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The Utility of Esophageal Motility Testing in Gastroesophageal Reflux Disease (GERD)

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Abstract

Purpose of Review Here, we discuss how esophageal motor testing plays important roles in patients with suspected gastroesophageal reflux disease (GERD). In addition to guiding appropriate placement of catheters for ambulatory reflux monitoring, esophageal high-resolution manometry (HRM) rules out confounding diagnoses, such as achalasia spectrum disorders, that can present with symptoms similar to that of GERD, but are managed very differently.

Recent Findings HRM performed with impedance in the post-prandial setting (PP-HRIM) can assess for rumination syndrome or supragastric belching, which should be directed towards behavioral interventions. The recent GERD Classification of Motor Function recommends a hierarchical approach, focusing on (1) the esophagogastric junction (EGJ), (2) the esophageal body, and (3) esophageal contraction reserve, which can be assessed with provocative maneuvers at HRM, such as multiple rapid swallows (MRS). This approach can inform the appropriate tailoring of antireflux surgery. Novel esophageal motility metrics, such as the EGJ-contractile integral from HRM, or post-reflux swallow-induced peristaltic wave indices from 24-h pH-impedance monitoring, may also assist with GERD diagnosis.

Summary Assessment of esophageal motor function can contribute in a significant manner to the care of patients with suspected GERD, particularly when esophageal symptoms do not improve with antisecretory therapy, and/or when surgical or endoscopic antireflux therapies are under consideration.

Keywords Esophageal motor testing · Esophageal function testing · Esophageal high-resolution manometry (HRM) · High-resolution impedance manometry (HRIM) · Gastroesophageal reflux disease (GERD) · Multiple rapid swallows (MRS) · Antireflux surgery (ARS) · Achalasia

Introduction

Gastroesophageal reflux disease (GERD), characterized by the reflux of gastric contents into the esophagus, is common; the prevalence in North America is estimated at 18–28% [1]. GERD is often diagnosed based on clinical evaluation of symptoms in practice, such as typical symptoms of heartburn and/or regurgitation [2]. Further, despite the limited specificity of this approach compared with objective esophageal testing in GERD diagnosis, symptomatic response to empiric proton pump inhibitor (PPI) therapy is associated with cost savings, may support potential GERD diagnosis, and is suggested by society guidelines [3–5]. On the other hand, after upper endoscopic evaluation, esophageal function testing is typically reserved for persistent symptoms refractory to PPI therapy, diagnostic uncertainty, pre-operative planning, and/or evaluation of atypical symptoms (such as cough) in clinical practice, with the recent Lyon Consensus forwarding the GERD diagnostic paradigm by defining parameters on ambulatory reflux testing that may guide management [6, 7•].

Here, we focus on how assessment of esophageal motor function can help guide the appropriate management of suspected GERD. Esophageal motor function—with respect to both the esophagogastric junction (EGJ) and the esophageal body—affects esophageal reflux burden, prompting the GERD classification of esophageal motor function [8•]. In this

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setting, esophageal high-resolution manometry (HRM) evaluates esophageal motor function in patients with esophageal symptoms that do not symptomatically respond to PPI therapy with unrevealing upper endoscopy, as well as prior to endoscopic or surgical antireflux intervention, and for appropriate positioning of catheters for ambulatory reflux monitoring [9, 10]. The Chicago Classification, now in its third iteration, facilitates the interpretation of HRM studies and the diagnosis of esophageal motor disorders through three cardinal metrics: (1) integrated relaxation pressure (IRP), which measures the adequacy of relaxation of the lower esophageal sphincter (LES) with swallowing; (2) distal contractile integral (DCI), which quantifies the vigor of esophageal body peristalsis; and (3) distal latency (DL), which confirms appropriate sequencing of esophageal peristalsis [11•, 12].

