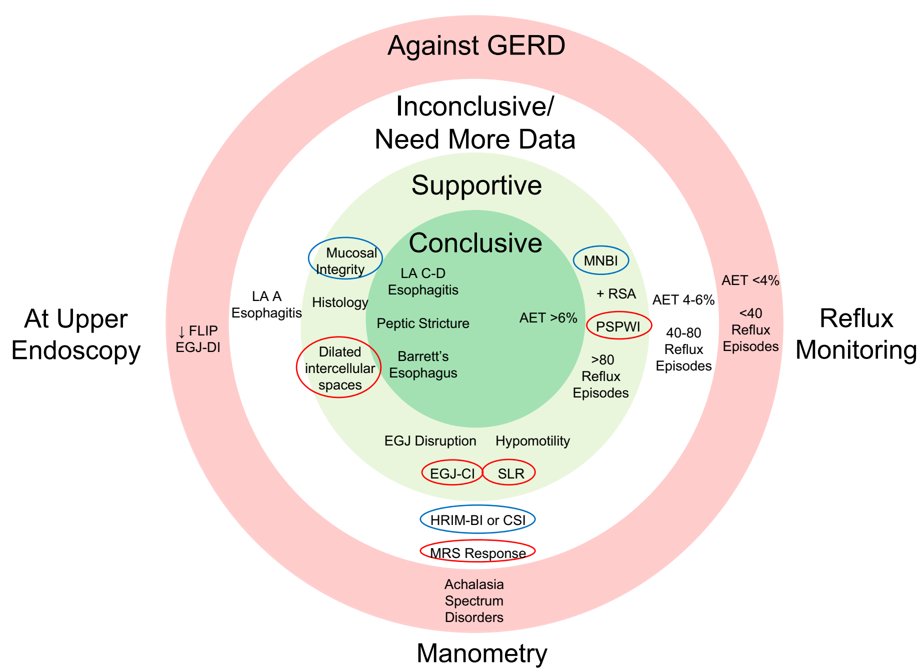

Fig. 1 Novel Techniques for GERD. From upper endoscopy, mucosal integrity (MI) and dilated intercellular spaces (DIS). From esophageal high-resolution manometry (HRM), esophagogastric junction-contractile integral (EGJ-CI), straight leg raise (SLR), baseline impedance (HRIM-BI), contractile segment impedance (CSI), and multiple rapid swallow (MRS) responses. From ambulatory reflux monitoring, mean nocturnal baseline impedance (MNBI) and post-reflux swallow-induced peristaltic wave indices (PSPWI). Blue circles indicate mucosal impedance-based tools; red circles indicate non-mucosal-impedance-based tools

Table 1 Novel tools for GERD diagnosis at upper endoscopy, esophageal high-resolution manometry (HRM), and ambulatory reflux monitoring

