Esophageal Motor Dysfunctions in Gastroesophageal Reflux Disease and Therapeutic Perspectives

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Gastroesophageal reflux disease (GERD) is a very common disease, and the prevalence in the general population has recently increased. GERD is a chronic relapsing disease associated with motility disorders of the upper gastrointestinal tract. Several factors are implicated in GERD, including hypotensive lower esophageal sphincter, frequent transient lower esophageal sphincter relaxation, esophageal hypersensitivity, reduced resistance of the esophageal mucosa against the refluxed contents, ineffective esophageal motility, abnormal bolus transport, deficits initiating secondary peristalsis, abnormal response to multiple rapid swallowing, and hiatal hernia. One or more of these mechanisms result in the reflux of stomach contents into the esophagus, delayed clearance of the refluxate, and the development of symptoms and/or complications. New techniques, such as 24-hour pH and multichannel intraluminal impedance monitoring, multichannel intraluminal impedance and esophageal manometry, high-resolution manometry, 3-dimensional high-resolution manometry, enoscopic functional luminal imaging probe, and 24-hour dynamic esophageal manometry, provide more information on esophageal motility and have clarified the pathophysiology of GERD. Proton pump inhibitors remain the preferred pharmaceutical option to treat GERD. The ideal target of GERD treatment is to restore esophageal motility and reconstruct the anti-reflux mechanism. This review focuses on current advances in esophageal motor dysfunction in patients with GERD and the influence of these developments on GERD treatment.

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Key Words
Esophageal motility disorders; Esophagogastric junction; Gastroesophageal reflux; Manometry; Pharmaceutical preparations

Introduction

Reflex of gastric contents into the esophagus induces esophageal symptoms of regurgitation and heartburn, and potentially, extraesophageal symptoms.1 In some patients with gastroesophageal reflux disease (GERD), frequent and severe reflux may result in reflux esophagitis. Available data indicate that GERD results from multiple predisposing factors in upper gastrointestinal dysmotility, which result in increased reflux and decreased defenses against the refluxate. The association of GERD with acid is actually the dislocation of acid secondary to motility disorders. Increased transient lower esophageal sphincter relaxation (TLESR), hypotensive lower esophageal sphincter (LES) or diaphragmatic crural dysfunction,
anatomical defects in the esophagogastric junction (EGJ), ineffective esophageal motility (IEM), abnormal esophageal bolus transport, and abnormal responses to multiple rapid swallowing (MRS) are closely associated with GERD. \(^1\) \(^2\) \(^3\) Recently, new techniques to detect esophageal functional defects, such as 24-hour pH and multichannel intraluminal impedance (MII) monitoring, MII and esophageal manometry (MII-EM), high-resolution manometry (HRM), 3-dimensional HRM, esophageal functional luminal imaging probe (EndoFLIP), and 24-hour dynamic esophageal manometry have improved our understanding of the pathogenesis of GERD and provided the basis for developing comprehensive and effective treatment programs. In this article, we reviewed recent advances in our understanding of esophageal motility dysfunction in GERD and discussed GERD therapeutic perspectives.

**Abnormal Motility in Gastroesophageal Reflux Disease and Its Association With Reflux Events**

The pathophysiological mechanisms of GERD include impaired anti-reflux defense and increased injury to the esophageal mucosa by refluxed contents. The former includes disruption of the anti-reflux barrier at the EGJ, decreased ability of the esophagus in clearing the refluxed contents, and reduced resistance of the esophageal mucosa to the refluxate.

**Disruption of the Anti-reflux Barrier at the Esophagogastric Junction**

The EGJ includes several structures, including the LES, diaphragmatic crura, and phrenoesophageal ligament, which form an anti-reflux barrier. Decreased function of the EGJ anti-reflux barrier manifests primarily as follows.

