



The target of therapies: pathophysiology of gastroesophageal reflux disease

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The fundamental abnormality in gastroesophageal reflux disease (GERD) is exposure of esophageal or supraesophageal epithelium to gastric secretions resulting in either histopathological injury or in the elicitation of symptoms. Some degree of gastroesophageal reflux and esophageal epithelial acid exposure, however, is considered normal or “physiological”. GERD results at the time when the balance between what the epithelium is exposed to (related to the frequency of acid reflux, the effectiveness of acid clearance, and the constituents of that reflux) and what that epithelium can tolerate tilts in favor of the aggressive forces. Significant aberrations in one or more potential pathophysiological factors can thus result in shifting from a compensated condition to a decompensated one with the consequent development of esophagitis or reflux symptoms, such as heartburn. Of the primary defensive factors preventing the clinical manifestations of GERD, esophagogastric junction (EGJ) competence, is the most fundamental and also the focus of new endoscopic therapies for GERD that are the subject of this monograph.

Under normal conditions, reflux of gastric juice into the distal esophagus is prevented as a function of the EGJ. The EGJ is an anatomically complex zone which functional integrity as an antireflux barrier has been variably attributed to intrinsic lower esophageal sphincter (LES) pressure, extrinsic compression of the LES by the crural diaphragm, the intra-abdominal location of the LES, integrity of the phrenoesophageal ligament, and maintenance of the acute angle of His promoting a “flap valve” function. Possibly each of these potential mechanisms of function is operant under specific conditions and the global function of the EGJ as an antireflux barrier is dependent the sum of the parts. The greater the

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dysfunction of the individual mechanisms of competence, the worse the overall antireflux function of the EGJ. By extension, the greater the degree of EGJ incompetence, the worse the severity of GERD.

Unfortunately, current medical therapies aimed at improving EGJ competence are minimally effective and GERD therapy has instead centered on reducing gastric acid secretion. Gastric acid secretion, however, is not fundamentally abnormal in GERD and pharmacologically reducing it represents a compensatory as opposed to a curative therapy. Nonetheless, it is a remarkably effective approach. In the uncommon circumstance that antisecretory therapy is not tolerated or is ineffective, antireflux surgery (most commonly a laparoscopic Nissen fundoplication) can be performed to restore EGJ competence. Even laparoscopic surgery, however, has the inherent risks of anesthesia and the occasional unpredictable adverse event, heightening the appeal of a non-surgical (yet also non-pharmacological) option. Thus, during the last few years a multitude of putative “endoluminal therapies” for GERD have emerged. These putative therapies can be mechanistically categorized into three groups: (1) radio-frequency energy delivery to the EGJ, (2) endoluminal suturing of the proximal stomach or distal esophagus, and (3) injection of non-absorbable inert material into luminal wall in the region of the EGJ. Each of the variations of these techniques is addressed individually in this monograph. All three methods are intended to alter the mechanical properties of the EGJ to reduce the occurrence of reflux. Although esophageal acid clearance, tissue resistance and causticity of the refluxate are also important factors in the pathogenesis of GERD, endoluminal therapies do not primarily target these pathophysiologic mechanisms. Thus, this review focuses on the anatomy and function of the EGJ as an antireflux barrier.

Functional constituents of the esophagogastric junction

Viewed as an impediment to reflux, the EGJ is generally viewed as the locus of a high-pressure zone at the distal end of the esophagus. Maintenance of that high-pressure zone ensures that the distal esophagus is sealed off from the stomach and thus protected from contact with potentially caustic gastric juice. Reflux occurs with either intermittent or constant compromise of that high-pressure zone. An added element to EGJ competence is the occurrence of EGJ opening and the degree to which the EGJ opens during periods that the high-pressure zone is compromised. Just as with the upper esophageal sphincter, it has become apparent that sphincter opening is not synonymous with sphincter relaxation, it is simply a permissive event.

As has been alluded to, the anatomy of the EGJ is complex. The tubular esophagus traverses the diaphragmatic hiatus and joins the stomach in almost a tangential fashion. Thus, in contemplating the contributors to the EGJ high-pressure zone, there are several potential contributors: the intrinsic LES, the influence of the diaphragmatic hiatus, and the muscular architecture of the gastric cardia that constitutes the distal aspect of the overall EGJ high-pressure zone. The

pathophysiology of each of these elements are discussed in ensuing sections but consider first the normal structure and function. The distal end of the esophagus is anchored to the diaphragm by the phrenoesophageal membrane that inserts circumferentially into the esophageal musculature in proximity to the squamocolumnar junction (SCJ). As determined by concurrent fluoroscopy and manometry, aided by the placement of a metal clip at the SCJ, the EGJ high-pressure zone extends from 1 to 1.5 cm proximal to the SCJ to about 2 cm distal to it (Fig. 1) [1].

