Managing Failed Anti-Reflux Therapy

Mark K. Ferguson and M. Brian Fennerty (Eds)

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Preface

Although GERD was initially described in the early 19th century, it is essentially a consequence of our modern day largesse. Dietary factors and associated obesity have combined with as yet other unknown factors (e.g. a decrease in the prevalence of *H. pylori*?) to make GERD one of the most common diseases affecting western society. It is estimated that up to 20 million adults in the United States suffer from GERD, and treatment of these individuals consumes approximately $10 billion annually, the majority of it for prescription drugs used to manage the disease and its symptoms. Fortunately, despite challenges presented by co-factors resulting in GERD (diet, obesity, etc.), therapy of GERD is largely successful. However, even a low failure rate for a therapy used in the management of GERD still results in large numbers of affected patients because of the high prevalence of this disease. Use of a conservative estimate of a failure rate of 5% translates to 1 million ineffectively treated and unhappy patients. How to manage these patients is the subject of this book.

Why is publication of this book important now? Several factors prompted us to work on this project. Mature results for proton pump inhibitor use are available, making this an appropriate time to review outcomes of PPI therapy of GERD. Similarly, mature results are now available for minimally invasive surgical therapy for GERD. In fact, results are sufficiently promising in the mid-term that some authors are recommending surgery over PPI use even for patients with only moderate GERD disease. In addition to defining the success of these therapies, the long-term results also illustrate important failure rates and help define characteristics of patients who are less likely to benefit from conventional treatment options.

Use of alternative therapies is now becoming quite common, particularly endoscopic treatments such as bulking agents, radiofrequency therapy, and plication procedures. The exact role of these modalities in the management of the typical patient with GERD will be defined in the next few years. A greater challenge is whether and how to use these techniques for patients who have already failed conventional therapy for GERD.

Given the complexity of causes underlying failures of GERD therapy, the approach to managing these patients should be multidisciplinary. For patients who have persistent GERD symptoms despite aggressive therapy, too often a single therapeutic approach is used to an extreme without consideration of alternative modalities, or even whether the symptoms are actually related to reflux. This may be because of the training, philosophical orientation, or lack of knowledge of the treating physician. To overcome some

of these shortcomings, we felt the time was propitious to produce a book describing management of medical and surgical failures from both medical and surgical perspectives.

The objectives of this book are to review current medical and surgical management of GERD, define what constitutes failure of such therapy, and describe approaches to management of such patients. We have enlisted a group of authors whose reputations in their specialties are universally recognized. Given the widespread incidence of GERD throughout western society, chapters are written for an international audience. Our goal was to outline a comprehensive approach to managing failed GERD therapy. However, ongoing advances in the pharmaceutical, endoscopic, and surgical instrumentation industries will always make such an effort incomplete. Our hope is that the reader is left with a framework for approaching these complex patients, and that any new information that arises can be fitted into this framework.

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The Epidemiology and Pathophysiology of Gastroesophageal Reflux Disease

Peter J. Kahrilas and John E. Pandolfino

Gastroesophageal reflux disease (GERD) is present in individuals with a symptomatic condition or histopathological alteration resultant from episodes of gastroesophageal reflux. Reflux esophagitis is present in a subset of GERD patients with lesions in the esophageal mucosa. However, reflux often causes symptoms in the absence of esophagitis.

Although GERD is widely reported to be one of the most prevalent clinical conditions afflicting the gastrointestinal tract, incidence and prevalence figures must be tempered with the realization that there is no "gold standard" definition of GERD. Thus, epidemiological estimates regarding GERD make assumptions; the most obvious being that heartburn is a symptom of GERD and that when heartburn achieves a certain threshold of frequency or severity, it defines GERD. A cross-sectional study surveying hospital employees in the United States in the 1970s found that 7% of individuals experienced heartburn daily, 14% weekly, and 15% monthly.[1] Ten years later, a Gallup survey of 1000 randomly selected persons found a 19% prevalence of weekly GERD symptoms.[2] Ten years later yet, a survey in Olmstead County found a 20% prevalence of at least weekly heartburn.[3] With respect to age, the Olmstead County data showed no correlation[3] whereas a recent report by El-Serag et al.[4] showed a slight correlation with advancing age ranging from a 24% weekly heartburn prevalence among 18–24 year olds to a 33% prevalence in those >55 years of age.