**Frequent transient lower esophageal sphincter relaxation**

When swallowing, the EGJ acts as a one-way valve, allowing food or liquid to enter the stomach from the esophagus and effectively prevents reflux of the gastric contents. TLESR is not associated with swallowing, which differs from LES relaxation caused by swallowing. The duration of TLESR is more than 10 seconds, which is longer than that of swallowing-induced LES relaxation (typically lasting 6-8 seconds), and there is no pharyngeal swallowing signal 4 seconds before and 2 seconds after LES relaxation. \(^6\)

TLESR spontaneously appears at either relatively stable LES pressures or after LES relaxation during normal swallowing. TLESR allows gas to move into the esophagus from the proximal stomach while preventing reflux of gastric contents. If TLESRs occur frequently, gastric contents may escape and reflux into the esophagus, especially within 15 minutes after eating (when there is an acid pocket), and gastric juice near the cardia may leak backwards into the esophagus and increase the incidence of postprandial reflux events. \(^7\)

The incidence of TLESR in GERD patients is more than two times that of healthy people. \(^4\) Other studies demonstrated that patients with GERD do not have more frequent TLESRs than healthy or asymptomatic controls, but instead, TLESRs in GERD patients are more likely to be associated with acid reflux. \(^5\) \(^10\) Pandolfini et al. studied TLESR using HRM and found that TLESR-induced EGJ opening was caused by LES relaxation, inhibited crural contraction, esophageal shortening, and increased gastric pressure. Also, in cases of incomplete TLESR, LES elevation is seen with HRM manometry, and ultrasonography shows esophageal muscle thickening 2 cm above the LES, indicating contraction of the esophageal longitudinal muscle, which may be the main cause of TLESR. \(^11\)

**Hypotensive lower esophageal sphincter, crural diaphragmatic dysfunction, or increased esophagogastric junction compliance without abnormal anatomy**

LES pressure in normal individuals is lowest after eating and highest at night. Even if the LES is relaxed, the pressure remains slightly higher than the intragastric pressure, to prevent reflux. This is important when the pressure difference between the stomach and esophagus is maximal (such as at end-inspiration), and gastro-esophageal reflux occurs when the resting LES pressure is abnormally low or the intragastric pressure is high. \(^12\) LES pressure at rest is maintained between 10-30 mmHg in healthy people. The LES resting pressure of patients with reflux esophagitis is significantly lower than that of healthy control \(^13\) or patients with non-erosive reflux disease (NERD), and the length of the LES is also shorter. \(^1\)

In obese patients with GERD, the intragastric pressure and mean gastroesophageal pressure gradient are significantly increased compared with those with a healthy body mass index, which also provides a perfect scenario for reflux. \(^14\)

At end-expiration, EGJ pressure is maintained mainly by the LES, and increased EGJ pressure during inspiration results from the strengthening effect of the crural diaphragm on the LES. Sun et al. \(^15\) found that crural diaphragmatic pressure in patients with GERD at resting was lower than that of healthy controls. The authors also found a significant increase in crural diaphragmatic pres-
sure during deep diaphragmatic breathing both for GERD patients and healthy subjects. With the development of HRM, a parameter similar to the distal contraction integral (DCI) concept has been proposed for measuring EGJ barrier function. This new parameter, the EGJ-contractile integral (EGJ-CI), involves calculating EGJ vigor (including dual contribution by the LES and diaphragmatic crura) during three respiratory cycles, then dividing by the value of the length of time of the cycles.16 Patients with GERD had a lower median EGJ-CI value compared with patients with functional heartburn.17 Patients with GERD with a defective EGJ-CI more frequently had positive reflux in impedance-pH monitoring or esophageal mucosal lesions at endoscopy than did patients with normal EGJ-CI values.17 This metric partially predicts abnormal esophageal acid exposure time and symptomatic outcome following anti-reflux therapy.18

Increased EGJ compliance is another pathophysiological abnormality in many patients with GERD.19,20 Excessive EGJ compliance allows more gastric contents to reflux into the esophagus and increases the frequency of TLESR, which is elicited by proximal gastric distention.21-23 EndoFLIP, which evaluates EGJ compliance during endoscopy, has shown that patients with GERD exhibited 2-3 fold increase in EGJ distensibility compared with controls, especially at 20-mL to 30-mL distention volumes.24,25

