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Review Article

Esophageal motor abnormalities in gastroesophageal reflux disorders

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Abstract

Gastroesophageal reflux disease (GERD), a prevalent condition with multifactorial pathogenesis, involves esophageal motor dysmotility as a key contributing factor to its development. When suspected GERD patients have an inadequate response to proton-pump inhibitor (PPI) therapy and normal upper endoscopy results, high-resolution manometry (HRM) is utilized to rule out alternative diagnosis such as achalasia spectrum disorders, rumination, or supragastric belching. At present, HRM continues to provide supportive evidence for diagnosing GERD and determining the appropriate treatment. This review focuses on the existing understanding of the connection between esophageal motor findings and the pathogenesis of GERD, along with the significance of esophageal HRM in managing GERD patients. The International GERD Consensus Working Group introduced a three-step method, assessing the esophagogastric junction (EGJ), esophageal body motility, and contraction reserve with multiple rapid swallow (MRS) maneuvers. Crucial HRM abnormalities in GERD include frequent transient lower esophageal sphincter relaxations, disrupted EGJ, and esophageal body hypomotility. Emerging HRM metrics like EGJ-contractile integral and innovative provocative maneuver like straight leg raise have the potential to enhance our understanding of factors contributing to GERD, thereby increasing the value of HRM performed in patients who experience symptoms suspected of GERD.

Keywords: *Esophageal motility, Gastroesophageal reflux disease, High-resolution esophageal manometry*

Introduction

Gastroesophageal reflux disease (GERD) is a common condition in which the contents of the stomach flow back into the esophagus, leading to troublesome esophageal or extra-esophageal symptoms and potential complications [1]. The prevalence of GERD worldwide is estimated to range between 7.4% and 19.6% [2], with variations depending on the country and the criteria used to define GERD symptoms. Despite being conventionally regarded as a disease caused by excessive acid, approximately half of GERD patients find minimal to no relief from pharmacological acid suppression [3,4]. The diverse range of symptoms and varying responses to treatment can be attributed to the complex and multifaceted nature of the underlying mechanisms that contribute to GERD.

The proposed pathogenesis of GERD includes factors such as inadequate saliva production, esophageal motor dysfunction, the presence of a hiatal hernia, the gastric acid pocket, gastric hypersecretion, delayed gastric emptying, and visceral hypersensitivity [5-7]. Gaining insight into the specific mechanism of reflux in an individual patient can be valuable in identifying the phenotype of GERD and determining the optimal therapeutic approaches for managing GERD. Among these factors, esophageal motor dysfunction stands as a significant pathophysiological mechanism, which can be detected through esophageal manometry.

Over the past few decades, conventional esophageal manometry has played a crucial role in diagnosing esophageal motility disorders. In recent years, high-resolution manometry (HRM) has emerged as the gold standard for assessing esophageal motor function, being utilized by more than 80% of motility centers globally [8]. The Chicago Classification, though helpful for identifying major motor disorders [9,10], was not originally designed to evaluate motor function in the context of GERD. The Lyon Consensus has made

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strides in establishing HRM and ambulatory reflux testing parameters for GERD, guiding its management [11,12]. While HRM alone cannot diagnose GERD, abnormal esophagogastric junction (EGJ) morphology (i.e. hiatus hernia), compromised EGJ barrier (especially using EGJ-contractile integral [EGJ-CI]), and esophageal hypomotility often link to abnormal acid exposure time or erosive esophagitis (ERD) [12-14].

In this review, we aim to provide a comprehensive overview of the current understanding regarding the relationship between esophageal motor findings and the pathogenesis of GERD. In addition, we also summarize the role of HRM and provocative testing in the clinical management of GERD.

Abnormal esophageal motility in gastroesophageal reflux disease

The most common motor abnormalities that contribute to the occurrence of reflux in GERD include frequent transient lower esophageal sphincter relaxations (TLESRs), disruption of the EGJ, and esophageal body hypomotility. These abnormalities may manifest in either the EGJ, esophageal body, or both.

Frequent transient lower esophageal sphincter relaxation

TLESRs serve as the main pathophysiologic mechanism responsible for initiating reflux. These frequent relaxations are characterized by prolonged and significant relaxation of the lower esophageal sphincter (LES) without the presence of swallowing, triggered by gastric distention [15]. Previous studies utilizing HRM demonstrated that TLESR-induced opening of the EGJ is a result of LES relaxation, crural diaphragm (CD) inhibition, esophageal shortening, and elevated gastric pressure [15,16]. TLESR is a physiological mechanism observed in both healthy individuals and patients with GERD. While ongoing debate persists regarding the frequency of TLESRs in GERD patients, it is consistently observed that the proportion of TLESRs associated with reflux is higher in GERD patients compared to controls [17,18].