Novel tool	Description	Normative ranges
Upper endoscopy	Advanced erosive esophagitis, long-segment Barrett's esophagus, or peptic esophageal stenosis represent conclusive evidence for GERD	
Dilated Intercellular Spaces (DIS)	Distances between esophageal epithelial cells evaluated with transmission electron microscopy or light microscopy; limited by lack of specificity for GERD, availability of equipment and expertise, associated cost and time burden	Control group means of 0.32 µm [13], 0.46 µm, [12] 1.2 µm [14]
Mucosal Impedance (MI)	Balloon probe at sedated endoscopy, with two arrays of impedance sensors along a 10-cm segment positioned above the squamocolumnar junction (MiVu, Diversatek, Milwaukee, WI); limited by equipment availability	Dedicated software generates contour maps of baseline impedance
Functional lumen imaging probe (FLIP)	8- or 16-cm long catheter-mounted compliant balloon positioned across lower esophagus at sedated endoscopy, with impedance planimetry sensors evaluating EGJ and esophageal dimensions and pressures (EndoFLIP, Medtronic, Minneapolis, MN); evidence of EGJ outflow obstruction would suggest against GERD in symptom generation; lack of consistent segregation of GERD from controls or reliable thresholds for GERD diagnosis at this time	EGJ-DI > 2–3 mm^2/mm Hg and EGJ diameter > 12–16 mm (in contrast, EGJ-DI < 2 mm2/mm Hg and EGJ diameter < 12 mm suggest EGJ outflow obstruction) [24]
Esophageal manometry	Serves to rule out confounding esophageal motor disorders, can evaluate for behavioral disorders, and informs tailoring of antireflux interventions	
EGJ Contractile Integral (EGJ-CI)	Distal contractile integral box forced across the EGJ (encompassing LES and CD for types 1–2 EGJ morphology, with exclusion of CD in type 3 EGJ morphology) that measures EGJ barrier vigor for three respiratory cycles during the landmark phase, indexed to the gastric baseline, and corrected for the duration of measurement; limited by absence of dedicated automated software analysis	Healthy volunteer 5th percentile values of 6.9–12.1 mm Hg-cm [37]
Straight Leg Raise (SLR)	Single leg raise to 45 degrees for 5 s, considered effective if intra-abdominal pressure increases by 50%, with intra-esophageal pressure (IEP) gradients measured 5 cm above the LES at baseline and during SLR	Increase in peak IEP < 100% [39] or < 11 mm Hg [38]
Baseline Impedance (BI)	Distal esophageal impedance values extracted during landmark (resting) phase or quiet overnight periods	> 1582 ohms [43]
Contractile Segment Impedance (CSI)	Distal esophageal impedance values extracted during peristaltic supine swallows, to maximize mucosal-sensor contact	> 500–1036 ohms [45, 46]
Multiple Rapid Swallows (MRS)	Five 2-mL supine liquid swallows < 3 s apart, with assessment of post-MRS distal contractile integral (DCI) as a measure of esophageal contractile reserve	MRS DCI: wet swallow DCI ratio > 1 [47]
Reflux monitoring	Distal esophageal acid exposure times (AET) > 6% represent confirmatory evidence for GERD; positive reflux-symptom association and elevated total numbers of reflux events represent supportive evidence	
Mean Nocturnal Baseline Impedance (MNBI)	Average of distal impedance values from three 10-min artifact-free periods during nocturnal sleep periods (1,2,3 AM)	> 2292 ohms [58]

Table 1 (continued)

Novel tool	Description	Normative ranges
Post-Reflux Swallow-Induced Peristaltic Wave (PSPW) Indices	Proportions of impedance-detected reflux episodes with a primary swallow (PSPW) bringing saliva to the distal esophagus (detected as drops in impedance) within 30 s; requires cumbersome manual calculation	> 61% [58]

EGJ esophagogastric junction, *LES* lower esophageal sphincter, *CD* crural diaphragm

may provide evidence of longitudinal rather than cross-sectional (as for catheter-based or wireless reflux monitoring) reflux exposure [12]. The spaces between esophageal epithelial cells may be quantitatively measured with transmission electron microscopy (TEM) [13, 14], but may also be evaluated via light microscopy [15, 16]. For TEM, biopsy specimens may be sliced into ultrathin sections, stained, and the suprabasal layer evaluated under magnification for subsequent intercellular space diameter (ISD) measurements [13, 14]. Based on TEM biopsy data, mean ISD appeared significantly higher among patients with confirmed GERD (0.87 µm) compared to controls (0.32 µm) or those with well-characterized functional heartburn (FH; 0.42 µm) [13]. For histopathologic examination of esophageal biopsies with light microscopy, DIS may be semi-quantitatively scored (as with a 0–3 scale; 0 (absent), 1 (mild), 2 (moderate), 3 (severe)) [15, 16]. Concordant with the differences observed with TEM data, average DIS scores were higher among those with reflux (erosive reflux disease, 1.91; non-erosive reflux disease (NERD), 1.75) compared to healthy controls (0.72) or FH (0.75) [15].