Ruling out Confounding Diagnoses in Suspected GERD

When patients present with suspected GERD, especially in the presence of typical symptoms of heartburn and regurgitation, without alarm symptoms such as dysphagia, empiric PPI therapy is generally appropriate [4, 5]. If esophageal symptoms persist in this setting, clinicians should first ensure compliance with optimally dosed PPI therapy [13]. If, however, symptoms persist despite compliance with optimally dosed PPI therapy, potential confounding etiologies for symptoms should be investigated. This work-up begins with upper endoscopy, which can identify complications of GERD (such as erosive esophagitis, peptic (reflux-mediated) strictures, adenocarcinoma) as well as other esophageal disorders (eosinophilic esophagitis, infectious esophagitis, squamous cell carcinoma). If symptoms persist despite antisecretory therapy and upper endoscopy and/or barium radiography are unrevealing, esophageal function testing is appropriate [7•].

Specifically, HRM can identify achalasia spectrum disorders, which can present with symptoms similar to that of GERD, such as heartburn, regurgitation, and/or chest pain [14]. The cardinal HRM metric of IRP, which quantifies LES relaxation with swallowing, has a sensitivity of 93–98% and specificity of 96–98% for a diagnosis of achalasia [15, 16]. However, achalasia spectrum disorders stem from pathophysiology distinct from GERD (particularly, incomplete LES relaxation) and are therefore managed quite differently, primarily with LES disruptive therapies [8•, 10]. In this fashion, standard fundoplication performed without LES disruption would worsen LES obstruction in patients with achalasia spectrum disorders, exacerbating symptoms. In a cohort of > 1000 patients at Washington University undergoing esophageal HRM prior to planned laparoscopic antireflux surgery (ARS), 2.5% had achalasia spectrum disorders and another 4.5% had esophageal body aperistalsis or severe hypomotility [17]. Together, therefore, 7% of this cohort had absolute or relative contraindications to the originally planned 360-degree fundoplication. In another cohort of > 100 patients from Amsterdam with suspected reflux symptoms that did not symptomatically respond to PPI who underwent HRM and 24-h pH-impedance monitoring, one-third had diagnoses other than GERD, including 2% with achalasia [18]. Such studies demonstrate that consideration of HRM is paramount in patients with esophageal symptoms not responding appropriately to optimal PPI therapy or prior to antireflux interventions in order to rule out confounding esophageal motor disorders, primarily achalasia spectrum disorders, which can present similarly to GERD but should not be directed to standard ARS.

Assessment for Behavioral Disorders

Another useful role of esophageal HRM in the evaluation of suspected GERD symptoms that do not resolve with PPI therapy is an assessment for behavioral disorders, such as rumination syndrome and supragastric belching. These presentations can overlap with GERD and cause diagnostic confusion, often going misdiagnosed by providers, with delays in appropriate management for these patients. Specifically, these disorders should be directed towards behavioral interventions, as opposed to maximization of antireflux therapy.

Rumination syndrome stems from post-prandial abdominal musculature contractions with increased intra-abdominal pressure, resulting in repetitive regurgitation of food contents with rechewing, reswallowing, and/or spitting out food [19]. The first-line therapy for rumination syndrome is behavioral modification with post-prandial diaphragmatic breathing with or without biofeedback [20, 21].

Excessive belching can be gastric or supragastric. Supragastric belching is characterized by the sucking or injection of pharyngeal air into the esophagus, followed by muscular contraction resulting in the abrupt expulsion of this air prior to reaching the stomach [22]. Potential treatment options for supragastric belching include speech therapy, biofeedback, diaphragmatic breathing, or hypnosis [23].

High-resolution impedance manometry (HRIM) can objectively detect episodes of rumination and supragastric belching, as well as transient LES relaxations (TLESRs) consistent with gastroesophageal reflux. TLESRs appear as inhibition of the diaphragmatic crura with LES relaxation for > 10 s, associated with retrograde movement of gastric contents into the esophagus [24•]. Rumination episodes are demonstrated by increased intragastric pressure > 30 mmHg above baseline, followed by retrograde flow of gastric contents into the esophagus, with increased esophageal pressure and upper esophageal sphincter (UES) relaxation [25]. Supragastric belches appear as EGJ contraction, negative intrathoracic pressures, and

UES relaxation, with aboral flow of air illustrated by increases in impedance, followed by expulsion of this air.

