

# Pathophysiology of GERD: Lower Esophageal Sphincter Defects

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## INTRODUCTION

The most common cause of gastroesophageal reflux disease (GERD) is lower esophageal sphincter (LES) dysfunction. The LES is a 3–4 cm high-pressure zone of muscular activity in the distal esophagus. The LES is anatomically and histologically distinct from the esophageal body. Manometric and radiographic studies can be used to identify the LES. Intraluminal manometry can detect the LES as a 2–4 cm high pressure region at the gastroesophageal junction. The basal pressure of the LES is 10–45 mmHg. LES pressures are asymmetric; a higher pressure can be detected at the left side of the LES where it is abutted by the diaphragm and gastric sling fibers (Figure 1). The crural diaphragm and gastric sling fibers provide structural support and contribute to LES pressure and competence. Ultrasound images demonstrate thicker muscle at the middle of the LES compared to the proximal and distal ends (2).

The LES can be distinguished from the esophageal body by its propensity to maintain tonic contraction. The ability of the LES to maintain a tone higher than structures proximal and distal is a result of spikes of calcium influx that are mediated by excitatory cholinergic neurons (1). Higher intracellular calcium levels are present in the resting LES compared to nonsphincteric esophageal muscle.

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The main function of the LES is to serve as a barrier to protect the esophageal mucosa and more proximal structures from potentially damaging substances in the stomach including gastric acid, pepsin, and bile salts. Incompetence in some form of the LES is the predominant determinant of GERD. The aim of this article is to review the three main LES sphincter defects that lead to GERD. These defects include transient LES relaxations, a chronically hypotensive lower esophageal sphincter, and the effects of a hiatal hernia on sphincteric function.

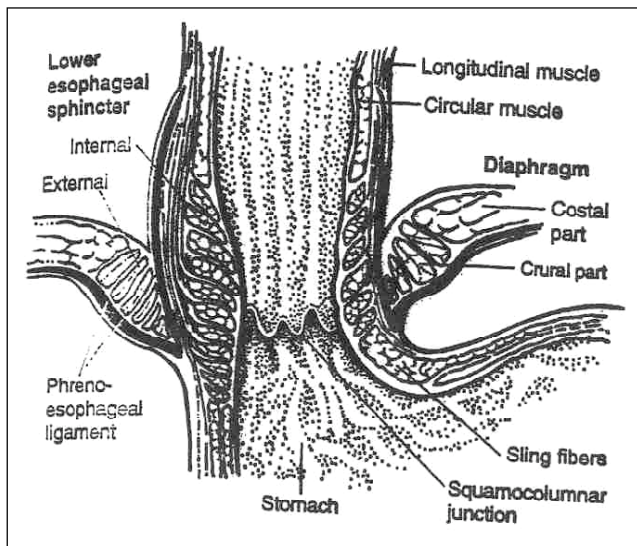
## TRANSIENT LOWER ESOPHAGEAL SPHINCTER RELAXATIONS

### Definition

Transient LES relaxations are the most frequent mechanism of reflux in people who have a normal LES resting pressure. Physiologically, a well functioning LES will remain closed except in three situations: 1) primary peristalsis 2) secondary peristalsis and 3) transient LES relaxations. Within two seconds after a swallow and the initiation of primary peristalsis, the cessation of excitatory cholinergic activity and release of nitric oxide and vasoactive intestinal peptide leads to LES relaxation. The LES remains relaxed for 5–10 seconds and then contracts. During secondary peristalsis, LES relaxation occurs as a reflex after distention of the proximal striated or more distal esophageal smooth muscle. In contrast to swallow-induced LES relaxation, transient LES relaxations are not associated

