Gastroesophageal Reflux Disease

From Pathophysiology to Treatment

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Contents

Esophageal Anatomy: The Antireflux Barrier

Leonardo de Mello Del Grande, Filipe de Pádua Brito Figueiredo, Fernando A. M. Herbella, Francisco Schlottmann, and Marco G. Patti

Abstract There is a transdiaphragmatic pressure gradient between the esophagus and the stomach. This gradient would lead inexorably to the reflux of gastric contents into the esophagus if not by the presence of a valvular mechanism at the level of the esophagogastric junction constituted by: (a) the lower esophageal sphincter; (b) the crural diaphragm; (c) the phrenoesophageal ligaments; (d) the angle of His; (e) the abdominal esophagus length; and (f) the Gubaroff valves. The study and understanding of the anatomy and physiology of the antireflux barrier is essential for the correct diagnosis and treatment of diseases in this region.

Keywords Gastroesophageal reflux · Anatomy · Esophageal hiatus · Diaphragm · Lower esophageal sphincter

Introduction

There is a transdiaphragmatic pressure gradient between the esophagus and the stomach. This gradient would lead inexorably to the reflux of gastric contents into the esophagus if not by the presence of a valvular mechanism at the level of the esophagogastric junction (EGJ). Despite the existence of this barrier, gastroesophageal reflux disease (GERD) is a very prevalent disease. This stimulated the study of this functional and anatomical barrier with a complex function to allow coordinated passage of contents into the stomach and gas ventilation but also prevent reflux episodes.

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The complex anatomy and physiology of this region has been the subject of debate for decades. Several factors have been identified including the intrinsic lower esophageal sphincter (LES), extrinsic compression of the LES by the pinchcock action of the crural diaphragm (CD), the length of esophagus under the abdominal pressure, and the angle of His.

Historical Aspects

The Interest in the EGJ is old and dates back to the time of *Hippocrates*, who called this region cardia. The definition of the limit between the esophagus and the stomach was not an anatomical consensus for a long time. At the seventeenth century, *Willis* described and illustrated the junction of circular muscular fibers of the esophagus and oblique fibers of the stomach as a collar named "*Loop of Willis*". A few years later, *Helvetius* (physician to Louis XV) described the oblique fibers too (*Helvetius collar*) [1]. At the end of the nineteenth century, several anatomists developed a special interest in this region. A fold in the lining of the esophagus over the cardiac sphincter is sometimes called "Braune's valvule", after *Christian Braune*, a professor of surgery and anatomy at Leipzig who described it in 1876. In 1883 *Leimer* described a discreet circumferential muscular narrowing in the distal esophagus and named it "lower physiological constriction". In 1903 *Wilhelm His* described the sling fibers of the stomach which cause a notch between the left lower esophagus and the stomach. He named it the incisura cardiac. In 1906, *Cunningham* began calling it the angle of His [2].

However, in the middle of the last century, the anatomical controversies have mostly involved the distal esophagus. Some questions were the presence or absence of a sphincter, the exact location of the EGJ, and the structure of the phreno-esophageal membrane. In 1950, *Lerche* used for the first time the term "inferior esophageal sphincter" for this muscle band [1, 3]. The phrenoesophageal membrane attaches the esophagus to the diaphragm and was originally described by *Galen.* The British surgeon *Allison* emphasized the role of this membrane in the anti-reflux barrier [4]. In 1922, *Chevalier Jackson* described the pinchcock effect caused by the crural compression. Although *Ambroise Pare* and *Morgagni* described diaphragmatic hernias, the modern concept of hiatal hernia is more recent [5].

The development of antireflux surgery from the 1950s onwards, the advent of endoscopy, manometry and radiology has created the modern concepts of the anti-reflux barrier and the link between EGJ anatomy and GERD.

The Anti Reflux Barrier Components

1. *The Lower Esophageal Sphincter*

The LES is traditionally described as a circular smooth muscle that is tonically contracted during rest which determines high pressure zone, located in the distal esophagus. The sphincter muscle is thicker than that of the adjacent esophagus and extends above the squamous columnar mucosal junction (2–3 cm) and the distal margin is about 2 cm distal to the squamous columnar junction. In this way, the upper portion of the muscle lies at the level of the diaphragmatic crura, while the lower portion is intra-abdominal, under the abdominal pressure. The total length of the muscle is normally about 2.4–4.5 cm [6].

Despite the relatively short length, the LES is formed by different muscle fibers (circular, oblique and sling), with different physiological characteristics, giving an asymmetrical pressure pattern. Moreover, the LES has a strongly circadian variation. Studies with endoscopic endoluminal imaging probe confirm this fact, showing that the region has different pressure depending on the location and the period of the day [7].

The LES has the important ability to maintain tone during rest and relax in coordination with pharyngeal swallow and esophageal peristalsis or transiently to relieve the sudden increase in pressure after meals through gas ventilation. Anatomical, myogenic, neurogenic, and humoral mechanisms all play a role in the maintenance of the anti-reflux barrier function and relaxation of the LES [6, 8].

The LES is the main component of the anti-reflux barrier and it is able to maintain its function even when other components are absent, as in patients with hiatal hernia without GERD.

2. *Crural Diaphragm*

The anatomical arrangement of the LES, hiatus and phreno-esophageal ligaments is a fundamental factor in the composition of the anti-reflux barrier. The upper portion of the LES lies in a hiatus created by the right crus of the diaphragm and is supported in the abdomen by the phrenoesophageal ligaments. This extrinsic pressure component conferred by the diaphragmatic crus associated with the basal pressure of the sphincter composes a high-pressure zone observed through manometry. The extrinsic pinching of the LES contributes not only to resting pressure, but more importantly, assists in supporting the LES segment in the correct position. Contraction of the crural diaphragm (CD) also substantially augments EGJ pressure during abdominal straining and abdominal compression [6–9].

The action of diaphragm during respiration creates an effect that imposes rhythmic pressure increments at the LES pressure. These pressure augmentations are directly proportional to the depth of inspiration when thoracic pressure reaches its lowest value [8].

In addition to positioning, there is a functional link between LES and CD. Interestingly, CD is selectively inhibited by esophageal distension, during vomiting and in association with transient LES relaxations [7].

3. ***Phrenoesophageal Ligaments***

The visceral peritoneum and phrenoesophageal ligaments help keeping the EGJ within the abdominal cavity. Phrenoesophageal ligaments are fibrous connective tissue extending from the muscle fibers of the diaphragm to the distal portion of the esophagus. There is an extension of the membrane 2 or 3 cm above the hiatus, transmitting abdominal pressure to this portion of the esophagus [8, 11].

4. ***Angle of His***

The acute angle formed between the esophagus and the gastric fundus (angle of His) creates a longer distance between the gastric fundus where the food is stored and the esophagus [9].

5. ***Others Anatomical Considerations***

Passive compression of abdominal esophagus by abdominal pressure can increase LES basal pressure [12]. Changes in anatomical and physiological interactions between EGJ and gastric fundus during respiration and on eating could create a functional "flap valve". This mechanism has been hypothesized to contribute to antireflux barrier [8].

Gubaroff valves or *plica cardiaca* consist in a cushion action of the distal esophageal mucosa at the level of the esophagogastric junction [9].

Figure 1 summarizes the main anatomic structures of antireflux barrier.

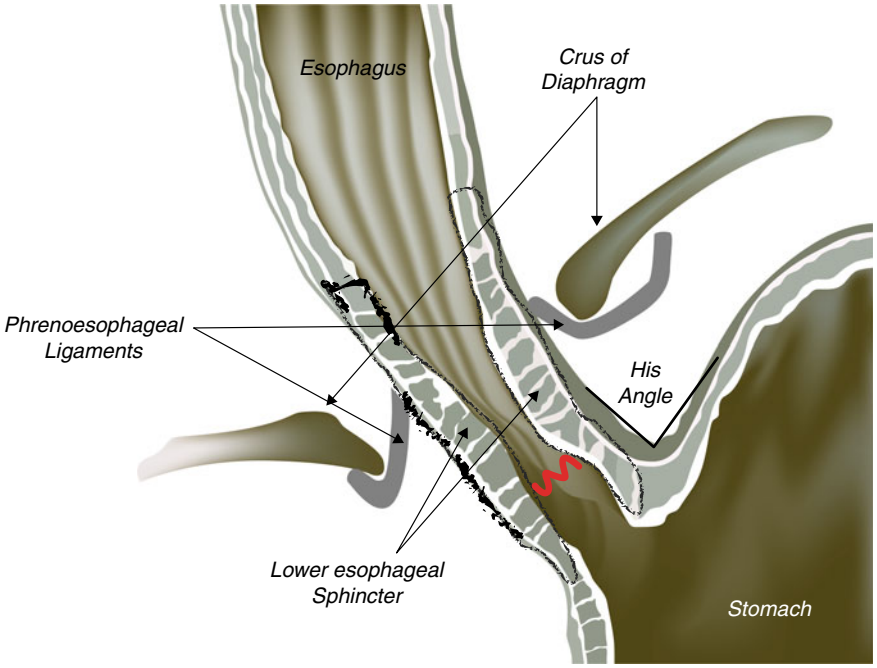

Fig. 1 The antireflux barrier

Conclusions

The antireflux barrier function is much more associated with the interaction of the different components than the isolated action of each one. This barrier is a complex, specialized and integrated anatomical and functional arrangement that allows swallowing and avoidance of reflux. The study and understanding of the anatomy and physiology of the antireflux barrier is essential for the correct diagnosis and treatment of diseases in this region.

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Pathophysiology of Gastroesophageal Reflux Disease

Rafael C. Katayama, Fernando A. M. Herbella, Marco G. Patti, and Francisco Schlottmann

Abstract Gastroesophageal reflux disease (GERD) pathophysiology is complex. It occurs when there is a disbalance between the transdiaphragmatic pressure gradient (positive intra-abdominal pressure and negative intra-thoracic pressure) and the intricate valve mechanism at the level of the esophagogastric junction. GERD may occur in different clinical scenarios affecting this balance such as: obesity, restrictive pulmonary diseases, hiatal hernia, and esophageal and gastric dysmotility. It is fundamental to understand GERD pathophysiology to properly guide therapy.

Keywords Gastroesophageal reflux disease · Obesity · Hiatal hernia · Pathophysiology

Introduction

Gastroesophageal reflux disease (GERD) pathophysiology is complex. It occurs when there is an imbalance between the transdiaphragmatic pressure gradient (positive intra-abdominal pressure and negative intra-thoracic pressure) and the intricate valve mechanism at the level of the esophagogastric junction (EGJ) [1–5] (Fig. 1).

An efficient barrier exists between the stomach and the esophagus, although normal individuals still present with small amount of physiological reflux [6, 7]. From the esophagus side the salivary production and the peristalsis play an important role in the esophageal clearance. From the EGJ side the lower esophageal sphincter (LES), the diaphragm, the angle of His, the Gubaroff valve and the phrenoesophageal

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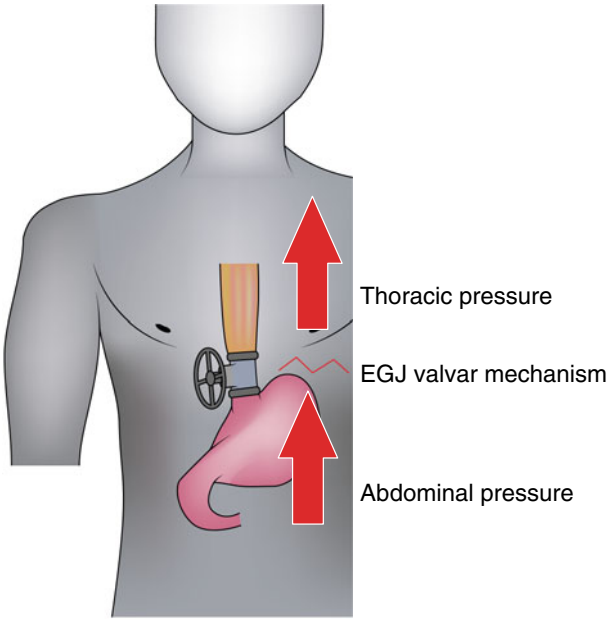

Fig. 1 Gastroesophageal reflux disease pathophysiology is based on a balance between the transdiaphragmatic pressure gradient and the valve mechanism at the level of the esophagogastric junction (EGJ)

membrane act together to compose the valvular mechanism [6]. When the transdiaphragmatic pressure overcomes this barrier, acid and bile rises into the esophagus and are responsible for an esophageal injury related to chemical damage of the mucosa [8]. The mucosal inflammation is due to the damage in the tight junction proteins of the esophageal epithelium, resulting in increased para-cellular permeability and dilated intercellular space (DIS). Through dilated intercellular spaces the noxious agents (gastric acid, bile, and pepsin) penetrate deep basal layers of the esophageal mucosa and provoke injury through inflammatory mediators [9–14]. This inflammation may act on nociceptors to provoke symptoms and dysmotility [8, 15–17].

Natural Anti-reflux Mechanism

1. ***Peristalsis***

Esophageal peristalsis is a very important mechanism in the clearance of the esophagus. A defective peristalsis is associated with GERD severity, both in terms of symptoms and mucosal damage, related to the time of exposure of the esophageal mucosa to chemical agents (acid and bile) [6].

It is known that 40–50% of patients with GERD have abnormal peristalsis. This dysmotility is particularly severe in about 20% of patients because of very low amplitude of peristalsis and/or abnormal propagation of the peristaltic waves (ineffective esophageal motility). A slower than normal esophageal clearance, increases the contact time of the refluxate which can eventually reach easier the upper esophagus and pharynx. Thus, these patients are prone to severe mucosal injury and frequent extra-esophageal symptoms such as cough [18–25].

2. ***Lower Esophageal Sphincter***

The LES is a smooth muscle, 3-4 cm in length, at the distal end of the esophagus that allows coordinated passage of food into the esophagus and gas venting after meals but also prevents reflux of contents into the esophagus [26, 27]. It acts by pressuring the transition between the esophagus and the stomach. An effective LES must have an adequate total and intra-abdominal length along with a satisfactory resting pressure. Although a defective LES is found in the majority of patients with GERD, up to 40% of patients with GERD have a normal LES pressure. This apparent contradiction is explained by the LES pressure being overcome by an increased transdiaphragmatic pressure gradient. In addition, transient LES relaxations (TLESR) may play a role. TLESR are defined as LES relaxations occurring in the absence of swallowing, lasting more than 10 s, that can be responsible of pathological reflux if too frequent [28–31].

3. ***Diaphragm and Intra-abdominal Esophagus Length***

The diaphragmatic crus is considered an extrinsic component of the gastroesophageal barrier [22]. It pinches the abdominal part of the esophagus at the level of the EGJ adding pressure to the LES. The presence of an intra-abdominal portion of the esophagus contributes to the valve mechanism, due to the effect of the abdominal pressure collapsing the esophageal wall [32–34]. This mechanism is lost in the presence of a hiatal hernia [35–37].

4. ***Angle of His***

The acute angle formed by the esophagus and the gastric fundus is called angle of His. The more acute the angle, the longer is the distance between the gastric fundus (where food is stored) and the EGJ, providing a barrier to the rise of the refluxate [6].

5. ***Gubaroff Valves***

Gubaroff valves consist of a cushion action of the distal esophageal mucosa at the level of the EGJ [2, 38].

Trans-Diaphragmatic Pressure

The thoracic pressure tends to be negative, promoting suction of the gastric contents, while the abdominal pressure tends to be positive, pushing the gastric contents towards the thorax. This gradient is normally balanced by natural valvular mechanisms [39, 40]. Nevertheless, there are situations in which this balance is disrupted. This can be related to the rise of intra-abdominal pressure (e.g. obesity) or to a decrease of the thoracic pressure (e.g. respiratory diseases) [41].

GERD in Different Clinical Scenarios

6. ***Obesity***

A defective LES is not always observed in patients with obesity. Moreover, some studies have shown an increased basal pressure of LES, probably linked to compensatory mechanisms to overcome the pressure gradient. TLESR, however, seems to be more frequent in obese individuals [38, 41–44].

The deposition of fat in the gastroesophageal junction can make this angle obtuse, worsening the valvular mechanism. Another concern is that salivation in patients with obesity is decreased and esophageal motility may be impaired in a quarter of obese individuals. Obese patients may also have increased intrathoracic pressure due to diaphragm elevation, with consequent decrease in pulmonary expansion. Intrathoracic pressure may also be increased by the frequent occurrence of obstructive apnea in these patients. Apnea itself may be a cause for GERD due to the increase of TLESR [45–47].

The main contributor of GERD in the setting of obesity is the raise in the intraabdominal pressure. The most prevalent reason for elevated abdominal pressure is obesity, a well-known independent risk factor for GERD. Abdominal fat deposition and abdominal circumference are directly related to the rise of abdominal pressure [30, 41].

7. ***Pulmonary Diseases***

Patients with obstructive pulmonary diseases or even professional glass blowers or singers, may have decreased thoracic pressure related to an increased respiratory effort and consequently more negative thoracic pressure, that may lead to a higher incidence of GERD [7, 30, 48, 49].

8. ***Hiatal Hernia***

Hiatal Hernia and GERD used to be considered synonyms. Currently, it is well known that these conditions can exist independently. However, hiatal hernia can disrupt most of the antireflux barrier and lead to GERD [50, 51] (Fig. 2).

Firstly, when the esophagus rises toward the thorax its distal portion loses the abdominal pressure who acts as part of the valve mechanism. Secondly, hiatus hernia

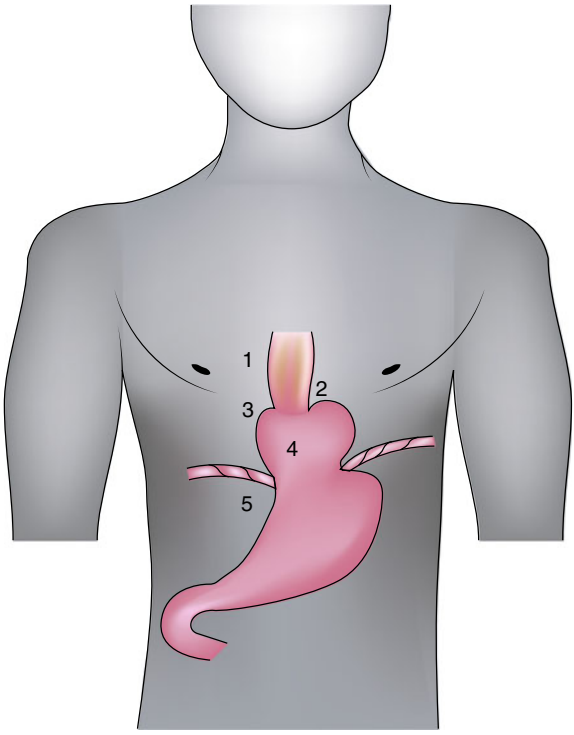

Fig. 2 Disruption of natural antireflux mechanisms by a hiatal hernia. (1) absence of intra-abdominal esophagus length; (2) angle of His becomes obtuse; (3) lower esophageal sphincter in a negative pressure environment; (4) pressurization of the herniated gastric pouch; (5) enlargement of the hiatus and diaphragm pinches the stomach not the esophagus

disrupts the angle of his, enlarges the esophageal hiatus and, not surprisingly, is associated with a more incompetent LES (the pinchcock action of the diaphragm is absent), defective peristalsis, more severe mucosal damage, and increased acid exposure. Moreover, TLESR is more frequent in patients with hiatal hernia [52–55].

9. *Esophageal Dysmotility*

Dysmotility may be found in almost half of the GERD patients with 20–30% having ineffective esophageal motility (Fig. 3). Adequate peristalsis is a crucial mechanism for esophageal clearance. Primary esophageal dysmotility might affect esophageal clearance and promote mucosa inflammation. Moreover, esophageal inflammation is associated with inefficient contractions.

It is not clear whether GERD is responsible for esophageal dysmotility, or it is the consequence of it. However, it has been demonstrated that when reflux is controlled by a fundoplication esophageal motility is usually improved [16, 17, 56, 57].

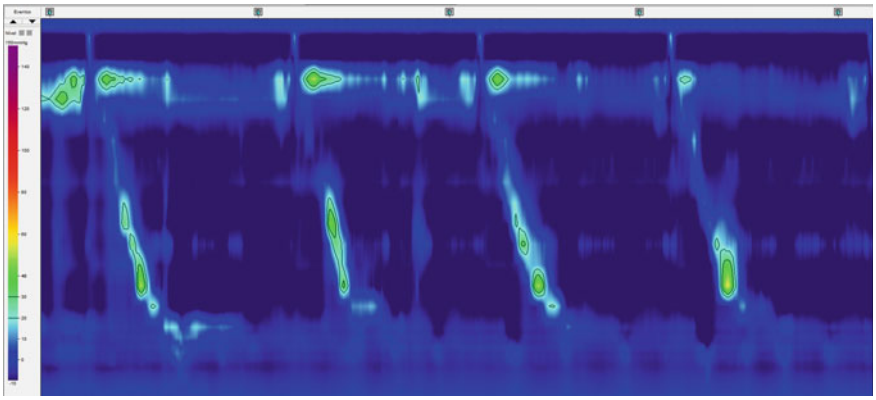

Fig. 3 Ineffective esophageal motility at esophageal high-resolution manometry in a patient with gastroesophageal reflux disease. Note a hypotensive lower esophageal sphincter

Refluxate Characteristics and GERD

Gastric and duodenal contents can reflux into the esophagus and adjacent organs. Gastric acid is recognized as harmful to the esophageal mucosa. Nonetheless, gastroesophageal refluxate may contain non-acid noxious agents including bile and pancreatic enzymes. It is known that this component of the refluxate is also injurious to the esophageal mucosa, promoting symptoms, and ultimately could be responsible for the development of Barrett's esophagus and esophageal adenocarcinoma [58–63]. Besides the constituents of the refluxate, symptom perception and mucosal damage also appear to be associated to the patterns of esophageal exposure and the volume of the refluxate. Individuals are more likely to perceive a reflux event if the refluxate has a high proximal extent and a large volume.

Conclusions

GERD pathophysiology is complex and multifactorial. Major players are the transdiaphragmatic pressure gradient and the valve mechanism at the EGJ. GERD may occur in specific clinical scenarios: obesity, restrictive pulmonary diseases, hiatal hernia, and esophageal and gastric dysmotility. It is fundamental to understand GERD pathophysiology to properly guide therapy.