With respect to esophagitis, even though endoscopic changes in the esophageal mucosa represent objective diagnostic criteria, it is less clear what proportion of heartburn sufferers are so affected. Early reports using ambulatory esophageal pH monitoring to define GERD found that 48–79% of patients with pathologic acid exposure had esophagitis.[5,6] More recent reports, perhaps less subject to selection bias, have suggested that the prevalence of esophagitis among the GERD population is lower, ranging from 19 to 45%.[7] Very recently, a population-based study found endoscopic esophagitis in 22% of 226 individuals with heartburn at least once weekly.[4] Similar to esophagitis, the prevalence of Barrett's metaplasia is difficult to determine in the absence of a characteristic symptom profile or population studies. Illustrative of this, an autopsy study suggested that fewer than one in six patients with Barrett's metaplasia was recognized clinically prior to death.[8]

GERD is equally prevalent among males and females, but there is a male preponderance of esophagitis (2:1 to 3:1) and of Barrett's metaplasia (10:1).[7] Pregnancy is associated with the highest incidence of GERD with 48–79% of pregnant women complaining of heartburn.[9] All forms of GERD affect Caucasians more frequently than other races. However, this trend may be changing in the United States suggesting it is at least partially influenced by geography.[4] In fact, there is substantial geographic variation in prevalence with very low rates in

Africa and Asia and high rates in North America and Europe.[10]

The role of Helicobacter pylori in GERD deserves special attention given the striking inverse time trends in the prevalence of GERD and H. pylori related peptic ulcer disease.[11] Epidemiological data reveal that GERD patients with esophagitis are less likely to have H. pylori infection.[12] H. pylori infection is also associated with a decreased prevalence of Barrett's metaplasia and esophageal adenocarcinoma.[13–15] Thus, epidemiological data clearly suggest a relationship between H. pylori and GERD. However, the details of that relationship are strongly dependent on the associated pattern of gastritis. If the dominant H. pylori strains within a population primarily result in corpus-dominant gastritis as in Japan,[14] the prevalence of GERD in that population will be lower than it would be in the absence of H. pylori infection. These epidemiological data have led some to believe that H. pylori should not be eradicated in patients with GERD. However, H. pylori is a risk factor for the development of peptic ulcer and gastric cancer causing many practitioners to be uncomfortable with that recommendation.

GERD Pathophysiology

The fundamental abnormality in GERD is exposure of esophageal epithelium to gastric secretions resulting in either histopathological injury or in the elicitation of symptoms. However, some degree of gastroesophageal reflux and esophageal epithelial acid exposure is considered normal or "physiological." GERD results when esophageal epithelial exposure to gastric juice exceeds what the epithelium can tolerate.

Under normal conditions, reflux of gastric juice into the distal esophagus is prevented as a function of the esophagogastric junction (EGJ). The EGJ is an anatomically complex zone whose functional integrity as an anti-reflux barrier has been attributed to a multitude of mechanisms. Quite possibly each of these potential mechanisms is operant under specific conditions and the global function of the EGJ as an anti-reflux barrier is dependent on the sum of the parts. The greater the dysfunction of the individual mechanisms of competence, the worse the overall anti-reflux integrity of the EGJ. By extension, the greater the degree of EGJ incompetence, the worse the severity of GERD.

Functional Constituents of the EGJ

Conceptualized as an impediment to reflux, the EGJ is generally viewed as a high-pressure zone at the distal end of the esophagus that isolates the esophagus from the stomach. The anatomy of the EGJ is complex. The tubular esophagus traverses the diaphragmatic hiatus and joins the stomach in a nearly tangential fashion. Thus, there are several potential contributors to EGJ competence, each with unique considerations: the intrinsic lower esophageal sphincter (LES), the influence of the diaphragmatic hiatus, and the muscular architecture of the gastric cardia that constitutes the distal aspect of the EGJ high-pressure zone.

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 mm Hg 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 mm Hg. Lesser fluctuations occur throughout the day with pressure decreasing in the postcibal state and increasing during sleep.[16] The genesis of LES tone is a property of both the smooth muscle itself and of its extrinsic innervation.[17] At any given moment, LES pressure is affected by myogenic factors, intraabdominal pressure, gastric distention, peptides, hormones, various foods, and many medications (Table 1.1).

To maintain the delicate balance between forward and backward flow, the LES has a complex neurological control mechanism involving both the central nervous system and peripheral enteric nervous system. Lower esophageal sphincter pressure is modulated by vagal afferents as well as both vagal and sympathetic efferents.[18] Efferent function is mediated through myenteric plexus neurons that can effect either LES contraction or relaxation. Synapses between the efferent vagal fibers and

Table 1.1. Factors that influence the LES pressure and tLESR frequency.