The LES is a 3 to 4 cm segment of tonically contracted smooth muscle at the EGJ. Resting LES tone varies among normal individuals from 10 to 30 mmHg relative to intragastric pressure and continuous pressure monitoring reveals considerable temporal variation. Large fluctuations of LES pressure occur with the migrating motor complex; during phase III, LES pressure may exceed 80 mmHg. Lesser fluctuations occur throughout the day with pressure decreasing in the post-cibal state and increasing during sleep [2]. The genesis of LES tone is a property of the smooth muscle itself and of its extrinsic innervation [3]. At any given moment, myogenic factors, intra-abdominal pressure, gastric distention, peptides, hormones, various foods, and many medications affect LES pressure.

To maintain the delicate balance between antegrade and retrograde flow, the LES has a complex neurological control mechanism involving the CNS and peripheral enteric nervous system. LES pressure is modulated by vagal afferents

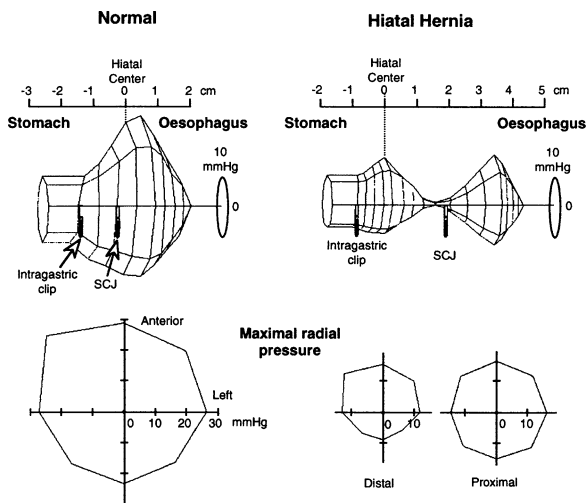


Fig. 1. Pressure topography of the EGJ of normal subjects (*left*) and hiatus hernia patients (*right*). Position zero on the axial scale is the midpoint of the diaphragmatic hiatus. The proximal clip indicates the position of the squamocolumnar junction (SCJ) and the distal clip marks the median position of the intragastric aspect to the EGJ as imaged endoscopically. All values of length and pressure are the medians of seven subjects in each subject study group. The bottom tracings represent maximal radial pressure for normals (*left*) and hiatus hernia subjects (*right*). Note the two peaks in the hiatus hernia group correlating to the above axial topography figures. (From Kahrilas PJ, Lin S, Chen J, et al. The effect of hiatus hernia on gastro-oesophageal junction pressure. *Gut* 1999;44: 476–82; with permission.)

and vagal and sympathetic efferents [4]. Efferent function is mediated through myenteric plexus neurons that can effect either LES contraction or relaxation. Synapses between the efferent vagal fibers and the myenteric plexus use a cholinergic system. The post-ganglionic transmitter effecting contraction is acetylcholine while several studies suggest that NO is the dominant inhibitory nonadrenergic-noncholinergic transmitter with VIP serving some type of modifying role [5,6].

Elegant anatomical studies suggest that the component of the EGJ high-pressure zone distal to the SCJ is largely a function of the opposing sling and clasp fibers of the middle layer of gastric musculature in the cardia [7,8]. In this region, the lateral wall of the esophagus meets the medial aspect of the dome of the stomach at an acute angle, defined as the angle of His. Viewed intraluminally, this region extends within the gastric lumen, appearing as a large fold that has been conceptually referred to as a flap valve because increased intragastric pressure would force the fold against the medial wall of the stomach, sealing off the entry to the esophagus (Fig. 2) [9,10]. As discussed, the distal aspect of the EGJ is particularly vulnerable to disruption as a consequence of anatomical changes at the hiatus.

Surrounding the LES at the level of the SCJ is the crural diaphragm, most commonly the right diaphragmatic crus. Two flattened muscle bundles arising

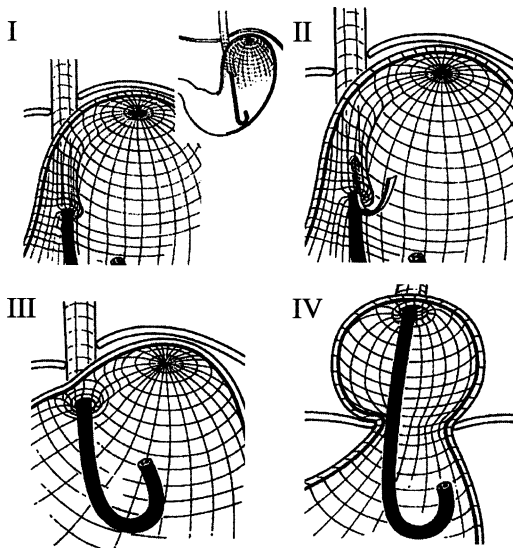


Fig. 2. Three dimensional representation of the progressive anatomical disruption of the gastroesophageal flap valve. (Grade I) Normal ridge of tissue closely approximated to the shaft of the retroflexed scope. (Grade 2) The ridge is slightly less well defined and opens with respiration. (Grade 3) The ridge is barely present and the hiatus is patulous. (Grade 4) There is no muscular ridge and the hiatus is wide open at all times (*Adapted from Hill LD, Kozarek RA, Kraemer SJ, et al. The gastroesophageal flap valve: in vitro and in vivo observations. Gastrointest Endosc* 1996;44:541–47; with permission.)