Abnormal esophagogastric junction local anatomy

With anatomical disruption of the EGJ or hiatal hernia, relaxation of the phrenoesophageal ligament, which is responsible for fixing the GEJ onto the diaphragm, makes a portion of the stomach move superior to the diaphragm. In such cases, 2 high-pressure zones are seen during esophageal HRM. Studies show that HRM has a high sensitivity of 92% and a specificity of 95% for detecting hiatal hernia.26 The Chicago classification describes 3 subtypes of EGJ based on the separation distance between the diaphragmatic crura and the LES: type I, no separation between the LES and diaphragmatic crura; type II, minimal separation (> 1 and < 2 cm); and type III, ≥ 2 cm of separation.27 A significant increase in esophageal acid exposure time, total number of reflux episodes, DeMeester score, and positive reflux-symptom association are seen when the separation between the LES and diaphragmatic crura widens (type III EGJ morphology).28,29 EGJ types I and II, with complete or partial overlap between the LES and diaphragmatic crura, have increased inspiratory pressure at the diaphragmatic crura. In contrast, patients with EGJ type III have complete LES-diaphragmatic crura separation and reduced inspiratory pressure.30 Also, hiatal hernia affects the location of the acid pocket, extending the duration of esophageal acid exposure. Unlike in healthy individuals, the acid pocket in patients with GERD and hiatal hernia is located superior to the diaphragm or in a hernia sac, during TLESR. This phenomenon is more prominent in patients with GERD and large hernia sacs, and reflux events are seen more frequently in these patients during TLESR.12,18 Obese patients are more likely to have EGJ disruption (leading to hiatal hernia).12

Impaired Esophageal Clearance of the Refluxate

Ineffective primary peristalsis

Studies using conventional water-perfused manometry and HRM have shown that IEM is the most common esophageal motility disorder. Previous studies divided IEM into lack of peristalsis, invalid contraction, synchronous contraction, and low-amplitude contraction.31 The newly-revised Chicago classification for esophageal motility disorders divided IEM into weak peristalsis (DCI < 450 mmHg·sec·cm) and no peristalsis (DCI < 100 mmHg·sec·cm) based on DCI in the HRM data.27 Patients with reflux esophagitis and those with NERD both have IEM although the incidence of IEM in patients with reflux esophagitis is higher than in patients with NERD (29% vs 15%, respectively; P = 0.030).32 IEM is more often associated with acid exposure, abnormal weakly-acidic reflux, and long-term acid reflux in patients with refractory GERD, and IEM severity parallels the degree of esophageal mucosal damage. Patients with reflux esophagitis had a lower DCI than patients without reflux esophagitis in one study (558 mmHg·sec·cm vs 782 mmHg·sec·cm, respectively; P = 0.045).33 To distinguish the contraction pattern from contractile vigor, the Chicago classification proposed small breaks (< 3 cm) and large breaks (> 5 cm) in the 20-mmHg isobaric contour. The latter is more common in patients with GERD, who have a pathological number of large breaks assessed by HRM, and are characterized by having a significantly prolonged reflux clearance in the supine position and higher esophageal acid exposure time.34

Abnormal secondary peristalsis

Primary esophageal peristalsis is mainly responsible for transporting the bolus inside the esophagus whereas secondary peristalsis clears the refluxate and swallowed food residue to empty the esophagus. Secondary peristalsis can be initiated by a variety of stimuli in the esophagus such as gas, balloon-dilatation, or water perfusion. Bolus-induced peristalsis can be initiated by intrinsic neural programs independent of vagal activity, but is influenced by vagal activity.36 Studies evaluating secondary peristalsis often involve
Abnormal esophageal bolus transport

Bolus transport is another method of assessing esophageal motility. Comparing patients with functional heartburn and with healthy individuals, patients with GERD often have more significantly abnormal bolus transport, which is represented by incomplete bolus transport and extended total bolus transport time. During MII-EM, 3 abnormal modes are seen in patients with GERD. The first invalid transport, in which transport signals in the proximal esophagus are seen and transport signals in the middle and distal esophagus are extended in a typical stepwise pattern. The corresponding peristaltic mode often has several pathological forms, such as weak contraction or synchronous peristalsis. The third abnormal mode is mixed transport with two-part signals. The first part is a signal that can be detected when swallowing a bolus, and the second part includes a peristaltic wave while there is no second swallowing, and which occurs within 4 seconds after the first signal. However, the corresponding peristaltic model remains unclear.