	Increase LES Pressure	Decrease LES Pressure	Increase tLESRs	Decrease tLESRs
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 $F_{2\alpha}$ Cisapride	Nitrates Calcium channel blockers Theophylline Morphine Meperidine Diazepam Barbiturates	Sumatriptan	Atropine Morphine Loxiglumide

the myenteric plexus are cholinergic. The postganglionic transmitter effecting contraction is acetylcholine whereas nitric oxide is the dominant inhibitory transmitter with vasoactive intestinal polypeptide serving some type of modifying role.[19,20]

Physiological studies clearly demonstrate that the EGJ high-pressure zone extends distal to the squamocolumnar junction (SCJ) thereby implying that the contributory structures reside in the proximal stomach as opposed to the distal esophagus.[21] Elegant anatomical studies attribute this distal portion of the EGJ high-pressure zone to the opposing sling and clasp fibers of the middle muscle layer of gastric cardia.[22] 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 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[23,24] (Figure 1.1). Of note, this distal aspect of the EGJ is particularly vulnerable to disruption as a consequence of anatomical changes at the hiatus because its entire mechanism of action is predicated on maintaining its native geometry.

Surrounding the LES at the level of the SCJ is the crural diaphragm, most commonly the right diaphragmatic crus. Two flattened muscle bundles arising from the upper lumbar vertebra incline forward to arch around the esophagus, first diverging like a scissors and then merging anterior with about a centimeter of muscle separating the anterior rim of the hiatus from the central tendon of the diaphragm[21,25] (Figure 1.2). 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 both 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 when electrical activity in the crural diaphragm is selectively inhibited

despite continued respiration.[26,27] This reflex inhibition of crural activity is eliminated with vagotomy. However, crural diaphragmatic contraction is augmented during abdominal compression, straining, or coughing.[28] Additional evidence of the sphincteric function of the hiatus comes from manometric recordings in patients after distal esophagectomy.[29] These patients still exhibited an EGJ pressure of about 6 mm Hg within the hiatal canal despite having sustained surgical removal of the smooth muscle LES.