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Clinical Presentation of Gastroesophageal Reflux Disease: Esophageal and Extraesophageal Manifestations

Fernando A. M. Herbella, Francisco Schlottmann, and Marco G. Patti

Abstract Gastroesophageal reflux disease may cause a variety of symptoms. Some of the symptoms are *esophageal,* such as heartburn, regurgitation, and dysphagia while others are defined as *extraesophageal* such as hoarseness, cough, asthma, aspiration, chest pain, water brush, and globus. It is also important to remember that in some patients (such as patients with pulmonary manifestations), the reflux can be asymptomatic or "silent" and be identified only by diagnostic testing.

Keywords Gastroesophageal reflux disease · Heartburn · Regurgitation · Chest pain · Dysphagia · Cough · Asthma · Aspiration

Introduction

Gastroesophageal reflux disease (GERD) may present with a myriad of clinical scenarios, from asymptomatic or "silent" (but noted by abnormal endoscopic or pHmonitoring test or even subclinical damage to the esophagus or adjacent organs) to a variety of symptoms.

The most widespread definition for GERD comes from the Montreal consensus that characterize GERD as "a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications" [1]. This vague definition does not include silent GERD and it is not practical in the real clinical scenario when trying to decide if a patient has indeed GERD. Despite the fact that surgeons have long insisted for a more objective diagnosis [2], only after the Lyon

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consensus that objective criteria to diagnose GERD was disseminated [3]. This all reflects the fact that even though clinical history, questionnaire data and response to medical therapy are the beginning of the investigation, they are insufficient to make a conclusive diagnosis of GERD in isolation.

GERD symptoms are *esophageal* (erroneously but classically also known as *typical*), such as heartburn, regurgitation, and dysphagia or *extraesophageal* (again, erroneously but classically also known as a*typical*), such as hoarseness, cough, asthma, aspiration, chest pain, water brush, and globus [4].

Esophageal Symptoms

Heartburn occurs due to the irritation of the esophageal mucosa by gastric contents, both acid and bile. Heartburn is a physiologic phenomenon that becomes pathologic when it is more frequent and severe, affecting the quality of life. It is felt in the retrosternal area, but it can extend upward, radiating toward the throat. It usually occurs post prandially, particularly after ingestion of spicy foods, fatty food, chocolate, and alcohol. Nocturnal heartburn can cause sleep disruption and impair next day activities. Heartburn can be caused by other disorders such as eosinophilic esophagitis, biliary disease, and gastritis. Sometimes, it can be the only symptom of myocardial ischemia. Patients with achalasia can also experience severe heartburn that does not respond to medications. In these patients the symptom is not due to reflux of gastric contents but rather to stasis and fermentation of food in the lower esophagus, because of the slow emptying caused by lack of peristalsis and a hypertensive and non-relaxing lower esophageal sphincter.

Heartburn is the most common symptom of GERD, but still with a suboptimal accuracy to diagnose GERD: a sensitivity of 73% and a specificity of 38% [5].

Regurgitation is the upward extent of the gastric refluxate into the hypopharynx or the mouth. Approximately 10% to 15% of patients with GERD have episodes of regurgitation at least 4 days per week, which determines a decrease in their quality of life. Factors that might induce regurgitation are eating large meals and bending over after eating. Regurgitation occurs more frequently in patients with and incompetent gastroesophageal junction and in the presence of large hiatal hernias. In addition to GERD, there are two other conditions that are associated with regurgitation: in achalasia patients, regurgitation is not caused by the reflux of gastric contents but rather by the upward extent of retained food in the esophagus, with no acid or bile. The other condition associated with regurgitation is rumination. In this condition the upward extent of gastric contents is a learned behavior, with the individual subconsciously causing the food to come back to the mouth and then swallow it again.

Regurgitation also has a suboptimal accuracy to diagnose GERD: a sensitivity of 61% and a specificity of 54% [5].

Dysphagia is difficulty swallowing, with patients having the feeling that the food is stuck in the throat or chest. Dysphagia can be caused by severe esophagitis or peptic stricture in patients with long standing GERD. It can also be “functional” in nature

due to abnormal esophageal peristalsis, which can be a cause or a consequence of the abnormal reflux. Dysphagia is also present in eosinophilic esophagitis and in achalasia (due the lack of peristalsis and the abnormal relaxation of the lower esophageal sphincter in response to swallowing).

Extraesophageal Symptoms

While it is quite easy to connect symptoms like heartburn, regurgitation, and dysphagia to the esophagus and particularly to GERD, it is quite challenging to attribute to pathologic reflux symptoms such as non-cardiac chest pain, cough and asthma, hoarseness or globus [6, 7].

GERD may cause a myriad of symptom mimicking diseases from the target organs (Fig. 1) [8].

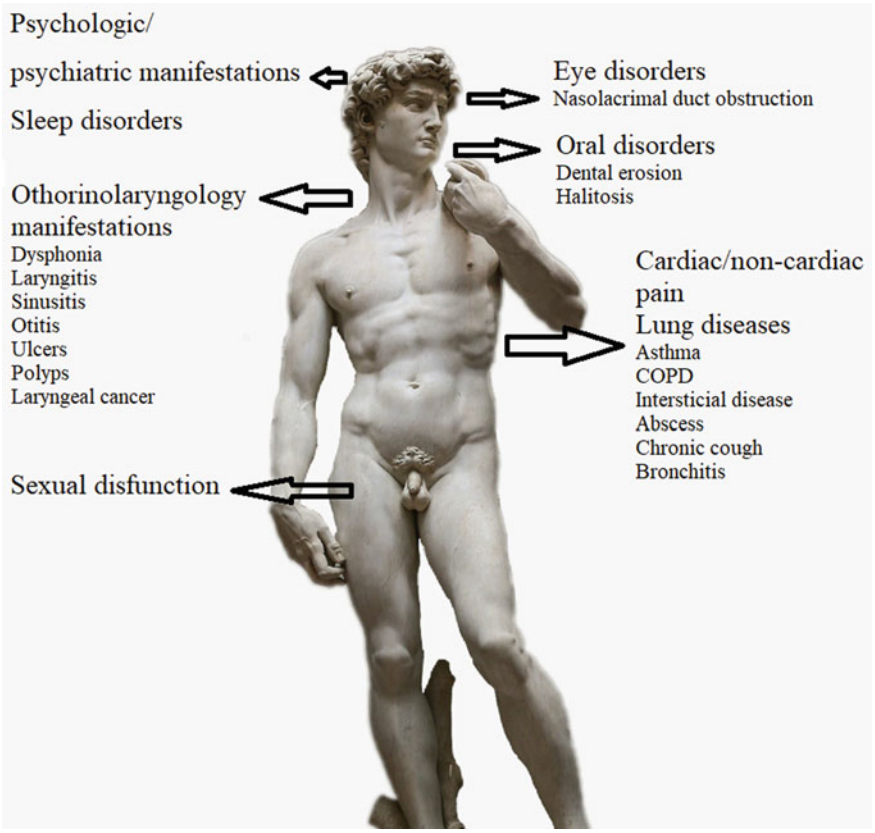

Fig. 1 Possible extraesophageal manifestations of gastroesophageal reflux disease

The following sections describe the more common GERD extraesophageal manifestations.

Ear-Nose-Throat Symptoms

Reflux laryngitis. Symptoms of reflux laryngitis include hoarseness and globus (feeling of lump in the throat) in addition to cough and dysphagia [9-11]. The most likely etiology for these symptoms is probably micro aspiration. The reflux most likely occurs at night when the pressure of the upper esophageal sphincter is lower.

These patients often manifest hypersalivation, also known as "water brash". The increased production of saliva is considered a defense mechanism thanks to the chemical neutralization of refluxed acid and the promotion of peristalsis, both two important components of the esophageal acid clearance mechanism.

Thoracic Symptoms

Non cardiac chest pain. Approximately 20–30% of patients with chest pain who undergo cardiac catheterization have normal or minimally diseased coronary arteries. This type of pain is termed "non-cardiac chest pain" and it is thought to be often of esophageal origin and secondary to either esophageal motility disorders such as achalasia or diffuse esophageal spasm or to abnormal reflux (which may be present in 25–50% of patients) [12, 13].

Pulmonary Symptoms

Cough and asthma can also be secondary to gastroesophageal reflux [14, 15]. There are two theories on how GERD might cause asthma: (A) vagal reflex; or (B) micro aspiration. The esophagus and the bronchial tree share embryonic foregut origins. Acid in the esophagus could stimulate acid-sensitive receptors causing a vagal reflex and bronchoconstriction. Micro aspiration of gastric contents into the tracheabronchial tree can also case bronchoconstriction. Medications used for the treatment of asthma might increase reflux. In addition, asthma might increase the negative intrathoracic pressure, therefore altering the thoraco-abdominal pressure gradient, thus favoring reflux. It is thought that about 50% of patients with asthma might have GERD.

Recently, studies have shown a very high prevalence of pathologic reflux, extending all the way the proximal esophagus and pharynx, in patients with idiopathic pulmonary fibrosis, suggesting that micro aspiration might play a role in its etiology along with other factors. GERD seems to also play a role in the rejection

after lung transplantation, the so called "bronchiolitis obliterans syndrome". In these patients, both pepsin and bile acids have been detected in the bronco alveolar lavage, suggesting aspiration of gastric contents.

Conclusions

GERD can affect directly or indirectly several organs apart from the esophagus and determine both esophageal and extraesophageal manifestations. The diagnosis of extraesophageal manifestations of GERD may be difficult, since symptoms mimic other diseases. Therefore, a high index of suspicion is often needed for a correct diagnosis.

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Refractory Gastroesophageal Reflux Disease. Real Reflux or Fake Reflux?

Francisco Schlottmann, Fernando A. M. Herbella, and Marco G. Patti

Abstract Clinicians are generally confident that a diagnosis of gastroesophageal reflux disease (GERD) can be made firmly from the clinical findings, and when a complaint is thought to be heartburn, acid-reducing medications are prescribed. Endoscopy is usually the first test performed on the assumption that it provides useful information for diagnosis and management. Esophageal manometry and pH monitoring (esophageal function tests—EFT) are seldom done early in the management, largely because other measures are reputed to be accurate enough for routine care. Unfortunately, this approach leads to a misdiagnosis of GERD—and missing the real cause of the symptoms—in 30 to 40% of patients. Therefore, a complete work-up is necessary—barium swallow, endoscopy, esophageal manometry, and pH monitoring—particularly when surgery is considered. Similarly, if a patient has persistent or recurrent foregut symptoms after fundoplication it is usually assumed that the operation has failed, and acid-reducing medications are often prescribed. Regrettably, most of these patients do not have persistent or recurrent pathologic reflux so that if EFT were performed early in the evaluation of symptomatic patients after fundoplication, improper and costly medical therapy could be avoided.

Keywords Gastroesophageal reflux disease · Proton pump inhibitors · Refractory GERD · Fundoplication

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Introduction

Clinicians are generally confident that a diagnosis of gastroesophageal reflux disease (GERD) can be made firmly from the clinical findings, and when a complaint is thought to be heartburn, acid-reducing medications are prescribed. Endoscopy is usually the first test performed on the assumption that it provides useful information for diagnosis and management. Esophageal manometry and pH monitoring (esophageal function tests—EFT) are seldom done early in the management, largely because other measures are reputed to be accurate enough for routine care. Unfortunately, this approach leads to a misdiagnosis of GERD (missing the real cause of the symptoms) in 30 to 40% of patients. Therefore, a complete work-up is necessary—barium swallow, endoscopy, esophageal manometry, and pH monitoring—particularly when surgery is considered.

Diagnostic Evaluation of GERD. Distinguishing "Real" from "Fake" Reflux.

Recently, the term "refractory GERD" has been used to describe patients that still experience foregut symptoms while on medical therapy. We feel that it is important to distinguish between "real reflux"—patients who have GERD but in whom the symptoms are not completely controlled by PPI therapy—and "fake reflux"—patients who have foregut symptoms which mimic GERD but are due to other causes. In these patients it is important to perform a full work-up that includes symptomatic evaluation, upper endoscopy, barium swallow, esophageal manometry, and pH monitoring to avoid improper and costly medical therapy and to miss the real cause of the symptoms.

Limitations of the Symptomatic Evaluation

GERD can manifest with typical symptoms such heartburn, dysphagia and regurgitation, and atypical symptoms such as cough, laryngitis, globus sensation, and chest pain. However, these symptoms have low sensitivity and specificity for the diagnosis of GERD. On the DIAMOND study the sensitivity and specificity for the symptom-based diagnosis of GERD in patients with heartburn and/or regurgitation was 62% and 67%, respectively [1]. Symptom response to a two-week course of 40 mg of esomeprazole did not add diagnostic precision. A subsequent study by Bytzer et al. showed the limited ability of the proton-pump inhibitory test to identify patients with GERD [2]. In this study, a positive response to the PPI test was observed in 69% of patients with GERD and in 51% of those without GERD.

Patti and colleagues studied in a large cohort of patients the role of esophageal function tests in the diagnosis of GERD [3]. Manometry and pH monitoring were performed in 822 patients with a clinical diagnosis of GERD based on symptoms and endoscopic findings (patients with Barrett's esophagus confirmed by biopsy were excluded). This study showed that 247 patients (group A; 30%) had normal reflux scores and 575 had an abnormal score (group B; 70%). It is of note that 80% of group A patients and 88% of group B patients had been treated with acid suppressing medications. Eventually, a different diagnosis was established in most patients from group A, such as cholelithiasis, irritable bowel syndrome, coronary artery disease. In addition, 18% of group A patients referred for antireflux surgery had a primary esophageal motility disorder such as achalasia [3].

Another study evaluated the role of a proper work-up in patients thought to have GERD and referred for antireflux surgery; 138 patients were referred for antireflux surgery with a diagnosis of GERD based on symptoms and endoscopy. Esophageal manometry and pH monitoring were performed in all patients before surgery. These tests showed that 4 patients had achalasia rather than GERD: among the remaining 134 patients, 78 (58%) had pathologic reflux and 56 patients (42%) had a normal score. There was no difference between the two groups with respect to the incidence of symptoms [4].

Patients with achalasia can also complain of heartburn that does not respond to medications, and they are often referred to as having refractory GERD. However, in these patients the symptom is not due to reflux of gastric contents into the esophagus but rather to stasis and fermentation of food in the distal esophagus because of the lack of peristalsis and the non-relaxing lower esophageal sphincter. For instance, a previous multi-center study evaluated 524 patients who were complaining of heartburn with manometry and pH monitoring [5]; 152 patients had been treated with acid reducing medications for an average of 29 months and were referred for antireflux surgery because of lack of response to medical therapy. All of them had achalasia and underwent a Heller myotomy with partial fundoplication. These data confirm the importance of esophageal manometry and pH monitoring in any patient considered for antireflux surgery to rule out achalasia and to establish a correlation between symptoms and episodes of reflux.

Limitations of Endoscopy in the Diagnosis of GERD

Esophagogastroduodenoscopy is very important in any patient with foregut symptoms to assess the esophageal mucosa and to rule out other pathology such as peptic ulcer disease or malignancy. However, it is very important to understand the limitations of this test.

The Los Angeles (LA) classification was introduced into practice to objectively describe the severity of esophagitis [6]. Based on the degree of damage, 4 levels are described: A, B, C, and D, with D being the least common and the most severe.

However, fewer than 50% of patients with typical GERD symptoms have endoscopically recognizable mucosal lesions [7]. In addition, there is major interobserver variability for grade A and B, which makes the diagnosis of GERD unreliable [8]. While the presence of Barrett's esophagus has been considered a strong indicator of pathologic reflux, it is very important to distinguish between long segment Barrett's esophagus ($\geq$3 cm) and short segment ($<$3 cm) according to the Prague classification. In this latter group, endoscopic findings are confirmed by biopsy in approximately 50% of patients only [9].

A Complete work–up: The Key for Success

Overall, we do know that medical therapy improves symptoms in most but not all patients with GERD. Antireflux surgery is an excellent option for patients with persistent symptoms such as regurgitation and for patients with complete symptomatic resolution on acid-suppressing therapy. However, proper patient selection is of paramount importance to achieve excellent outcomes. Patti et al. analyzed the causes of failed antireflux surgery and determined that an incomplete pre-operative work-up was one of the 3 most common causes of failure, the other two being wrong indications for the operation and failure to execute the proper technical steps [10].

The importance of the preoperative diagnostic workup before antireflux surgery was highlighted by a panel of experienced gastroenterologists and surgeons which reached an evidence and experience-based consensus about the work-up of patients with foregut symptoms, particularly if surgery is considered. Patients should be evaluated by symptomatic evaluation, barium swallow, upper endoscopy, esophageal manometry, and pH monitoring [11]. A 4-h gastric emptying study should be reserved for patients with significant nausea, vomiting and bloating or in those with retained food in the stomach after an overnight fast on endoscopy.

In patients with idiopathic pulmonary fibrosis, bronchoscopy with bronchoalveolar lavage and essay for pepsin should be performed to determine the presence of aspiration.

Persistent Symptoms After Antireflux Surgery: Distinguishing "Real" from "Fake" Reflux

The presence of foregut symptoms after fundoplication is often considered proof that the operation has failed, with the need to start acid-reducing medications again. This approach assumes that the presence of pathologic reflux can be made confidently based on the symptomatic evaluation only. Usually, the first test that is performed is an endoscopy, while manometry and pH monitoring are rarely done early in the management of these patients. However, many studies have shown that this approach

is wrong in about 30–40% of patients, stressing the importance of an early and objective evaluation by esophageal function tests [12–14].

Previous research has shown that GERD is absent in most patients taking acid-suppressing medications after Nissen fundoplication [12]. They studied 86 patients who had foregut symptoms after Nissen fundoplication using manometry and pH monitoring. They found that only 23% (20 of 86) of all patients and only 24% (9 of 37) of those taking acid-suppressing medications had abnormal esophageal acid exposure on the 24-h pH study. Similar results were obtained by Galvani et al. who evaluated with esophageal function tests 124 patients who developed symptoms after laparoscopic fundoplication (average 17 months postoperatively) [13]. Sixty-two patients (50%) were taking acid reducing medications. They found that 76 (61%) patients had normal esophageal acid exposure while the acid exposure was abnormal in 48 patients (39%). Only 20 (32%) of the 62 patients who were taking acid-reducing medications had reflux postoperatively [13]. In a similar study, Bernardi et al. assessed 32 patients who had GERD like symptoms nonresponding to acid suppression after fundoplication [14]. Ambulatory pH testing showed that only 5 (9%) had a pathologic amount of reflux.

Overall, these studies show that the presence of symptoms after fundoplication for GERD is an unreliable index of pathologic reflux and that esophageal function tests should be performed early in the evaluation as most patients have a normal reflux profile.

Conclusions

GERD diagnosis based on symptoms and/or endoscopic findings is unreliable. A proper diagnostic work up including endoscopy, barium swallow, esophageal manometry, and pH monitoring is necessary to confirm the diagnosis of GERD. Patients with GERD like symptoms after antireflux surgery should also undergo a thorough diagnostic work up to assess the presence or not of pathologic reflux.

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Radiologic Evaluation of Gastroesophageal Reflux Disease

André V. Santana, Fernando A. M. Herbella, Rodrigo P. Polízio, and Fernando D. Tamamoto

Abstract Gastroesophageal reflux disease (GERD) evaluation requires a complete work-up. Each different test studies esophageal/hiatal anatomy and physiology from different perspectives. Radiologic tests, barium swallow and computerized tomography, have been underutilized by surgeons and gastroenterologists alike; however, they may bring a different perspective of the interface between hiatal hernias and the esophageal/hiatal anatomy. Radiologic tests should not be considered diagnostic tests for GERD but could play a role in evaluating patients with GERD, especially when surgical treatment is considered, showing a different anatomical view compared with the other tests.

Keywords Gastroesophageal reflux disease · Radiology · Esophagram · Computed tomography

Introduction

Gastroesophageal reflux disease (GERD) evaluation requires a complete work-up. Each different test evaluates the esophageal/hiatal anatomy and physiology from different perspectives. Radiologic tests have been underutilized by surgeons and gastroenterologists alike. A variety of factors justify the decrease in use of this tests, including less experienced radiologists that prefer to dedicate themselves to more modern test such as magnetic resonance; the argument that they are time-consuming and technically demanding and the sense that upper digestive endoscopy is sufficient to study the esophageal/hiatal anatomy and diagnose GERD [1]. Despite contrary thoughts, radiologic tests can show information that the other exams are unable to provide, helping surgeons to have the valuable data to plan surgical treatment.

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Barium esophagram can evaluate swallowing function, esophageal motility, gastroesophageal reflux, and morphologic abnormalities. This test should be considered in all candidates for antireflux surgery (ARS) to evaluate global anatomy for structural problems, a recommendation of the consensus of the Esophageal Diagnostic Advisory Panel [2].

Computed tomography (CT) cannot diagnose GERD, but new image reconstruction software is an excellent tool to evaluate hiatal hernias (HH) and the interaction of the esophagus, esophagogastric junction (EGJ) and stomach with other organs and structures.

Both radiologic tests may be useful for distinguishing GERD from other pathologic conditions involving the esophagus and the stomach, guiding decisions about additional diagnostic tests, medical or surgical treatment.

Barium Esophagram or Esophagography

Barium esophagram or esophagography is a non-invasive and low-cost test, widely available. This test is done with oral (or tube in some situations) intake of barium contrast followed by radiographs or fluoroscopy. This test does not require sedation and permits a 2-dimensional (2D) morphologic evaluation of the esophagus, the EGJ and the stomach.

This test can evaluate disorders, such as achalasia, GERD and morphologic abnormalities in the pharynx and esophagus, such as neoplasia, diverticulum, strictures or presence and size of HH. Esophagram is a good test to diagnose anatomic failure after antireflux surgery or HH repair [3, 4], showing the location of the fundoplication in respect to diaphragm and the morphologic appearance of the fundoplication.

Technique

The esophagram can be done with single or double contrast. The single-contrast technique uses only barium contrast, and the double-contrast technique uses an effervescent agent and barium contrast. Barium may be offered fluid or mixed with food or even pills to assess bolus transit.

The single-contrast esophagram has an overall sensitivity of 50–75% for detecting GERD, *versus* 90% with the double-contrast technique [1] that can detect superficial ulcers or mucosal edema which suggest the presence of esophagitis. The study should be performed as a multiphasic examination, including dynamic evaluation and lateral and frontal spot images of pharynx and cervical esophagus, to detect structural abnormalities, such as a Zenker diverticulum. A videorecorded examination helps to evaluate the esophagus dynamically, showing peristalsis, bolus transport, and reducibility of HH.

The test is followed by upright views of the esophagus with oral barium contrast to detect tumors or GERD; views of cardia and gastric fundus to detect tumors, achalasia, rings or strictures; and prone spot images to view gastroesophageal reflux.