Further, diagnostic criteria based on HRIM performed in the post-prandial setting (PP-HRIM) have been proposed based on observation of these episodes. In this setting, patients consume a solid refluxogenic test meal, with up to 90 min of post-prandial HRIM monitoring. Supragastric belching may be defined as greater than two episodes/h, with or without TLESRs, and rumination syndrome as at least one rumination episode/h, with or without TLESRs or supragastric belches. Based on these definitions, in a study of 94 PPI-nonresponders at Northwestern selected to undergo PP-HRIM over a 6-year period, 42% had supragastric belching and 20% had rumination syndrome [24•]. Therefore, in this cohort, albeit selectively referred by expert esophagologists, 62% had behavioral patterns and 45% had behavioral patterns in the absence of increased TLESRs, representing patients who should be directed towards behavioral therapies instead of maximization of antireflux therapies.

GERD Classification of Esophageal Motor Function

The motor function and structural integrity of the EGJ and esophageal body have important implications for reflux burden, as these entities can facilitate retrograde movement of gastric contents through the EGJ into the esophagus and/or impaired clearance of refluxate [2]. A recently proposed classification scheme to evaluate esophageal motor findings in GERD focuses on a three-step hierarchical approach: (1) the EGJ as antireflux barrier, (2) esophageal body motor function, and (3) assessment of esophageal contraction reserve with provocative maneuvers at HRM [8•]; Table 1.

Step 1. Assessment of the EGJ

The EGJ antireflux barrier may be described in both structural (EGJ morphology types) and motor (i.e., normal or hypotensive) terms. Using HRM, EGJ morphology is defined by localizing the LES and crural diaphragm (CD), which together compose the EGJ. The separation between the LES and CD facilitates the characterization of the EGJ morphology into three types on HRM: (I) superimposed LES and CD (no hiatus hernia), (II) axial separation of the LES and CD by < 3 cm, and (III) axial separation of the LES and CD by > 3 cm [11•, 26]. In this manner, HRM is highly sensitive (92%) and specific (95%) for hiatus hernia detection, superior to upper endoscopy or barium radiography alone [27]. When a hiatus hernia is present (EGJ morphology types II or III), this separation weakens the antireflux barrier and contributes to gastroesophageal reflux [26, 28, 29].

Table 1 Gastroesophageal reflux disease (GERD) classification of esophageal motor function

Esophagogastric junction (EGJ)	Intact Hypotensive Hiatus Hernia Both hypotensive and hiatus hernia
Esophageal body	Intact Fragmented peristalsis Ineffective esophageal motility Absent contractility
Contraction reserve	Contraction reserve Absence of contraction reserve

In addition to EGJ morphology, EGJ resting motor function may be described by HRM. Although conventional manometric parameters such as end-expiratory and mean baseline LES pressures have published normative values and are typically reported with HRM studies, the EGJ-contractile integral (EGJ-CI) metric takes into account inspiratory augmentation in the setting of the length and tone of the EGJ antireflux barrier [8•]. The EGJ-CI metric may segregate physiologic from pathologic esophageal reflux burden and changes appropriately with surgical intervention, such as fundoplication [30–32].

The combination of EGJ morphology type and motor assessment defines EGJ phenotypes. Normal EGJ resting pressures and type I EGJ morphology are consistent with an intact EGJ antireflux barrier, suggesting TLESRs as the probable etiology of gastroesophageal reflux in these patients [33]. On the other hand, abnormal EGJ antireflux barrier phenotypes can include a hiatus hernia (types II or III EGJ morphology), hypotensive EGJ, or both [8•].