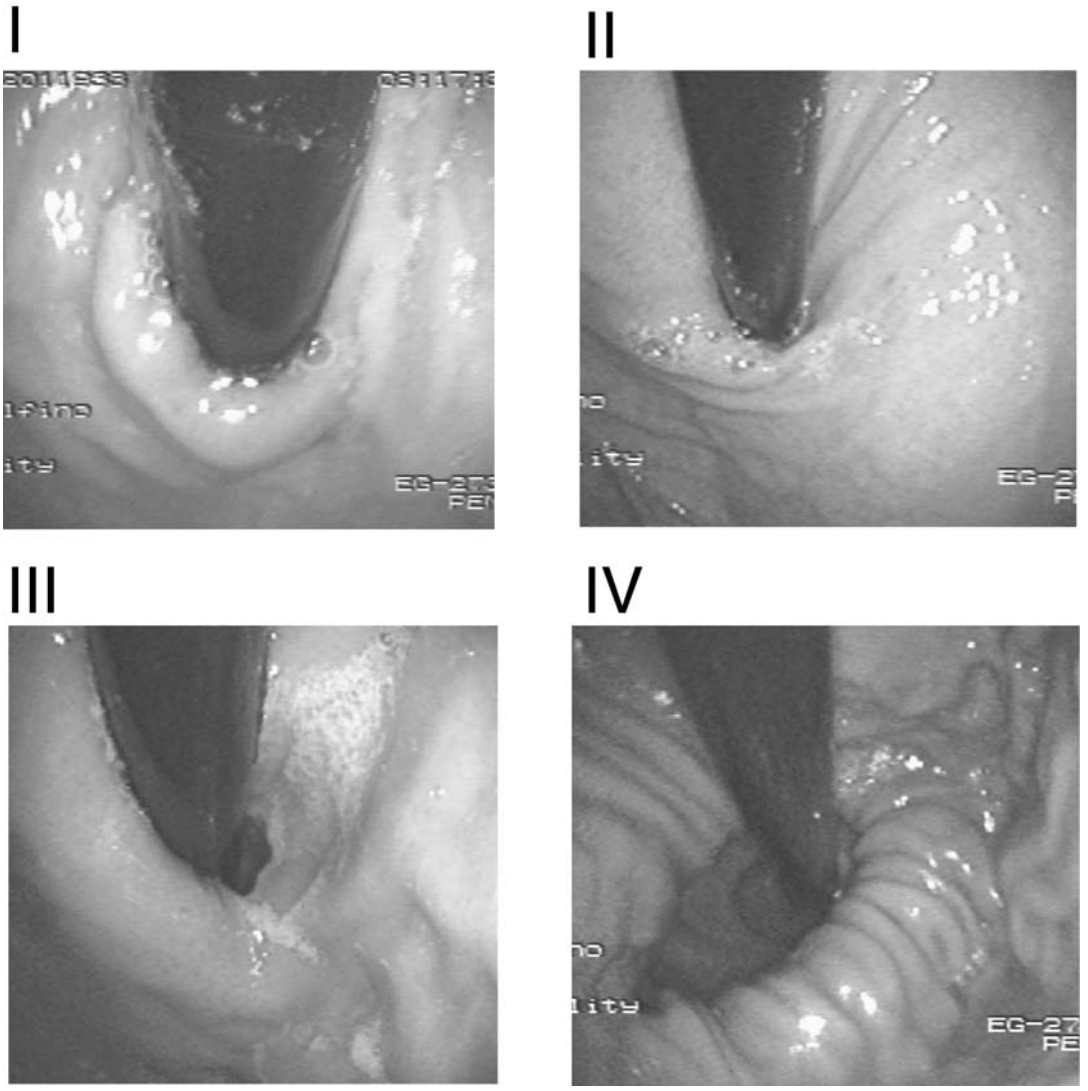

Figure 1.1. Three-dimensional representation of progressive anatomical disruption of the gastroesophageal flap valve as viewed with a retroflexed endoscope. Grade I, Normal ridge of tissue closely approximated to the shaft of the retroflexed scope. Grade II, The ridge is slightly less well defined and opens with respiration. Grade III, The ridge is barely present and the hiatus is patulous. Grade IV, There is no muscular ridge and the hiatus is wide open at all times (Reprinted from Hill et al.,[24] Copyright 1996, with permission from the American Society for Gastrointestinal Endoscopy.)

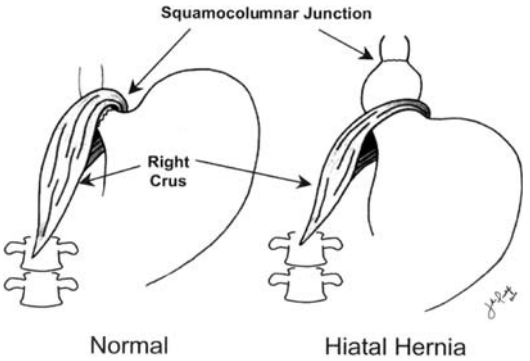

Figure 1.2. Anatomy of the diaphragmatic hiatus. The right crus makes up the muscular component of the crural diaphragm. Arising from the anterior longitudinal ligament overlying the lumbar vertebrae. A single muscle band splits into an anterior and posterior muscular band, which cross each other to 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. (Reprinted with permission from Pandolfino and Kahrilas.[81])

Mechanisms of EGJ Incompetence in GERD

Physiologically, the EGJ must perform seemingly contradictory functions. During swallowing it must facilitate the esophagogastric flow of swallowed material while 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 caustic gastric juice but also be able to transiently relax and permit gas venting. 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 intraabdominal segment of the LES may be important in preventing reflux associated with swallowing, the crural diaphragm may be of cardinal importance during episodes of increased intraabdominal pressure, and basal LES pressure may be of primary importance during restful recumbency. 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 (tLESRs), 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 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.[30] These observations support the hypothesis that the functional integrity of the EGJ is dependent on both 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 both 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 preexisting 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 LES Relaxations

Compelling evidence exists that tLESRs 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).[31,32] Of note, prolonged manometric recordings have not consistently demonstrated an increased frequency of tLESRs in GERD patients compared with normal controls.[33] However, the frequency of acid reflux (as opposed to gas reflux) during tLESRs has been consistently reported to be greater in GERD patients.[34]

Recognizing the importance of tLESRs in promoting reflux, investigators have attempted to define this reflex using physiological and pharmacological manipulations. The dominant stimulus for tLESRs is distension of the proximal stomach, not surprising given that tLESR is the physiological mechanism for belching.[35] Transient LES relaxation can be experimentally elicited by either gaseous distension of the stomach or distension of the proximal stomach with a barostat bag. 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 responsible for eliciting this reflex.[36] The most likely candidate for the afferent receptor is the intraganglionic lamellar ending, or IGLE.[37] Intraganglionic lamellar endings are found at the receptor end of vagal afferents innervating the gastric cardia and can be shown physiologically to fire in direct proportion to applied tension.[38] The frequency of tLESRs is also increased by assuming an upright posture.[33,39] The vagal afferent mechanoreceptors in the gastric cardia then project to the nucleus tractus solitarii in the brainstem and subsequently to the dorsal motor nuclei of the vagus. Finally, dorsal motor nucleus neurons project to inhibitory neurons localized within the myenteric plexus of the distal esophagus. Furthermore, tLESR is an integrated motor response involving not only LES relaxation, but also crural diaphragmatic inhibition and contraction of the costal diaphragm.[32,40] The tLESR reflex is abolished by vagotomy.[32] Recently, animal and human experiments have demonstrated that tLESRs can be inhibited by gamma aminobutyric acid receptor type B agonists (such as baclofen), suggesting a potential new approach to the treatment of GERD.[41–44]