Therefore, although further work is warranted for better understanding of its role, evaluation of DIS (among other histopathologic findings, such as basal cell hyperplasia and papillary elongation) may have utility in distinguishing NERD from FH in patients with refractory heartburn at endoscopy [13, 15, 16]. Notably, other data have not demonstrated increased DIS in the distal esophagus or postcricoid larynx among patients with GERD or laryngitis compared to controls, at baseline or after acid suppressive therapy, raising doubts over DIS as an objective marker to diagnose GERD [14]. Additional considerations limiting DIS from widespread use at present include the potential lack of specificity for GERD (DIS have been described in other processes), the associated cost and time burden for analysis, availability of TEM and pathology expertise, normative ranges, and variability of measurements.

Mucosal Impedance (MI)

Impedance measures the resistance to the current of flow between adjacent sensors; esophageal MI reflects mucosal permeability and integrity (inversely correlating with DIS and reflux exposure) [17]. While esophageal MI can be extracted from high-resolution impedance manometry or pH-impedance tracings, it may also be measured with a balloon probe with a 10-cm segment equipped with two arrays of impedance sensors (positioned above the squamocolumnar junction at sedated endoscopy) that provide real-time baseline impedance values; dedicated software generates MI contour patterns and disease probabilities (MiVu, Diversatek Healthcare, Milwaukee, WI) [18, 19]. Lower esophageal MI values are significantly decreased among patients with erosive or non-erosive GERD or eosinophilic esophagitis (EoE) compared to those without GERD [20].

Further, MI patterns along the esophageal axis illustrated by this device show promise to differentiate GERD, EoE, and non-GERD processes at the time of endoscopy. Specifically, in contrast to GERD and EoE, patients without GERD have higher MI values across all of the measured esophagus [19]. While patients with EoE have low MI measurements across all of the measured esophagus, those with GERD have low MI values in the distal esophagus that recover (or increase) moving proximally from the EGJ up the esophageal axis (or with acid suppressive therapy) [19]. These MI patterns may identify patients with GERD (AUC = 0.67), EoE (AUC = 0.84), and non-GERD (AUC = 0.83) [19]. Although MI performed at index endoscopy has exciting potential to decrease diagnostic and treatment latency in GERD evaluation, increased accessibility and inclusion of clinical data in prediction models will augment its clinical utility.

Endoscopic Functional Lumen Imaging Probe (FLIP)

FLIP, which is performed at the time of sedated upper endoscopy, leverages impedance planimetry technology through volumetric distension of a catheter-mounted balloon positioned across the lower esophagus (EndoFLIP, Medtronic, Minneapolis, MN) [21, 22]. FLIP can provide information on the distensibility and dimensions of the EGJ and esophagus in real-time, as well as secondary peristaltic patterns. While the role of FLIP in achalasia spectrum disorders is increasingly well-characterized (with EGJ distensibility indices (EGJ-DI) of < 2 mm^2/mm Hg and/or smaller maximum EGJ diameters < 12 mm supportive of outflow obstruction as opposed to GERD in symptom generation) [23, 24], its role in GERD diagnosis is less defined. Specifically, although there is promising utility for FLIP in the intra-operative tailoring of antireflux interventions to optimize clinical outcomes [25, 26], investigations have not consistently segregated patients with GERD from controls based on EGJ-DI, nor are there are not reliable published thresholds for GERD diagnosis [27]. Although clinical guidance suggests against the use of FLIP to diagnose GERD in routine clinical practice [2, 22], with further study and refinement FLIP may yet afford insights into GERD pathophysiology and potentially contribute to GERD diagnosis.

High-Resolution Manometry (HRM)

Beyond its significant conventional value in the management of patients with suspected GERD (such as ruling out confounding esophageal motor disorders, evaluating for behavioral disorders, and tailoring antireflux wraps) [6–9, 28], esophageal HRM also facilitates the acquisition of novel metrics that reflect reflux burden and can augment GERD diagnosis.