The quality of esophagram is highly variable among radiologists and institutions. A standardized protocol is suggested [2], showing the most important aspects of anatomy and function: presence and type of HH, reducibility of HH in the upright position, presence and level of gastroesophageal reflux, esophageal motility and peristalsis, presence of diverticulum, and provocative maneuvers, such as Valsalva or Trendelemburg position.

Gerd Evaluation

The patient is placed in supine position to collect contrast in the gastric fundus. In patients with GERD, barium contrast flows to esophagus spontaneously. If necessary, provocative maneuvers can be performed: change to supine right posterior oblique position to permit the view of barium contrast flows past the EGJ and Valsalva maneuver to increase intraabdominal pressure (Fig. 1).

Fluoroscopy could also establish the volume, level, frequency, and duration of gastroesophageal reflux episodes, based on the volume (small or large) of contrast refluxed, distending the esophagus.

A low-magnification image should be done to estimate the height and width of the barium column in the esophagus when gastroesophageal reflux is found. Patients with GERD may present esophageal dysmotility, shown as weakened or absent peristalsis in the thoracic esophagus (Fig. 2). Esophagram can also show anatomical defects in patients with GERD, like HH, Schatzki ring, strictures or mucosal edema and erosion (Fig. 3).

Radiologic abnormalities are found in 30–47% of patients with GERD detected at pH-monitoring [5, 6]. Gastroesophageal reflux identified by esophagram has a low sensitivity (40%) and specificity (85%) [6] for GERD diagnosis, with a poor correlation with 24-h pH-monitoring. The provocative maneuvers realized in esophagram

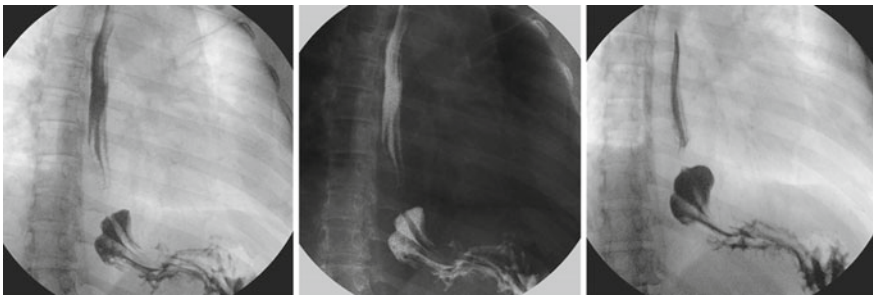

Fig. 1 Gastroesophageal reflux in a barium esophagram with Valsalva maneuver

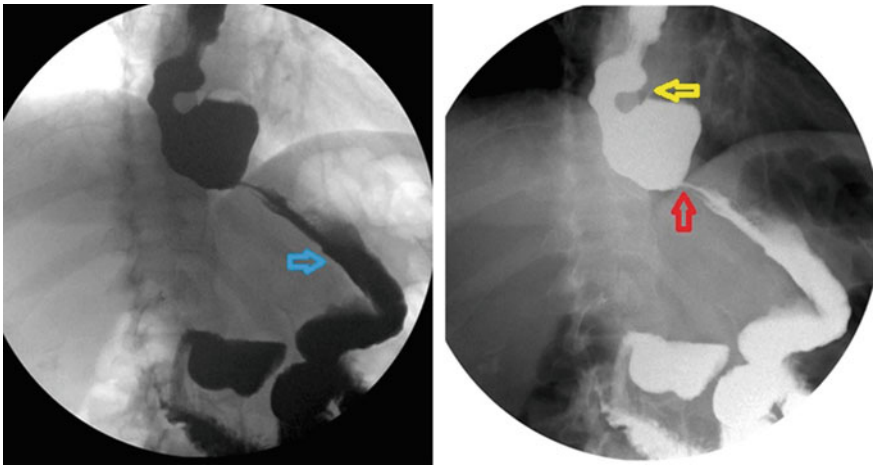

Fig. 2 Patient with Sleeve Gastrectomy (blue arrow). Sliding hiatal hernia (red arrow), gastroesophageal reflux and esophageal dysmotility with tertiary waves (yellow arrow)

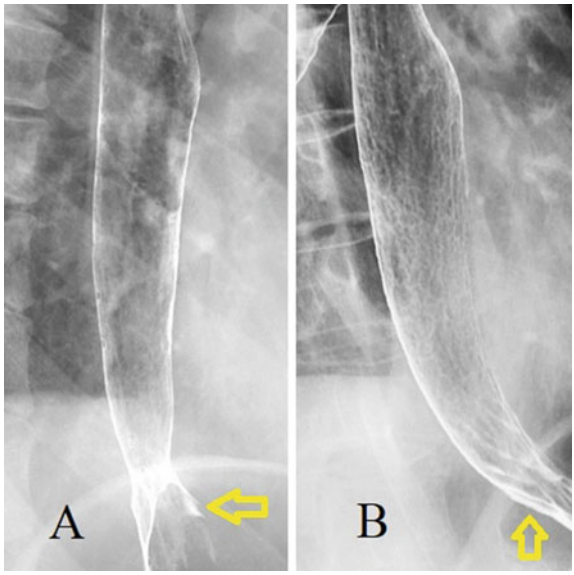

Fig. 3 Double-contrast esophagram showing a peptic stricture (arrow—A) and esophagitis with mucosal edema and linear erosion (arrow—B)

could induce reflux, but this event does not correspond to an abnormal reflux on pH-monitoring. It must be remembered; however, that GERD detected by this method represents a single episode of reflux under provocative maneuvers. It does not replace prolonged pH monitoring.

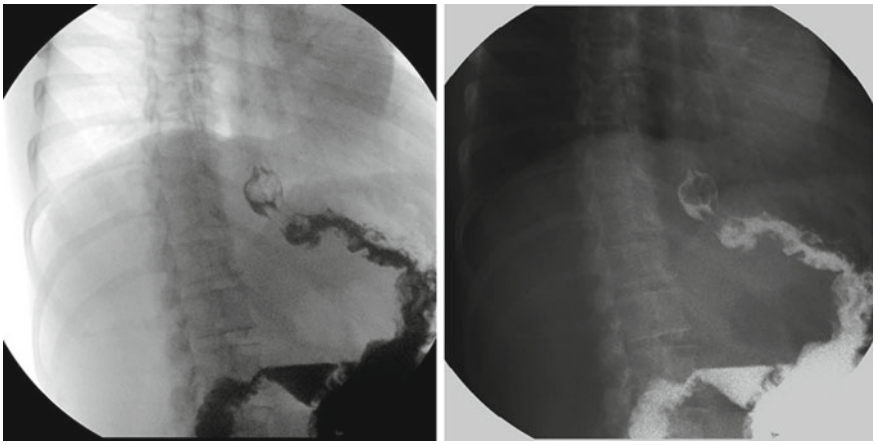

Fig. 4 Type I Hiatal Hernia (Sliding Hernia) in a barium esophagram

Hiatal Hernias

HH are classified in four types [7]: type I (sliding hernias), type II (paraesophageal hernias), type III (paraesophageal hernias with herniation of the EGJ and various degrees of stomach) and type IV (giant hernias, that involves herniation of other organs or visceras). The sliding hernia is the most common (90%) type of HH and directly associated with GERD (Fig. 4).

The EGJ is demarcated by a mucosal junction ring (B ring) or by the gastric rugae mucosa. HH is diagnosed when the EGJ is located more than 2 cm above the diaphragm. This test can diagnose type I, II and III HH, but is not a good test for type IV. The esophagram is able to differentiate between a type I to a type III HH, an advantage when compared to endoscopy, that can be inaccurate for this purpose. A previous study, however, showed poor correlation between HH size in esophagram *versus* hiatal size measured during ARS [8].

Computed Tomography

CT scan images are acquired in multidetector scanners. The images can be visualized in axial, coronal or sagittal plan, and may be reconstructed in a 3-dimension (3D) view, showing the esophagus, the stomach, the diaphragm, and the relationship with all the structures around the EGJ. The technique of this test is variable. A CT of thorax and/or abdomen with oral or venous contrast could be realized to visualize the structures of the EGJ (Figs. 5 and 6).

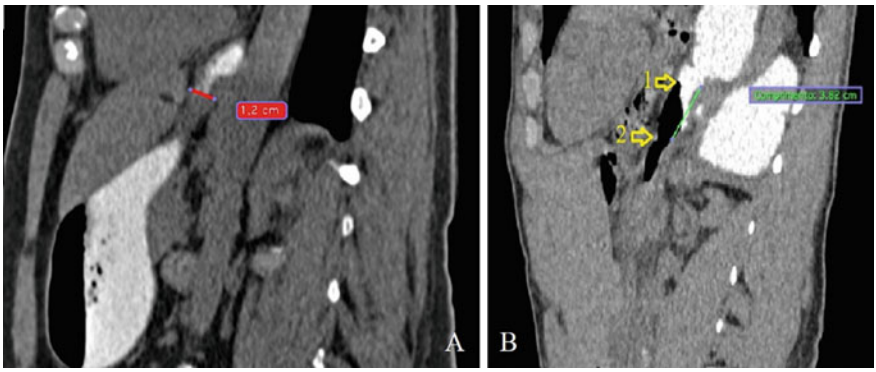

Fig. 5 A Computed tomography sagittal section showing absence of hiatal hernia, and antero-posterior diameter of hiatus of 1.2 cm; B A type III hiatal hernia with EGJ-hiatus distance of 3.82 cm

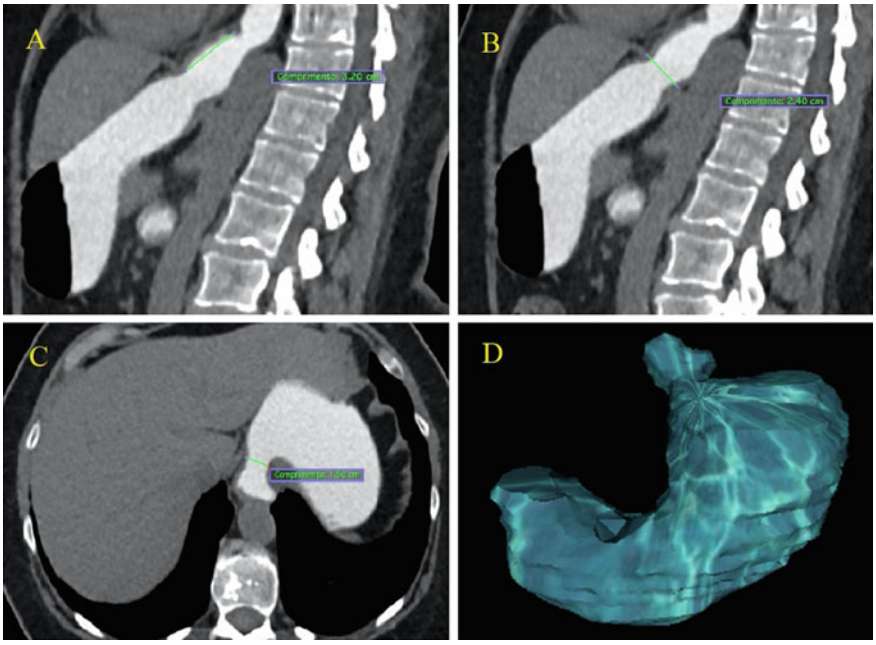

Fig. 6 Type I hiatal hernia. A Distance of the esophagogastric junction to hiatus of 3.2 cm in sagittal CT section with oral contrast. B Anteroposterior diameter of the hiatus of 2.4 cm in a sagittal CT section. C Side-to-side diameter of the hiatus of 1.50 cm in axial CT section. D Gastric reconstruction in 3D, with demonstration of the herniated stomach

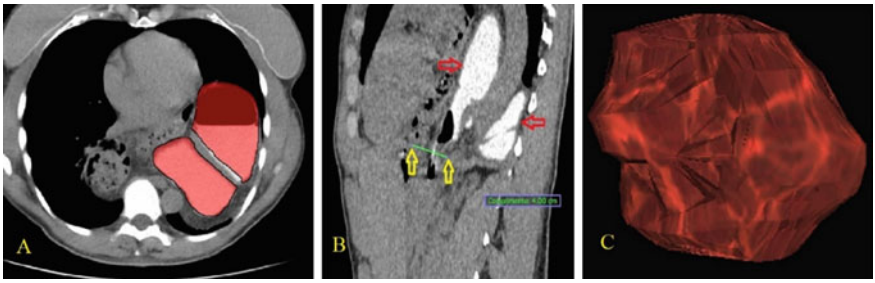

Fig. 7 A Axial CT section showing the entire stomach (red) in an intrathoracic position. B CT sagittal section showing the entire stomach (red arrows) above the diaphragm, with a large hiatal defect, with an anteroposterior diameter of 4 cm. C 3D image reconstruction, showing 100% of the herniated volume, associated with gastric volvulus

CT is probably the best test to diagnose and evaluate type IV HH (Fig. 7). HH is diagnosed by identifying EGJ markers above the level of the esophageal hiatus of diaphragm. The EGJ markers are the abrupt change in the tubular contour of esophagus to the sacular form of stomach or the gastric rugae mucosa [9, 10].

Hiatal surface area (HSA) can be measured by CT. As an independent antireflux mechanism, acting as a sphincter, the pathological enlargement of esophageal hiatus of diaphragm could play a role in the pathogenesis of GERD and HH. The mean HSA is 2.5 cm^2 in asymptomatic patients and 6.9 cm^2 in HH subjects [9]. HSA higher than 3.5 cm^2 has 81% sensibility and 88% specificity to presence of HH [11].

CT cannot diagnose GERD. However, a large HSA is associated with HH and GERD, correlated with a reduced LES pressure and increased acid reflux, in a mixed population of hernia-positive and hernia-negative subjects [9]. The average HSA in patients with GERD is 6.7 cm^2, versus 4.0 cm^2 in patients without GERD [11]. HSA is negatively correlated with LES pressure by manometry and positively correlated with GERD by pH monitoring [8]. In patients without HH in CT, HSA do not correlate with GERD [9].

CT can be helpful for surgeons who are planning ARS or HH repair. A large hiatal defect based on CT measurements is a predictor of a complex surgical repair and technique approach, potentially requiring relaxing incision in the diaphragm, use of mesh or gastropexy [11, 12].

The use of high-resolution CT is increasing with better images. Modern software allows advance in image processing, with a 3D reconstruction of unique organs or structures, helping for a clinical utility of preoperative imaging evaluation (Fig. 8) [13]. Recurrent hiatal hernias can also be well evaluated by CT (Figs. 9 and 10).

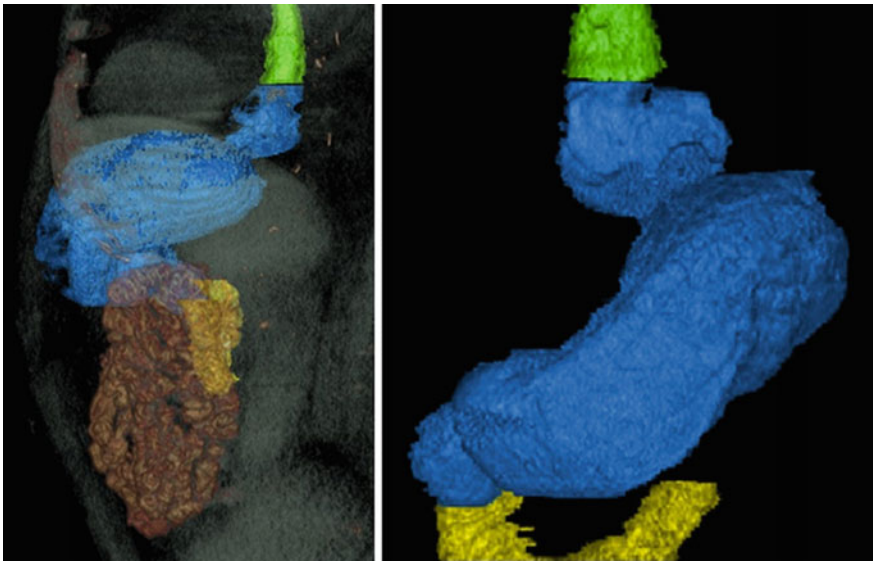

Fig. 8 3D computed tomography images showing a recurrent hiatal hernia

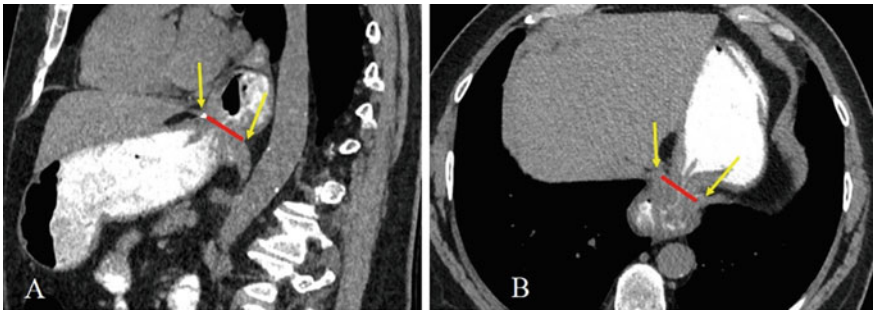

Fig. 9 Recurrent hiatal hernia showed in a high-resolution computed tomography; A anteroposterior diameter of hiatus; B lateral diameter of hiatus

Conclusions

The understanding of the interface between HH and the esophageal hiatus anatomy may help comprehend the pathophysiology of HH and GERD. Radiologic tests should not be considered diagnostic tests for GERD. However, they certainly play a role during the evaluation of these patients, especially when surgical treatment is considered, showing a different anatomical view compared with other tests.

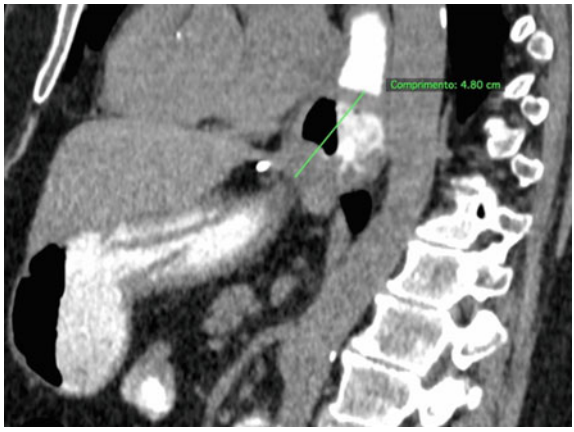

Fig. 10 A sagittal section of computed tomography image showing a recurrent hiatal hernia, with distance of esophagogastric junction to hiatus of 4.8 cm

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Endoscopic Evaluation of Gastroesophageal Reflux Disease

Francisco Schlottmann, Manuela Monrabal Lezama, Fernando A. M. Herbella, and Marco G. Patti

Abstract Patients with typical gastroesophageal reflux disease (GERD) symptoms can initiate medical therapy without further testing. In patients with dysphagia or other alarm symptoms, multiple risk factors for Barrett's esophagus, diagnostic uncertainty, and/or poor response to medication an endoscopy is recommended. In this chapter, common endoscopic findings in patients with GERD are discussed.

Keywords Gastroesophageal reflux disease · Endoscopy · Esophagitis · Erosive GERD · Barretts · Esophagus

Introduction

Gastroesophageal reflux disease (GERD) is one of the most common disorders seen by primary care physicians, gastroenterologists, and surgeons. In the US, it is estimated that GERD affects around 20% of the adult population [1]. Typical clinical symptoms include heartburn, regurgitation, and dysphagia. However, patients might also present a wide variety of symptoms making the clinical diagnosis quite challenging. Therefore, a thorough work up with endoscopic, imaging and functional studies is needed in selected patients.

An esophagogastroduodenoscopy (EGD) is one of the most common studies performed in patients with clinical diagnosis of GERD. In this chapter, we will discuss indications for EGD and frequent endoscopic findings in patients with GERD.

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Indications for EGD

GERD is often empirically diagnosed and treated based on the clinicians' symptom assessment. Patients with classic GERD symptoms (i.e., heartburn and regurgitation) can be treated with an 8-week trial of empiric proton pump inhibitors (PPIs) once daily before a meal. In patients with good response to this 8-week empiric trial of PPIs, we can attempt to stop medication and continue with clinical follow-up [2].

On average, around 70% of patients with esophagitis and 50% of patients with non-erosive reflux disease (NERD) will obtain symptom relief from a PPI trial [3]. In patients with atypical symptoms such as chronic cough, laryngitis or chest pain, PPI response rates are significantly lower than with heartburn, thereby diminishing the utility of the PPI trial approach for diagnosis [4].

Endoscopy as first for evaluation of GERD is recommended for patients with dysphagia or other alarm symptoms (i.e., gastrointestinal bleeding or weight loss) and for patients with multiple risk factors for Barrett's esophagus [2]. In patients with diagnostic uncertainty and/or poor response to PPIs an EGD should also be performed to evaluate for potential GERD complications (i.e., peptic stricture, Barrett's esophagus, esophageal adenocarcinoma) and to detect possible alternative diagnoses that might modify therapy (i.e., eosinophilic esophagitis) [5]. An endoscopy is also mandatory in patients evaluated for antireflux surgery.

Endoscopic Findings

An EGD is useful to determine the presence and severity of esophagitis. The most widely used classification is the Los Angeles (LA) classification (Table 1). LA grade A refers to one or more mucosal breaks no longer than 5 mm, not bridging the tops of two mucosal folds (Fig. 1). LA grade B refers to one or more mucosal breaks more than 5 mm long, not extending between the tops of two mucosal folds (Fig. 2). LA grade C is defined by one or more mucosal breaks bridging the tops of mucosal folds involving less than 75% of the circumference (Fig. 3). LA grade D is defined by one or more mucosal breaks bridging the tops of mucosal folds involving more than 75% of the circumference (Fig. 4).

Unfortunately, there is a high interobserver variability for the determination of the LA grade, mainly for low-grade esophagitis [6]. In addition, the presence of low-grade esophagitis, particularly LA grade A, is non-specific and can be found in asymptomatic controls [7, 8]. High-grade esophagitis LA grade C or D, Barrett's esophagus, or peptic stricture and considered confirmatory evidence for GERD [5].