LES (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 when a hypotensive LES is overcome and "blown open" in association with an abrupt increase of intraabdominal pressure.[45] Manometric data suggest that this rarely occurs when the LES pressure is >10 mm Hg[45,46] (Figure 1.3). It is also a rare occurrence in patients without hiatus hernia.[30] Free reflux is characterized by a decrease in intraesophageal pH without an identifiable change in either intragastric pressure or LES pressure. Episodes of free reflux are observed only when the LES pressure is within 0–4 mm Hg of intragastric pressure. A wide-open or patulous hiatus will predispose to this free reflux as both the intrinsic and extrinsic sphincter are compromised.

A puzzling clinical observation, and one that supports the importance of tLESRs, is that only a minority of patients with GERD have a fasting LES pressure value of <10 mm Hg.[47] This observation can also be reconciled when 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. However, there is probably a larger population of patients susceptible to strain-induced or free reflux when their LES pressure periodically decreases as a result of specific foods, drugs, or habits (Table 1.1).

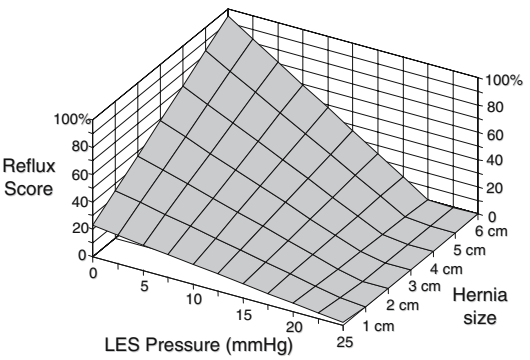

Figure 1.3. Model of the relationship between the LES pressure, size of hernia, and the susceptibility to gastroesophageal reflux induced by provocative straining maneuvers as reflected by the reflux score on the *z* axis. The overall equation of the model is: reflux score = 22.64 + 12.05 (hernia size) − 0.83 (LES pressure) − 0.65 (LES pressure × hernia size). The hernia size is in centimeters, and the LES pressure is in millimeters of mercury. The multiple correlation coefficient of this equation for the 50-subject data set was 0.86 ($R^2 = .75$). 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. (Reprinted with permission from Sloan et al.[45])

The Diaphragmatic Sphincter and Hiatus Hernia

Physiological studies by Mittal et al.[48] have clearly demonstrated that the augmentation of EGJ pressure observed during a multitude of activities associated with transient increases in intraabdominal pressure is attributable to contraction of the crural diaphragm. With hiatus hernia, crural diaphragm function is potentially compromised both by its axial displacement[49] and potentially by atrophy consequent from dilatation of the hiatus.[50] The impact of hiatus hernia on reflux elicited by straining maneuvers was demonstrated in studies in normal volunteers compared to GERD patients with and without hiatus hernia.[45] Of several physiological and anatomical variables tested, the size of hiatus hernia was shown to have the highest correlation with the susceptibility to strain-induced reflux. 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.[49]

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.[51] 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.[52] However, simulating reduction of the hernia by repositioning the intrinsic sphincter back within the hiatal canal and arithmetically summing superimposed pressures 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.[49] This is likely the result of disruption of the EGJ segment distal to the SCJ attributable to the opposing sling and clasp fibers of the gastric cardia.[22] 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.[53]

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 intraabdominal cavity. A flap valve is formed by a musculomucosal fold created by the entry of the esophagus into the stomach along the lesser curvature. Increased intraabdominal or intragastric pressure can decrease the angle of His and compress the subdiaphragmatic 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.[24] demonstrated the presence of a gastroesophageal pressure gradient in cadavers without a hiatal hernia. They also showed that the ability of the EGJ in cadavers to resist reflux in the face of increased intraabdominal pressure could be increased by surgically accentuating the length of the flap valve. Hill et al. then went on to define a grading scheme based on endoscopic inspection of the gastroesophageal flap valve (Figure 1.1). Two endoscopic studies have reported that this grading scheme correlated with the severity of reflux disease.[24,54] Most recently, an investigation using wireless pH monitoring found a strong correlation between the degree to which individuals are susceptible to exercise-induced reflux and flap valve grade.[55] No such correlation existed with LES pressure. Because exercise-induced reflux is presumably strain induced, this supports the importance of the flap valve as a defensive mechanism.