Esophagogastric Junction-Contractile Integral (EGJ-CI)

EGJ-CI is a novel HRM metric that can quantify the vigor of the antireflux barrier, the high-pressure zone constituted by the lower esophageal sphincter (LES) and the crural diaphragm (CD), that defends against reflux [5]. While earlier described as an LES pressure integral across a 10-s recording window [29], EGJ-CI values were subsequently standardized by forcing the distal contractile integral (DCI) analysis box on HRM software across the LES and CD during the landmark (resting) phase [30], with the contractile integral measured across three consecutive respiratory cycles (to minimize the effects of respiratory variation) above the gastric baseline (Fig. 2) [31]. The calculated contractile integral is then divided by the duration of these three cycles, to yield a time-independent measurement [31, 32]. Of note, in type 3 EGJ morphology (LES and CD separation of ≥ 3 cm), the CD component should be excluded for calculation of EGJ-CI [5, 9].

EGJ-CI measurements have shown value in GERD diagnosis. Italian data demonstrated that patients with GERD based on pH-impedance data had significantly lower median EGJ-CI values compared to those with FH (negative endoscopy and pH-impedance monitoring; 11 vs 22 mm Hg-cm) [32]. Likewise, data from Washington University demonstrated that mean EGJ-CI values were significantly lower when AET was abnormal, offering an optimal threshold value of 39 mm Hg-cm to predict abnormal AET [30]. Korean data proposed a threshold of 30 mm Hg-cm for prediction of GERD (sensitivity 78%, specificity 82%) [33]. Further work has suggested that not only do low EGJ-CI values associate with abnormal reflux burden [34], but that surgical intervention can result in superior outcomes in the setting of low EGJ-CI, particularly when esophageal body motor function is intact [35]. These findings likely reflect that low EGJ-CI values help identify GERD patients with marked antireflux barrier dysfunction. Further, EGJ-CI can quantify changes in EGJ barrier function with antireflux surgical intervention, with differences noted between complete and partial fundoplication in GERD [36].

While the Lyon Consensus on GERD diagnosis noted that EGJ-CI represents a promising GERD metric, it acknowledged dramatic numeric variations in the literature (potentially reflecting discrepancies in acquisition) that warrant further understanding and standardization before more widespread adoption [5]. Since that time, international normative EGJ-CI ranges have been published based on 484 healthy volunteers, finding 5th percentile EGJ-CI values of 6.9–12.1 mm Hg-cm, with variations based on manufacturer and gender [37]. Increasing data (including clinical outcomes) with standardized methodology and measurement (as with dedicated software tools) may facilitate more widespread use of EGJ-CI as a summary metric of antireflux barrier function and vigor.

Straight Leg Raise (SLR)

SLR is a novel manometric maneuver that can also help assess EGJ antireflux barrier function and augment GERD diagnosis. While LES-CD pressure typically augments to prevent gastroesophageal reflux in patients without GERD during instances of increased intra-abdominal pressure (IAP), this protective mechanism may not be present in patients with GERD, in whom this increased pressure may be transmitted into the thoracic cavity [38]. To perform SLR during HRM, the patient raises one leg off the bed above 45 degrees and holds it in place for at least 5 s, with the maneuver considered effective if the IAP increases by 50% during SLR [39].