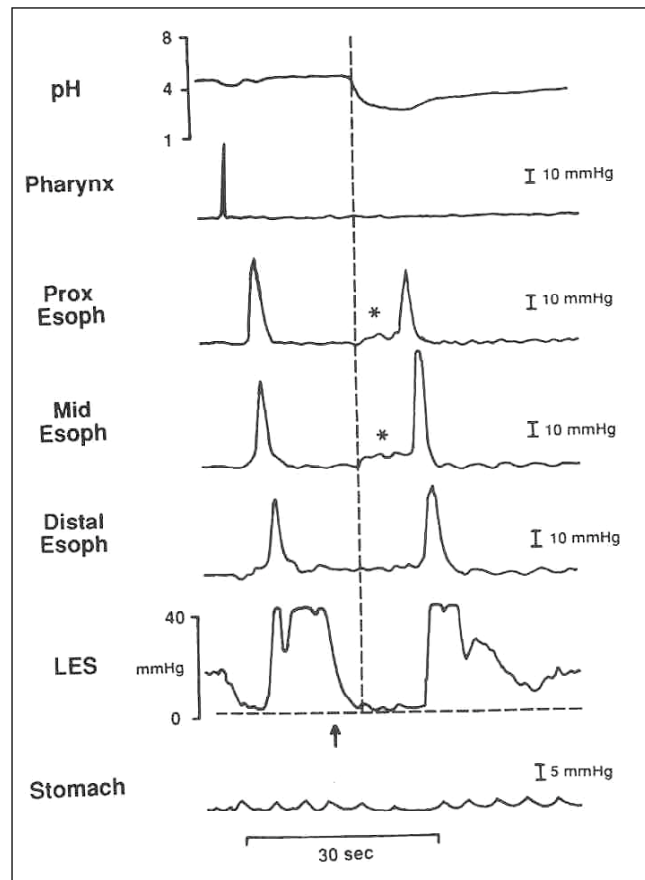
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**Figure 1.** Anatomy of the esophagogastric junction. (From Mittal RK, et al. *N Engl J Med*, 1997;336:924, with permission.)

mainly with pharyngeal contraction or esophageal peristalsis and persist for more than 10 seconds (3). Transient LES relaxations may occur immediately after the completion of a normal swallow-induced LES relaxation or may occur spontaneously on a background of stable LES pressure (4) (Figure 2). Lower esophageal pressure waves that have a synchronous onset and are unrelated to swallowing may be present with episodes of transient LES relaxations (5). Transient LES relaxations are complete, usually relaxing to within 2 mm Hg of intragastric pressure. Studies show that transient LES relaxations, instead of being isolated to the LES, are coordinated with inhibition of the crural diaphragm, inhibition of primary peristalsis, and inhibition of the gastric fundus (6,7). The inhibition of multiple structures that are fundamental to LES competence may explain the greater propensity to reflux observed with transient LES relaxation compared to swallow-induced LES relaxation. Transient LES relaxations are a physiologic response to gastric distention that lead to gastric-gas venting and avoidance of gastrointestinal bloating, and may occur with belching, vomiting, or rumination. Not surprisingly, transient LES relaxations are the primary cause of post-prandial reflux (5). They are less common in a supine position compared to a sitting position and do not commonly occur during sleep (8,9).