Non-erosive reflux disease (NERD), however, represents the more common phenotypic presentation of GERD and includes patients who have typical symptoms without any mucosal breaks at endoscopy. For instance, it is estimated that erosive esophagitis is evidenced in only around 30% of treatment-naïve patients

Table 1 Los Angeles classification of esophagitis

Los Angeles classification of esophagitis	
Grade A	Mucosal breaks ≤ 5 mm long, none of which extends between the tops of the mucosal folds
Grade B	Mucosal breaks > 5 mm long, none of which extends between the tops of two mucosal folds
Grade C	Mucosal breaks that extend between the tops of ≥ 2 mucosal folds, but which involve < 75% of the esophageal circumference
Grade D	Mucosal breaks which involve ≥ 75% of the esophageal circumference

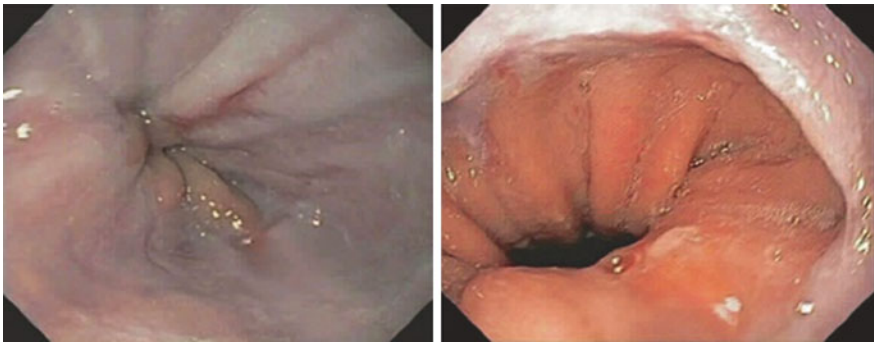

Fig. 1 Esophagitis LA grade A (From Foregut Surgery: Achalasia, Gastroesophageal Reflux Disease and Obesity. Editors Marco G. Patti, Marco Di Corpo, Francisco Schlottmann. Spinger 2020)

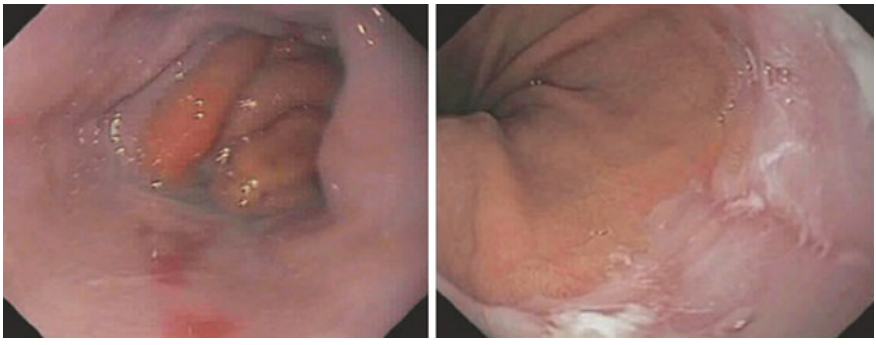

Fig. 2 Esophagitis LA grade B (From Foregut Surgery: Achalasia, Gastroesophageal Reflux Disease and Obesity. Editors Marco G. Patti, Marco Di Corpo, Francisco Schlottmann. Spinger 2020)

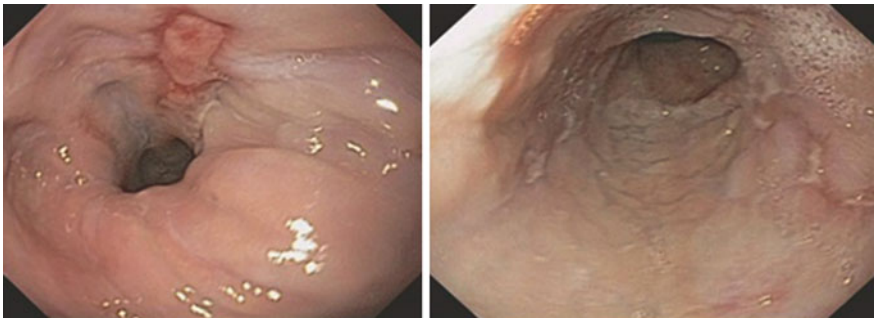

Fig. 3 Esophagitis LA grade C (From Foregut Surgery: Achalasia, Gastroesophageal Reflux Disease and Obesity. Editors Marco G. Patti, Marco Di Corpo, Francisco Schlottmann. Spinger 2020)

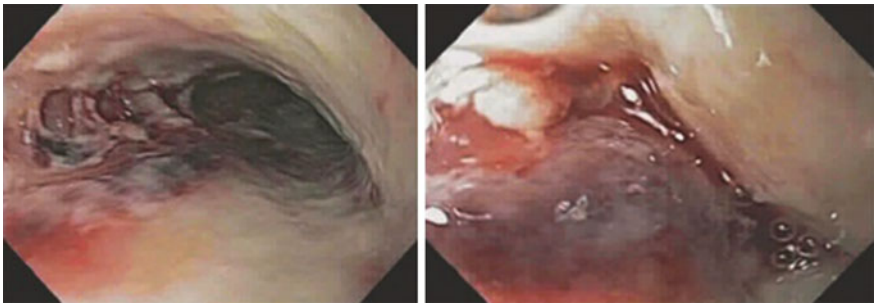

Fig. 4 Esophagitis LA grade D (From Foregut Surgery: Achalasia, Gastroesophageal Reflux Disease and Obesity. Editors Marco G. Patti, Marco Di Corpo, Francisco Schlottmann. Spinger 2020)

with heartburn and in less than 10% of patients taking PPIs [9, 10]. Therefore, the majority of patients with GERD will actually have normal findings in the EGD.

Barrett's esophagus (BE) is defined as the presence of at least 1 cm of metaplastic columnar epithelium (*salmon-colored mucosa*) replacing the stratified squamous epithelium normally lining the distal esophagus (Fig. 5).

BE is observed in around 5–15% of patients with chronic GERD [11, 12]. A segment of < 3 cm is defined as short-segment BE, while a segment ≥ 3 cm is defined as long-segment BE. In order to provide a uniform description of BE, the Prague classification is currently recommended [13]. The classification measures the circumferential extent of metaplasia (C) and the maximal extent of metaplasia (M) (Fig. 6). The presumptive diagnosis of BE should always be confirmed histologically.

Finally, a relatively common endoscopic finding in patients with GERD is the presence of a hiatal hernia (Fig. 7). Patients with large hiatal hernias often present higher grades of esophagitis, higher prevalence of BE, and higher amount of pathologic reflux on pH monitoring [14].

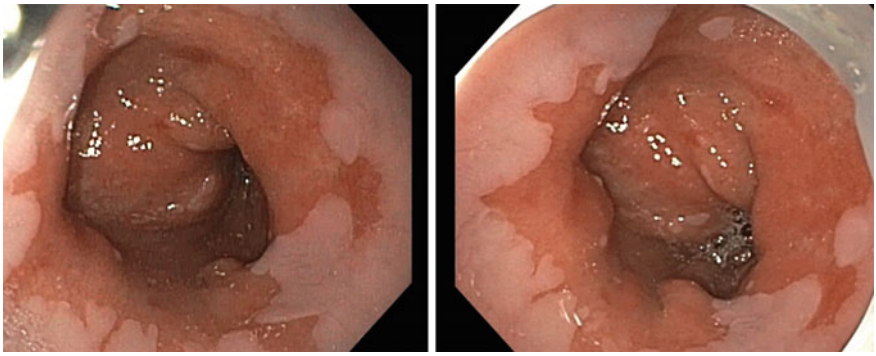

Fig. 5 Endoscopic images of a patient with Barrett's esophagus. Salmon-colored mucosa replaces the normal white pale mucosa lining the distal esophagus

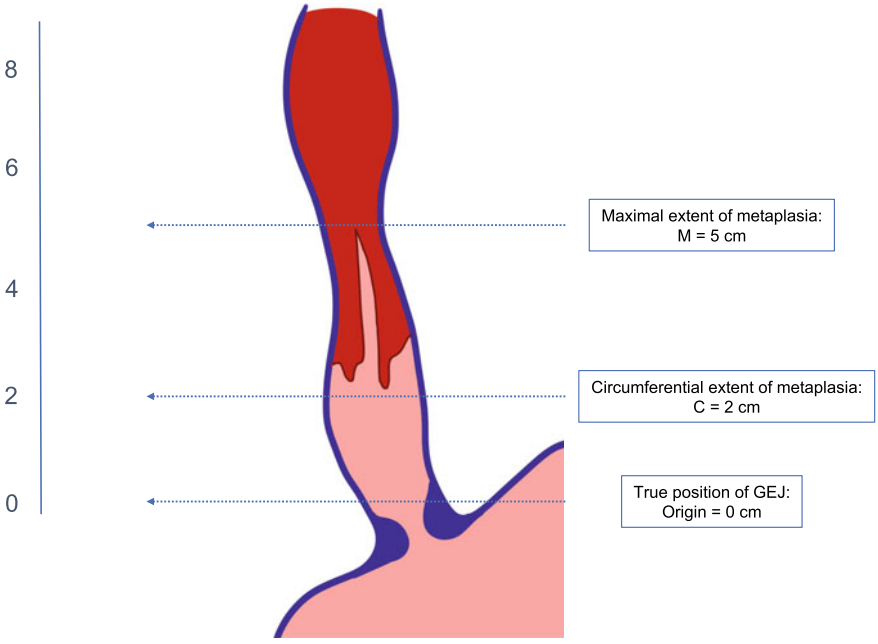

Fig. 6 Prague Classification for Barrett's esophagus. In this case, classified as C2 M5

Overall, EGD findings can be clinically relevant and specific for GERD. However, we should be aware that this study has a low sensitivity for the diagnosis of GERD as many patients affected by this disorder will present normal endoscopic findings.

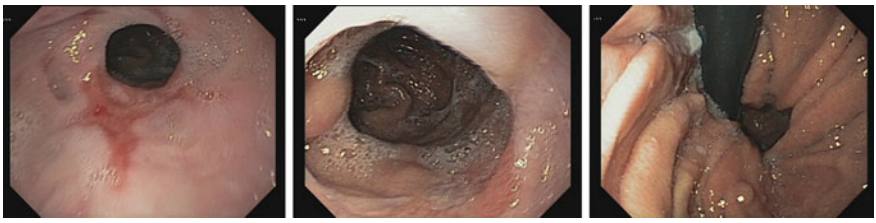

Fig. 7 Endoscopic images of a patients with LA grade C esophagitis and hiatal hernia

Conclusions

Although an endoscopy is not a necessary prerequisite to initiate therapy for typical GERD symptoms, it is a valuable diagnostic tool in these patients as it can assess the presence or severity of esophagitis, determine the presence of GERD complications, and/or rule out other disorders that can mimic GERD.

Conflicts of Interest

The authors have no conflicts of interest.

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Esophageal Manometry and Ambulatory pH Monitoring

Rafaella Orlow, Fernando A. M. Herbella, Marco G. Patti, and Francisco Schlottmann

Abstract Symptoms are inaccurate to diagnose gastroesophageal reflux disease (GERD). A complete objective work-up is necessary including esophageal manometry and pH monitoring. Esophageal manometry determines the exact placement of the pH monitoring catheter, may guide the type of operation, excludes primary motility disorders, and provides a baseline comparison in case of poor outcomes after the operation. pH monitoring provides information beyond the presence of GERD, including the severity, pattern and the temporal correlation between reflux and symptoms.

Keywords Gastroesophageal reflux · Esophageal motility disorders · High-resolution manometry · Ambulatory pH-monitoring

Introduction

Gastroesophageal reflux disease (GERD) has a broad spectrum of clinical presentation because variables such as the height of reflux, tissue resistance and amount of reflux play important roles [1]. Esophageal and extraesophageal symptoms may be part of the presentation and symptoms are clearly inaccurate to diagnose the disease [2]. Even complex and dedicated GERD questionnaires fail to accurately diagnose the disease [3]. Symptoms are even worse predictors for GERD after foregut operations [4].

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Primary esophageal motility disorders (PEMD) symptoms may also mimic GERD and are, again, not accurate enough [5]. Surgeons have been repeatedly calling for a need for objective evaluation for GERD and esophageal motility [6]. Only recently, however, has this view reached the clinical world [7].

This chapter presents esophageal manometry and ambulatory pHmonitoring in GERD evaluation.

Esophageal Manometry

Indications and Contraindications

In the setting of GERD, esophageal manometry has the important indication to locate the lower esophageal sphincter (LES) to determine the exact placement of the pH monitoring catheter. Catheter placement by pH step-up and endoscopic determination of the squamous-columnar junction have been shown to be imprecise [8, 9]. Another indication is to exclude PEMD or involvement of the esophagus in systemic diseases, such as in the setting of dysphagia or connective tissue diseases.

Esophageal manometry is especially important in candidates for antireflux operation. Esophageal motility may guide the type of operation for some, PEMD are excluded, and a baseline comparison is provided in case of poor outcomes after the operation.

It must be emphasized that esophageal manometry does not diagnose GERD. An abnormal LES is not synonym of GERD since other natural antireflux mechanisms may compensate for it and a normal LES does not exclude GERD since an abnormal transdiaphragmatic pressure gradient may overcome the LES [10].

Indications for esophageal manometry are summarized in Table 1.

Contraindications are only relative and may be related to intolerance to the catheter that is becoming more common with new generations [11]; coagulopathy that may lead to nasal bleeding; nasal obstruction; or esophageal stenosis. Some of these contraindications can be solved with endoscopic-guided placement of the catheter. Inability to trespass the LES (such as in large hiatal hernias) is not a contraindication to do the test because the study of the esophageal body offers valuable information

Table 1 Indications for esophageal manometry in the setting of gastroesophageal reflux disease

• Location of the lower esophageal sphincter to determine the exact placement of the pH monitoring catheter
• Exclusion of primary esophageal motility disorders
• Exclusion of esophageal involvement in systemic diseases
• Determination of esophageal motility before antireflux surgery
• Baseline esophageal motility determination before antireflux surgery

and the endoscopic-guided placement can also be used if the study of the LES is mandatory (such as to determine LES relaxation in a troubled postoperative case).

Technique

At least 6 h of fasting is necessary to reduce emesis and aspiration during intubation [12]. Medications that may alter esophageal motor function (including calcium channel blockers, nitrates, prokinetics, adrenergic antagonists, opiate antagonists or agonists, anticholinergic agents, tricyclic antidepressants, etc.) must be stopped prior to the test [12].

The study begins in the supine position, following catheter placement, a minimum of 60 s of quiet rest allows for an adaptation period, following which catheter position is confirmed using a minimum of three deep inspirations. Next, a baseline period of at least 30 s is captured to enable identification of lengths and basal pressure of the upper and lower sphincters.

Following this, ten wet swallows are performed. There should be at least 30 s between wet swallows to avoid effects of deglutitive inhibition.

Finally, the current guideline suggests one multiple rapid swallow sequence and change in position although the real usefulness of these provocative maneuvers is still elusive [13].

Interpretation

We will show the interpretation of high-resolution manometry that constitutes the current gold standard test although very useful data can also be obtained with conventional manometry still in use in several places [14]. High-resolution manometry interpretation is mostly guided by the Chicago Classification, now in the 4.0 version [13].

The Lower Esophageal Sphincter and the Esophagogastric Junction

A defective LES is not synonym with GERD, as mentioned before, but it may add to the understanding of pathophysiology, diagnosis, and therapy choice in some difficult cases. LES basal pressure; however, does not affect operative outcomes [14].

Esophageal manometry is able to measure LES basal pressure by different parameters (mid-respiratory, expiratory, and EGJ-CI) although neither showed superiority over the others in our experience [15]. Relaxation (residual) pressure is measure

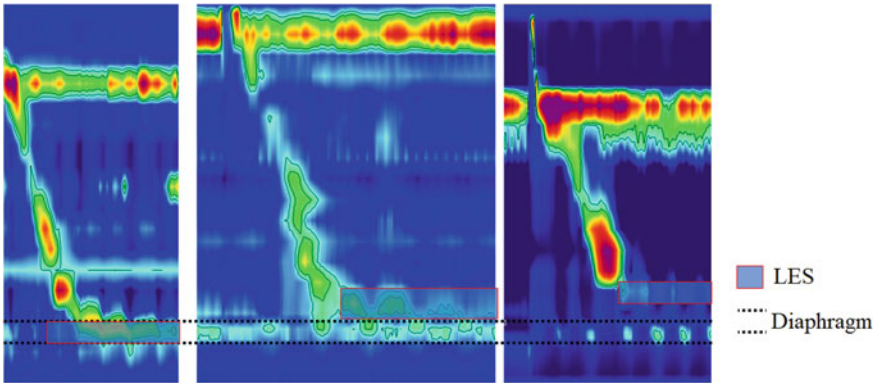

Fig. 1 Esophagogastric junction types by esophageal manometry. Type 1. There is complete overlap of diaphragmatic pressure and lower esophageal sphincter pressure components. Type II there is double-peaked pressure zone 1–2 cm part. Type IIIa is the separation greater than 2 cm

by the integrated relaxation pressure (IRP), defined by the mean pressure of 4 s of greatest post-deglutive relaxation in a 10 s gap, triggered at the beginning of a swallow [16]. Shorter LES total length and intraabdominal length also make the LES defective [17].

The morphology of the esophagogastric junction (EGJ) can be assessed by manometry. The intrinsic (smooth muscle) component of the LES must coincide with the extrinsic (diaphragmatic) component (EGJ type 1). A progressive disjunction of these components defines other EGJ types—manometric representation of a hiatal hernia (Fig. 1). Sensitivity for the diagnosis of hiatal compared to other tests is low (50%) since the limits of the esophagus are different for each test and the esophageal hiatus could be so weak and enlarged that it can ne not detected by manometry [18].

Esophageal Body

Esophageal body motility is normal in the presence of adequate force and coordination of the esophageal muscles in order to push the bolus down to the stomach. Most motility disorders associated with GERD are defined by abnormalities of the esophageal body. It must be remembered that esophageal motility disorders may be considered primary disorders only in the absence of GERD. If GERD is present, the motility abnormality is considered secondary, and treatment is directed toward reflux. It is also important to remember that even in the presence of manometric changes in GERD, there is no difference in the outcome in relation to surgical treatment (laparoscopic Nissen fundoplication) [19].

Force (contraction vigor) is determined by the distal contractility integral (DCI) calculated as the product of the mean amplitude of contraction in the distal esophagus

(mmHg) times the duration of contraction (s) times the length of the distal esophageal segment (cm) [16]. Waves can be failed, weak, normal or hypercontractile based on the DCI.

Coordination is determined by the distal latency (DL) calculated as the time interval between the beginning of the upper esophageal sphincter relaxation and the transition from the esophageal body to the epiphrenic ampulla [16]. Waves can be premature or normal.

Ineffective esophageal motility

Ineffective esophageal motility is the dysmotility most common in GERD patients [20]. It is a disease of force and defined by the presence of $\geq 70\%$ ineffective swallows or $\geq 50\%$ failed waves [13] (Fig. 2).

Absent contractility

Absent contractility is the most severe expression of lack of force. It is defined by 100% failed peristalsis [13] (Fig. 3). It can be found in patients with GERD and diseases of the connective tissue or end-stage GERD with esophageal wall fibrosis.

Hypercontractile esophagus

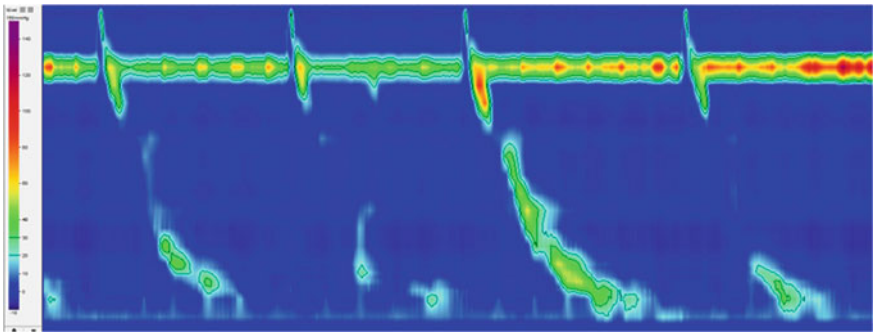

Fig. 2 Manometric tracings of ineffective esophageal motility

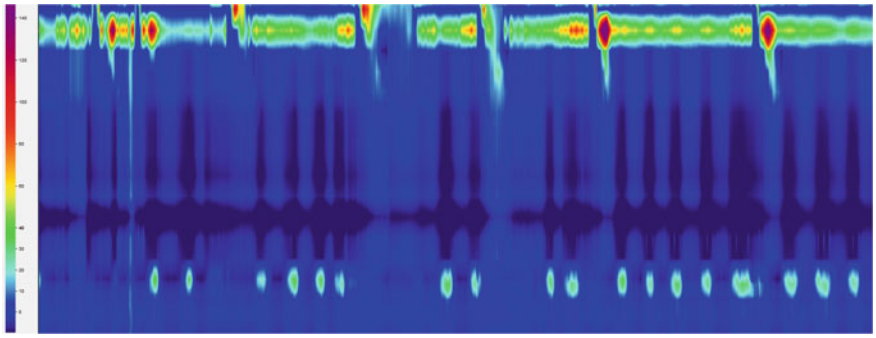

Fig. 3 Manometric tracings of absent contractility

Hypercontractile esophagus (previously nutcracker and jackhammer) is a disease of force to the exaggeration. It is defined by excessive peristaltic vigor in at least 20 of the swallows. Symptoms are necessary for a clinically significant diagnosis [13] (Fig. 4).

Distal esophageal spam

Distal esophageal spam follows ineffective esophageal motility as the second most common dysmotility associated to GERD [20]. It is a disease of coordination defined by the presence of at least 20% of premature contractions with normal contractile vigor. Symptoms (dysphagia/chest pain) are necessary for a clinically significant diagnosis [17] (Fig. 5).