Mechanical Properties of the Relaxed EGJ

For reflux to occur in the setting of a relaxed or hypotensive sphincter, it is necessary for the relaxed sphincter to open. Recent physiological studies exploring the role of compliance in GERD reported that GERD patients without and particularly with hiatus hernia had increased compliance at the EGJ compared with normal

subjects[56] and patients with fundoplication.[57] These experiments utilized 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 intragastric pressure, and 3) for a given distention pressure the EGJ opened about 0.5 cm wider. Still significant, but lesser compliance related changes were demonstrated in the non-hernia GERD patients (Figure 1.4). These alterations of EGJ mechanics are likely secondary to a disrupted, distensible crural aperture and may be the root causes of the physiological aberrations associated with GERD.

Increased EGJ compliance may help explain why patients with hiatus hernia have a distinct mechanistic reflux profile compared with patients without hiatus hernia.[30] 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" to the EGJ because the extrinsic sphincteric mechanism is chronically disrupted. Thus, the only prerequisite for reflux becomes LES relaxation, be that in the setting of swallow-induced relaxation, tLESR, or a period of prolonged LES hypotension.

Increased compliance may also help explain why GERD patients may be more likely to sustain acid reflux in association with tLESRs compared with asymptomatic subjects. In an experiment that sought to quantify this difference, normal subjects exhibited acid reflux with 40–50% of tLESRs compared with 60–70% in patients with GERD.[33] 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 above flow equation, flow is directly proportional to EGJ diameter to the fourth power and inversely proportional to the length of the narrowed segment and the viscosity of the gas or liquid traversing the segment. Should tLESRs occur in the context of an EGJ with

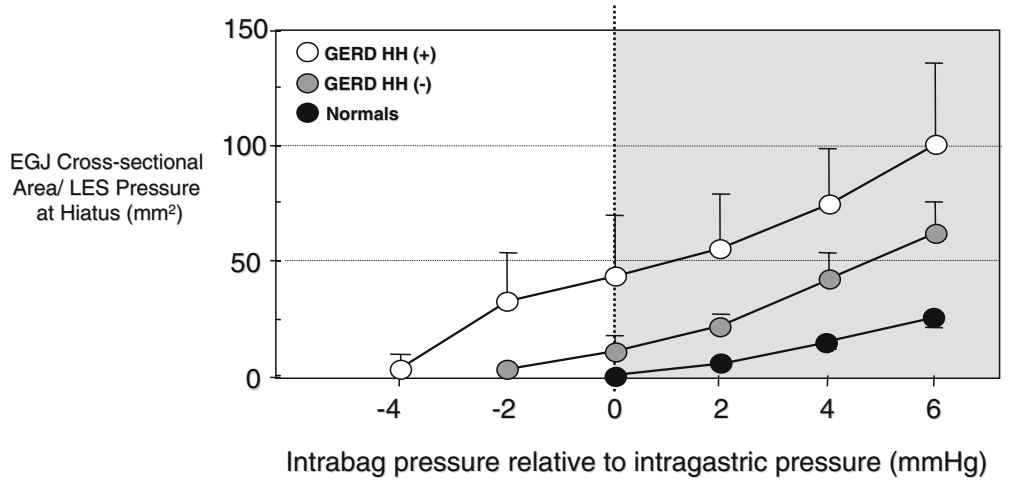

Figure 1.4. Esophagogastric junction cross-sectional area as a function of distention pressure. Cross-sectional area at intrabag pressures >0 mm Hg was significantly increased in the non-hiatus hernia (NHH) GERD patients compared with normal subjects ($P < .0001$) and in the hiatus hernia (HH) patients compared with the NHH patients ($P < .005$). At pressures ≤0 mm Hg, the EGJ cross-sectional area of HH GERD patients was significantly greater than both the NHH GERD patients and normals ($P < .05$). At pressures <0 mm Hg, there was no significant difference between NHH GERD patients and normals. Thus, NHH GERD patients exhibited similar distensile properties to HH patients at pressures greater than intragastric pressure and similar to normal subjects at pressures less than or equal to intragastric pressure. (Reprinted from Pandolfino et al.,[56] Copyright 2003, with permission from the American Gastroenterological Association.)