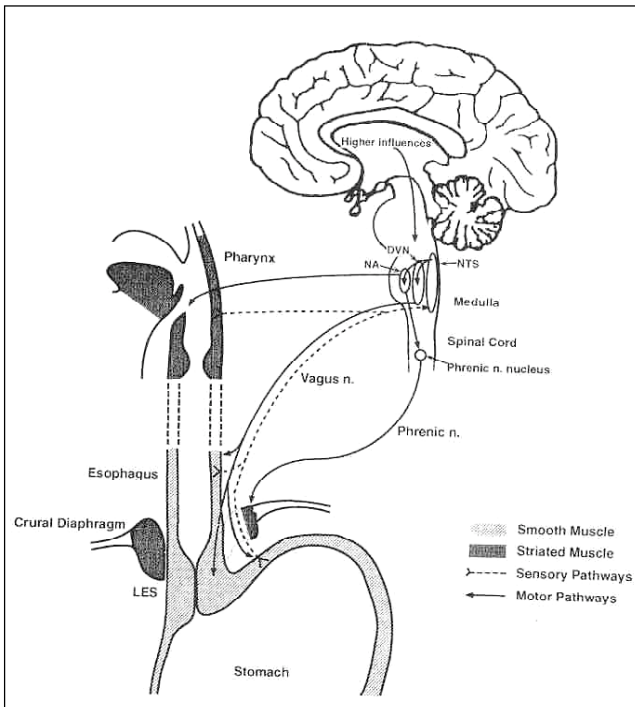
**Figure 2.** Transient LES relaxations can occur immediately after the completion of a normal swallow (marked with an arrow), or spontaneously on a background of stable LES pressure (marked by an asterisk). (From Mittal RK, et al. *Gastro*, 1995;109, with permission.)

### Physiology

Transient LES relaxations are predominantly mediated by a vagal nerve reflex. Proximal gastric distention triggers mechanoreceptors in the gastric cardia (10). One recent study found stretch receptors to be more relevant than tension receptors in triggering transient LES relaxations (11). Afferent fibers from the gastric cardia project to the nucleus tractus solitarius in the brainstem and subsequently to the dorsal motor nucleus of the vagus either directly or via interneurons (12). Neuronal stimulation of the dorsal motor nucleus of the vagus excites vagal efferent neurons that project

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**Figure 3.** Schematic representation of the neural pathway that controls transient LES relaxations. Sensory signals from the receptors in the gastric cardia, pharynx, and esophageal body and integrated in brain stem nuclei which trigger motor responses in the LES, stomach, pharynx and esophageal body, and inhibition of the crural diaphragm. DMV, dorsomotor nucleus of the vagus nerve; NA, nucleus ambiguus; NTS, nucleus tractus solitaries; PN, phrenic nerve nucleus. (From Mittal RK, et al. *Gastro*, 1995;109, with permission.)

to the LES and generates transient LES relaxation (13) (Figure 3). Truncal vagotomy in dogs has been shown to terminate transient LES relaxation (14). Acetylcholine, cholecystinin-A, nitric oxide, and GABA<sub>B</sub> are important agents in the formation of transient LES relaxations. Acetylcholine is released by the vagus nerve and by the myenteric plexus. Cholecystinin is released from intestinal cells after meals and nitric oxide is the neurotransmitter released at the postganglionic site in the vagal pathway. Antagonists to acetylcholine (15), cholecystinin-A (16), and nitric oxide (16) can inhibit transient LES relaxations. GABA<sub>B</sub> is present in the nucleus tractus solitarius and its agonists, such as baclofen, have been shown to

inhibit transient LES relaxations (17). These agents may be useful targets for future GERD therapies.

While gastric distention and vagal stimulation appears to account for the primary factor in transient LES relaxation, some evidence suggests that pharyngeal stimulation directly triggers transient LES relaxation or may lower the threshold for triggering by gastric distention. This pharyngeal stimulation is not associated with a complete pharyngeal contraction (18). Further studies are needed to clarify a potential pharyngeal-related reflex leading to transient LES relaxation. Finally, intraduodenal administration of fat may trigger transient LES relaxations through cholecystinin-A release (19).

### Relationship to GERD

Transient LES relaxations account for 70%–100% of reflux episodes in normal subjects and for 63%–74% of reflux episodes in patients with GERD (9,20). While transient LES relaxations are common in normal subjects and in patients with GERD, it is clear that differences must exist between normal subjects and patients in regard to triggering of transient LES relaxations to account for the variable existence of GERD. Many studies have evaluated potential mechanisms to explain the relation of the pathogenesis of GERD to transient LES relaxations.