Disruption of anti-reflux barrier at the esophagogastric junction

Disruptions in the EGJ barrier can arise from motor deficiency (hypotensive EGJ), morphological abnormalities (hiatus hernia), or a combination of both factors. These disruptions can contribute to the development of GERD and related symptoms. HRM, with its ability to assess the functionality and structure of the EGJ, provides valuable information about its characteristics.

Hiatal hernia

The morphology of the EGJ determines the relationship between two significant components: the intrinsic LES and the CD. A disrupted anti-reflux barrier occurs when these two elements are spatially detached, thus indicating the presence of a hiatal hernia and facilitating the reflux of gastric content into the esophagus [19,20]. According to the Chicago Classification, there are three subtypes of EGJ morphology on HRM: (i) type I, superimposed LES and CD (no hiatus hernia), (ii) type II, axial separation of the LES and CD by <3 cm, and (iii) axial separation of the LES and CD by more than 3 cm [9,10]. Research has shown that HRM achieves a high sensitivity of 92% and specificity of 95% in the detection of hiatus hernia. It has been found to be superior to both upper endoscopy (73%) and barium radiography (73%) when used individually for this purpose [21]. In the presence of a hiatus hernia (particularly EGJ morphology type III), the separation weakens the anti-reflux barrier, leading to a substantial rise in esophageal acid exposure time, total reflux episodes, and DeMeester score [22,23].

Hypotensive esophagogastric junction

In addition to morphological changes, the presence of reflux is also linked to a hypotensive EGJ [19,24]. A hypotensive EGJ is identified when the basal pressure of the LES is below 10 mmHg [25]. Studies have shown that the mean LES pressure is significantly lower in patients with ERD and nonerosive reflux disease (NERD) compared to healthy individuals and those with functional heartburn [26,27]. Furthermore, populations referred for surgical management of GERD are more likely to exhibit low LES resting pressure [28]. Nevertheless, there is a lack of studies that utilize traditional manometric parameters like end-expiratory and mean baseline LES pressures to assess the effectiveness of EGJ barrier function. Currently, a novel metric called EGJ-CI is calculated similarly to the distal contractile integral (DCI) using a box that covers the LES and CD during three respiratory cycles above a gastric pressure threshold. To eliminate the influence of time, the calculated "DCI" is divided by the duration of the three respiratory cycles and expressed in units of mmHg·cm [29]. Studies have shown that EGJ-CI effectively differentiates between a normal and abnormal reflux burden and accurately reflects changes after fundoplication [30-33]. Tolone *et al*. proposed a cutoff value of 5 with high sensitivity (89%) and specificity (63%) to distinguish GERD from functional heartburn [22]. Another study indicated that borderline reflux patients with lower EGJ-CI scores (<21.2 mmHg) respond better to anti-reflux treatments [33]. However, it is not in routine clinical use due to variations in calculation methods, leading to a broad range of normal values.

Esophageal body hypomotility

Esophageal hypomotility disorders are the most common motility abnormalities among pH-metry-confirmed GERD cases [7,28]. In HRM, the vigor of esophageal body contractions is assessed using the DCI, where a value <450 mmHg·s·cm corresponds to an average distal contraction amplitude of <30 mmHg, defining ineffective peristalsis [34]. Esophageal hypomotility can present in different levels of severity, such as ineffective esophageal motility (IEM) and absent contractility. Fragmented peristalsis, characterized by the presence of breaks measuring ≥5 cm in the peristaltic contour, has been incorporated into the definition of IEM in Chicago Classification version 4.0 (CCv4.0) [35]. This change is motivated by the infrequent occurrence of this pattern and the clinical relevance of a break exceeding 5 cm in peristaltic integrity [13,36].