Initial data suggested that larger intra-esophageal pressure (IEP) gradients (between baseline and SLR, measured 5 cm above the LES) of ≥ 100% predicted abnormal AET on reflux monitoring (sensitivity 71%, specificity 75%),

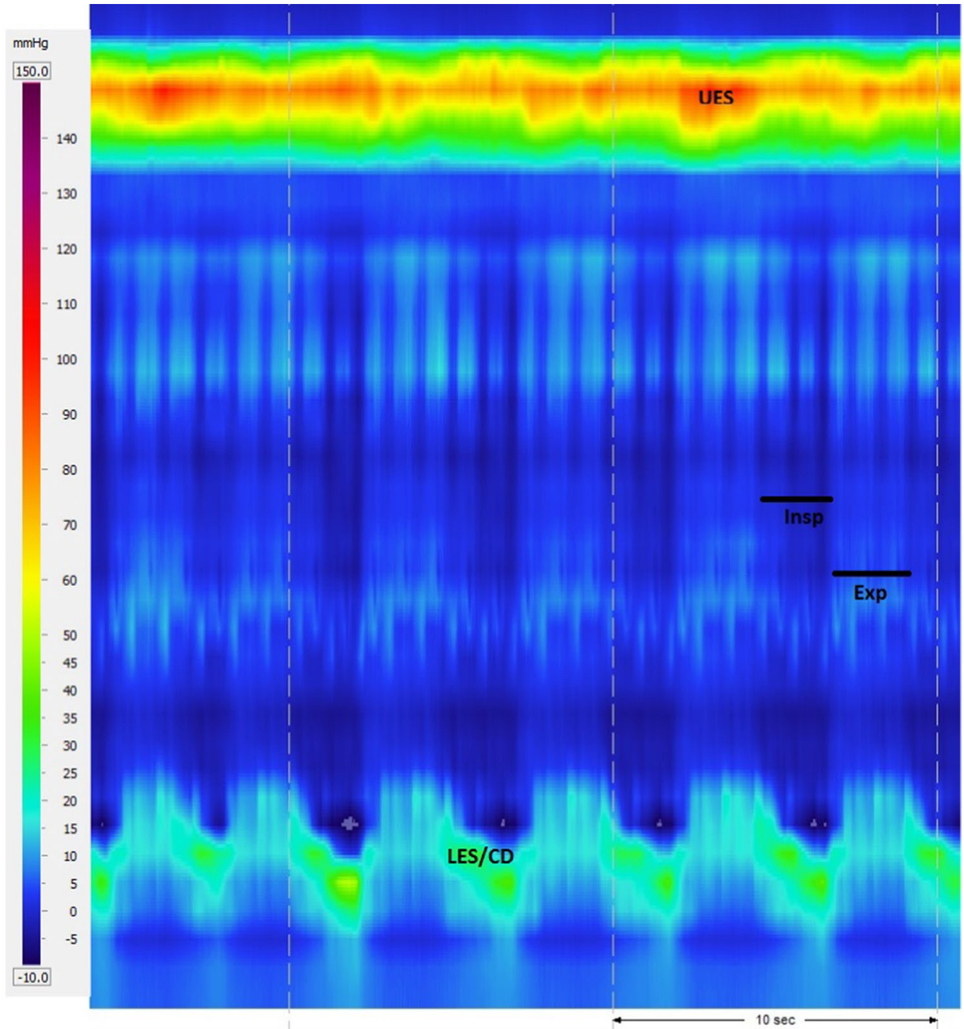

Fig. 2 Measurement of Esophagogastric Junction Contractile Integral (EGJ-CI) on High-Resolution Manometry (HRM). The distal contractile vigor (DCI) HRM software tool (red rectangle) is forced over the EGJ (encompassing the lower esophageal sphincter (LES) and crural diaphragm (CD) for types 1 and 2 EGJ morphology) to cover three respiratory cycles during the landmark (resting) phase, above the gastric baseline pressure. Dividing the acquired value by the duration of the three respiratory cycles corrects for respiration and provides a time-independent metric

particularly in the absence of hiatus hernias (type I EGJ morphology) [39]. Interestingly, EGJ-CI was not associated with peak IEP gradients in this cohort [39]. Further, among an Asian population with ineffective esophageal motility (IEM), transient hiatal separation during SLR was associated with higher AET [40]. Robust international data across 295 patients found that peak IEP during SLR was higher among patients with GERD (29.7 vs 13.9 mm Hg) [38]. Regardless of the presence of a hiatus hernia, a threshold of an 11 mm Hg increase in IEP from baseline to SLR predicted abnormal AET > 6% with sensitivity 79% and specificity 85% [38]. While further data are warranted for routine clinical adoption, inclusion of SLR at HRM with evaluation of IEP gradients can contribute to GERD diagnosis and help identify patients who may benefit from antireflux interventions.