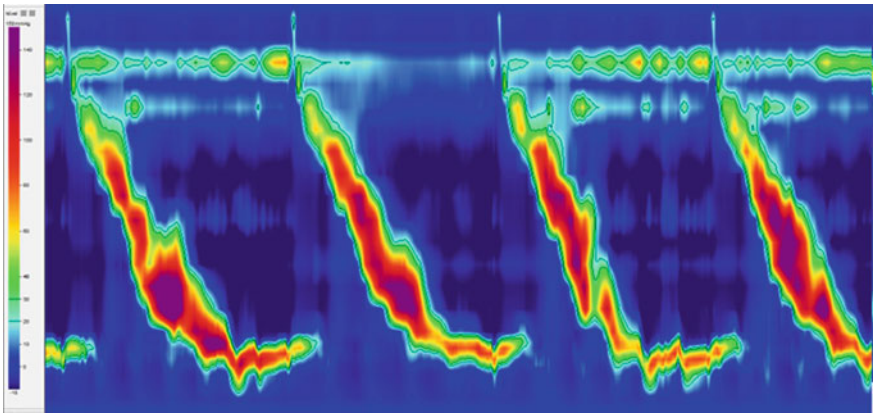

Fig. 4 Manometric tracings of hypercontractile esophagus

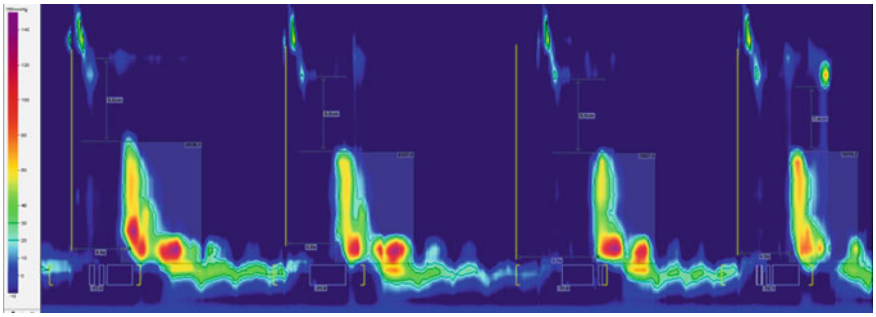

Fig. 5 Manometric tracings of distal esophageal spam

Upper Esophageal Sphincter

Manometric evaluation of the upper esophageal sphincter (UES) has been neglected due to technical limitations of manometry equipment; incipient knowledge of the both the anatomy and physiology of the pharyngo-upper esophageal area; and not inclusion of the UES in the current guidelines. Some authors disregard the study of the UES in routine manometric studies [21].

UES basal (resting) pressure is frequently measured at the point of higher pressure. The interpretation of this parameter is difficult for diverse reasons: the reference values for normality vary wildly; the pressure is not constant during the test; it is under certain voluntary control; and it is elusive the pressure necessary of the UES to act as a real valve preventing supraglotic reflux. Intuitively, a hypertonic UES would be anticipated in patients with GERD as a compensatory response to prevent aspiration. However, the manometric profile of the UES in patients with GERD is characterized by a short and hypotonic UES in most patients, and this profile is more pronounced in patients with extraesophageal symptoms [21].

Ambulatory pH Monitoring

Indications and Contraindications

Typical indication for pHmonitoring is the diagnosis of GERD. Current guidelines, different from previous ones that privileged symptoms, advocate objective GERD diagnosis by pHmonitoring when other tests, especially upper digestive endoscopy, are not conclusive for this diagnosis. Thus, the Lyon consensus states that pH monitoring should be performed in the suspicion of GERD and absence of esophagitis grade Los Angeles C/D or long segment Barrett's esophagus [22].

We believe; however, that pH monitoring provides information beyond the presence of GERD, including the severity, pattern and the temporal correlation between reflux and symptoms The confirmed presence of GERD does not guarantee that symptoms are caused by GERD and GERD may occur silently, such as in pulmonary diseases associated with GERD (Table 2).

Contraindications are similar to the esophageal manometry.

Technique

Ambulatory pH monitoring can be performed with transnasal catheters or wireless capsules attached to the esophageal mucosa, and it can be associated to intraluminal impedance measurements [23].

Table 2 Indications for ambulatory pH monitoring

GERD diagnosis	• Clinical suspicion not supported by other tests such as endoscopy • Possible "silent" GERD
Causality between GERD and symptoms	• Extra-esophageal symptoms
GERD severity evaluation	• DeMeester Score • Pattern (supine, upright, combined)
Pre-operative work-up	• Certainty of the diagnosis • Baseline comparison in cases of poor outcome
Post-operative work-up	• Post-operative symptoms

Catheters are more disconformable but cheaper, more reliable and allow multiple sensors to detect the height of reflux. Wireless capsules are expensive, there is a significant loss of data due to radio interference, chest pain may occur due to the presence of the capsule, there is a risk of early or too late detachment of the capsule, but they are more tolerable and allow monitoring for periods longer than 24 h.

Combined pH-impedance monitoring has impedance electrodes in addition to pH sensor(s) and allows identification of reflux episodes irrespective of pH. There are criticisms to pHimpedance due to the rarity of isolated non-acid reflux [24]. Some authors advocate pHimpedance during the use of acid-blockers. We honestly do not see a justifiable use of it since GERD may not be properly diagnosed with acid blockade.

Interpretation

GERD Diagnosis

pHmonitoring is the gold standard test to diagnose GERD. There is a threshold between physiologic (normal) acid exposure and pathologic (abnormal) acid exposure This is measured by the acid exposure time (AET)—the percentage of time that the esophagus was acidic (pH < 4) during the time of monitoring—or by the DeMeester Score. The DeMeester score is a composite score based on points attributed to each standard deviation above the mean value for 6 parameters: (1) total number of episodes of reflux; (2) % total time esophageal pH < 4; (3) % upright time esophageal pH < 4; (4) supine time esophageal pH < 4; (5) number of reflux episodes $\geq$ 5 min; and (6) longest reflux episode (minutes) (Fig. 6).

Although the DeMeester score is more complex and shows other characteristics such as esophageal clearance, both parameters (AET and DeMeester score) are equivalent for GERD diagnosis [25]. AET is considered pathologic > 6%. Lyon Consensus determined a gray zone in the 4–6% area when GERD is possible but not definitive.

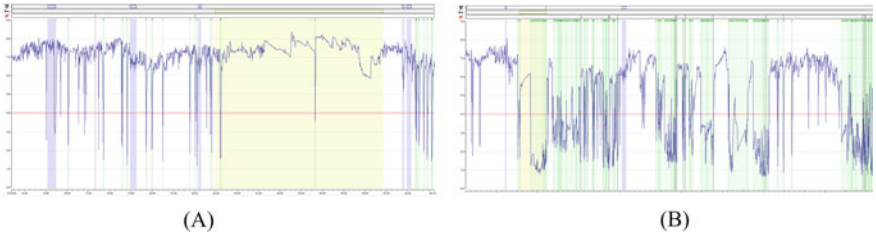

Fig. 6 pH monitoring traces showing physiologic reflux—DeMeester Score 9 (**A**) and pathologic reflux—DeMeester Score 82 (**B**). The red horizontal line represents pH = 4. All lines below the red line indicate an episode of reflux (green rectangles).

This gray zone studied from the DeMeester score perspective; however, shows that most patients have GERD in this zone indeed [26].

GERD Pattern

GERD may occur predominantly in the upright or supine position or still in a combined pattern (bipositional). The pattern is determined by the % of time the esophagus is acidic in each position (Fig. 7).

These patterns may indicate severity of the disease with worse presentations in supine and biposicional [27]. For some investigators, the pattern is also prognostic for surgical therapy [28].

GERD Severity

DeMeester score figures clearly correlate with GERD severity [25]. AET correlation with GERD severity has not been sufficiently studied. DeMeester score better correlates with severity since poor esophageal clearance (estimated by the number

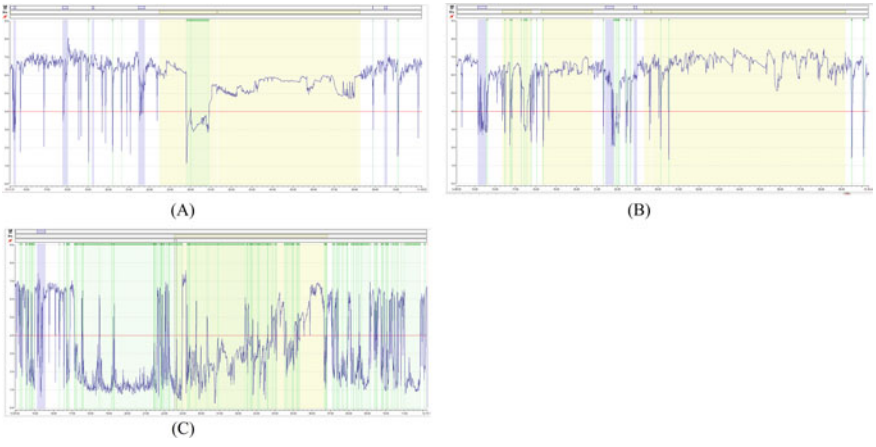

Fig. 7 Gastroesophageal reflux disease patterns by pH monitoring. Predominantly in supine position (**A**), upright position (**B**), or biposicional (**C**). Yellow rectangles indicate supine periods. Green rectangles indicate episodes of reflux

of reflux episodes ≥ 5 min and the longest reflux episode) and supine reflux episodes have a stringer proportionality in the final score, two characteristics associated to clinical severity.

Reflux Height

The addition of multiple (usually 2) sensors in the same catheter allows the estimation of the height that the reflux episodes reach. The interpretation of the height of reflux is; however, very difficult due to a lack of an accepted reference value for proximal reflux and lack of technique standardization [29].

Symptoms

pH monitoring may determine the temporal association between symptoms and episodes of reflux. There are different metrics to calculate this association (Fig. 8).

A simple proportion of symptoms associated to GERD *versus* all symptoms defines the symptom index (SI) and is positive when > 50%. It has the criticism that 2 times reported symptom with 1 correlated to reflux has SI 50% while 200 times reported symptoms with 100 correlated to reflux has the same SI. The advantage is the simplicity and easy understanding by the referring physician not used to the other parameters.

A more robust metric consists of the Symptom Association Probability (SAP), which considers the presence or absence of reflux and/or symptoms for each 2-min segment of the study and computes a statistical probability of symptoms and reflux episodes occurring just by chance. When the likelihood just by chance is < 5% (i.e., $p < 0.05$), SAP is > 95%, and hence positive. It has a non-intuitive interpretation to non-experts.

SI and SAP are complementary and cannot be directly compared to each other [30].

Conclusions

GERD is a complex disease with a heterogeneous symptom profile and a multifaceted pathogenic basis that defies a simple diagnostic algorithm or categorical classification. A complete work-up that includes esophageal manometry and pHmonitoring is necessary.

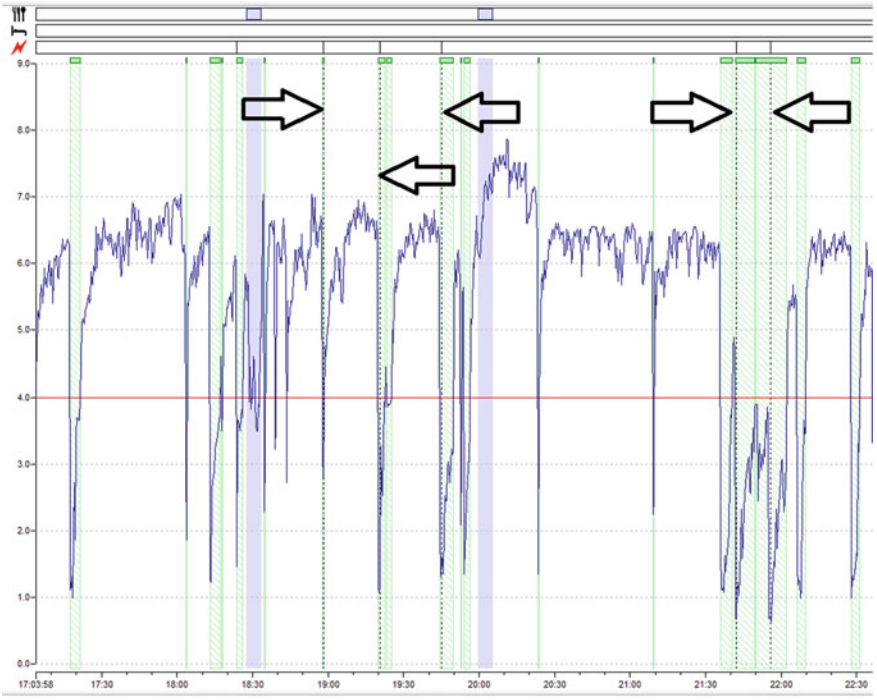

Fig. 8 Positive association between symptoms and episodes of reflux. Vertical dotted lines and arrows represent symptoms moments that coincide with episodes of reflux (green rectangles)

Conflicts of Interest

The authors have no conflict of interest to declare.

GERD: gastroesophageal reflux disease.

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Medical Therapy for Gastroesophageal Reflux Disease

Jeremy Klein and Robert T. Kavitt

Abstract Lifestyle modifications remain first line treatment for gastroesophageal reflux disease (GERD). However, these modifications alone may not be effective for patients with severe or refractory symptoms. Several medications currently exist for the treatment of GERD. Proton pump inhibitors (PPIs) potently and irreversibly block the final step of gastric parietal cell acid production and are used in most patients. With more attention and research into PPI side effects, many primary care providers and gastroenterologists are reassessing PPI prescribing patterns. As with many medications, timing for dose adjustment or therapy discontinuation is patient specific. This chapter provides a thorough description of all the available medications for the treatment of GERD.

Keywords GERD · PPI (proton pump inhibitor) · Acid reflux · Heartburn · Esophagitis · Antacids · Histamine-2-receptor antagonists (H2RA) · Potassium competitive acid blockers (P-CABs)

Lifestyle Modifications

Lifestyle modifications remain first line treatment for gastroesophageal reflux disease (GERD). These modifications limit the pathologic reflux of acidic gastric contents into the esophagus [1, 2]. Recommendations can be grouped into three categories: avoidance of foods that precipitate reflux (caffeine, chocolate, peppermint, alcohol, fatty foods), avoidance of spicy/acidic foods that promote heartburn (citrus, grapefruit, orange, tomatoes), and behaviors that improve lower esophageal sphincter (LES) functioning (smoking cessation, avoidance of recumbent position for 2–3 h

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after meals, raising head of bed, sleeping in left lateral decubitus position, and weight loss) [3].

Prior studies show laboratory evidence that alcohol, carbonation, tobacco, high-fat foods, peppermint, citrus, and chocolate can exacerbate GERD by reducing LES tone and contractility [4]. Thus, it is physiologically feasible that decreasing exposure to these agents could improve reflux symptoms. However, few controlled studies produced convincing evidence that lifestyle modifications improve GERD symptoms [3]. The evidence base for many lifestyle modifications is equivocal as controlled studies are difficult to perform. Several randomized controlled trials found head of bed elevation, left-side down sleeping, and weight loss improved GERD symptoms [5–7]. LES tone can also be decreased by hormones such as estrogen and progesterone during pregnancy [8]. Lifestyle modifications, including avoiding triggers, are the foundation for all GERD treatment because it is safe, low risk, easy, and physiologically potential for symptomatic benefit.

Postprandial recumbency and raising the head of the bed 6–8 inches uses the protective effect of gravity to improve esophageal acid exposure and promote esophageal healing [5, 9, 10]. Data around the timing of meals prior to bedtime has been conflicting. A small prospective trial showed that participants eating 6 h prior to supine position (sleeping) had less reflux episodes compared to participants that ate 2 h prior to bedtime. [11] Thus, it is recommended to avoid eating less than 2 h before sleeping.

Studies show a dose-dependent relationship between BMI and GERD symptoms [7, 12, 13]. Therefore, weight loss continues to be a recommendation for overweight patients with GERD. Overweight individuals tend to eat more processed fats and consume known dietary triggers of GERD. They also have increased intra-abdominal pressure leading to higher gastroesophageal pressure gradients and increased incidence of hiatal hernias [14]. A Norwegian prospective population-based study of women found lowering BMI by >3.5 kg/m^2 led to less GERD symptoms and can augment anti-reflux therapy [7]. Similarly, logistic regression analysis of the 2000 Nurses' Health Study questionnaire found losing >3.5 kg/m^2 was associated with a 40% risk reduction of GERD symptoms [12]. Weight loss can also improve LES functioning and decrease esophageal acid exposure [15]. Even with lifestyle interventions, these modifications alone may not be effective for patients with severe or refractory symptoms.

Non-proton Pump Inhibitor-Based Medical Therapy

Non-absorbable Agents

Antacids

Antacids are inorganic salts varying in formulation (chewing gum, chewable, liquids) and potency (greatest to least): calcium carbonate, sodium bicarbonate, magnesium, aluminum salts [16]. Chewing gums offer repetitive esophageal exposure leading to sustained symptom relief and pH control [17]. Unfortunately, antacids do not affect the volume of acid secretion and calcium carbonate formulations are associated with gastric acid-rebound. Along with neutralizing gastric acid, antacids exert a potent effect on increasing esophageal pH [18]. Antacids are likely as effective as H2Rs in healing esophagitis [19].

Limited head-to-head studies exist showing significant symptomatic improvement with antacids compared to placebo or other anti-reflux medications. In general, antacids are well tolerated but can cause adverse effects at higher doses and/or prolonged use. Magnesium compounds can worsen diarrhea, aluminum-based antacids can cause constipation and calcium-based antacids can cause worsened bloating/flatulence. They are short-acting, lasting around 60 min per dose [20]. Given the lack of systemic absorption, antacids (aside from magnesium trisilicate and sodium bicarbonate due to side effects) are first line for pregnant patients [21]. For patients with mild GERD symptoms, antacids remain a safe, cheap, on-demand, and fast acting over-the-counter option for temporary heartburn relief.

Alginate

Alginates are natural polysaccharide polymers of variable composition that create a mechanical barrier to reflux. Gastric acid plus alginate precipitates a viscous gel of near-neutral pH. This mechanical barrier acts as a gel raft that pushes the postprandial acid pocket further from the gastro-esophageal junction [22]. These effects reduce reflux for up to 4 h after dose [23]. In patients with non-erosive GERD, alginates (along with alginate-antacid combination) effectively reduce symptoms compared to placebo [24]. A 2017 meta-analysis showed a trend towards alginates being less effective at symptom reduction compared to H2Ras and PPIs, but this finding was not statistically significant [23]. Additionally, one study found the combination antacid-alginate formulation more effective than antacid alone in controlling postprandial esophageal acid exposure [25]. The main adverse effect is constipation from the aluminum hydroxide. Alginates are likely most effective in patients with postprandial predominant pyrosis and can be used as adjunctive therapy for patients on PPIs [26].

Sucralfate

Sucralfate is an aluminum non-absorbable salt that coats gastric and esophageal mucosa. Use is reserved for pregnant patients as it was found more effective than placebo in controlling GERD symptoms [27]. Sucralfate (along with antacids) are minimally secreted in breast milk and considered safe during lactation [21]. A randomized, double-blind, placebo controlled study at 6 centers in Germany showed superiority of sucralfate compared to placebo for symptomatic management of non-erosive GERD [28]. Current recommendations do not support sucralfate in non-pregnant patients.

Inhibitors of Transient Lower Esophageal Sphincter Relaxations (TLESRs)

For patients on PPI maintenance therapy, GERD symptoms may persist because of continued reflux of gastric contents despite adequate gastric acid suppression. To combat this, agents that inhibit transient lower esophageal sphincter relaxations (TLESRs) have been developed. TLESRs can be inhibited through various pathways, predominately via gamma-aminobutyric acid (GABA) and metabotropic glutamate receptor 5 (mGluR5). TLESRs can also be reduced through lifestyle measures such as sleeping in the left lateral decubitus position [29]. Baclofen (a GABA-B agonist) is one of the few agents that reduce TLESRs and reflux symptoms. A mGluR5 antagonist, Mavoglurant, has been shown to reduce meal-time reflux in a small randomized clinical trial though more research is needed [30].

One RCT of patients with GERD showed that baclofen decreased the number of upright reflex episodes and improved belching/overall symptom score compared to placebo [31]. Additionally, a meta-analysis of 9 randomized controlled trials found that baclofen reduced the average length of reflux episodes, amount of episodes, and the incidence of TLESRs compared to placebo [32]. As Baclofen crosses the blood–brain barrier, dose-related adverse effects such as drowsiness and confusion are possible along with nausea/vomiting. Baclofen before meals can be an adjunctive therapy for patients on maintenance PPI with ongoing symptoms.

Anti-secretory Agents

Histamine-2 Receptor Blockers (H2RAs)

H2RAs bind competitively and reversibly to H2 receptors on parietal cells to reduce histamine binding and subsequent gastric acid production. They are offered over-the-counter (Famotidine and Cimetidine) or by prescription (Famotidine, Cimetidine,

and Nizatidine). These agents are another common anti-reflux option, often used for patients on PPIs with persistent nocturnal symptoms. Nocturnal acid breakthrough (NAB) occurs in over 70% of patients on PPI therapy [33, 34]. H2Ras last longer compared to antacids but are not as rapid acting (concentrations peak on average 2 h after dosing).

A meta-analysis of 8 randomized controlled trials found adding H2RA at bedtime decreased the amount of nocturnal reflux episodes [35]. However, studies have found repeated nightly use causes tolerance (tachyphylaxis) to occur in as short as days to weeks [36]. Meta-analysis has shown H2RAs are inferior to PPI alone for symptom relief and treating erosive esophagitis [37]. Another meta-analysis of 13 randomized controlled trials found 80 mg of Famotidine the most effective H2RA for short-term relief [38]. H2RAs are pregnancy category B and are considered safer than PPIs. The main side effects of H2RAs as a class are headache, drowsiness, and fatigue from central antihistamine effects. Prolonged high-dose Cimetidine has been linked to gynecomastia, impotence, and galactorrhea [39] (Table 1).

Potassium Competitive Acid Blockers (P-CABs)

P-CABs compete with potassium and bind selectively to the proton pump ATPase (alpha subunit). This causes a rapid, dose-dependent, and reversible inhibition of gastric parietal cell acid production [40]. Various P-CABs have been developed since 1980 with the prototype SCH28080 from Schering-Plough Corporation. This compound failed to make it to practice because of hepatotoxicity concerns and non-superiority to PPIs [41]. The first P-CAB, Revaprazan, made it to clinical practice in South Korea and India in 2007 [40]. A recent 2019 phase 3 multi-center randomized controlled clinical trial in South Korea found a novel P-CAB, Tegoprazan (50 or 100 mg daily) non-inferior to esomeprazole 40 mg daily in treating erosive esophagitis [42].