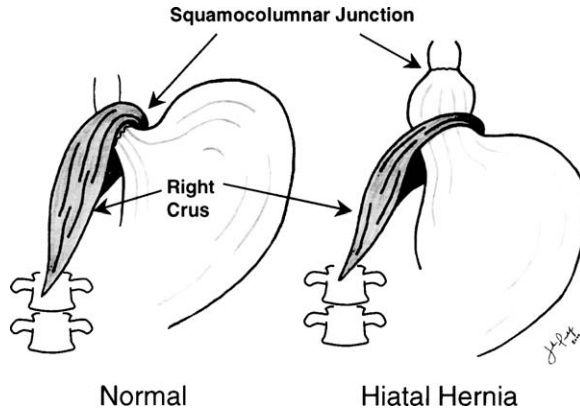


Fig. 3. Anatomy of the diaphragmatic hiatus. The right crus makes up the muscular component of the crural diaphragm. Arising from the anterior longitudinal ligament overlying the lumbar vertebrae. A single muscle band splits into an anterior and posterior muscular band, which cross each other to form the walls of the hiatal canal and then fuse anteriorly. With hiatus hernia the muscle becomes thin and atrophic limiting its ability to function as a sphincter. (From Pandolfino JE, Kahrilas PJ. Esophageal Motility Abnormalities in Barrett's Esophagus. In: Sharma P, Sampliner RE, editors. Barrett's Esophagus and Esophageal Adenocarcinoma. Malden: Blackwell Science; 2001. p. 35–44, with permission.)

from the upper lumbar vertebra incline forward to arch around the esophagus, first diverging like a scissor and then merging anterior with about a centimeter of muscle separating the anterior rim of the hiatus from the central tendon of the diaphragm (Fig. 3) [8,11,12]. The hiatus is a teardrop shaped canal and is about 2 cm along its major axis. Recent physiological investigations have advanced the “two sphincter hypothesis” for maintenance of EGJ competence, suggesting that the intrinsic smooth muscle LES and the extrinsic crural diaphragm serve a sphincteric function. Independent control of the crural diaphragm can be demonstrated during esophageal distension, vomiting, and belching at the time electrical activity in the crural diaphragm is selectively inhibited regardless of continued respiration [13,14]. This reflex inhibition of crural activity is eliminated with vagotomy. On the other hand, crural diaphragmatic contraction is augmented during abdominal compression, straining or coughing [15]. Additional evidence of the sphincteric function of the hiatus comes from manometric recordings in patients after distal esophagectomy [16]. These patients still exhibited an EGJ pressure of about 6 mm Hg within the hiatal canal despite having sustained removal of the smooth muscle LES.

Mechanisms of EGJ incompetence in GERD

Physiologically, the EGJ must perform seemingly contradictory functions. During swallowing it must facilitate the esophago-gastric flow of swallowed material whereas at the same time preventing reflux of gastric content into

esophagus that is otherwise favored by a positive abdomen-to-thoracic pressure gradient. During rest the EGJ must, again, contain gastric juice but also be able to transiently relax and permit gas venting without allowing reflux of caustic gastric juice. These functions are accomplished by the delicate interplay of anatomical elements and physiological responses of the EGJ.

The dominant mechanism protecting against reflux varies with physiological circumstance. For example, the intra-abdominal segment of the LES may be important in preventing reflux associated with swallowing, the crural diaphragmatic may be of cardinal importance during episodes of increased intra-abdominal pressure, and basal LES pressure may be of primary importance during restful recumbence. As any of these protective mechanisms are compromised the deleterious effect is additive resulting in an increasing number of reflux events and consequently increasingly abnormal esophageal acid exposure.

Investigations have focused on three dominant mechanisms of EGJ incompetence: (1) transient LES relaxations, without anatomic abnormality, (2) LES hypotension, again without anatomic abnormality, or (3) anatomic distortion of the EGJ inclusive of, but not limited to, hiatus hernia. Which reflux mechanism dominates seems to depend on several factors including the anatomy of the EGJ. Whereas tLESRs typically account for up to 90% of reflux events in normal subjects or in GERD patients without hiatus hernia, patients with hiatus hernia have a more heterogeneous mechanistic profile with reflux episodes frequently occurring in the context of low LES pressure, straining, and swallow-associated LES relaxation [17]. These observations support the hypothesis that the functional integrity of the EGJ depends on the intrinsic LES and extrinsic sphincteric function of the diaphragmatic hiatus. In essence, gastroesophageal reflux requires a “two hit phenomenon” to the EGJ. Patients with a normal EGJ require inhibition of the intrinsic LES and extrinsic crural diaphragm for reflux to occur: physiologically this occurs only in the setting of a tLESR. In contrast, patients with hiatal hernia may exhibit pre-existing compromise of the hiatal sphincter. In that setting reflux can occur with only relaxation of the intrinsic LES, as may occur during periods of LES hypotension or even deglutitive relaxation.