Ineffective esophageal peristalsis

Ineffective swallows are characterized by swallows with a large break (>5 cm), weak swallows (DCI 100–450 mmHg·s·cm), and failed swallows (DCI <100 mmHg·s·cm). Recent evidence indicates that ≥50% of failed swallows [13] or ≥70% of ineffective swallows predict abnormal acid exposure in GERD patients [13,14]. Severe peristaltic dysfunction (≥70% ineffective swallows) is linked to impaired bolus clearance [13,37], increased supine acid exposure [38,39], and esophageal mucosal injury [13,40,41]. Yet, a diagnostic threshold of 50% ineffective swallows is less reliable for detecting abnormal bolus transit and reflux burden compared to >70% ineffective swallows [13,37,42]. As a result, the diagnostic criteria for IEM in CCv4.0 have become more stringent, requiring a minimum of 80% ineffective swallows or at least 50% failed peristalsis [10]. Furthermore, IEM is more likely to occur in patients with ERD, increasing severity of GERD, and Barrett's esophagus, compared to those with NERD and physiologic acid exposure [43-45]. These findings suggest that IEM may play a role in the pathogenesis of GERD [13,14,37-41].

Absent peristalsis

In the esophageal body, there can be a complete absence of contractility, which is characterized by 100% failed peristalsis (DCI <100 mmHg·s·cm) while maintaining a normal integrated relaxation pressure (IRP) in both the supine and upright positions according to CCv. 4.0 [10]. This severe form of esophageal body hypomotility was detected in 3.2% of GERD patients who were undergoing assessment for anti-reflux surgery [28]. In addition, the absence of contractility has been linked to a significantly elevated esophageal acid burden [42]. When dealing with absent contractility, borderline IR*P* values should prompt consideration of the possibility of type I achalasia. It is crucial to conduct supportive testing if dysphagia is the predominant symptom. While there is no specific treatment to restore peristalsis, GERD patients with absent contractility can manage symptoms with aggressive PPI therapy, lifestyle modifications, and posture adjustments [35].

Abnormal secondary peristalsis

Primary esophageal peristalsis is responsible for propelling the bolus through the esophagus, while secondary peristalsis aids in clearing residual refluxate to facilitate esophageal emptying. Secondary peristalsis, which can be stimulated by factors such as gas, balloon distention, or water perfusion, contributes to 90% of reflux clearance, especially during sleep [46]. GERD patients, especially those with IEM, demonstrate significant impairments in the triggering of secondary peristalsis on both conventional manometry and HRM, in contrast to normal subjects or GERD patients with normal esophageal motility [46-48].

Impaired esophageal body contraction reserve

The use of provocative maneuvers, especially MRSs, has been commonly employed during HRM to assess deglutitive inhibition during repetitive swallows, as well as the contractile response subsequent to the final swallow in the sequence [49]. The contractile reserve refers to the enhancement of esophageal body contraction following MRS. It is quantified by calculating the ratio between the post-MRS DCI and the average DCI of nonfailed single swallows, with a value of ≥1 [35]. A normal MRS response necessitates intact inhibitory and excitatory neural pathways for coordinated regulation of the esophageal body and LES, coupled with sufficient muscle reserve to effectively respond to the stimulation following MRS [49,50]. The correlation between MRS response and esophageal acid burden has been observed [42]. Recent studies have indicated that MRS ratio is notably lower in GERD patients with abnormal pH results [51]. This ratio demonstrates an inverse relationship with esophageal acid exposure time while also showing a direct association with baseline impedance and effective chemical clearance, as measured by the postreflux swallow-induced peristaltic wave index [42,51]. Moreover, the lack of contractile reserve on MRS in patients with IEM can potentially predict the occurrence of dysphagia following fundoplication [52,53], as well as the persistence or development of IEM after anti-reflux surgery [54]. This underscores the significance of HRM in diagnosing esophageal motor abnormalities in GERD patients before they undergo anti-reflux surgery, aiding in the selection of the most suitable type of fundoplication (complete or partial) to prevent the occurrence of dysphagia.

Indication for esophageal motor testing in the diagnosis of gastroesophageal reflux disease

When patients continue to experience GERD symptoms despite empirical PPI therapy or exhibit alarm features (anemia, dysphagia, or weight loss), the initial investigation starts with upper endoscopy. This procedure helps in identifying complications associated with GERD (e.g. ERD, stricture, Barrett's esophagus, and adenocarcinoma) as well as other structural or inflammatory esophageal disorders like eosinophilic esophagitis. If the upper endoscopy reveals normal esophageal mucosa, further esophageal functional testing, including HRM and ambulatory pH monitoring, should be conducted to confirm the diagnosis of GERD or to explore other alternative diagnoses that mimic GERD [11,55].