Due to their potency and long duration of action, PCABs remain an active interest for refractory GERD. At the time of publication, TAK-438 (Vonoprazan—10 mg or 20 mg daily) is the only P-CAB currently under FDA review for use in GERD (Table 2). It has already been approved for GERD treatment in Japan (2015) and Helicobacter Pylori treatment in the USA (2022). A recent 2022 meta-analysis of 19 studies found Vonoprazan superior to PPI in treating erosive esophagitis, but non-inferior to PPIs in non-erosive esophagitis [43]. Unlike PPIs, P-CABs are not prodrugs, do not require acid activation, and reach maximum plasma concentration in around 2 h with longer half-life of ~9 h compared to ~2 h for most PPIs [44]. Moreover, P-CABs slowly dissociate from the proton pump and maintain mucosal activity for up to 24 h after administration [45]. The main adverse effects of Vonoprazan is diarrhea and, unlike early P-CABs, no hepatotoxicity was noted [44]. The safety profile at 52 weeks is like lansoprazole [46]. In adults with erosive esophagitis, a non-inferiority randomized trial between PPIs and PCABs showed higher healing rates at 8 weeks with Vonoprazan 20 mg compared to lansoprazole 30 mg [47]. At

Table 1 Detailed pharmacokinetic data for H2-Receptor antagonists along with common adverse effects

	Brand name	Formulation	Dose (mg)	Max dose (mg)with CrCl < 30 ml/min	Bioavailability (%)	Time to peak (range, hours)	Renal clearance (%) Oral | IV		Hepatic clearance (%) Oral | IV		Adverse effects (in order of incidence)
Famotidine	Pepcid	Tablet	10, 20, 40	20	40	1–3.5	25–30	65–80	50–80	25–30	Agitation, headache, diarrhea > constipation, dizziness
		Suspension	40 mg/ 5 ml								
		Intravenous	20								
Cimetidine	Tagamet	Tablet	200 – 800	600	80	1–2	40	50–80	60	25–40	Headache, gynecomastia, agitation, dizziness, drowsiness, diarrhea
		Solution	400 mg/ 6.67 ml								
Nizatidine	Tazac, Axid	Capsule	150, 300	150	70	1–3	57–65	75	22	25	Headache, dizziness, pruritus
		Solution	15 mg/ ml								

Rare adverse effects <1% not included

24 weeks, similar rates of healing were seen between Vonoprazan 10 and 20 mg with both superior to lansoprazole 15 mg [47]. This effect was more pronounced in patients with more severe LA grade esophagitis C/D [47]. More robust head-to-head comparisons of PPI versus P-CAB therapy is needed to assess maintenance therapy for GERD. P-CABs have the potential to augment future anti-reflux care, particularly for patients with erosive disease or PPI-refractory symptoms.

Proton Pump Inhibitors (PPIs)

Brief History of PPIs

Proton pump inhibitors (PPIs) potently and irreversibly block the final step of gastric parietal cell acid production. PPIs were developed in the late 1970s, put into practice in the late 1980s, and remain cornerstone in acid suppression therapy. Timoprazole was the first PPI found to covalently bind and inhibit the gastric proton pump. However, rat models found Timoprazole caused thyroid enlargement and thymic degeneration; halting it's clinical use [48].

Omeprazole, a derivative of the former Timoprazole, was the most potent inhibitor of gastric acid secretion without the prior concerns of thyroid dysfunction, thymus atrophy, or necrotizing vasculitis. Omeprazole was taken to human trials in 1982 then launched as Losec in Europe (1988) and as Prilosec in the United States (1990) [48]. Since induction, a 1995 meta-analysis of 30 double-blind prospective trials showed 20 mg of omeprazole daily had greater therapeutic benefit compared to H2RA in symptom resolution, healing erosive esophagitis, duodenal ulcer, gastric ulcers, relapse reduction, maintenance therapy [49, 50]. Moreover, a 1996 meta-analysis demonstrated PPIs superior to H2RAs, sucralfate, and placebo for heartburn relief and healing of erosive esophagitis [51]. In a 2013 Cochrane review of 34 trials with empiric PPI use, PPIs were deemed more effective than H2RAs in relieving heartburn [52].

Currently, PPI usage goes beyond GERD and includes the treatment of peptic ulcer disease, NSAID-induced ulcer prevention, Helicobacter pylori eradication, and Zollinger-Ellison syndrome. As of 2022, there are 6 PPIs (Omeprazole (OTC), Esomeprazole (OTC), Lansoprazole, Dexlansoprazole, Pantoprazole, and Rabeprazole) approved by the FDA for reflux treatment with various formulations: intravenous, enteric-coated, gelatin capsules, coated granules, immediate release, delayed release, multiple-unit pellet system (MUPS), among others [53] (Table 3). Since 2013, PPI use continues to increase as an empiric PPI trial (4–8 weeks) remains the recommended initial approach to typical GERD symptoms in patients without alarm symptoms [2].

Table 2 Pharmacokinetics of Vonoprazan (novel PCAB) and common adverse effects

	Brand name	Formulation	Dose (mg)	Max dose (mg) with CrCl <30 ml/min	Bioavailability (%)	Half-life (hours)	Time to peak (range, hours)	Hepatic metabolism enzyme	Adverse effects
Vonoprazan	Takecab	Tablet	10, 20	Use not recommended	Unknown	7.7	1.5–5.0	CYP3A4	Diarrhea/constipation, nausea/vomit, abdominal pain, rash

Rare adverse effects <1% not included

Table 3 Proton pump inhibitors pharmacodynamics, formulations, and common adverse effects (ordered by incidence)

	Brand name	Over the counter?	Formulation (IV, DR, capsule, suspension, ODT)	Dose (mg)	Bioavailability (~%)	Half-life (hours)	Time to peak (range, hours)	Hepatic Metabolism Enzyme	Adverse Effects (in order of incidence)
Omeprazole	Prilosec	Yes	Tablet-DR	20	30–40	0.5–1.2	0.5–3.5	CYP2C19	Headache, abdominal pain, diarrhea, nausea, dizziness, rash, upper respiratory infection
			Capsule-DR	10, 20, 40					
			Suspension	10, 20					
	Zegerid (sodium bicarbonate)		Packet	2.5 – 10					
Pantoprazole	Protonix	No	Tablet-DR	20, 40	77	0.8–2.0	2–3	CYP2C19, CYP3A4	*Headache, diarrhea, upper respiratory tract infection, rash, hypersensitivity reaction, myalgia
			Packet	40					
			Intravenous	40					
Esomeprazole	Nexium	Yes	Tablet-DR	20	64 - 90	1.0–1.5	1.5	CYP2C19	Headache, abdominal pain, diarrhea, constipation, dizziness
			Packet	2.5 – 40					
			Capsule-DR	20, 40					
			Intravenous	20, 40					
Lansoprazole	Prevacid	Yes	Capsule-DR	15, 30	80 - 85	0.9–2.1	1.7	CYP2C19	Abdominal pain, diarrhea, headache, constipation, dizziness
			Suspension						
			Dissolvable						
Dexlansoprazole	Dexilant	No	Capsules-DR	30, 60	—	1–2	1–2, 4–5	CYP2C19, CYP3A4	Headache, diarrhea, upper respiratory tract infection
Rabeprazole	Aciphex	No	Sprinkle	5, 10	52	1–2	2–5	CYP2C19	Abdominal pain, diarrhea, vomiting, Headache, pharyngitis
			Tablets-DR	20					

*Higher incidence with IV versus oral formulations. Rare adverse effects <1% not included

*Rare adverse effects <1% not included

Pharmacology of PPIs

PPIs covalently bind to cysteine residues (all PPIs bind cysteine 813) of the H^+/K^+ ATPase thus inhibiting the ATP dependent, 1:1 exchange of intracellular hydrogen for extracellular potassium [54]. PPIs are weak bases that selectively accumulate in stimulated parietal cell canaliculi. This stimulation occurs in response to meals via various secretagogues such as gastrin, histamine, and acetylcholine that induce acid secretion from gastric parietal cells via neurocrine, paracrine, and hormonal stimuli [55]. This acidic environment allows accumulation (1000-fold greater than the concentration of PPI in blood), conversion, and subsequent protonation of the prodrug to the activated cation [54, 56]. As a result, acid secretion can be delayed and is inhibited until replacement pumps are synthesized in a process that can take up to 48 h [54]. Proton pump recovery is independent of the PPI dose. It is recommended to take PPIs at least 30 min prior to meals to exert their antacid effect on activated proton pumps. If PPIs are combined with other anti-secretory or antacid agents then the PPI effect will be dampened as gastric acid secretion relies on negative feedback [55].

In a prolonged fasted state, many proton pumps are inactive, with greater potential for activation and acid release upon stimulus exposure. Therefore, PPIs are more effective in this setting when a larger number of proton pumps are activated [57]. Not all parietal cells or proton pumps are simultaneously activated due to this dynamic process. As a result of this and the PPI plasma half-life of ~90 min, orally dosed PPIs inhibit around 70% of proton pumps [54]. Yet, because of the irreversible binding of the active PPI metabolite, PPIs exert an inhibitory effect on acid secretion for up to 48 h [54]. On once daily PPI dosing, acid inhibition takes about 2–3 days to achieve steady state [54]. Oral bioavailability is high, on average about 85%, for all PPIs [53].

PPIs are protein-bound and mainly metabolized via hepatic CYP2C19 and 3A4 enzymes with CYP activity varying between individual phenotypes. Some Europeans and North Americans are genetically rapid metabolizers, which can explain a lack of treatment response [53]. Others are poor metabolizers that lack CYP2C19 (3% of Caucasians and 15%-20% of Asians) leading to prolonged half-life and systemic drug exposure [54]. The drug-drug interactions and side effects from cytochrome P450 metabolism are discussed below.

Omeprazole

Omeprazole was developed in the 1970s and approved by the FDA in 1989. Omeprazole is offered over-the-counter (20 mg) and as intravenous, capsules, tablets, immediate release (IR), delayed-release, multiple-unit pellet system (MUPS), and oral suspension. It has lower bioavailability at ~35%, the fastest onset (0.5–3.5 h), and the shortest half-life (0.5–1 h) compared to other PPIs [53]. Omeprazole-IR/sodium

bicarbonate suspension is non-enteric coated, rapid acting, and superior to pantoprazole delayed-release, esomeprazole, and lansoprazole in reducing nocturnal acid breakthrough symptoms [58, 59]. This is likely due to sodium bicarbonate acting as a buffer to rapidly neutralize gastric acid, thus activating more proton pumps and protecting the uncoated tablet [60]. However, clinical significance remains at question after a 2015 phase 3 clinical trial did not find immediate-release omeprazole superior to delayed-release in self-reported symptom improvement [61]. Further studies are needed to evaluate immediate-release and the correlation between intragastric pH, heartburn relief, and quality of life. Omeprazole is the only PPI that is safety class C during pregnancy because of increased fetal mortality in animal models [21].

Esomeprazole

Esomeprazole is an isomer of omeprazole, approved by the FDA in 2001 for the treatment of GERD and erosive esophagitis. It is available in 20 mg or 40 mg, intravenous, liquid, immediate-release, delayed-release, and multiple-unit pellet system (MUPS) formulations. The oral bioavailability after 40 mg daily increased with repeated doses up to 90% after day 5 with a half-life of ~1.5 h [62]. A 2006 meta-analysis of 10 studies reported a 5% relative increase in erosive esophagitis healing probability at 8 weeks with esomeprazole compared to pantoprazole, lansoprazole, and omeprazole (number-needed-to-treat of 25) [63]. Other studies have found esomeprazole 40 mg more effective at controlling intragastric pH (mean percentage of time with pH >4 over 24 h) compared to omeprazole 40 mg, pantoprazole 40 mg, rabeprazole 20 mg, or lansoprazole 30 mg once daily [64–66]. When divided into two doses per day, even better intragastric pH control was achieved with esomeprazole 40 mg twice daily compared to other PPIs [67]. Despite numerous meta-analyses reporting greater efficacy of esomeprazole, the clinical significance of these differences is to be seen [68].

Pantoprazole

Pantoprazole was first approved in Germany in 1994 and then in 2000 by the FDA for treatment of erosive esophagitis [69]. At the time, it was the first PPI available in intravenous and oral formulations (delayed-release, oral suspension). In 2001, the FDA approved IV Pantoprazole 40 mg once daily for 7–10 days in patients with GERD and a history of erosive esophagitis unable to tolerate oral medication [69]. Unlike other PPIs, serum concentration is not dose-dependent [70]. Pantoprazole binds to cysteine 822 residues which make it more stoichiometrically challenging for reducing agents (such as glutathione) to reverse pantoprazole activity. Thus, pantoprazole reversal relies more heavily on de novo pump synthesis [71].

In a study of 603 patients with erosive esophagitis, results showed pantoprazole 40 mg/day offered early esophagitis healing and had the highest healing rates at 4 and 8 weeks compared to other pantoprazole doses [72]. However, pantoprazole offered no difference in endoscopic healing rates at 4 or 8 weeks compared to omeprazole 20 mg/day or lansoprazole 30 mg/day [73]. Other studies comparing pantoprazole 40 mg/day to esomeprazole 40 mg/day found patients taking pantoprazole had less symptomatic episodes at one week [74] and faster first time nocturnal symptom relief [75]. With robust data in over 100 clinical trials, pantoprazole is an established safe, well-tolerated, and effective PPI.

Lansoprazole

Lansoprazole (LAN) comes in delayed release oral disintegrating tablet and a novel fast disintegrated tablet (LFDT) that is easily swallowed with or without water [56, 76]. The fast-disintegrating tablet is easily mixed into drinks/food; this improves patient convenience and tolerability for older individuals, children, patients with dysphagia, nothing-per-oral (NPO) status, and those with nasogastric tubes. Several studies suggest that compared to omeprazole, lansoprazole offers more effective acid control with a quicker onset of action (~1.5 h) [77]. Along with above formulations, lansoprazole comes in intravenous, liquid suspension, and 15 mg or 30 mg capsules [53]. Compared to other PPIs, lansoprazole has the highest oral bioavailability around 80% and a longer half-life of ~1.6 h [53].

Dexlansoprazole

Dexlansoprazole is available in 30 mg and 60 mg delayed release capsules and oral disintegrating tablet. The delayed release formulation offers longer half-life than other PPI agents [78]. The granule composition has different pH dissolution properties that allows for around 25% of drug release into the proximal duodenum and the remaining portion in small bowel. This prolongs plasma concentration, reaching peak ~2 h and then again at 5 h after administration [78]. Unlike other PPIs, dexlansoprazole reaches higher plasma concentration when administered 30 min after a meal. For those unable to adhere to meal-time restrictions, dexlansoprazole takes the onus off patients [79]. A meta-analysis of 11 randomized trials found 4 weeks of dexlansoprazole 30 mg is more efficacious compared to esomeprazole (40 mg; RR: 2.17, 95% CI: 1.39–3.38) in controlling GERD symptoms [80].

Rabeprazole

Rabeprazole, approved in 2002, is available in 10 mg, 20 mg, delayed and extended-release 50 mg tablets. It has a slower onset than other PPI at 2–5 h with a half-life of 1–2 h [53]. The extended release formulation is gradually absorbed throughout the small intestine and colon to improve serum half-life [53]. One Canadian study of 248 healthy volunteers found rabeprazole-DR 20 mg had superior nocturnal acid suppression compared to esomeprazole 40 mg [81]. A different study, in patients with erosive esophagitis, found Rabeprazole-ER was not superior to esomeprazole in improving heartburn symptoms or esophageal healing [82]. Compared to other PPIs, Rabeprazole 20 mg is the most potent PPI available and can be used second line in patients with persistent symptoms after an initial PPI trial.

Drug Interactions

PPIs are highly protein-bound and metabolized largely via the CYP2C19 pathway (though pantoprazole and dexlansoprazole also have CYP3A4 metabolism) [53]. Individuals metabolize PPIs at different rates due to genetic variations in the CYP pathway [56]. Omeprazole and esomeprazole have the highest percentage of CYP2C19 metabolism conferring the greatest drug-drug interaction risk [53]. Less drug-drug interactions are seen with lansoprazole, pantoprazole, dexlansoprazole, and rabeprazole due to the affinity for CYP3A4 degradation [53]. Along with effects on cytochrome degradation, PPIs can affect the solubility/bioavailability of medications that rely on a more acidic gastric environment [83].

Observational research over the past 15 years has focused on the potential interaction between clopidogrel and PPIs given clopidogrel requires CYP2C19 activation [84]. This concern is greatest with CYP2C19-dependent PPIs: omeprazole and esomeprazole. Retrospective data review has offered conflicting insight into this interaction. Despite the proposed risk of decreased clopidogrel activation, multiple randomized trials have not shown an increased risk of adverse cardiovascular events with clopidogrel and PPI co-ingestion [85]. Moreover, it is theorized that separating administration by 12–20 h (~3 clopidogrel half-lives) will prevent competitive CYP inhibition and limit clinically significant interaction [86, 87]. Along with clopidogrel, concomitant administration of PPI with various medications (such as mycophenolate, levothyroxine, digoxin, etc.) can increase the risk for adverse effect [84]. These drug interactions are detailed in Table 4.

Table 4 Proposed long-term adverse effects of PPI therapy

Adverse effect	Odds ratio[a], hazard ratio[b]	Conclusion/mechanism
Chronic kidney disease	1.17[a] [88], 4.35 [121]	Increased incidence of AKI via acute interstitial nephritis (AIN) along with variable/indolent kidney injury than typical immune-mediated drug nephrotoxicity that can contribute to CKD progression [120, 125]
C. Difficile Infections	2.26[a] [88], 1.71[b] [97]	Lack of gastric acid allows for the survival of the toxin-forming vegetative state. Loss of microbial diversity in the colon after PPI use leading to diminished endogenous barriers to *C. difficile* infection
SIBO (Small intestinal bacterial overgrowth)	1.71 [97]	Hypochlorhydria (gastric acid deficiency) predisposing patients to small intestinal bacterial overgrowth (SIBO)
Enteric infections	1.33[a] [88]	Similar to *C. Difficile* mechanism. Dysbiosis and diminished gut barrier; altered gut flora in setting of elevated gastric pH
Pneumonia	1.02[a] [88], 1.89[c] [90]	Decreased gastric acid along with micro-aspiration of gastric contents
Fractures	0.96[a] [88]	Altered calcium absorption, direct inhibition of osteoclast activity, and gastrin-mediated parathyroid hyperplasia
Dementia	1.20[a] [88, 128]	PPIs can inhibit V-type ATPases in microglial cells leading to less β-amyloid degradation and subsequent amyloid-β (Aβ) protein deposition
All-cause mortality	1.03[a] [88]	Due to the above proposed risks and cumulative adverse effects

Commonly reported and studied adverse effects of long-term PPI therapy with Odds Ratio from the COMPASS trial [88]. Odds Ratio = [a] Hazard Ratio = [b], Adjusted Relative Risk = [c]

Long-Term PPI Therapy: Safety Concerns

Over the past 10 years, safety concerns of prolonged PPI therapy have been well documented. Especially in an era of technology, information accessibility, and over-the-counter medications, it is important that patients have an accurate understanding of PPI risks and benefits. Many adverse events linked to PPIs are associations made from epidemiologic studies. These putative adverse effects include pneumonia, acute kidney injury, gastrointestinal infections, nutritional deficiencies, osteoporosis, dementia, and others. Many reported effects lack evidence of causality plus limitations from inherent biases and confounding variables. A 2019 randomized placebo-controlled prospective clinical trial with 17,598 patients and ~3 years of follow-up did not find any statistically significant adverse effects associated with pantoprazole use [88]. This is the largest prospective trial assessing adverse effects of PPI use.

As a drug class, PPIs are overall well-tolerated with a few nonspecific side effects. These include but are not limited to headaches, dizziness, rash, nausea, vomiting, abdominal pain, constipation, diarrhea [89]. When medication is halted, these side effects dissipate.

PPI use has been linked to community (CAP) and hospital acquired pneumonia (HAP), hypothesized due to micro-aspiration of gastric contents. Concern for this link grew in 2004 after JAMA published a study reporting a positive dose–response and an adjusted relative risk of 1.89 for patients on PPI versus those that stopped [90]. This association was further assessed in a systematic review of 26 studies that found outpatient PPI use conferred a 1.5-fold increased risk of CAP [91]. Another large pharmacoepidemiologic cohort study found PPIs linked to a 30% increased odds of HAP [92]. Some studies suggest this risk is greatest within 30 days of starting PPI therapy [91, 93], decreasing the likelihood that PPIs could directly cause pneumonia in such a time frame. Other studies suggest this association is limited by comorbid conditions, temporal feasibility, and protopathic bias where early symptoms of pneumonia were falsely attributed to GERD and treated with PPIs [94–96].

Along with pneumonia, PPIs and its associated hypochlorhydria (gastric acid deficiency) has been linked to gastrointestinal infections like small intestinal bacterial overgrowth (SIBO) and *Clostridium difficile* infection (CDI). Prior studies evaluating SIBO risk from PPI use have been conflicting with a 2018 meta-analysis conferring moderate risk (pooled OR 1.71) [97]. This relative risk increases eightfold when SIBO is diagnosed with duodenal aspirates [98]. However, objective findings of SIBO do not always correlate with symptomatic and clinically relevant infection.

For CDI, *C. difficile* spores are not sensitive to gastric acid. Therefore, it is hypothesized that the lack of gastric acid allows for the survival of the toxin-forming vegetative state [96]. Another explanation is the loss of microbial diversity in the colon after PPI use leading to diminished endogenous barriers to *C. difficile* infection [99–102]. A meta-analysis of 56 studies found PPI use significantly associated with increased risk of CDI (including when stratifying for study type), though these studies are limited again by bias from observational/retrospective design [103]. Other studies have found that concurrent PPI and *C. difficile* treatment does not increase risk of CDI recurrence [102].

There is also consideration regarding micronutrient malabsorption due to altered gastric microbiome and the less acidic environment. Of particular concern is the absorption of calcium, B12, magnesium, and iron. Gastric acid facilitates ionized calcium release from calcium salts [101], though PPIs have less effect on calcium contained in dairy and water-soluble calcium salts [104]. Studies have yet to show strong evidence that chronic PPI exposure causes B12 deficiency, though a case–control study from 2013 found an increased odds risk for B12 deficiency in patients that had been prescribed a PPI [105]. Like B12, gastric acid is needed for optimal iron reduction and absorption. A case–control study found PPI use >2 years and higher dose were associated with increased risk of iron deficiency anemia [106]. Another case–control study found a positive dose–response and time-response relationship to chronic PPI use >1 year and risk of iron deficiency [107]. Gastric acid is also important for the absorption of non-heme iron, which requires an acidic environment

to facilitate reduction of ferric iron to ferrous state [108]. More prospective research is needed to determine if PPIs cause clinically significant iron deficiency [106].

Alterations in serum magnesium is another adverse effect of active research despite magnesium absorption occurring passively throughout the small intestine independent of gastric acid. The mechanism is not fully elucidated and current meta-analyses literature is not conclusive as prior study populations were heterogenous [109]. Yet, some studies found serum magnesium levels recovered quickly after PPI discontinuation (an effect not seen with H2-blockers) [110]. Patients on PPIs are also resistant to magnesium supplementation [110]. These findings led to a 2011 FDA safety announcement about the potential link between PPI exposure >1 year and hypomagnesemia. Still, the 2022 ACG Clinical Guidelines do not recommend routine monitoring or supplementation of magnesium, calcium, B12, or iron for patients on PPI therapy [4].