One important discovery that addresses this difference is that GERD patients have a greater amount of reflux during transient LES relaxations (60%–70%) compared to normal subjects (40%–50%) (20,21,22). The mechanism for this is unclear, however an attractive hypothesis must be that transient LES relaxations may last for a longer time in patients with GERD compared to normal subjects. Unfortunately, studies have not supported this hypothesis, and have instead found that the duration of transient LES relaxations are similar in patients with GERD and normal subjects (22,23). Another possibility is that patients with GERD experience more frequent episodes of transient LES relaxations compared to normal subjects. While some studies have shown that patients with GERD have a higher frequency of transient LES relaxations (3–8 per hour) when compared to normal subjects (2–6

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per hour) (24,25), other studies have not supported these results (18). A higher frequency of postprandial transient LES relaxations has been found to occur in GERD patients compared to normal subjects (26).

The addition of abdominal straining has been postulated to lead to reflux during episodes of transient LES relaxations. Abdominal straining occurs during 15%–20% of transient LES relaxations and can increase the likelihood of reflux from 30%–60% (22,23). However, the presence of abdominal straining during reflux episodes has not been shown to differ between normal subjects and patients with reflux disease (4).

Patients with GERD may differ from normal subjects in their quality of refluxate. Patients with GERD may reflux acid while normal patients may reflux air or non-acid liquid. This is suggested by studies using intraluminal impedance monitoring where reflux in GERD patients consists of an increased proportion of liquid as opposed to isolated gas reflux (27,28). A recent study by Pandolfino, et al postulates that the variation in reflux quality present in transient LES relaxation in GERD patients can be due to a wider opening of the esophagogastric junction (29). This study used a combination of barostat, manometric, and fluoroscopic methods and showed that at distention pressures greater than intragastric pressure, the esophagogastric junction cross-sectional opening area was significantly greater in patients with GERD (with or without a hiatal hernia) compared to normal controls. Increased water flow rates were also observed in patients with GERD (29). Therefore, a significantly larger cross-sectional esophagogastric junction area may translate into increased gastric flow rates and account for the difference in the quality and quantity of reflux between patients with GERD and normal subjects experiencing transient LES relaxations.

In summary, transient LES relaxations account for the majority of reflux events in GERD and normal subjects. Patients with GERD experience a higher frequency of liquid reflux events, a qualitative difference in reflux content, a greater cross-sectional opening of the esophagogastric junction, higher liquid flow rates across the esophagogastric junction, and perhaps higher numbers of relaxations, particularly postprandially, in association with transient LES relaxation episodes compared to controls.

## HYPOTENSIVE LOWER ESOPHAGEAL SPHINCTER

### Definition

LES hypotension is another sphincter defect that contributes to the pathogenesis of GERD. LES hypotension is a less common cause of GERD compared to transient LES relaxations. LES hypotension is defined by a low resting sphincter pressure (<10 mmHg) and can result in an insufficient barrier to prevent GERD.

### Physiology

LES hypotension occurs by primary neurogenic and myogenic failure of the LES muscle (30). The complex pathophysiology of LES hypotension is not known for certain. However, neurogenic dysfunction represented by a decrease in excitatory cholinergic input and increase in inhibitory mediators including nitric oxide can lead to LES hypotension (31). Therefore, medications such as nitrates may decrease LES pressure. Calcium is another important agent involved in LES hypotension. A decrease in calcium release from intracellular storage occurs in LES myogenic failure and explains why agents such as calcium channel blockers may decrease LES pressure (32).

### Relationship to GERD

A hypotensive LES leads to GERD by two mechanisms: stress reflux or free reflux (32). Stress reflux occurs when an abrupt increase in intraabdominal pressure overwhelms LES pressure. In the presence of a normal LES, a positive pressure gradient exists between the abdomen and thorax. This pressure gradient normally increases substantially during exercise, coughing, sneezing, or other actions associated with abdominal muscle contraction to provide adequate defense against reflux of gastric contents. People who have a hypotensive LES have a lower threshold of experiencing GERD events during these episodes compared to people with a competent sphincter as a result of their inability to maintain this protective pressure gradient (21). Dent and colleagues showed that abdominal compression alone does not lead to reflux. However, contraction of abdominal wall muscles in



the presence of reduced LES pressures significantly increases the occurrence of reflux (21).