Excluding major motility disorders in suspected gastroesophageal reflux disease

Based on research conducted in Amsterdam, it was observed that among patients who did not experience improvement with PPI therapy and underwent HRM and pH-impedance monitoring, approximately 30% received diagnoses other than GERD. This included 2% who were diagnosed with achalasia [56]. Another study, involving a sample size of over 1000 patients who underwent HRM before laparoscopic anti-reflux surgery, identified that 7% of them had either achalasia or severe hypomotility disorders. These findings acted as absolute or relative contraindications to the initially planned complete fundoplication procedure [28]. In such cases, the utilization of HRM becomes crucial for patients presenting with esophageal symptoms that do not adequately respond to PPI therapy or before undertaking anti-reflux surgery, as it helps to rule out achalasia and other major esophageal motility disorders.

Evaluation for behavioral disorders

Esophageal HRM can also serve as a valuable tool in assessing suspected symptoms of GERD that persist despite PPI therapy by examining the presence of behavioral disorders such as rumination syndrome and supragastric belching [57-59]. The occurrence of these disorders may overlap with GERD, leading to diagnostic confusion, frequently resulting in misdiagnosis by health-care providers and delays in providing appropriate management to patients. In particular, the focus for addressing these conditions should be on behavioral interventions rather than solely relying on maximizing anti-reflux therapy. Possible treatment approaches for behavioral disorders encompass behavioral modification, diaphragmatic breathing, biofeedback, speech therapy, and hypnosis [57,60].

Application of high-resolution manometry for the functional diagnostic assessment of gastroesophageal reflux disease

The current CCv4.0 of esophageal motor disorders primarily focuses on identifying abnormal bolus transit in individuals with dysphagia and chest pain [10]. However, this classification system does not specifically address the evaluation of motor function in the context of GERD. As a response to this, the International GERD Consensus Working Group has recently introduced a three-step hierarchical method for assessing esophageal motor findings in individuals with GERD [7,61].

Step 1: Assessment of morphology and function of esophagogastric junction

In the stepwise algorithmic classification of esophageal motor findings, the first step involves assessing the EGJ barrier by considering both basal pressure and morphology. If the EGJ barrier is intact, with normal resting pressures and morphology, it suggests that TLESR is the most likely mechanism contributing to reflux. An abnormal EGJ barrier may include a hiatus hernia (types II or III EGJ morphology), a hypotensive LES, or a combination of both.

Step 2: Assessment of esophageal body motor function

Next, the assessment focuses on the esophageal body motor function, which plays a crucial role in the clearance of refluxate. Among patients with GERD, the most frequently encountered esophageal body motor pattern is normal peristalsis [28,62]. The severity of esophageal body hypomotility can vary, ranging from IEM to absent contractility. Research studies have demonstrated that the reflux symptom burden and abnormal acid exposure time are correlated with the severity of dysmotility, with the highest burden observed in absent contractility [14,63]. Furthermore, esophageal body hypomotility can coexist with an abnormal EGJ barrier, which further intensifies the burden of esophageal reflux [64].

Step 3: Assessment of contractile reserve of the esophagus

When there is hypomotile esophageal body function, evaluating contractile reserve involves analyzing the findings of MRS during HRM. The presence of contractile reserve is indicated as an augmentation of esophageal body contraction following MRS compared to the mean DCI obtained from single liquid swallows (post-MRS DCI: mean wet-swallow DCI ratio > 1). For a reliable evaluation of contractile reserve, it is recommended to conduct a minimum of three MRS sequences, taking into consideration the most optimal MRS sequence [65]. In current HRM protocols, the incorporation of contraction reserve assessment has become standard practice, particularly when defining cases of IEM [35].

Integrating impedance analysis into HRM for assessing bolus transport in gastroesophageal reflux disease

Bolus transport assessment is a method to evaluate esophageal motility. Multichannel intraluminal impedance with esophageal manometry can assess both esophageal motility and detect abnormal bolus transport during swallowing simultaneously. Individuals with GERD frequently exhibit notably disrupted bolus transport, characterized by incomplete bolus transport and prolonged total bolus transit time [66]. Abnormal bolus transport is also linked to GERD severity. A study discovered that liquid and viscous bolus transport was notably reduced in ERD compared to NERD or functional heartburn patients, with longer transport durations in ERD [44]. Contractile segment impedance (CSI), a technique combining HRM with impedance, measures esophageal mucosal integrity during esophageal contractions. This approach is convenient, is faster, and provides better mucosal contact with the impedance sensor during smooth muscle contraction [67]. Recent research has demonstrated that it is equally effective in assessing GERD, comparable to mean nocturnal baseline impedance [68].