Transient lower esophageal relaxations

Compelling evidence exists that transient LES relaxations are the most frequent mechanism for reflux during periods of normal LES pressure (> 10 mm Hg). Transient LES relaxations occur independently of swallowing, are not accompanied by peristalsis, are accompanied by diaphragmatic inhibition, and persist for longer periods than do swallow-induced LES relaxations (> 10 seconds) (Fig. 4) [18–20]. Prolonged manometric recordings have not demonstrated an increased frequency of transient LES relaxations in GERD patients compared to normal controls [21]. The frequency, however, of acid reflux (as opposed to gas reflux) during transient LES relaxations has been reported to be greater in GERD patients [21].

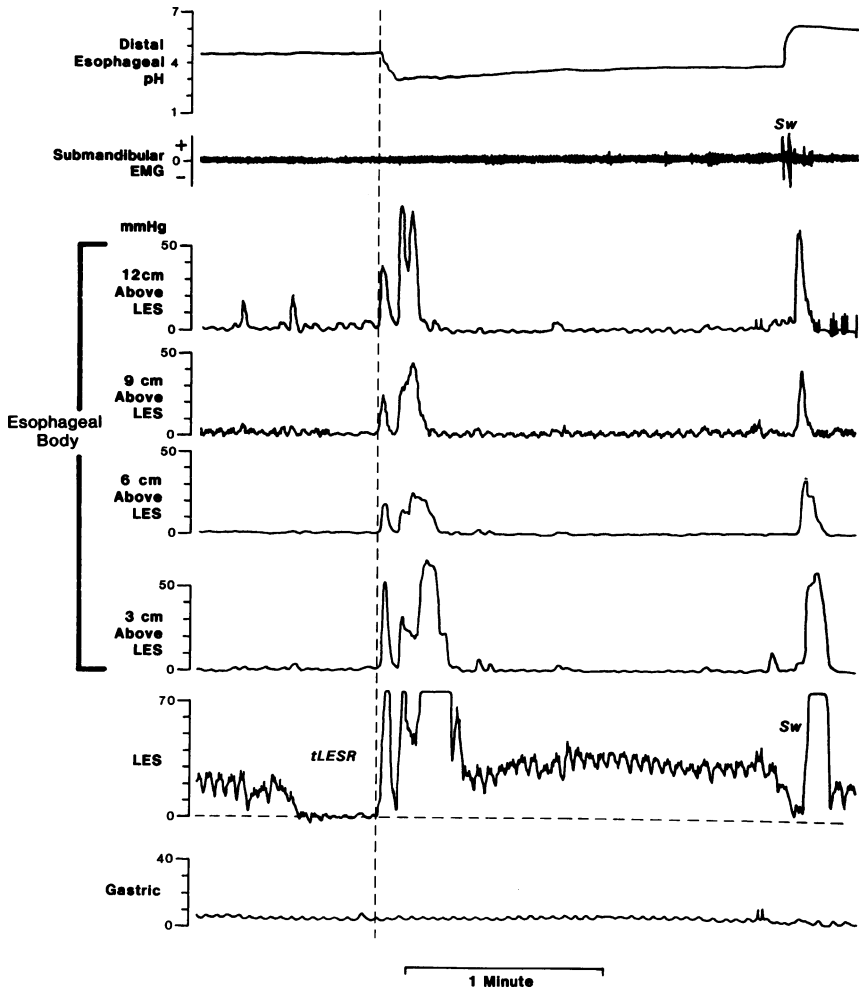


Fig. 4. Example of a transient LES relaxation recorded in an asymptomatic individual. LES pressure is referenced to gastric pressure with the horizontal dotted line (0 mm Hg) representing mean intragastric pressure. Note that the transient LES relaxation persisted for almost 30 seconds, whereas the swallow-induced LES relaxation to the right (Sw) persisted for only 5 seconds. Also note the absence of a submental electromyographic (EMG) signal during the transient LES relaxation indicating absence of a pharyngeal swallow. Finally, the associated esophageal motor activity is different in the two types of LES relaxation: the swallow induced is associated with primary peristalsis whereas the transient LES relaxation is associated with a vigorous, repetitive “off contraction” throughout the esophageal body. (From Kahrilas PJ. Cigarette smoking and gastroesophageal reflux disease. *Dig Dis* 1992;10:61–71; with permission.)

Recognizing the importance of transient LES relaxations in promoting reflux, investigators have attempted to define this reflex using physiological and pharmacological manipulations. The dominant stimulus for transient LES relaxation is distension of the proximal stomach, not surprising given that transient LES relaxation is the physiological mechanism for belching [22]. Transient LES relaxation can be experimentally elicited by either gaseous distension of the stomach or distension of the proximal stomach with a barostat bag. Gastric distension activates vagal afferent mechanoreceptors in the gastric cardia that project to the nucleus tractus solitarius in the brainstem and subsequently to the dorsal motor nuclei of the vagus. Furthermore, the degree to which tLESR frequency is augmented by gastric distension is directly related to the size of hiatus hernia suggesting that the associated anatomical alteration affects the function of the afferent mechanoreceptors believed responsible for eliciting this reflex [23]. The transient LES relaxation reflex is abolished by vagotomy [19].