Free reflux occurs when reflux travels from the stomach to the esophagus without restraint. Free reflux is defined by a decline of intraesophageal pH without an identifiable change in LES or intragastric pressure. Free reflux is observed only when LES pressure is within 0–4 mmHg of intragastric pressure and is in essence really a common cavity between the stomach and esophagus (20).

LES hypotension may be transient or constant. Transient hypotension may occur in response to a myriad of foods or drugs (Table 1). Only a small percentage of patients with GERD have persistent LES hypotension. Interestingly, individuals with a normal LES pressure experience heartburn after eating certain foods such as fried or spicy foods. In contrast, patients with very low LES pressures report heartburn symptoms with a much broader range of foods (33). In some cases, LES hypotension may have a secondary cause. For example, a grossly hypotensive LES can be associated with scleroderma, diabetes mellitus, and pregnancy.

Scleroderma is one of the most well recognized causes of severe LES hypotension. The majority of patients with scleroderma have esophageal involvement (34). Autonomic neurologic dysfunction, esophageal smooth muscle atrophy and fibrosis of the muscularis propria may be prominent and of pathogenic importance (35,36). These anatomic alterations result in the hallmark signs of esophageal scleroderma: LES hypotension and aperistalsis of the distal esophagus (36). These findings can be detected with manometric or radiographic barium studies. Scleroderma patients can have profound GERD symptoms as well as regurgitation and dysphagia. Patients experience significant symptoms due to a combination of acid reflux across a hypotensive LES and an increased acid exposure time related to impaired esophageal peristalsis (37). GERD-related complications may occur including peptic strictures and Barrett's esophagus. Radiographic studies may show a dilated, atonic esophagus with air esophagram (38). Endoscopy may reveal high-grade esophagitis, Barrett's esophagus, and strictures. Interestingly, studies have found that the severity and extent of GERD is more closely related to ineffective esophageal peristalsis compared to LES hypotension (39).

**Table 1**  
**Factors Decreasing LES Pressure**

<b>Foods</b>	<b>Neural Agents</b>
Chocolate	β-Adrenergic agonists
Ethanol	α-Adrenergic antagonists
Peppermint	Anticholinergic agents
Caffeine	
<b>Hormones</b>	<b>Other</b>
Cholecystokinin	Theophylline
Progesterone	Smoking
Secretin	Morphine, meperidine
Glucagon	Calcium-blocking agents
Somatostatin gastric inhibitory polypeptide	Diazepam
Vasoactive intestinal polypeptide	Dopamine

LES hypotension and low-normal LES pressure has been noted in some patients with diabetes mellitus (39,42). Decreased LES pressure in patients with diabetes mellitus may also occur with decreased peristaltic amplitudes. Although autonomic dysfunction is a characteristic of diabetes mellitus that can affect the

**Table 2**  
**Highlights**

**Transient LES relaxation**

- Most common cause of reflux
- Triggered by proximal gastric distention
- Associated with mild GERD

**Hypotensive LES**

- Low resting sphincter pressure (<10 mmHg)
- Associated with stress and free reflux
- Related to severe GERD in patients with scleroderma

**Sliding hiatal hernia**

- Pathophysiologic factor in at least 50% GERD cases
- Increases likelihood of reflux from low LES pressure, deglutitive relaxation, and abdominal muscle straining
- GERD severity correlates to hernia size

entire gastrointestinal tract, studies have not detected a correlation between the presence of peripheral or autonomic neuropathy and esophageal manometry abnormalities (40). A psychiatric component associated with esophageal motility abnormalities in diabetic patients has been suggested (41). The clinical significance of esophageal motility abnormalities in patients with diabetes mellitus is unclear as some studies have found that not all diabetic patients with LES hypotension have symptoms (42).