PPI use can feasibly impact bone health from altered calcium absorption, direct inhibition of osteoclast activity, and gastrin-mediated parathyroid hyperplasia [111]. Some observational studies including two large meta-analysis have found a modest association between PPI use and hip or vertebral fracture risk [112–114]. However, like other PPI side effects, the clinical relevance and causal relationship of PPI use and bone health remains controversial, especially given that fracture risk is a complex and confounded composite outcome [115, 116]. In 2010 the FDA announced a safety warning for the possible link between long-term PPI use and hip, wrist, and spine fracture risk. This caution statement was revised in 2011 to exclude fracture risk associated with short term OTC PPI use due to lower doses and less exposure time. More recent meta-analysis in 2018, 2020 and 2022 report conflicting findings between PPI and bone mineral density. While fracture incidence trended higher in PPI users, there has not been convincing evidence linking PPI to decreased bone mineral density [114, 117, 118]. The 2022 ACG Clinical Guidelines do not recommend additional bone mineral density screening for patients on PPIs [4].

Multiple meta-analyses and retrospective population-based studies have linked PPIs to acute kidney injury (AKI), acute interstitial nephritis (AIN), risk of chronic kidney disease (CKD), CKD progression, and end-stage renal disease (ESRD) [119–121]. A nested population based, case–control study in New Zealand found AIN occurred at a higher rate in current PPI users compared to past PPI users (patients not on PPI >90 days prior to AIN diagnosis) [120]. Another large retrospective cohort study found an association between PPI exposure and AKI incidence (adjusted odds ratio 4.35, 3.14–6.04, $p < 0.0001$) [121]. Similar studies have found an increased incidence of CKD in patients exposed to PPI therapy [121]. CKD risk also increases with prolonged exposure [119, 122] and higher PPI doses [123]. A retrospective cohort analysis of ~ 125,000 PPI users found over 50% of patients had PPI-associated chronic renal injury irrespective of predisposing AKI [124]. This, along with other studies, points toward more variable and indolent kidney injury than typical immune-mediated drug nephrotoxicity [120, 125]. Thus, preceding AKI cannot be reliable used as an indicator of PPI toxicity and routine monitoring of kidney function is not standard of care [4]. However, patients with other risk factors and comorbidities may warrant closer creatinine monitoring and necessity of PPI therapy addressed.

Lastly, data suggests that PPI use may exacerbate development of dementia in elderly patients [126]. Mouse models have shown PPIs can inhibit V-type ATPases in microglial cells leading to less β-amyloid degradation and subsequent amyloid-β (Aβ) protein deposition [127]. However, studies have been conflicting [128, 129] and a recent 2020 meta-analysis did not show a significant relative risk of PPI use and dementia [118]. Especially in older patients who are subject to polypharmacy, confounding comorbidities, and dementia development, it is challenging to draw conclusions from PPI exposure and dementia progression/risk [104].

In 2021, results were released from the COMPASS randomized controlled trial that added more real-word context to the contentious adverse effects discussed above. The main study objective was to assess cardiovascular outcomes over 3 years for patients on various doses of rivaroxaban with or without aspirin. In addition, the study had PPI-related arms containing 17,598 patients at 580 centers. The trial found, over 3 years, that almost all adverse effects were not statistically significant. However, they did report pantoprazole use led to a slight statistically significant increased risk of enteric infections (1.33; 95% confidence interval, 1.01–1.75) [88]. However, the other adverse effects were not statistically significant. The composite odds ratios are detailed in Table 4. More prospective studies or randomized clinical trials are needed to further contextualize the severity and clinical significance of the many reported adverse effects of PPIs.

Approach to Pharmacologic Therapy

For patients with typical mild reflux symptoms >2 episodes per week without erosive esophagitis or red flag alarm features (dysphagia, odynophagia, weight loss, recurrent vomiting), a step-up approach can be utilized. In this approach, treatment may start with antacids and H2RAs with subsequent dose adjustments in 4 weeks until symptoms are controlled. If symptoms persist, patients should trial daily PPI therapy for 4–8 weeks. If symptoms resolve, it is reasonable to consider PPI on-demand therapy with as needed antacids/H2RA. On the other hand, if symptoms persist then it is important to ensure patients are taking their PPI 30 min prior to meals. If medication adherence is confirmed, then patients may switch to a more potent PPI and/or escalate to twice daily dosing.

For patients with erosive disease or frequent severe reflux symptoms, a step-down strategy can be employed. These patients may benefit from daily PPI for 8 weeks instead of 4 weeks [130]. If symptoms resolve, then stepping down to H2RAs for maintenance is a feasible approach. If symptoms persist after 8 weeks of PPI therapy, dosing frequency is increased to twice daily [131]. Those that do not respond to twice daily PPI after 12 weeks are deemed to have refractory disease, which can occur in up to 30% of patients with GERD [132]. One clinical trial of patients with mild esophagitis on esomeprazole 40 mg found prolonging therapy from 4 to 8 weeks reduced symptom relapse [130]. Current recommendations are to continue maintenance PPI therapy while exploring other diagnostics and procedural options [4]. This

includes an endoscopy off PPI for at least 2 weeks to evaluate for erosive disease and exclude Eosinophilic Esophagitis with biopsies. These patients are also appropriate for pH testing, esophageal manometry, and consideration for pH-impedance to further understand their GERD phenotype.

Many studies and clinical trials have sought to discover how to select the optimal PPI and dosing. PPI potency and efficacy is often assessed using time with gastric pH >4 as an objective marker. PPI and gastric pH have a linear dose–response with a ceiling effect seen at 70 mg of omeprazole and with three-times daily dosing [133]. In addition, esomeprazole 20 mg and omeprazole 20 mg had similar time of gastric pH > 4 [134]. As a class, PPIs maintained gastric pH > 4 for 15–21 h per day as compared to 8 h daily with H2RAs [51]. The World Health Organization proposed that omeprazole 20 mg is equivalent to rabeprazole 20 mg, esomeprazole 30 mg, lansoprazole 30 mg, dexlansoprazole 30 mg, and pantoprazole 40 mg [133]. Vonoprazan 10 mg daily is more potent and equivalent to 60 mg of omeprazole [133]. Despite doses greater than 20 mg per day offering superior acid control and esophagitis healing, it remains uncertain whether this translates to any symptomatic/clinical benefit [135].

For some patients with incomplete responses, switching to another PPI is a feasible approach given the variation of intragastric pH control [53]. A double-blind, randomized study found that for patients with persistent heartburn on lansoprazole 30 mg, increasing to twice daily lansoprazole was as effective as switching to esomeprazole 40 mg [136]. Yet, almost 10% of patients remain symptomatic on twice daily PPI [137]. Those with persistent symptoms unresponsive to initial PPI trial could be genetically rapid drug metabolizers. These patients may benefit from switching to PPIs with limited CYP2C19 metabolism, such as rabeprazole or pantoprazole (lowest cytochrome induction or inhibition amongst benzimidoles) [53]. A randomized control trial of patients on daily PPI showed 20% had symptomatic improvement when increasing to twice-daily PPI or switching PPI [138].

Since reflux symptoms are so prevalent, PPIs continue to be amongst the most prescribed medications in many countries [139]. With more attention and research into PPI side effects, many primary care providers and gastroenterologists are reassessing PPI prescribing patterns. As with many medications, timing for dose adjustment or therapy discontinuation is patient specific. Studies have demonstrated lower healthcare costs, improved symptom relief, and unchanged quality of life with full-dose PPI step-down approach compared to H2RA and low-dose PPI step-up strategies [140]. For patients with mild symptoms, one study found omeprazole 10 mg had similar symptomatic remission at 1 year compared to omeprazole 20 mg (77% vs. 83% respectively) [141]. Another multi-center study reported 80% success rate of step-down from omeprazole 20 mg to omeprazole 10 mg [142].

More studies need to be done to assess the clinical significance of PPI discontinuation and subsequent rebound acid hypersecretion. Current evidence points towards tapering patients who have been on PPI therapy for greater than 6 months. For patients with mild to moderate GERD, decreasing maintenance PPI dose offered less symptom relapse compared to “on-demand” PPI or class switch to H2RA [139].

Conclusions

Several medications currently exist for the treatment of GERD. PPIs block the final step of gastric parietal cell acid production and are used in the vast majority of patients. With more attention and research into PPI side effects, many primary care providers and gastroenterologists are reassessing PPI prescribing patterns. As with many other medications, dose adjustment or therapy discontinuation should be tailored for each specific patient.

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Endoscopic Management of Gastroesophageal Reflux Disease

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Abstract Gastroesophageal Reflux Disease (GERD) is a common gastrointestinal malady with increasing prevalence. GERD is typically diagnosed clinically and treated with proton-pump inhibitors. Endoscopy has proven important in the diagnosis of GERD. Moreover, endoscopic techniques for managing GERD have been employed. This chapter reviews current and future approaches in the endoscopic diagnosis and management of GERD.

Keywords Gastroesophageal reflux disease · Endoscopy · Bravo pH testing · Transoral incisionless fundoplication · Anti-reflux mucosectomy

Introduction

Gastroesophageal reflux disease (GERD) is a troublesome gastrointestinal disorder in which gastric contents move retrograde into the esophagus leading to the classic symptoms of heartburn and regurgitation. In the United States, GERD is the most common gastrointestinal disorder with a prevalence of 18–28% [1, 2]. It is estimated that 30–40% of all adults experience reflux in their life time with 20–28% reporting weekly symptoms [1, 3]. Annually, GERD is associated with a significant economic impact of $9–10 billion dollars [4]. The bulk of these expenses is due to direct costs including medical management of GERD, diagnostic procedures and hospitalizations with the remainder due to indirect costs related to lost work productivity and time taken off [5].

GERD is the result of an incompetent lower esophageal sphincter (LES) leading to loss of barrier function. Typically, the LES consists of tonically contracted smooth muscle that prevents pathologic reflux. This anti-reflux valve is augmented from the

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components of extrinsic pressure from the diaphragmatic crura as well as positive intraabdominal pressure. The angle of His also provides an additional anatomy barrier to prevent reflux of contents in the gastric fundus [6]. In 60% of cases, the LES is incompetent leading to a loss of anti-reflux mechanism. The remainder of patients experience GERD due to transient LES relaxation [7]. Furthermore, hiatal hernias can displace the LES into the negative pressure thoracic cavity leading to longer transient LES relaxation, decreased baseline tone and shorter esophageal length. LES dysfunction can further be compounded by functional disorders including gastroparesis and esophageal dysmotility [6].

The typical symptoms of GERD, heartburn and regurgitation, are caused by direct reflux of gastric and duodenal contents with subsequent inflammatory-mediated activation of nociceptors. Pathologic reflux can also result in atypical symptoms such as chronic cough, asthma, hoarseness, laryngitis, chest pain, and dyspepsia resulting in significant morbidity and impaired quality of life. Furthermore, long-standing reflux can impair the protective barrier of the esophageal mucosa and lead to erosive disease. This predisposes individuals to developing esophageal metaplasia, Barrett's esophagus, and subsequent malignant transformation, esophageal adenocarcinoma [6].

GERD is typically a clinical diagnosis based on the presence of symptoms of heartburn. Patients undergo a trial of proton pump inhibitors (PPIs) as empiric treatment for GERD. If patient symptoms do not improve or if concerning symptoms, such as dysphagia, weight loss or hematemesis are present, then additional diagnostic testing is completed. This typically begins with upper endoscopy and objective pH monitoring. At times, esophageal manometry and gastric emptying studies are also indicated.

Endoscopic examination is an integral adjunct in the diagnosis of GERD. It allows for examination of the esophageal mucosa and distinguishes between erosive and non-erosive disease. Endoscopy is also important in identifying the sequelae of GERD including Barrett's esophagus and esophageal adenocarcinoma. Anatomic defects, such as hiatal hernia, that can lead to pathologic reflux can also be visualized with endoscopy. Ambulatory pH monitoring can be completed with an endoscopically placed probe which provides objective measurements of both acid and non-acid reflux. Advances in endoscopic imaging as well as pH monitoring has increased the sensitivity and specificity in the diagnosis of GERD.

Treatment of GERD begins with lifestyle modifications and medical management with PPIs, though its use does not necessarily decrease reflux episodes. For those with refractory disease and those unwilling to take PPIs long-term, anti-reflux surgery (ARS) has been the standard of care. Traditionally, ARS, consisting of repair of hiatal hernia when present and creation of a fundoplication, has been enlisted in refractory cases of GERD or when patients cannot take PPIs long-term. ARS is an effective treatment for GERD, however, with complications such as gas-bloat and dysphagia as well as the desire for less invasive options, endoscopic treatments for GERD have been developed.

This chapter details modern day techniques and advances in the endoscopic diagnosis and management of GERD.

Endoscopic Diagnosis of GERD

GERD is typically diagnosed based on the presence of subjective heartburn and regurgitation. Patients are usually trialed on a course of empiric PPIs for 4–8 weeks. However, heartburn and regurgitation are only found in 54% and 28% of patients and fewer than 50% of patients respond to PPIs. Furthermore, a PPI trial only has a 78% sensitivity and 54% specificity for GERD [8]. This can lead to diagnostic uncertainty in a significant number of patients presenting with reflux symptoms.

Endoscopy is subsequently indicated in cases of PPI failure, alarm symptoms and as part of the routine work-up prior to anti-reflux surgery. Endoscopy visualizes the esophageal mucosa and can detect GERD related injury seen in erosive disease. It also characterizes the lower esophageal sphincter and detects the presence of hiatal hernias. Endoscopic analysis is often combined with objective analysis of acid and non-acid reflux with a pH monitor.

Endoscopic Examination for GERD

Current guidelines indicate objective evaluation for GERD with endoscopy for persistent or worsening symptoms despite a trial of PPIs, the presence of alarm symptoms or extra-esophageal symptoms [9]. Alarm symptoms such as dysphagia, weight loss, or hematemesis may point to an underlying malignancy causing reflux. Another indication would be for patients who are unable to wean off PPI and as part of the routine work up for anti-reflux surgery.

Endoscopy is usually completed in the ambulatory setting. Gross examination includes identification of erosive esophagitis (EE) or non-erosive disease (NERD). Erosive esophagitis reflects damage to the esophageal mucosa from reflux with loss of its physiologic protective mechanisms. Esophagitis is calculated with the Los Angeles (LA) Classification based on the length and number of mucosal breaks. There are four categories with the LA classification system, LA Grade A–D (Table 1). Recent consensus described LA Grade A and LA Grade B, was borderline and inconclusive for GERD and can be found in normal individuals [10].

Table 1 Los Angeles classification of esophagitis

Los Angeles classification of esophagitis	
Grade A	Mucosal breaks ≤5 mm long, none of which extends between the tops of the mucosal folds
Grade B	Mucosal breaks >5 mm long, none of which extends between the tops of two mucosal folds
Grade C	Mucosal breaks that extend between the tops of ≥2 mucosal folds, but which involve <75% of the esophageal circumference
Grade D	Mucosal breaks which involve ≥75% of the esophageal circumference

Barrett's esophagus (BE) is another phenotype of GERD seen on endoscopy. BE is visualized as salmon-colored mucosa extending proximal from the gastroesophageal junction (GEJ) and represents mucosal metaplasia from normal squamous epithelia to intestinal-type columnar epithelia. It is the only known precursor for esophageal adenocarcinoma with a 0.11% annual conversion risk [11]. BE is graded based on the Prague classification system [12]. The Prague classification characterizes BE based on its circumferential extent, the "C" criteria, and maximum proximal extension, the "M" criteria. Visualization of BE is an indication for biopsy and subsequent surveillance.

The presence of EE has a 95% specificity for the diagnosis of GERD [13]. However, EE is only seen in 70% of patients with GERD [14]. The incidence of EE may be under reported as only macroscopic changes to the esophageal mucosa on white light examination can be visualized. Advanced imaging techniques can detect earlier changes to the esophageal mucosa.

The American Society for Gastroenterology (ASGE) included the use of advanced imaging to detect the presence of mucosal abnormalities [15]. Narrow band imaging (NBI) filters green and blue light to detect early proliferative changes to the esophageal mucosa. NBI improves detection of abnormal vascular and micro-erosions in NERD [16]. NBI is commercially available with a 94.2% and 97.5% specificity for BE based on irregular mucosal and vascular patterns [17]. Confocal laser endomicroscopy (CLE) employs a special endoscope or probe to obtain confocal images at 1000 magnification, however, is no longer in use due to its costs. Other methods of advanced endoscopic imaging include chromoendoscopy with acetic acid or methylene blue. These were not found to meet standards for detecting dysplasia and showed high variability [18]. Autofluorescence is another imaging technique that can detect mucosal lesions based on difference in tissue fluorescence. This technique was found to have a higher sensitivity for GERD when compared to standard endoscopic imaging (77% vs 21%), but with only a 53% specificity [19].

Endoscopy also examines the lower esophageal sphincter for the presence of hiatal hernia. The presence of a hiatal hernia relocates the LES from the positive-pressure abdominal cavity to the low-pressure thoracic cavity resulting in decreased tonic contraction and longer transient LES relaxations. The presence of hiatal hernia may also cause the LES complex to lose its extrinsic compression from the diaphragmatic crura. Identification of a hiatal hernia has a strong association with the development of reflux and its sequelae [20].

Endoscopic examination of the hiatus entails measuring the axial length of a hernia when present as well as grading the degree of hiatal disruption. The Hill Classification characterizes the amount of crural disruption based on endoscopic imaging. The hiatus is given a grade from 1 – 4. The Hill Classification was found to have a strong association with a diagnosis of GERD [21, 22].

Recent guidelines from the American Gastroenterological Association determine that the diagnosis of GERD is based on endoscopic visualization of LA Grade B, C, or D esophagitis, long-segment BE or an acid exposure time (AET) $\geq$6% for two or more days based on ambulatory pH testing [9].

Ambulatory pH Testing

Ambulatory pH testing is the only objective monitor for GERD. It can detect the presence of acid reflux in patients with non-erosive disease. Endoscopic placement of a wireless probe 5 cm proximal to the lower esophageal sphincter can measure reflux episodes and esophageal pH for a study duration of 48–96 h. The pH probe measure episodes of reflux when esophageal pH is less than 4.

Prior to testing, patients should be off histamine-2 antagonists for 3 days and PPIs for 14 days. Placement of the pH probe is often completed in conjunction with endoscopic examination. Patients are typically provided a data recorder to measure episodes of oral intake, changes in positioning and onset of GERD-related symptoms.

A primary metric of esophageal pH monitoring is acid exposure time (AET). AET is defined as the percent of time that the esophageal environment is at a pH of less than 4. An AET >6% is considered abnormal, while an AET <4% is considered normal and in between values being indeterminate [10, 13]. An adjunctive measure to AET is the number of reflux episodes with >80 reflux episodes in a 24 h period being abnormal [13]. pH monitoring also identifies the association between reflux episodes and patient's subjective symptoms. The Symptom Associated Probability (SAP) and Symptom Index (SI) reflect the temporal association between acidic reflux events and onset of symptoms. SAP is a reflection of the likelihood a symptom is associated with reflux and SI reflects the magnitude of the association. SAP and SI are good indicators for symptom improvement with treatment of GERD [23]. Strong correlation is seen when SAP >95% or SI >50% [9].

Endoscopic Treatment of GERD

Initial management for GERD involves lifestyle modifications and treating with PPIs. PPIs are useful in making refluxate less acidic, but does not change the number of reflux episodes. Furthermore, a PPI trial is ineffective in 25–42% of patients [24]. Anti-reflux surgery (ARS) is considered in patients who do not respond to PPIs. Many patients, given concerns for PPI side-effects and costs with long-term use, also elect for ARS.

ARS is an effective treatment for GERD with lower long-term use of PPIs and improved symptom control. ARS allows for repair of hiatal hernia, localization of the LES in the intra-abdominal position and increasing basal LES pressure with fundoplication. Patients undergoing ARS are less likely to require anti-reflux medications, have improved symptom resolution and better quality of life [25]. However, associated dysphagia and gas bloat is present in up to 24% and 15% of patients, respectively [26].

Endoscopic approaches have also been developed for management of GERD. These techniques are less invasive and are an alternative to traditional ARS. However, though endoscopic approaches improve LES function, they are unable to address

hiatal hernias. As a result, patient selection is very important for endoscopic anti-reflux therapy. In general, good candidates should not have severe esophagitis (LA grade C/D or BE) or esophageal dysmotility and should not have a large hiatal hernia. Specifically, patients should either have no hiatal hernia or a hiatal hernia less than 2 cm in axial length (Hill Grade 1 or 2). The best candidates are those who respond well to PPIs. Furthermore, an endoscopic anti-reflux procedure should not preclude a patient from receiving future ARS.

Radiofrequency Ablation (RFA)

RFA is one of the earliest endoscopic treatments for GERD. The Stretta device (Restech Corporation, Houston, Texas, US) found FDA approval in 2000 under its original manufacturer (Curon Medical, Inc.). The Stretta catheter consists of four radio-frequency probes that is advanced to the LES over a guidewire. Radiofrequency energy is then applied at six levels from 2 cm above to 2 cm below the Z-line. It is postulated that RFA leads to tissue remodeling. This is thought to decrease compliance of the LES complex and result in fewer transient LES relaxations.

Long-term studies of Stretta reveals normalization in quality-of-life scores in 72% of patients with 54% of patients off PPIs at 10 years follow up [27]. However, there was no significant improvement in objective GERD measurements as LES pressure remained unchanged and AET returned to pre-treatment values at 8 year follow up [28]. When compared to ARS, the percentage of patients off PPI were similar, but ARS was superior in terms of improved quality of life [29]. Concerningly, a meta-analysis found that compared to sham treatment, Stretta did not provide significant changes in objective GERD outcomes, ability for patients to discontinue PPI, or quality of life [30].

Transoral Incisionless Fundoplication (TIF)

The TIF creates an endoscopic fundoplication similar to the traditional surgical approach. The TIF procedure was first approved by the FDA in 2007. The current iteration, EsophyX 2.0, (EndoGastric Solutions, Inc., Redmond, WA, US) is a two-operator device and creates a 2–3 cm long, 270°, esophagogastric plication. The TIF device draws in the gastric wall with a helical retractor and suction device to fold the fundus over the esophagus and create a full thickness plication with polypropylene T-fasteners. This technique creates a fundoplication to strengthen the LES high-pressure zone and bolsters the angle of His to restore the flap-valve mechanism.