Abnormal bolus transport is also often related to the severity of GERD. Savarino et al found that the incidences of complete liquid bolus and viscous bolus transports in reflux esophagitis patients were significantly lower than those in patients with either NERD or functional heartburn. The duration of bolus transport in patients with reflux esophagitis was also longer than that in patients with either NERD or functional heartburn.

Abnormal multiple rapid swallowing

MRS testing to assess peristaltic reserve has been advocated as an adjunct to standard high resolution manometry. During traditional water-perfused manometry or pressure measurement combined with impedance testing, 10 independent swallows are often required, and the time interval between 2 swallows is 20-30 seconds. MRS involving 5 swallows (2 mL each) in rapid sequence (separated by 2-3 seconds) occurs often during drinking or eating in daily life; therefore, current detection methods do not comprehensively reflect actual esophageal motility. MRS may depress the central and peripheral nervous system and inhibit esophageal smooth muscle contraction and cause complete and persistent LES relaxation. The last swallow of the MRS process is followed by a series of more powerful esophageal contractions and LES contractions after relaxation. A normal MRS response requires not only complete inhibitory and excitatory mechanisms to regulate coordi-
nation between the esophageal body and the LES, but also requires esophageal smooth muscle integrity to respond to the strong stimulation at the end of MRS.\textsuperscript{50,52} The MRS response was abnormal in 65% of patients with IEM in one study.\textsuperscript{50} A more recent study\textsuperscript{53} showed that post MRS contractile DCI and the preoperative ratio of esophageal peristalsis DCI to wet swallowing (WS) DCI (MRS/WS) were lower in impedance- and pH test-positive patients compared with negative patients. Post-MRS contractile DCI and the MRS/WS ratio were also correlated with esophageal acid exposure time, baseline impedance values, and post-reflux swallow-induced peristaltic wave index.\textsuperscript{53} Low baseline impedance values were related to impaired esophageal mucosal integrity and increased sensitivity to acid stimulation in patients with functional heartburn.\textsuperscript{54} The post-reflux swallow-induced index, as a measure of impaired chemical clearance, is a primary pathophysiological mechanism in GERD.\textsuperscript{35} The value of assessing DCI ratio is controversial, and investigators are recommended to simply use contraction amplitude < 450 mmHg·sec·cm as a benchmark for ineffective motility. It is likely that manometry with additional MRS testing can better evaluate clinically relevant motor dysfunction, better assess ineffective bolus transit, and better predict treatment efficacy.\textsuperscript{56} Strong results following MRS testing in patients with IEM suggests peristaltic reserve and may predict success with prokinetic treatment.

We summarized the esophageal motor dysfunctions and link to reflux in GERD patients in Table 1.

**Therapeutic Perspectives in Esophageal Motility Disorders for Patients With Gastroesophageal Reflux Disease**

The Asia-Pacific consensus on GERD emphasizes that proton pump inhibitors (PPI) remain the preferred pharmaceutical in GERD treatment.\textsuperscript{57} Therapy to suppress acid production reduces aggressive risk factors in GERD treatment but cannot improve motility dysfunction(s) causing reflux, such as TLESR, low LES pressure, or reduced clearance ability. Improving motility is an essential component of GERD treatment (Table 2).