GERD frequently accompanies pregnancy and has been reported to occur in 60%–70% of pregnant women (43). LES hypotension appears to contribute to the pathogenesis of GERD in these individuals. Women who experience heartburn during pregnancy have reduced LES pressures compared to pregnant women without heartburn and normal subjects (44). High levels of sex hormones, particularly progesterone, have been found to decrease LES pressure (43,44). LES competence appears to become impaired early in pregnancy, prior to the onset of symptoms (45). Increased abdominal pressure by the gravid uterus exerts an additive effect with low LES pressure to cause reflux. This explains why most women who have low LES pressure during pregnancy do not experience reflux until the third trimester of pregnancy (43). GERD has not been found to significantly affect the health of the mother or the well-being of the fetus (4).

In summary, LES hypotension is associated with stress and free reflux events. Persistent LES hypotension can occur in diseases such as scleroderma and results in severe esophagitis, Barrett's esophagus, and peptic strictures.

## HIATAL HERNIA AND THE DIAPHRAGMATIC SPHINCTER

### Definition

A sliding or direct hiatal hernia (type I) is the most common hernia and the type most frequently associated with GERD (47,48). A sliding hiatal hernia occurs when a portion of the gastric cardia protrudes above the diaphragm and is endoscopically defined as a proximal dislocation of the squamocolumnar mucosal junction 2 cm or more above the diaphragmatic hiatus (49).

### Physiology

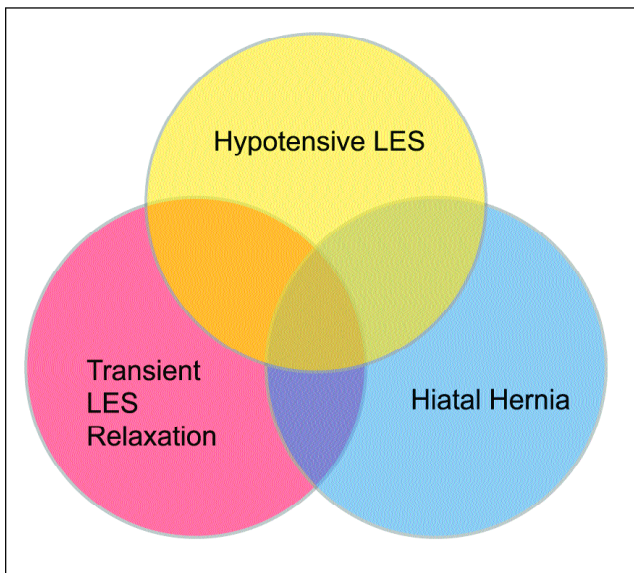
The crural diaphragm is a dynamic and powerful component of LES function. During forceful contraction of the crural diaphragm, LES pressure can quickly increase from 15–30 mm Hg to more than 100–200 mm Hg (50). Alternatively, crural diaphragm relaxation occurs in concert with esophageal distention, swallow-induced LES relaxation, and transient LES relaxations (51). Proximal displacement of the LES in the presence of a hiatal hernia decreases structural support normally provided by the crural diaphragm, since the crural diaphragm is no longer aligned next to the LES. The cause of a hiatal hernia is unknown but has been speculated to occur by the acquired stretching of diaphragmatic crural facial attachments to the esophagogastric junction (52). Another hypothesis is that a hiatal hernia forms as a response to acid-induced shortening of the esophagus (1). However, most patients with a hiatal hernia do not have GERD (53).