Novel provocative maneuver in gastroesophageal reflux disease: straight leg raise

The straight leg raise (SLR) maneuver, designed to create a scenario resembling EGJ outflow obstruction by increasing intra-abdominal pressure, has been recently proposed to evaluate the integrity of the EGJ during HRM [69-71]. Rogers *et al*. conducted a study demonstrating that assessing the trans-EGJ pressure gradient during SLR can effectively determine the integrity of the EGJ barrier. They discovered that a decrease or absence of trans-EGJ pressure during SLR is more commonly observed in patients with type 3 hiatal hernia [69]. Furthermore, they observed that an increase in peak intra-esophageal pressure of ≥100% during SLR is associated with pathologic GERD [70]. Moreover, even in patients considered to have a normal EGJ structure based on standard HRM investigation criteria, the identification of transient hiatal separation induced by SLR can predict acid reflux burden, particularly in the context of IEM [71]. In addition, performing SLR during HRM while measuring the impedance value of the CSI can enhance the ability to identify GERD due to the better mucosal contact with impedance sensors [68]. In a recent multicenter study which examined the clinical value of SLR maneuver in symptomatic

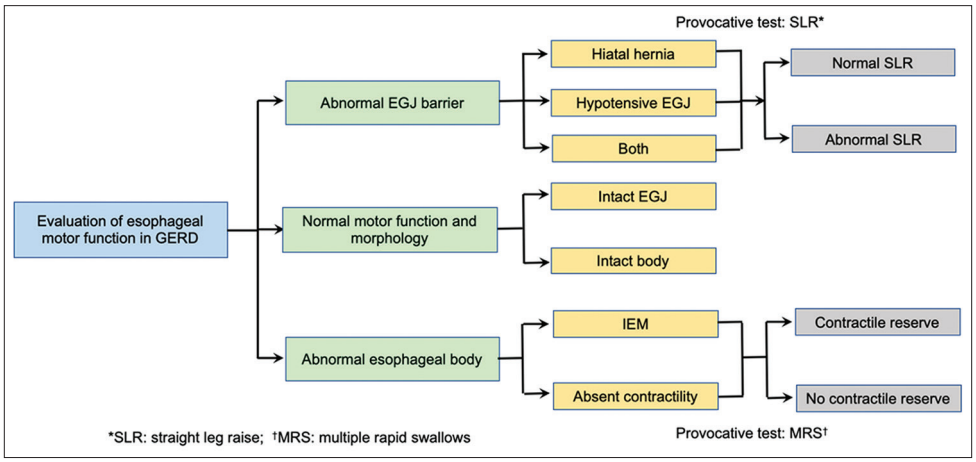

Figure 1: Investigating motor findings in GERD: A comprehensive analysis of EGJ and esophageal body characteristics. GERD: Gastroesophageal reflux disease; EGJ: Esophagogastric junction; IEM: Ineffective esophageal motility; SLR: Straight leg raise; MRS: Multiple rapid swallows

GERD patients, they demonstrated that an increase in intra-esophageal pressure of 11 mmHg during SLR achieves a sensitivity of 79% and specificity of 85% in identifying pathologic GERD [72]. Therefore, the SLR serves as a simple provocative test for evaluating the integrity of the EGJ barrier and predicting the acid reflux burden. This has the potential to enhance the diagnostic value of HRM in cases where GERD is suspected or when the available diagnostic evidence is inconclusive. A modified three-step algorithm incorporating the finding of SLR is proposed for evaluating esophageal motor function in GERD [Figure 1].

Conclusions

The pathogenesis of GERD is multifactorial, including esophageal motor dysmotility, of which the most key abnormalities are TLESRs, EGJ dysfunction, and esophageal body hypomotility. In suspected GERD patients who have an inadequate response to PPI therapy and normal upper endoscopy results, HRM is employed to evaluate confounding esophageal motor conditions and rule out behavioral disorders like rumination or supragastric belching. A three-step algorithm is suggested for evaluating esophageal motor function in GERD, incorporating findings related to EGJ and esophageal body motility, as well as assessing of contraction reserve during HRM. Newly developed HRM metrics such as EGJ-CI and innovative provocative maneuvers like the SLR test hold promise in providing a more precise understanding of pathophysiologic factors associated with GERD. These advancements have the potential to enhance the diagnosis and management of patients with suspected GERD symptoms. However, further outcome studies are necessary to validate their effectiveness.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

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