**Lifestyle and Dietary Modifications**

Obesity may weaken the anti-reflux barrier at the EGJ and is relevant to GERD pathogenesis.\textsuperscript{57,58} Weight loss is considered an appropriate lifestyle modification to improve GERD symptoms by lowering intragastric pressure and reducing the reflux frequency. However, it remains unknown whether weight loss can reverse ana-

| Table 1. Esophageal Motility Disorders and Link to Reflux in Gastroesophageal Reflux Disease Patients |
|---|---|---|
| **Category** | **Abnormality** | **Detection method** | **Link to reflux** |
| Anti-reflux barrier at EGJ | Frequent TLESR | HRM | Postprandial acid reflux $\uparrow$ |
| | Hypotensive LES | HRM/conventional manometry | Reflux esophagitis $\uparrow\uparrow$ |
| | Shorter length of LES | HRM/conventional manometry | Reflux esophagitis $\uparrow\uparrow$ |
| | EGJ-CI/lower rural diaphragmatic pressure | HRM/conventional manometry | Acid exposure $\uparrow$ |
| | Increased EGJ compliance | EndoFLIP | Erosive mucosal lesion $\uparrow\uparrow$ |
| | Hiatal hernia | HRM | More reflux $\uparrow\uparrow\uparrow$ |
| Esophageal body motility | Ineffective primary peristalsis | HRM/dynamic manometry | Acid, weakly-acidic reflux $\uparrow$ |
| | Decreased effective secondary peristalsis | Pressure and pH-impedance dynamic monitoring | Long-term acid reflux $\uparrow$ |
| | Long duration of esophageal bolus transport | MII/MII-EM | Esophageal mucosal damage $\uparrow\uparrow\uparrow\uparrow$ |
| | Abnormal multiple rapid swallowing | HRM | Common in refractory GERD |
| | | | Response to long acid reflux $\downarrow$ |
| | | | Erosive esophagitis and complication $\uparrow\uparrow\uparrow\uparrow$ |
| | | | Reflux esophagitis $\uparrow\uparrow$ |
| | | | Acid exposure time $\uparrow$ |
| | | | Predict efficacy of prokinetics $\uparrow$ |

EGJ, esophagogastric junction; TLESR, lower esophageal sphincter relaxation; LES, lower esophageal sphincter; EGJ-CI, esophagogastric junction-contractile integral; HRM, high-resolution manometry; EndoFLIP, endoscopic functional luminal imaging probe; MII, multichannel intraluminal impedance; MII-EM, multichannel intraluminal impedance and esophageal manometry; GERD, Gastroesophageal reflux disease.
tomical disruption of the EGJ. Sun et al reported that diaphragm biofeedback training for 30 minutes in the fasting state in the initial 8 weeks combined with rabeprazole, and then training 20 minutes twice a day in the fasting state at home for 6 months with acid depression on demand therapy, diaphragm biofeedback increased crural diaphragm tension and GEJ pressure significantly at 8 weeks evaluation, but without change in LES pressure, long term training decreased the usage of acid depression during 6 months follow-up.

**Medical Treatment Options**

Currently, prokinetic agents used to treat GERD include dopamine receptor antagonists (metoclopramide and domperidone), serotonin receptor agonists (mosapride, tegaserod, and prucalopride), and prokinetic drugs with dual modes of action (tripride and trimebutine maleate). Prokinetic drugs can accelerate gastric emptying, increase resting LES pressure, or enhance esophageal clearance of the refluxed contents. Ndraha performed a randomized double-blind study to compare the efficacy of 2 weeks’ administration of a PPI (omeprazole, 20 mg per os every 12 hours) and the combined administration of a PPI and a prokinetic (domperidone, 10 mg per os every 8 hours), and found that combination therapy resulted in a significant improvement in reflux symptoms compared with patients receiving the PPI alone (reflux symptom score: 4.6 ± 3.3 vs 7.5 ± 5.9, respectively; \( P = 0.020 \)). A separate study showed that mosapride decreased the threshold value of the gas volume required for inducing secondary peristalsis to improve the efficacy of secondary peristalsis. Prucalopride, a selective high-affinity serotonin receptor agonist, reduced the number of persisting or weakly and/or non-acid reflux episodes in 4 patients with constipation. It is important to note that the potencies of some PPIs decrease at low pH, and delayed gastric emptying may affect their acid-suppression ability; therefore, improved gastric motility can promote PPI potency. Combined prokinetic therapy should be considered for patients with significant esophageal motility disorders, delayed gastric emptying, and severe GERD. Acotiamide, a novel prokinetic, is a selective acetylcholinesterase inhibitor and enhances the actions of cholinergic neurons. It was observed that acotiamide can reduce TLESRs and enhancing esophageal bolus clearance in healthy subjects. These observed effects would be favorable for treating patients with GERD and future research is needed.