Step 2. Assessment of the Esophageal Body

Next, HRM evaluates the motor function of the esophageal body, which is responsible for the clearance of esophageal refluxate. The most commonly encountered esophageal body motor pattern among GERD patients is normal (or intact) peristalsis, defined by the Chicago Classification as appropriate contraction vigor (DCI > 450 mmHg s cm) and the absence of > 5 cm breaks in the 20-mmHg peristaltic contour [17, 34]. However, in the setting of GERD, esophageal body motor function may be seen along a gradient, ranging from intact peristalsis to increasingly abnormal motor patterns, which include fragmented peristalsis (with breaks > 5 cm but preserved esophageal body contraction vigor), ineffective esophageal motility (at least 50% ineffective swallows, characterized by DCI < 450 mmHg s cm), and absent contractility (all swallows with DCI < 100 mmHg s cm) (Fig. 1) [8, 11]. These abnormal esophageal HRM studies, characterized by fragmentation or hypomotility, are more commonly found with increased esophageal reflux burden, and in the setting of erosive esophagitis or Barrett's esophagus [35, 36]. In particular, the

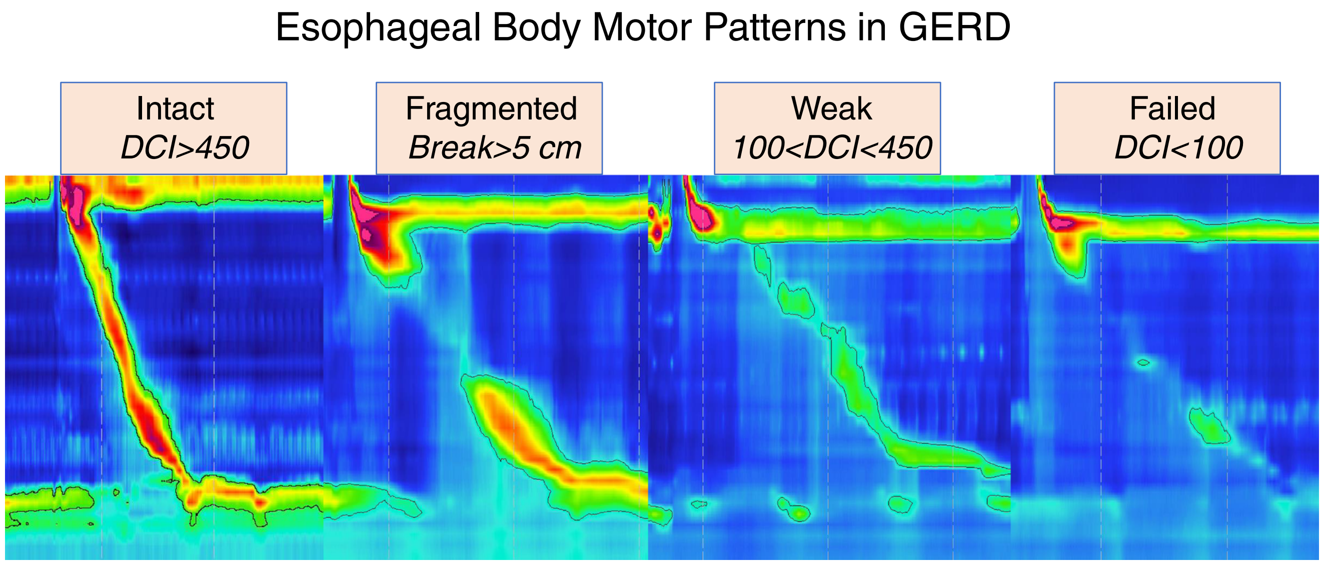

Fig. 1 Esophageal body motor patterns in gastroesophageal reflux disease (GERD) (adapted with permission from C. Prakash Gyawali)

presence of esophageal body hypomotility correlates with increased supine esophageal reflux burden [37, 38].