Lower esophageal sphincter (intrinsic sphincter) hypotension

Gastroesophageal reflux disease can occur in the context of diminished LES pressure either by strain-induced or free reflux. Strain-induced reflux occurs at the time a hypotensive LES is overcome and “blown open” in association with an abrupt increase of intra-abdominal pressure [24]. Manometric data suggest that this rarely occurs at the time the LES pressure is greater than 10 mm Hg [24,25]. It is also a rare occurrence in patients without hiatus hernia [17]. Free reflux is characterized by a fall in intra-esophageal pH without an identifiable change in either intragastric pressure or LES pressure. Episodes of free reflux are observed only at the time the LES pressure is within 0 to 4 mm Hg of intragastric pressure. A wide open or patulous hiatus will predispose to this free reflux as the intrinsic and extrinsic sphincter are compromised.

A puzzling clinical observation, and one that supports the importance of transient LES relaxations, is that only a few patients with gastroesophageal reflux disease have a fasting LES pressure value of < 10 mm Hg [26]. This observation can also be reconciled at the time one considers the dynamic nature of LES pressure. The isolated fasting measurement of LES pressure is probably useful only for identifying patients with a grossly hypotensive sphincter; individuals constantly susceptible to stress and free reflux. There is, however, probably a larger population of patients susceptible to strain induced or free reflux at the time their LES pressure periodically decreases as a result of specific foods, drugs, or habits (Table 1).

The diaphragmatic sphincter and hiatus hernia

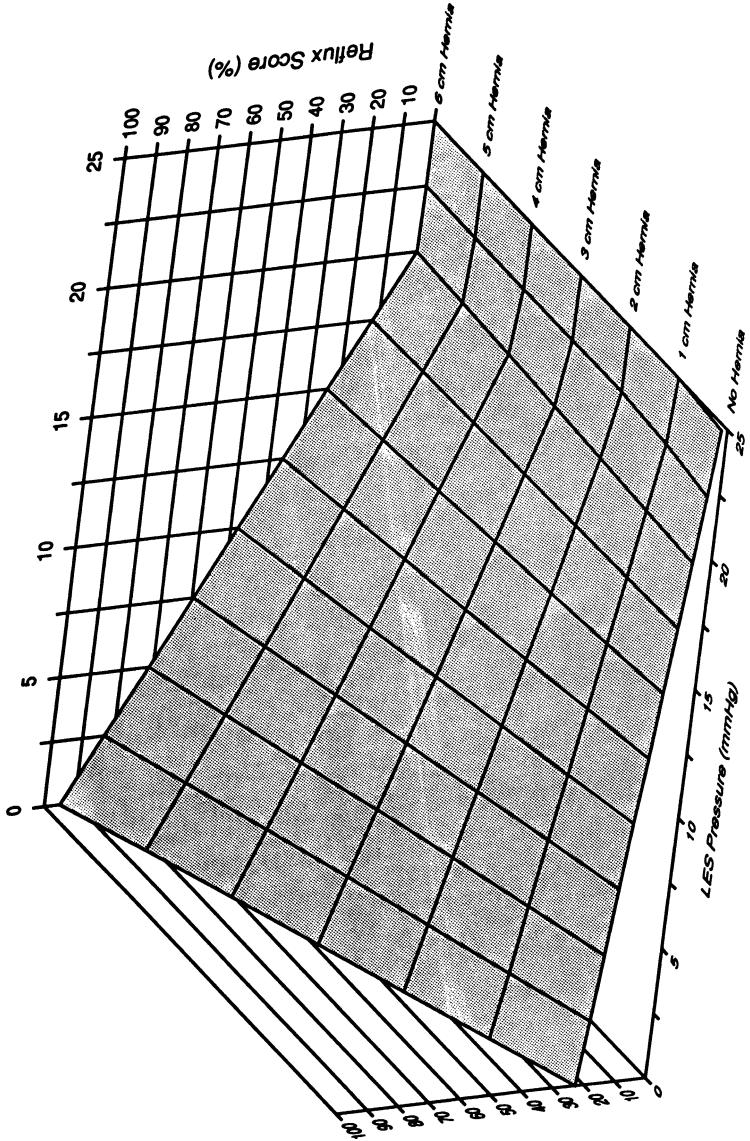
Physiological studies by Mittal et al [27] have clearly demonstrated that the augmentation of EGJ pressure observed during a multitude of activities associated with transient increases in intra-abdominal pressure is attributable to contraction of the crural diaphragm. With hiatus hernia, crural diaphragm function is poten-

Table 1
Factors that influence the lower esophageal sphincter pressure and tLESR frequency