**Endoscopic or Surgical Treatment**

Anti-reflux surgery is the final choice for patients with GERD and unsatisfactory outcomes after conservative treatment. Motility in the esophageal body is an indicator predicting outcomes following fundoplication. Seo et al reported that the presence of absent esophageal motility did not affect the outcome of fundoplication. Specifically, there were no significant differences between patients with absent esophageal motility and those with normal esophageal motility before surgery for dysphagia scores 3 months and 6 years after surgery (11.1 vs 10.9, respectively; \( P = 0.943 \) and 8.9 vs 7.6, respectively; \( P = 0.315 \)). Shake et al reported that the preoperative MRS/WS ratio was > 1.0 in only 11.1% of patients with long-term dysphagia after anti-reflux surgery. Therefore, MRS and its

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Table 2. The Possible Therapeutic Targets of Dysmotilities in Gastroesophageal Reflux Disease Patients

| Dysmotilities | Therapeutic methods | Validated/potential efficacies |
|---------------|---------------------|--------------------------------|
| Frequent TLESR | Acotiamide          | Improve gastric accommodation  |
|               |                     | Number of TLESRs ↓64             |
| EGJ-CI/lower rural diaphragmatic pressure | Diaphragm biofeedback | Crural diaphragm tension ↑ |
| Hypotensive LES | Prokinetics | LES pressure ↑ |
|               |                     | Reflux episodes ↓60,61          |
| Ineffective primary peristalsis | Prokinetics | Combined with PPI for severe GERD62 |
| Decreased effective secondary peristalsis | Mosapride | Improve secondary peristalsis57 |
| Overlap with delayed gastric empty | Prokinetics | Combined with PPI |
| Presumed high intragastric pressure | Weight loss in obesity | Reflux frequency ↓ |
| Co-exist with hiatal hernia and/or failed to medical therapy | Fundoplication | Normalized of ineffective peristalsis Enhance LES pressure65,66 |

TLESR, lower esophageal sphincter relaxation; EGJ-CI, esophagogastric junction-contractile integral; LES, lower esophageal sphincter; EGJ, esophagogastric junction; PPI, proton pump inhibitors; GERD, gastroesophageal reflux disease.
related indicators could be important factors predicting outcomes following anti-reflux surgeries.

The ideal target of GERD treatment is to reconstruct a normal anti-reflux mechanism. Deprez and Fasse prescribed omeprazole (40 g/day for 3-6 months) for patients with GERD and saw significant improvement in esophageal motility. Ravi et al found that the amplitude of distal esophageal contraction increased significantly after fundoplication in patients with GERD, and that esophageal peristalsis normalized after surgery in patients with either weak peristalsis or ineffective peristalsis before surgery. However, other researchers suggest that combined prokinetic therapy and anti-reflux surgery does not improve esophageal motility, including resting LES pressure, amplitude of distal esophageal contraction, and incidence of frequent IEM. Such research groups attest that it is difficult to restore esophageal motility and reconstruct the anti-reflux mechanism to prevent GERD recurrence.

Conclusion

With a growing understanding of GERD pathophysiology, there are clearly a number of shortcomings in our knowledge of esophageal motility, the need for intubation, limited examination time, lack of understanding regarding the impact of bolus continuity on esophageal peristalsis, and inability to comprehensively detect esophageal clearance during reflux. Combined 24-hour dynamic manometry and MII monitoring evaluate esophageal motility and reflux events are anticipated to help identify effective methods to treat refractory GERD.

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