High-Resolution Impedance Manometry (HRIM) Baseline Impedance (BI)

As transnasal catheter-based ambulatory reflux monitoring can be cumbersome to perform, uncomfortable for patients, and limited to a cross-sectional evaluation that may not adequately capture day-to-day variations in reflux burden, acquisition of distal esophageal BI values at the time of the landmark (resting) phase or overnight periods of high-resolution impedance manometry (HRIM) may circumvent some of these limitations for GERD evaluation and afford insights into longitudinal reflux burden as a surrogate of esophageal mucosal integrity [41]. While BI acquired from HRIM catheters may have some correlation with the more thoroughly studied and characterized mean nocturnal baseline impedance (MNBI) acquired from pH-impedance tracings at corresponding channels on testing off antisecretory therapy, this correlation appears limited for BI measured by HRIM and pH-impedance, especially proximally [41, 42]. Regardless, in a cohort from the Mayo Clinic, patients with supine and total AET ≥ 5% had significantly lower mean BI values than those with AET < 3% (1061 vs 2814 ohms); a threshold of 1582 ohms was 86% sensitive and 89% specific for GERD [43].

Contractile Segment Impedance (CSI)

Because BI acquired from resting phases at HRIM may be compromised by inconsistent or incomplete contact between the esophageal mucosa and the sensors on the catheter, acquisition of impedance values during esophageal peristaltic contractions (maximizing mucosal-sensor contact), may enhance the accuracy of GERD diagnosis. CSI values are extracted from the distal esophagus during protocol supine swallows at HRM [44]. Among patients undergoing HRIM and pH-impedance off therapy, not only did CSI inversely correlate with AET, but distal esophageal CSI also had numerically higher area under receiver operating characteristic curves (AUROC) for pathologic AET compared to HRIM-BI and MNBI [44]. Likewise, a Taiwanese cohort showed increased AUROC for CSI over HRIM-BI for GERD, but also observed an increased AUROC for CSI with the SLR maneuver [45]. Among a cohort of 40 patients, an optimized distal CSI threshold was 91% sensitive for an AET > 4%, with a negative predictive value of 96% [46]. With further data and prospective validation in the future, there is the possibility for impedance data (from HRM or MI) to potentially rule out pathologic GERD in selected clinical settings without requiring the costs, invasiveness, and discomfort of conventional ambulatory reflux monitoring.

Multiple Rapid Swallow (MRS) Responses

MRS is performed by administering 5 2-mL supine liquid swallows < 3 s apart, and primarily evaluates for esophageal contractile reserve, with potential implications for dysphagia and/or esophageal motor function after antireflux surgery (Fig. 3) [47–49]. Not only is the incorporation of MRS recommended for the classification of esophageal motor findings in GERD [9], but MRS is also included in the standardized manometric protocol recommended by the Chicago Classification version 4.0 [50]. In health, a physiologic MRS response consists of LES relaxation and deglutitive inhibition followed by an augmented esophageal body contraction, with vigor exceeding that of the single wet swallows [28].