	Increase LES pressure	Decrease LES pressure	Increase transient LES relaxations	Decrease transient LES relaxations
Foods	Protein	Fat Chocolate Ethanol Peppermint	Fat	
Hormones	Gastrin Motilin Substance P	Secretin Cholecystokinin Glucagon Gastric inhibitory polypeptide Vasoactive intestinal polypeptide Progesterone	Cholecystokinin	
Neural agents	α -Adrenergic agonists β -Adrenergic antagonists Cholinergic agonists	α -Adrenergic antagonists β -Adrenergic agonists Cholinergic antagonists Serotonin	L-arginine	Baclofen L-NAME Serotonin
Medications	Metoclopramide Domperidone Prostaglandin F _{2a} Cisapride	Nitrates Calcium channel blockers Theophylline Morphine Meperidine Diazepam Barbituates	Sumatriptan	Atropine Morphine Loxiglumide

tially compromised by its axial displacement [1] and potentially by atrophy consequent from dilatation of the hiatus [28]. The impact of hiatus hernia on EGJ susceptibility to reflux elicited by straining maneuvers was demonstrated in studies in normal volunteers compared to GERD patients with and without hiatus hernia [24]. Of several physiological and anatomical variables tested, the size of hiatus hernia revealed the highest correlation with the susceptibility to strain-induced reflux (Fig. 5). The implication of this observation is that patients with hiatus hernia exhibit progressive impairment of the diaphragmatic component of EGJ function proportional to the extent of axial herniation [1].

Another effect that hiatus hernia exerts on the anti-reflux barrier is to diminish the intraluminal pressure within the EGJ. Relevant animal experiments revealed that simulating the effect of hiatus hernia by severing the phrenoesophageal ligament reduced the LES pressure and that the subsequent repair of the ligament restored the LES pressure to levels similar to baseline [29]. Similarly, manometric studies in humans using a topographic representation of the EGJ high pressure zone of hiatus hernia patients revealed distinct intrinsic sphincter and hiatal canal



pressure components, each of which was of lower magnitude than the EGJ pressure of a comparator group of normal controls (Fig. 1) [30]. Simulating reduction, however, of the hernia by arithmetically repositioning the intrinsic sphincter back within the hiatal canal resulted in calculated EGJ pressures that were practically indistinguishable from those of the control subjects. Along with previous investigations these data also demonstrated that hiatus hernia reduced the length of the EGJ high-pressure zone [1]. This is likely caused by disruption of the EGJ segment distal to the SCJ attributable to the opposing sling and clasp fibers of the gastric cardia [7]. It is also the likely explanation for the clinical correlation established in a multitude of surgical publications that EGJ competence is inversely related to manometrically defined EGJ length [31].

Gastroesophageal flap valve

In addition to the two sphincters described above, another mechanism of barrier function at the EGJ lies in the positioning of the distal esophagus in the intra-abdominal cavity. A flap valve is formed by a musculo-mucosal fold created by the entry of the esophagus into the stomach along the lesser curvature. Increased intra-abdominal or intragastric pressure can decrease the angle of His and compress the sub-diaphragmatic portion of the esophagus, thereby preventing reflux during periods of abdominal straining. Although the clinical relevance of this concept has been controversial, several studies have helped bolster its validity. Hill et al [9] demonstrated the presence of a gastroesophageal pressure gradient in cadavers without a hiatal hernia. They also showed that ability of the EGJ in cadavers to prevent reflux in the setting of increased intra-abdominal pressure could be increased by surgically accentuating the length of the flap valve. Hill and colleagues then went on to define a classification grading scheme based on endoscopic inspection of the gastroesophageal flap valve (see Fig. 2). Two endoscopic studies have reported that this grading scheme correlated with the severity of reflux disease [9,32]. In addition to its deleterious effect on the LES, hiatus hernia may also cause disruption of the gastroesophageal flap valve. Grade 3 and 4 flap valves are almost always associated with hiatus hernia; axial displacement decreases the prominence of the musculo-mucosal fold that makes up the gastroesophageal flap valve [9]. Consequently, the angle of His is also increased and there is no longer a subdiaphragmatic segment of the esophagus to be compressed at the time intra-abdominal pressure rises.

Fig. 5. Model of the relationship between the lower esophageal sphincter (LES) pressure, size of hernia, and the susceptibility to gastroesophageal reflux induced by provocative maneuvers as reflected by the reflux score on the Z axis. The overall equation of the model is: reflux score = 22.64 + 12.05 (hernia size) - 0.83 (LES pressure) - 0.65 (LES pressure x hernia size). The hernia size is in cm, and the LES pressure is in mm Hg. The multiple correlation coefficient of this equation for the 50 subject data set was 0.86 ($R^2 = 0.75$). Thus, the susceptibility to stress reflux is dependent on the interaction of the instantaneous value of LES pressure and the size of the hiatus hernia. (From Sloan S, Rademaker AW, Kahrilas PJ. Determinants of gastroesophageal junction incompetence: hiatal hernia, lower esophageal sphincter, or both? *Ann Intern Med* 1992;117:977–82; with permission)

Mechanical properties of the relaxed EGJ

In contemplating the occurrence of reflux in the setting of a relaxed or hypotensive sphincter it is also necessary to consider other mechanical attributes of the system that may account for a relaxed sphincter remaining closed in one case and physically open in another; one such attribute is the compliance, or distensibility of the sphincter. Acquired anatomic changes inclusive of, but not restricted to, hiatus hernia may alter the compliance at the relaxed EGJ thereby decreasing the resistance to gastroesophageal flow.