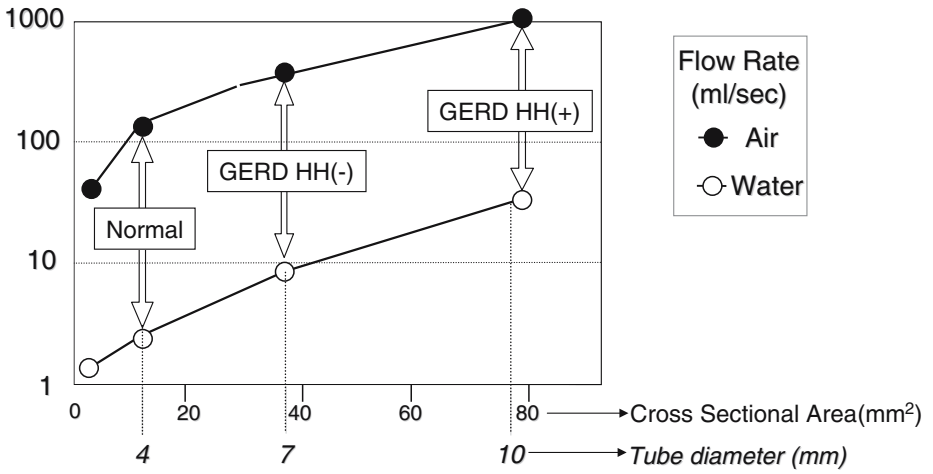

Figure 1.5. Simulated flow rates of water and air across the EGJ using a hydrostat or barostat and short lengths (1 cm) of polyurethane tubing. The diameter of the tubing used to model each group simulates cross-sectional area observed with distention pressures of 4 mm Hg in the three study groups (normal, GERD without hiatus hernia, GERD with hiatus hernia). Given that 57 mL/s was the greatest flow rate attainable with the barostat, higher air flow rates were extrapolated from liquid flow rates using a liquid/air viscosity ratio of 55 : 1. At cross-sectional areas simulating normal subjects, flow of air is preserved whereas flow of liquid is minimal. In contrast, the flow of liquid is significantly increased in both GERD groups.

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 illustrating the flow rates of gas and liquid through tubing simulating the aperture size of normal controls and GERD patients with and without hiatus hernia (Figure 5). 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 II gastroesophageal flap valve or defects in the LES musculature.

Esophageal Acid Clearance

After an acid reflux event, the duration of time that the esophageal mucosa remains acidified to a pH of <4 is termed the esophageal acid clearance time. Acid clearance begins with peristalsis that empties the refluxed fluid from the esophagus and is completed by titration of the residual acid by swallowed saliva. This was demonstrated in an elegant study using radiolabeled 0.1 N hydrochloric acid.[58] Aspirating saliva from the mouth prolonged acid clearance, suggesting that it was the swallowed saliva rather than peristalsis that restored esophageal pH. It requires approximately 7 mL of saliva to neutralize 1 mL of 0.1 N hydrochloric acid, with 50% of this neutralizing capacity attributable to bicarbonate. The typical rate of salivation is 0.5 mL/min.[58] Thus, in individuals with normal esophageal emptying, maneuvers that increase salivation such as oral lozenges or gum chewing hasten acid clearance whereas hyposalivation prolongs acid clearance. Of note, although salivation virtually ceases during sleep,[59] some acid clearance is still achieved attributable to bicarbonate secretion from esophageal submucosal glands.[60]

Prolongation of esophageal acid clearance among patients with esophagitis was demonstrated along with the initial description of an acid clearance test.[61] Subsequent investigations have demonstrated heterogeneity within the patient population such that about half of the GERD patients had normal clearance values,

whereas the other half had prolonged values.[62,63] Ambulatory pH monitoring studies suggest that this heterogeneity is at least partially attributed to hiatus hernia, because this subset of individuals tended to have the most prolonged supine acid clearance.[64] Clinical data also suggest that prolonged acid clearance correlates with both the severity of esophagitis and the presence of Barrett's metaplasia.[65–67] From what we know regarding the mechanisms of acid clearance, the two main potential causes of prolonged esophageal acid clearance are impaired esophageal emptying and impaired salivary function.