Step 3. Assessment of Esophageal Contraction Reserve

Particularly in the setting of hypomotile esophageal body motor patterns, provocative maneuvers performed at HRM can evaluate for augmentation of esophageal body contraction, consistent with contraction reserve. The most widely utilized provocative maneuvers at HRM for this purpose are multiple rapid swallows (MRS) and the rapid drink challenge (RDC) [39•]. The MRS maneuver is composed of five liquid swallows performed 2 to 3 s apart, and the RDC maneuver refers to free drinking of 100–200 mL of water. With these maneuvers, the repetitive swallows should result in deglutitive inhibition of esophageal body contraction with LES relaxation, to be followed typically by robust esophageal body peristalsis [40]. With MRS, an increase in esophageal body contraction vigor (as quantified by the DCI) in response to the MRS maneuver compared with the mean DCI of the single wet swallows (WS) is consistent with the presence of esophageal peristaltic reserve (MRS DCI:WS DCI ratio > 1). At least three MRS sequences should ideally be performed at the HRM study to reliably evaluate esophageal contraction reserve, with the best MRS sequence being considered as there can be significant swallow-to-swallow variation even in patients with seemingly normal esophageal motility [41].

MRS responses correlate with esophageal reflux burden. Among 103 endoscopy-negative heartburn patients with normal HRM divided according to abnormal (distal esophageal acid exposure time (AET) > 4.2% and > 54 total reflux events) or normal (neither parameter present) 24-h pH-impedance reflux monitoring studies, MRS DCI and MRS DCI:WS DCI ratios were significantly lower among those patients with abnormal pH-impedance studies, with inverse correlations noted between MRS DCI or MRS DCI:WS DCI ratios and esophageal reflux burden as quantified by distal esophageal AET [42]. Evaluation of esophageal contraction reserve can also help inform surgical planning in GERD, as discussed below.

Tailoring of Antireflux Surgery Based on Esophageal Motor Function

ARS, traditionally comprised of complete (360°, Nissen) or partial (180° or 270°) fundoplication, mechanically augments EGJ function and reduces gastroesophageal reflux burden. However, dysphagia can occur (or persist) after ARS, due to either morphologic EGJ abnormalities or esophageal body dysmotility. For example, dysphagia is more common after laparoscopic fundoplication compared with pharmacologic GERD therapy (short-term, 13% vs 4%, RR 3.6; medium-term 10% vs 2%, RR 5.4) [43]. Although outcome data are limited, findings of severe esophageal body hypomotility may guide treatment teams toward a partial—as opposed to complete—fundoplication to minimize the risk of post-operative dysphagia. For example, for post-myotomy fundoplication, rates of post-operative dysphagia at 6 years were significantly higher among patients with complete versus partial fundoplication (39% vs 10%, $p = 0.03$) [44]. For GERD, rates of post-operative dysphagia at 2 years were higher for complete versus partial fundoplication, specifically among patients with esophageal dysmotility [45].

In the setting of abnormal esophageal body motor patterns, evaluation of contraction reserve with MRS can help inform the surgical approach and tailor the fundoplication most appropriately. MRS has value in predicting dysphagia after fundoplication, with abnormal pre-operative MRS responses found more commonly among those with post-operative dysphagia [46]. Specifically, the proportions of patients with evidence of esophageal contraction reserve (MRS DCI:WS DCI ratio > 1) on pre-operative HRM studies differed based on the presence of post-operative dysphagia: 78% of normal controls, 64% of those without post-operative dysphagia, 44% of those with early dysphagia (< 3 months post-operatively), and 11% of those with late dysphagia (> 3 months post-operatively), demonstrating that a lack of augmentation with MRS was associated with late post-operative dysphagia [47•]. Additional studies suggest that MRS responses differ between ineffective esophageal motility (IEM) phenotypes in the setting of ARS. When patients were stratified into four IEM phenotypes (resolved IEM, persistent IEM, developed IEM, or no IEM) based on pre-operative and post-operative HRM testing, the cohorts with persistent IEM or those who developed IEM after ARS had significantly lower augmentation with MRS, compared with the group without IEM, and the likelihood of appropriate augmentation with MRS was highest in those with resolved IEM or no IEM [48]. These data suggest that the evaluation of esophageal body contraction reserve with MRS maneuvers at HRM prior to ARS can help inform the surgical approach (partial versus complete fundoplication) to best minimize the risk of post-operative dysphagia.