Recent physiologic studies exploring the role of compliance in GERD reported that GERD patients with hiatus hernia had increased compliance at the EGJ compared to normal subjects [33] and patients with fundoplication [34]. These experiments used a combination of barostat-controlled distention, manometry, and fluoroscopy to directly measure the compliance of the EGJ. Several parameters of EGJ compliance were shown to be increased in hiatus hernia patients with GERD: (1) the EGJ opened at lower distention pressure, (2) the relaxed EGJ opened at distention pressures that were at or near resting intra-gastric pressure, and (3) for a given distention pressure the EGJ opened about 0.5 cm wider (Fig. 6) [35]. These alterations of EGJ mechanics are likely

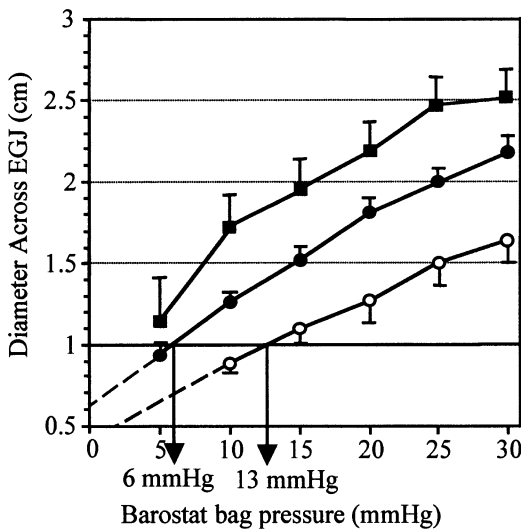


Fig. 6. EGJ opening diameter during deglutitive relaxation. The EGJ diameter was typically 0.5 cm wider among the hernia patients compared to the controls at every distention pressure. The SCJ diameter in hernia patients was typically 0.6 cm wider at each distention pressure. The threshold distention pressure required to achieve a 1 cm EGJ opening diameter in each subject group was substantially lower amongst the hernia patients compared to controls (6.0 mm Hg versus 13.0 mm Hg, $P < 0.005$). (From Pandolfino JE, Shi G, Curry J, Joehl RJ, Brasseur JG, Kahrilas PJ. Esophagogastric junction distensibility: a factor contributing to sphincter incompetence. *Am J Physiol Gastrointest Liver Physiol* Jun 2002;282(6):G1052-8; with permission.)

secondary to a disrupted, distensible crural aperture and may contribute to the physiological aberrations associated with hiatus hernia and GERD.

Increased EGJ compliance may help explain why patients with hiatus hernia have a distinct mechanistic reflux profile compared to patients without hiatus hernia [36]. Anatomical alterations, such as hiatal hernia, dilatation of the diaphragmatic hiatus, and disruption of the gastroesophageal flap valve may alter the elastic characteristics of the hiatus such that this factor is no longer protective in preventing gastroesophageal reflux. In that setting, reflux no longer requires “two hits” because the extrinsic sphincteric mechanism is already disrupted. Thus, the only prerequisite for reflux becomes LES relaxation, be that in the setting of swallow-induced relaxation, tLESRs, or a period of prolonged LES relaxation.

Increased compliance may also help explain why GERD patients may be more likely to sustain acid reflux in association with tLESRs compared to asymptomatic subjects. In an experiment that sought to quantify this difference, normal subjects exhibited acid reflux with 40%–50% of tLESRs compared to 60%–70% in patients with GERD [21]. This difference may be the result of increased EGJ compliance and its effect on trans-EGJ flow.

$$\text{Trans - EGJ flow} = \Delta P \times R^4 / C \times L \times \eta$$

In the flow equation, flow is directly proportional to EGJ diameter to the fourth power and inversely proportional to the length of the narrowed segment

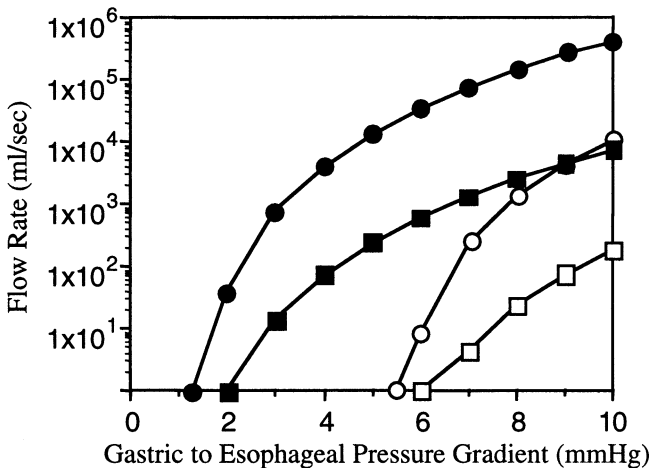


Fig. 7. The modeled effect of increased EGJ compliance on retrograde flow. Volume flow (Q) (mL/s) is estimated using a simplified mathematical model based on Newton’s law of motion as detailed in the text. From the equation it is evident that flow is highly dependent on diameter given that it is factored to the fourth power. Note that for a given value of the gastric to esophageal pressure gradient flow is 2 to 3 orders of magnitude greater for the hernia group compared to normal subjects for either air or water and that within each group flow rate of air is about 2 orders of magnitude greater than for water. (From Pandolfino JE, Shi G, Curry J, Joehl RJ, Brasseur JG, Kahrilas PJ. Esophagogastric Junction Distensibility: A factor contributing to sphincter incompetence. *Am J Physiol Gastrointest Liver Physiol* Jun 2002;282(6):G1052-8; with permission.)