Because peristaltic reserve relates to the clearance of refluxate, it follows that inadequate MRS responses may be associated with reflux burden, particularly in the setting of esophageal hypomotility. Among 103 Italian patients with pH-impedance data, peristaltic vigor during MRS was inversely correlated with AET [51]. However, data from Washington University of 191 patients found that contraction reserve based on MRS was not associated with AET in patients with normal HRM studies, but that contraction reserve was associated with reflux burden (particularly upright AET) in patients with nonsevere IEM [52]. Further data exploring the relationships between esophageal motor

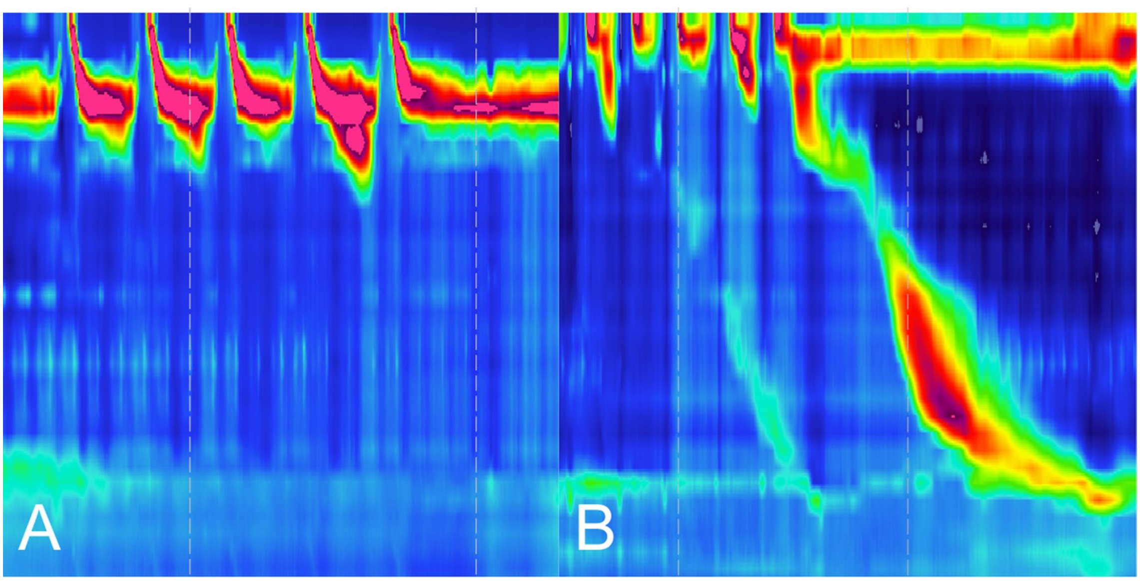

Fig. 3 Multiple Rapid Swallow (MRS) Responses on High-Resolution Manometry. **A** An abnormal MRS response, with expected lower esophageal sphincter (LES) relaxation and deglutitive inhibition, but without augmented esophageal peristalsis following the MRS maneuver. **B** A physiologic or normal MRS response, with LES relaxation and deglutitive inhibition, followed by augmented, vigorous esophageal body peristalsis

function, contractile reserve, reflux burden, and clinical outcomes will help facilitate how MRS can be most optimally utilized in GERD diagnosis.

Ambulatory Reflux Monitoring

Mean Nocturnal Baseline Impedance (MNBI)

As previously discussed for MI, HRIM-BI, and CSI, esophageal mucosal impedance has shown value as a measure of longitudinal reflux exposure and mucosal damage. While there is data suggesting some discriminatory value of MNBI in on-therapy pH-impedance monitoring [53], these impedance-based metrics have typically been acquired off PPI therapy; medical or surgical antireflux therapy can increase values in patients with GERD, reflecting recovery of mucosal integrity [54]. Early data from pH-impedance monitoring demonstrated a negative correlation between distal (but not proximal) esophageal baseline impedance (acquired at 2-h intervals across the study) and AET [55]. Further data have shown that lower esophageal baseline impedance can differentiate patients with GERD from FH [16].

Subsequently, standardized acquisition of MNBI has been proposed as the average of impedance values (at 3 and/or 5 cm above the LES) over quiet, recumbent 10-min periods around 1, 2, and 3 AM to minimize any interference from swallows or reflux events [56, 57]. In a large cohort of patients with PPI-responsive heartburn, a proposed threshold for distal MNBI off 2292 ohms identified pH-positive GERD with 86% sensitivity and 86% specificity [58]. Among a cohort of 266 patients tested off PPI therapy, those with elevated AET had lower distal but similar proximal MNBI values as those with physiologic AET [59]. Further, after 3 years of follow-up, distal esophageal MNBI was predictive of symptomatic improvement after medical or surgical antireflux therapy [59].