Novel Esophageal Motility Metrics

Esophagogastric Junction-Contractile Integral

As introduced above, the novel EGJ-CI metric can be acquired from HRM studies, incorporating respiratory variation into assessment of the EGJ barrier. In practice, measurement of the EGJ-CI can be performed by constraining the HRM software box used to calculate DCI over the EGJ (LES and CD) for a duration of three respiratory cycles, indexed to the gastric pressure, and dividing by this duration [7•, 8]. Although reported normative ranges of EGJ-CI vary based on the exact method of acquisition, the recent Lyon Consensus proposes further focus on this EGJ-CI metric to quantify EGJ antireflux barrier function [7•]. Multiple studies have demonstrated that the EGJ-CI can segregate among different subsets of patients with GERD (such as abnormal ambulatory reflux monitoring studies and/or erosive esophagitis) based on barrier function [30, 31, 49]. It has also been shown that a low EGJ-CI may predict a superior symptomatic response to ARS versus medical therapy [30] and that EGJ-CI values augment appropriately with ARS [32].

Post-Reflux Swallow-Induced Peristaltic Wave Index

Under normal circumstances, gastroesophageal refluxate triggers a vagally mediated esophagosalivary reflex that generates primary peristalsis—or triggers distention-related secondary peristalsis, together known as the post-reflux swallow-induced peristaltic wave (PSPW), which clears refluxate and helps to neutralize esophageal mucosal acidification [7•]. This peristalsis can be seen on pH-impedance studies and may be defined as an antegrade 50% decline in impedance relative to pre-swallow baseline, which progresses from proximal to distal esophageal impedance channels and is then followed by ≥ 50% return to pre-swallow baseline impedance levels in the distal channels [50]. The PSPW index (PSPWI) may then be calculated from pH-impedance studies as the ratio of the number of reflux events that are followed within 30 s by a PSPW to the total number of reflux events in the study [51].

Although manual review of 24-h pH-impedance studies is required at present for calculation of PSPWI, this novel motility metric shows tremendous promise. PSPWI, while not affected by medical antireflux therapy, is lower in untreated erosive GERD than in untreated nonerosive GERD, and lower in both groups compared with controls [50–52]. In fact, PSPWI may even outperform other pH-impedance parameters in identifying patients with GERD, increasing the diagnostic yield of ambulatory reflux monitoring [51]. At pH-impedance monitoring performed on PPI therapy, PSPWI was associated with PPI responsiveness [53]. Further, the PSPWI shares a direct correlation with MRS DCI and MRS DCI:WS DCI ratios (Spearman correlation coefficients 0.63–0.67, $p < 0.001$) [42].

Conclusions

In patients with suspected GERD, esophageal motility testing, primarily with HRM, has significant utility in diagnosis and management, beyond localization of landmarks for catheter-based reflux monitoring. For those patients with suspected GERD who do not have an adequate symptomatic response to medical antireflux therapy and whose upper endoscopy is unrevealing, HRM is used to evaluate for confounding esophageal motor diagnoses, such as achalasia spectrum disorders. Achalasia spectrum disorders represent a contraindication to standard fundoplication without myotomy and are managed very differently from GERD, primarily with LES disruptive approaches. HRM catheters equipped with impedance channels can be used in the post-prandial setting (PP-HRIM) for evaluation of rumination episodes or supragastric belching, which can overlap with GERD and lead to diagnostic confusion but are most effectively managed with behavioral treatments. The GERD classification of motor function proposes a three-step evaluation, consisting of assessment of the EGJ (both morphological and motor facets), esophageal body, and esophageal contraction reserve. Evaluation of contraction reserve is best performed by assessing for augmentation of esophageal body peristalsis (as measured by DCI) in response to MRS maneuvers at HRM, by a simple ratio with mean WS DCI. Contraction reserve can guide selection of the appropriate wrap to minimize the risk of post-operative dysphagia in patients with GERD who have abnormal esophageal body motor patterns. Emerging esophageal motility metrics, such as EGJ-CI gleaned from HRM studies or the PSPWI acquired from pH-impedance tracings, demonstrate promise in improving the diagnosis and management of patients with suspected GERD symptoms.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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