and the viscosity of the gas or liquid traversing the segment. Should tLESRs occur in the context of an EGJ with increased compliance, wider opening diameters will occur under a given set of circumstances and trans-EGJ flow will increase. The impact of this difference in opening diameter is evident in the modeled data of Fig. 7 illustrating the predicted flow rates of gas and liquid in individuals with and without hiatus hernia [35]. Note that, because of the reduced opening diameter, the normal EGJ acts as a mechanical filter selectively permitting flow of gas while limiting that of water. Patients without obvious hiatus hernia may still have increased compliance secondary to more subtle defects at the EGJ not readily evident using current radiographic or endoscopic methods of evaluation. These defects may be more akin to minor anatomical variants of the EGJ such as a grade 2 gastroesophageal flap valve or defects in the LES musculature.

Targets of intraluminal GERD therapy

With the above brief overview of the mechanisms of EGJ competence and incompetence as background, briefly consider the role of the “endoluminal therapies” for GERD that are emerging. Again, these putative therapies can be mechanistically categorized into three groups: (1) radio-frequency energy delivery to the EGJ, (2) endoluminal suturing of the proximal stomach or distal esophagus, and (3) injection of non-absorbable inert material into luminal wall in the region of the EGJ. All three methods are intended to alter the mechanical properties of the EGJ to reduce the occurrence of reflux and, perhaps, the content of the refluxate. In each case, the alterations imposed on the EGJ have the potential of decreasing the compliance of the EGJ and the frequency of tLESRs. Altered compliance may result from scarring in the case of radiofrequency technique, plication in the case of the various suturing techniques, or by thickening the luminal wall in the case of injection therapies. The effect on tLESR frequency is potentially mediated either by direct damage to the vagal afferent mechanoreceptors or a secondary effect as a result of altering the mechanical properties of those mechanoreceptors.

Although the above discussion serves as a conceptual framework on which to base hypotheses regarding efficacy and mechanism of action of intraluminal therapies, ultimately there is no substitute for data and currently, as will become apparent throughout this monograph, minimal mechanistic or efficacy data currently exist. Now that there are tools, the challenge is to optimally use them and to optimally select the patient on whom to use them. With respect to optimal use, the authors leave that to the discussion of the ensuing investigators. In terms of the target population, consider Table 2 describing subgroups of GERD patients. The endoluminal therapies are unlikely to have relevance to either the Barrett’s population or the erosive esophagitis population. These patient groups usually have large hiatus hernias and, consequently, major defects in acid clearance and reflux of increased frequency. Clearance problems are currently not a target of endoluminal

Table 2
Theoretical paradigm for endoluminal treatments of GERD subtypes

Pathophysiological mechanisms of gastroesophageal reflux	Relative importance of individual reflux mechanisms in GERD subtypes				Endoluminal treatments that could theoretically modulate
	Barrett's metaplasia	Erosive esophagitis	Endoscopy negative GERD	Extra-esophageal GERD	
tLESR frequency	+/-	+/-	+/-	+/-	Radiofrequency ablation
Esophageal sensitivity	Normal or decreased	Normal or increased	Normal or increased	Normal	Radiofrequency ablation
% tLESR coupled with acid reflux	+++	+++	++	++	All (decrease compliance)
LES hypotension	++++	++++	+	+	Implantation techniques
LES opening	++++	++++	+	+	All (decrease compliance)
Esophageal acid clearance	++++	++++	+/-	+/-	No relevant data

therapies and hence, unlikely to be benefited. The most likely target populations thus become the endoscopy negative reflux population and perhaps the supra-esophageal reflux disease population. In these instances reducing the reflux frequency and volume may have merit. In addition, esophageal sensitivity may be dampened by radiofrequency ablation of vagal afferents in the distal esophagus.

Summary

Recognition of the importance of anatomical and mechanical factors in the pathogenesis of GERD has led to attempts that modify these mechanisms by endoluminal therapies. Although these alterations of EGJ anatomy and function appear minor at first glance, one must be cautious not to upset the delicate balance maintained by this complex anatomic zone. Performing a procedure that effects retrograde flow will inevitably also affect antegrade flow to some degree. The challenge will be to find a middle ground whereby GERD symptoms are not exchanged for symptoms such as dysphagia and gas bloat. With respect to endoluminal therapies, the authors are at an early stage of development and much more work is needed to define the relevant mechanical variables that need to be modified and to define the patient populations most appropriate for these interventions.

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