### Relationship to GERD

A sliding hiatal hernia has been shown to be a significant pathophysiologic factor in at least 50% of GERD cases (48). A sliding hiatal hernia disrupts the alignment of the crural diaphragm and leads to reflux by three mechanisms: 1) disruption of the “pinchcock effect” of crural contraction, 2) lowering LES pressure, and 3) creation of a wider cross sectional opening of the esophagogastric junction (54,57). A recent study by Pandolfino, et al observed that the esophagogastric junction opens to greater diameter during LES relaxation in patients with a hiatal hernia compared to asymptomatic normal subjects (30). This study also found that the esophagogastric junction opens at very low pressures (<0 mmHg) in patients with a hiatal hernia and therefore explains why they may experience reflux during deglutitive relaxation (31). Further studies have explored the pathophysiology of GERD in patients with a hiatal hernia. These studies focus on esophageal acid exposure time, reflux episode frequency, association with LES hypotension and transient LES relaxations, and hiatal hernia size.

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**Figure 4.** LES defects associated with GERD.

GERD patients with a hiatal hernia experience higher esophageal acid exposure and more frequent reflux episodes compared to patients without a hiatal hernia (59). These findings may be due to increased susceptibility to reflux and by prolonged acid clearance in patients with a hiatal hernia. Increased reflux in GERD patients with a hiatal hernia appear to be explained by an increased number of reflux episodes caused by low LES pressure, swallow-associated normal LES relaxations, deep inspiration, and straining (51). Transient LES relaxations may also occur in patients with a hiatal hernia but whether they appear to occur more frequently compared to normal subjects is controversial (51,60).

The size of a hiatal hernia has been found to be an important factor in the severity of GERD. Larger hiatal hernias >3 cm in length as measure endoscopically are associated with significant increases in esophageal acid exposure (61). The increase in esophageal acid exposure may be explained by impaired refluxate clearance that has been observed in patients with nonreducing hiatal hernias that are greater than 2 cm in length compared to smaller, reducing hiatal hernias (61,62). Since large hiatal hernias are associated with increased esophageal acid exposure and impaired refluxate clearance, it is logical that a significant correlation between hernia size and severity of esophagi-

tis has also been documented (57). As exemplified by one study, hiatal hernia length in GERD patients with erosive esophagitis was  $2.55 \pm 0.35$  cm compared to  $0.7 \pm 0.18$  in GERD patients with nonerosive esophagitis ( $P < 0.0001$ ) (57). The majority of patients with severe esophagitis and Barrett's esophagus have a hiatus hernia of 2 cm or greater (56).

In summary, the presence of a sliding hiatal hernia disrupts the anatomy of the LES and increases the likelihood of reflux events associated with low LES pressure, deglutitive relaxation, and abdominal muscle straining. Esophageal acid exposure and esophagitis grade are increased with larger, non-reducing hiatal hernias compared to smaller reducing hernias. Furthermore, the presence of a hiatal hernia is associated with advanced degrees of GERD including severe esophagitis and Barrett's esophagus.

## CONCLUSION

The pathogenesis and severity of GERD is predominantly attributed to anatomic and physiologic LES dysfunction. Mild to moderate non-erosive reflux disease is most commonly due to transient LES relaxations. More severe GERD including erosive esophagitis is usually associated with a hypotensive LES or a hiatal hernia. Furthermore, the degree of esophagitis in patients with GERD correlates with hiatal hernia size and extent of LES hypotension.

To conceptualize LES defects associated with GERD as isolated events is overly simplistic. Instead, LES defects exert an additive effect and act in concert to increase the susceptibility to gastroesophageal acid reflux (Figure 4). This concept is supported by the observation that the presence of both a hiatal hernia and a hypotensive LES are associated with severe gastroesophageal junction incompetence and an increased susceptibility to GERD (62). The combination of a hiatal hernia and hypotensive LES have also been associated with erosive esophagitis (55). Although controversial, a hiatal hernia has also been observed to increase the frequency of transient LES relaxations in patients with GERD (60). The pathophysiology of GERD involves complex interactions between multiple LES defects and remains an important area of ongoing investigation.



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