Impairments of Esophageal Emptying

Impaired esophageal emptying in reflux disease was inferred by the observation that symptoms of gastroesophageal reflux improve with an upright posture, a maneuver that allows gravity to augment fluid emptying. Subsequently, two mechanisms of impaired esophageal emptying have been identified: peristaltic dysfunction and superimposed reflux associated with nonreducing hiatus hernias. Peristaltic dysfunction in esophagitis has been described by a number of investigators. Of particular significance are failed peristalsis and hypotensive peristaltic contractions (<30 mm Hg) which result in incomplete emptying.[68] As esophagitis increases in severity, so does the incidence of peristaltic dysfunction.[47] More recent investigations of peristaltic function have labeled this "ineffective esophageal motility," defined by the occurrence of >30% of hypotensive or failed contractions.[69] With respect to the reversibility of peristaltic dysfunction, recent studies show no improvement after healing of esophagitis by acid inhibition,[70] or by anti-reflux surgery.[71] Most likely, the acute dysfunction associated with active esophagitis is partially reversible but that associated with stricturing or fibrosis is not.

Hiatus hernia also can impair esophageal emptying. Concurrent pH recording and scintigraphy above the EGJ showed that impaired clearance was caused by reflux of fluid from the hernia sac during swallowing.[72] This observation was subsequently confirmed radiographically in an analysis of esophageal emptying in patients with reducing and nonreducing hiatus hernias.[73] The efficacy of emptying was significantly diminished in both hernia groups when compared with normal controls. Emptying was particularly impaired in the nonreducing hiatus hernia patients who exhibited complete emptying with only one-third of test swallows. The patients with nonreducing hernias were the only group that exhibited retrograde flow of fluid from the hernia during deglutitive relaxation, consistent with the scintigraphic studies.

Salivary Function

The final phase of esophageal acid clearance depends on salivation. Just as impaired esophageal emptying prolongs acid clearance, diminished salivary neutralizing capacity has the same effect. Diminished salivation during sleep, for instance, explains why reflux events during sleep or immediately before sleep are associated with markedly prolonged acid clearance times. Similarly, chronic xerostomia is associated with prolonged esophageal acid exposure and esophagitis.[74] However, no systematic difference has been found in the salivary function of GERD patients compared with controls. One group of subjects shown to have prolonged esophageal acid clearance times attributable to hyposalivation is cigarette smokers. Even those without symptoms of reflux disease exhibited acid clearance times 50% longer than those of nonsmokers and the salivary titratable base content was only 60% of the age-matched nonsmokers.[75]

In addition to bicarbonate, saliva contains growth factors that have the potential to enhance mucosal repair. Epidermal growth factor (EGF), produced in submaxillary ductal cells and duodenal Brunner's glands, has been extensively studied.[76] In animal models, EGF has been shown to provide cytoprotection against irritants, enhance the healing of gastroduodenal ulceration, and decrease the permeability of the esophageal mucosa to hydrogen ions.[76–78] However, studies have not shown consistent differences in EGF concentration in esophagitis or Barrett's metaplasia patients,[79,80] making it impossible to implicate perturbations of growth factor secretion in the pathogenesis of GERD.

Summary

Gastroesophageal reflux disease is likely the most prevalent condition afflicting the gastrointestinal tract in the United States with typical estimates finding 14–20% of the adult population afflicted on at least a weekly basis. The most clearly subset of GERD patients have esophagitis wherein excessive exposure of the esophageal epithelium to gastric acid and pepsin results in erosions, ulcers, and potential complications of these. However, most afflicted individuals will not have endoscopic evidence of esophagitis. Paradoxically, as esophagitis has become less of a problem, at least in part because of more effective treatments, the issue of symptom control has become a more substantial one.

From a pathophysiological viewpoint, GERD results from the excessive reflux of gastric contents into the distal esophagus. Under normal conditions, this is prevented as a function of the anti-reflux barrier at the EGJ, the integrity of which is dependent on the delicate interplay of a host of anatomical and physiological factors including the integrity of the LES, tLESRs, and anatomical degradation of the EGJ inclusive of, but not limited to, hiatus hernia. In fact, considerable investigative focus is now aimed at describing the subtle aberrations of the EGJ that may contribute to the root causes of GERD. The net result is of an increased number of reflux events, an increasing diversity of potential mechanisms of reflux, and a diminished ability of the stomach to selectively vent gas as opposed to gas and gastric juice during tLESRs.

Once reflux has occurred, the duration of resultant esophageal acid exposure is determined by the effectiveness of esophageal acid clearance, the dominant determinants of which are peristalsis, salivation, and, again, the anatomical integrity of the EGJ. About half of GERD patients have abnormal acid clearance and the major contributor to this is hiatus hernia. Abnormalities of acid clearance are probably the major determinant of which GERD patients are most prone to developing esophagitis as opposed to symptomatic GERD.

In summary, GERD is a multifactorial process involving both physiological and anatomical abnormalities. These abnormalities exhibit a complicated interplay that degrades the ability of the EGJ to contain gastric juice within the stomach and to effectively clear the esophagus of gastric juice once reflux has occurred.

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