MNBI can be especially helpful as adjunctive evidence in settings of equivocal reflux evidence. Among patients with borderline or inconclusive AET of 4–6% on ambulatory reflux monitoring, international data showed that those with low MNBI responded to antireflux therapy at rates similar to those with abnormal AET > 6% [60]. Similarly, among an Italian cohort with inconclusive GERD (AET 4–6%), abnormal MNBI was more common among PPI responders compared to non-responders (91% vs 30%) [61]. This data, among other lines of investigation, support the role of MNBI analysis in complementing AET in GERD diagnosis and guiding management.

Post-reflux Swallow-Induced Peristaltic Wave (PSPW) Indices

In addition to secondary peristalsis facilitating volume clearance of refluxate, primary swallows following reflux episodes help deliver saliva to neutralize esophageal mucosal acidification, providing chemical clearance [2]. The PSPW index may be calculated as the proportion of reflux events followed within 30 s by a swallow-induced peristaltic wave [62]. Data from healthy subjects show that the use of this accepted time window between a reflux episode and PSPW of 30 s results in a near-optimal probability of a chance association of about 30% (a time window of 29 s would be associated with the very lowest probability of random association) [63].

Early data showed that the PSPW index was significantly lower in erosive reflux disease (15–16%) and NERD (31–33%) compared to FH or controls (67–75%), regardless of testing on or off PPI therapy [62]. Large cohort data proposed a threshold of 61% for PSPW index based on ROC analysis, with sensitivity 99% and specificity 92% for pH-positive GERD [58]. The stability of PSPW index values regardless of PPI status does not apply to impedance-based metrics, which differ in GERD based on antireflux therapy. International data found that patients with normal PSPW indices had significantly lower reflux burden than those with low PSPW indices, regardless of the presence or absence of contraction reserve [64]. Further, PSPW indices represent an independent predictor of PPI-refractory GERD [53]. Among the previously mentioned Italian cohort with inconclusive GERD, abnormal PSPW indices were more common among PPI responders compared to non-responders (86% vs 23%) [61]. Further data from Italy suggests that PSPW indices, individually and when combined with MNBI, may even link PPI-responsive heartburn to GERD better than AET in some clinical settings [65]. Although potentially cumbersome to manually calculate from pH-impedance tracings with current software, accumulating data highlight the significant adjunctive value of PSPW indices and MNBI in GERD evaluation, particularly in the setting of equivocal conventional metrics, such as borderline AET.

Conclusions

- For patients with suspected GERD symptoms not responsive to PPI therapy, the conventional clinical paradigm recommends upper endoscopy, followed by consideration of esophageal function testing, if without confirmatory evidence for GERD or an alternate explanation for symptoms.

- The esophagogastric junction contractile integral and straight leg raise maneuver at esophageal HRM afford insights into the EGJ antireflux barrier.
- Mucosal impedance-based reflux metrics, whether extracted from a dedicated balloon catheter at endoscopy, from HRIM as baseline or contractile segment impedance, or from pH-impedance tracings as MNBI, reflect esophageal mucosal integrity and demonstrate at least adjunctive value in GERD diagnosis.
- Esophageal contraction reserve on multiple rapid swallows at HRM and post-reflux swallow-induced peristaltic wave indices from pH-impedance tracings reflect different but complementary parameters helpful in the evaluation of reflux clearance and GERD.
- Better understanding and thoughtful adoption of novel reflux metrics and techniques can help facilitate a more patient-centric, individualized approach to GERD diagnosis and management.

Declarations

Conflict of interest The authors disclose no relevant conflicts of interest.

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