The TIF procedure has been shown to decrease transient LES relaxation and LES distensibility [31]. In a cohort of 57 patients undergoing TIF, at an 8 year follow up, 78% of patients felt adequate relief of symptoms with a significant improvement in

quality of life [32]. Following TIF, ambulatory pH monitoring showed normalization of pH scores in 95% of patients with intact fundoplication [33]. A recent meta-analysis showed significant improvements in quality-of-life scores and pH scores with a 2% adverse event rate. Furthermore, 89% of patients were no longer using PPIs [34]. When compared to ARS, objectively, ARS was more likely to have higher LES pressure and decreased acid exposure, but TIF provided the most improvement in quality of life and symptom relief [35]. The TIF procedure has also been applied as an adjunct to GERD predisposing procedures, namely the sleeve gastrectomy and peroral endoscopic myotomy.

Anti-reflux Mucosectomy (ARMS) and Anti-reflux Mucosal Ablation (ARMA)

ARMS and ARMA are endoscopic treatments for GERD that do not use proprietary, treatment specific devices. ARMS, first reported in 2014, was discovered incidentally during endoscopic mucosal resection (EMR) of BE around the LES. Following resection of a crescent of mucosa, the patient reported improvement in GERD symptoms with objective improvement in esophageal acid exposure [36]. It is thought that mucosal contracture and scarring helps to narrow and strengthen the LES. ARMS can be completed either with cap-EMR or endoscopic submucosal dissection (ESD) techniques. In 2020, Inoue et al., published a pilot study of ablation of the LES mucosa with similar improvement in pH score and quality of life [37]. Short term results of ARMS showed normalization of pH scores in 72.5% of patients with 69.4% of patients off PPI at 1 year [38]. Sustained improvement in AET was seen at three years follow up. When compared to ARS, ARMS had significantly shorter operative time, length of stay and decreased pain. There was also no significant difference between quality of life [39].

Conclusions

Endoscopic approaches to the diagnosis of GERD are well established while endoscopic therapies continue to be developed and studied. It becomes important to balance the costs of these innovations with their practical utility. Endoscopic therapy for GERD has been shown to be safe and efficacious. As more treatment options are developed, it will become increasingly vital to determine the best option on a patient-by-patient basis. Furthermore, substantial education and training in these procedures must be completed to increase accessibility of these novel techniques.

Conflict of Interest The authors have no conflicts of interest.

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Laparoscopic Antireflux Surgery

Francisco Schlottmann, Fernando A. M. Herbella, and Marco G. Patti

Abstract Antireflux surgery should be considered if there is partial control of symptoms (e.g., persistence of regurgitation or cough despite medical therapy), presence of large hiatal hernia, poor compliance to medication, refusal to take PPIs for a long time, or complications related to medical therapy. The success of antireflux surgery will rely on a careful patient selection, a comprehensive preoperative work-up, and a properly executed operation. We present a detailed step-by-step description of the surgical technique of laparoscopic antireflux surgery.

Keywords Gastroesophageal reflux disease · Antireflux surgery · Laparoscopy · Hiatal Hernia · Total fundoplication · Partial fundoplication

Introduction

Gastroesophageal reflux disease (GERD) is a common disorder; in the US it affects around 20% of the adult population and the incidence has risen in the last decades due to the high prevalence of obesity [1]. The disease has an important economic impact in the healthcare system, with direct costs of approximately $10 billion per year (mostly related to the broad use of proton pump inhibitors (PPIs) [2, 3].

The treatment of GERD has three main objectives: control symptoms, improve patients' quality of life, and prevent GERD-related complications (i.e., bleeding,

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esophageal stenosis, Barrett's esophagus and/or esophageal adenocarcinoma). The majority of patients are properly managed with lifestyle modifications and PPIs.

Antireflux surgery should be considered if there is partial control of symptoms (e.g., persistence of regurgitation or cough despite medical therapy), presence of large hiatal hernia, poor compliance to medication, refusal to take PPIs for a long time, or complications related to medical therapy [4].

The success of antireflux surgery will rely on a careful patient selection, a comprehensive preoperative work-up, and a properly executed operation [5–7].

Preoperative Work-Up

The clinical evaluation should include complete history assessing the presence, duration, and severity of typical (heartburn, regurgitation, and dysphagia) and atypical (e.g. cough, hoarseness, chest pain) symptoms. Clinical response to PPIs should also be evaluated.

Unfortunately, diagnosis of GERD solely based on symptoms is often wrong because the clinical presentation is heterogenous and symptoms overlap with many other gastrointestinal disorders. Therefore, several tests should be performed preoperatively:

Esophagogastroduodenoscopy (EGD): An EGD is useful to determine the severity of esophagitis (Table 1) and for detecting GERD-related complications such as strictures, Barrett´s esophagus or cancer. In addition, other disorders that might mimic GERD can be ruled out (e.g. eosinophilic esophagitis, gastritis or peptic ulcer). Patients with non-erosive GERD might have a normal EGD.

Barium esophagram: This test offers relevant anatomical information such as the presence and size of hiatal hernia, strictures or esophageal shortening.

Esophageal high-resolution manometry: The esophageal manometry is very important to rule out primary esophageal motility disorders (e.g. achalasia) that can mimic GERD due to the presence of similar symptoms (dysphagia, regurgitation, heartburn). In addition, it is needed for the correct placement of the pH monitoring probe (5 cm above the upper border of the lower esophageal sphincter). Finally, it

Table 1 Los Angeles classification of esophagitis

Los Angeles classification of esophagitis	
Grade A	Mucosal breaks $\leq$5 mm long, none of which extends between the tops of the mucosal folds
Grade B	Mucosal breaks >5 mm long, none of which extends between the tops of two mucosal folds
Grade C	Mucosal breaks that extend between the tops of $\geq$2 mucosal folds, but which involve <75% of the esophageal circumference
Grade D	Mucosal breaks which involve $\geq$75% of the esophageal circumference

might help for tailoring the fundoplication (a partial fundoplication is preferred in patients with GERD and severe esophageal dysmotility).

Ambulatory pH monitoring: This study is the gold standard for the diagnosis of GERD because it objectively determines pathologic acid exposure and correlates specific symptoms with episodes of reflux.

Surgical Technique

Positioning of the Patient and Surgical Team

After induction of general endotracheal anesthesia, an orogastric tube is inserted to keep the stomach decompressed. The patient is positioned supine in low lithotomy position with the lower extremities extended on stirrups, with knees flexed 20°-30°. The surgeon will stand between the patient's legs (Fig. 1).

Troubleshooting: Pneumatic compression devices for legs are recommended for prophylaxis against deep vein thrombosis.

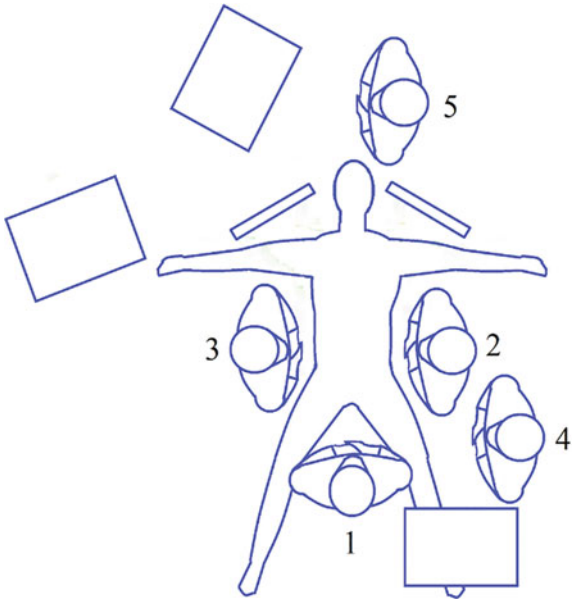

Fig. 1 Positioning of the patient and surgical team. (1) surgeon, (2) first assistant, (3) second assistant, (4) scrub nurse, and (5) anesthesiologist

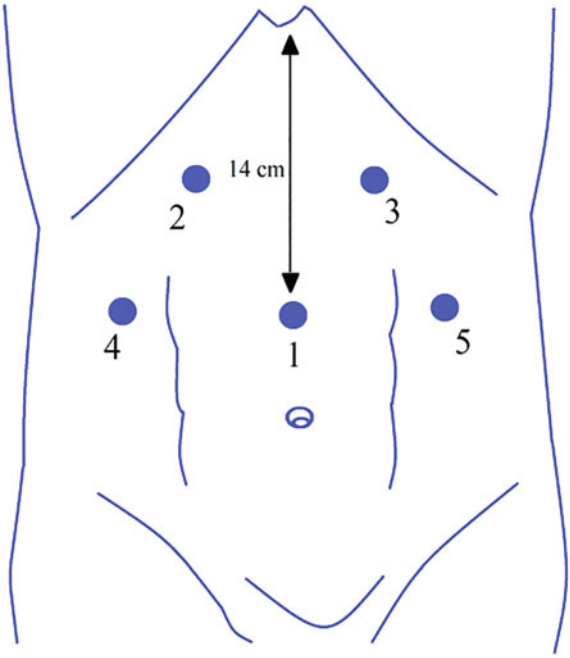

Fig. 2 Ports placement for laparoscopic antireflux surgery. (1) camera, (2) surgeon, (3) surgeon, (4) liver retractor (could be replaced for a subxiphoid port for Nathanson retractor), (5) assistant port

Trocar Placement

A total of five laparoscopic ports are used for the operation (Fig. 2).

Troubleshooting: Care must be taken during the introduction of the first port in the supraumbilical area. We recommend using an optical trocar to obtain access.

Division of the Gastrohepatic Ligament

Initially, the left segment of the liver should be retracted. Then the gastrohepatic ligament is divided starting above the caudate lobe of the liver towards the right crus (Fig. 3). The right crus is separated from the esophagus with blunt maneuvers and the posterior vagus nerve is identified. The right crus should be dissected all the way down towards the junction with the left crus (Fig. 4).

Troubleshooting: Care must be taken with a potential accessory left hepatic artery originating from the left gastric artery.

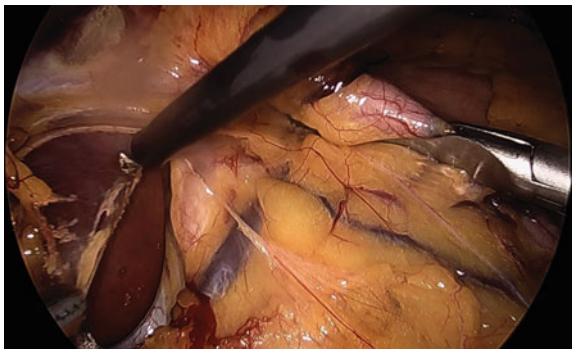

Fig. 3 Division of the gastrohepatic ligament

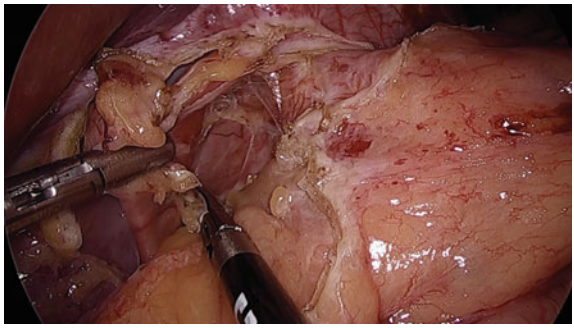

Fig. 4 Dissection of the right crus

Division of the Phrenoesophageal Membrane

The phrenoesophageal membrane is divided just above the esophagus (Fig. 5). The anterior vagus should be identified at this point and left attached to the esophageal wall. The left pillar of the crus is then separated from the esophagus, and dissected bluntly downward toward the junction with the right crus.

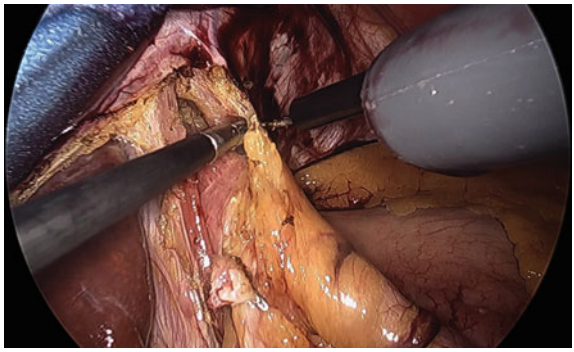

Fig. 5 Division of the phrenoesophageal membrane

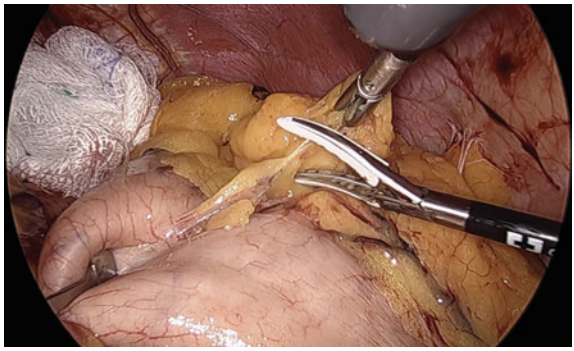

Fig. 6 Division of short gastric vessels

Troubleshooting: Injury of the anterior vagus nerve is prevented by lifting gently the peritoneum and phrenoesophageal membrane away from the esophagus and leaving the nerve attached to the esophagus.

Division of Short Gastric Vessels

The short gastric vessels are taken down with a vessel sealing device starting from a point midway along the greater curvature of the stomach towards the fundus and all the way to the left pillar of the crus. This step is important in order to obtain a tension-free fundoplication afterwards (Fig. 6).

Troubleshooting: Short gastric vessels should be transected cautiously without excessive traction in order to avoid bleeding from the spleen.

Placement of Penrose Drain and Mediastinal Dissection

A posterior window under the esophagus is opened with blunt dissection (Fig. 7). The window is then enlarged and a Penrose drain is passed around the esophagus, incorporating both the anterior and posterior vagus nerves. Retracting the esophagus away from the hiatus helps performing an extensive mediastinal dissection, which is needed to obtain at least 3 cm of esophagus below the diaphragm.

Troubleshooting: The Penrose drain should be secured with a large clip or a loop suture tie. In case the pleura is opened during mediastinal dissection, the anesthesiologist should be promptly notified. Reducing pneumoperitoneum pressure is usually enough to avoid respiratory events.

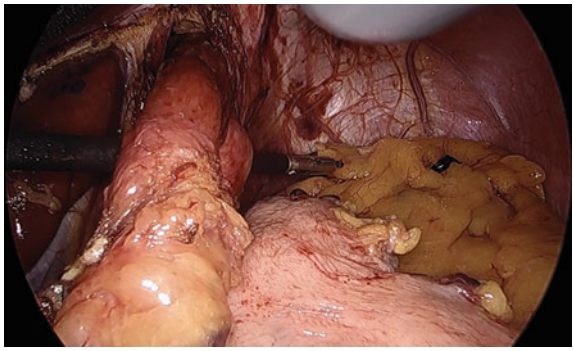

Fig. 7 Posterior window behind the esophagus that will be used to place the Penrose drain

Closure of the Esophageal Hiatus

The hiatus is properly exposed by retracting the esophagus upward and toward the patient's left with the Penrose drain. The closure of the crura is done with interrupted non-absorbable sutures (e.g. 2–0 silk or polyester). The first stitch should be placed just above the junction of the two pillars. Additional stitches are placed 1 cm apart, and a space of about 1 cm should be left between the uppermost stitch and the esophagus (Fig. 8).

Troubleshooting: The closure of the crura should not be too tight to avoid postoperative dysphagia. A closed grasper should slide easily between the esophagus and the crura.

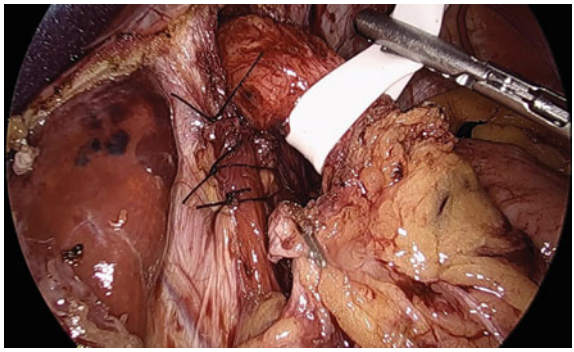

Fig. 8 Closure of the hiatus with interrupted non-absorbable sutures

Fundoplication

The fundus is passed behind the esophagus and a "shoe-shine" maneuver is performed to verify sufficient fundic mobilization (Fig. 9). There are two main types of fundoplication during an antireflux operation: total 360° fundoplication (Nissen fundoplication) or partial posterior 240–270° fundoplication (Toupet fundoplication). Both types of fundoplication are very effective for controlling abnormal reflux [8, 9]. A partial fundoplication is recommended for patients with severe esophageal dysmotility.

Total 360° Fundoplication: A bougie is inserted into the esophagus to prevent postoperative dysphagia. The gastric fundus is passed behind the esophagus, and the left and right sides of the fundus are wrapped with a Babcock above the gastroesophageal junction during the placement of the first stitch. We use 3 stitches of nonabsorbable material (2–0 silk or polyester) at 1 cm intervals to approximate the right and left side of the fundoplication. A short (about 2 cm in length) and floppy wrap should be created (Figs. 10 and 11).

Partial Posterior Fundoplication: The gastric fundus is passed behind the esophagus and the right and left sides of the fundus are separately sutured to the esophagus

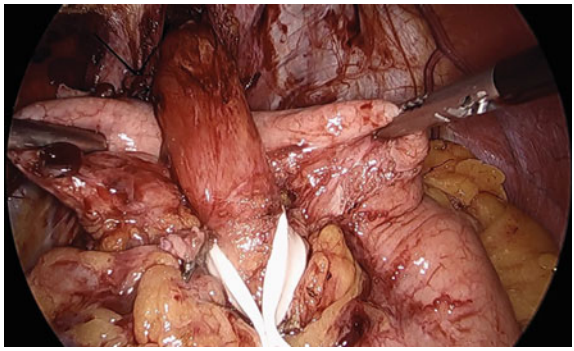

Fig. 9 "Shoe-shine" maneuver to verify sufficient fundic mobilization

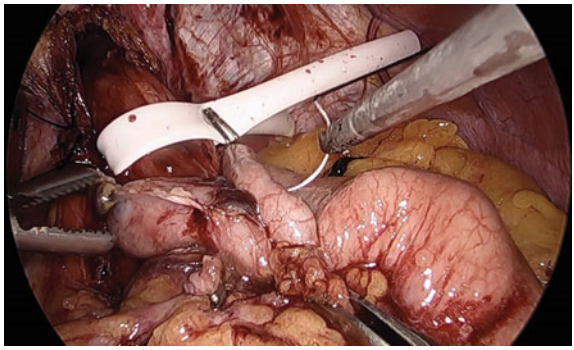

Fig. 10 First stitch of the total 360° fundoplication

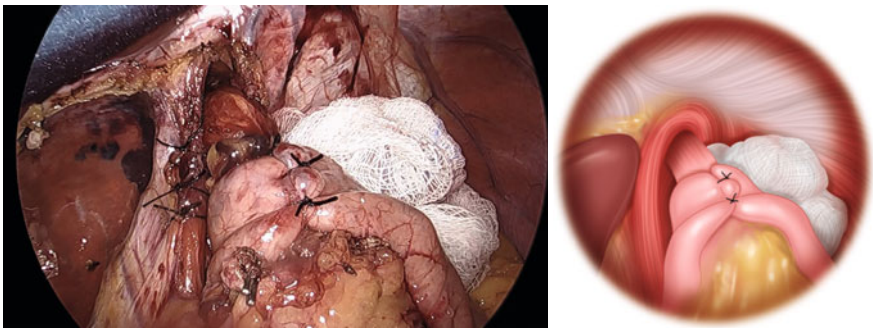

Fig. 11 Completed total 360° fundoplication

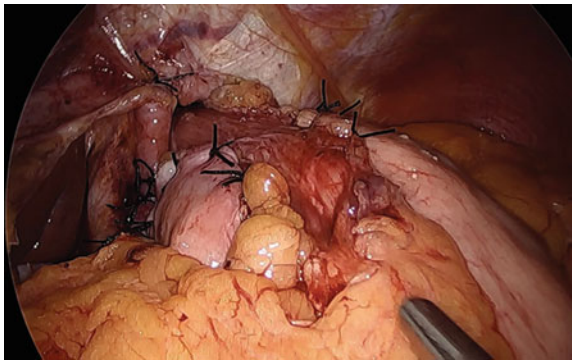

Fig. 12 Completed partial posterior fundoplication

leaving the anterior esophageal wall uncovered. Three stitches of non- absorbable material (2–0 silk or polyester) are placed on each side (Fig. 12).

Troubleshooting: A free-tension fundoplication is critical for the success of the operation.

Final Inspection

The bougie is smoothly removed from the esophagus by the anesthesiologist and the Penrose drain is cut and removed. After checking for adequate hemostasis, the liver retractor, instruments and trocars are removed under direct vision. The fascia of the 10–12 mm ports should be closed.

Postoperative Care

Patients can start with clear liquids the day of the operation, and then advance to soft diet as per tolerance. Most patients are discharged within 48 h with instructions to avoid meat, bread, and carbonated beverages for the following two weeks. PPIs should be discontinued after 6 weeks.

Conflict of Interest The authors have no conflicts of interest.

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Robotic Antireflux Surgery

Emiliano G. Manueli Laos, Francisco Schlottmann, and Mario A. Masrur

Abstract Gastroesophageal reflux disease (GERD) is a prevalent disease. Although most patients are adequately treated with medication, some will eventually require antireflux surgery. The robotic platform offers significant technical advantages over laparoscopy that help obtaining optimal surgical outcomes.

Keywords GERD · Hiatal hernia · Robotic surgery · Fundoplication

Introduction

Gastroesophageal reflux disease (GERD) is a prevalent disease with almost half of all adults reporting GERD symptoms at least once in their lives. GERD is mostly related to disorders affecting the lower esophageal sphincter (LES), such as higher frequency of relaxations, decreased LES contractility, higher intraabdominal pressure, and/or anatomical abnormalities like hiatal hernias [1].

There are 4 types of hiatal hernia: Type I or sliding hernia, in which the distal portion of the esophagus and the stomach cardias slide through the esophageal hiatus into the posterior mediastinum. Type II or paraesophageal hernia, where a portion or the totality of the stomach comes through the esophageal hiatus in parallel to the esophagus. Type III or mixed hernia is a combination of the two previously mentioned hernias, where the esophagus and the stomach are herniated through the hiatus.

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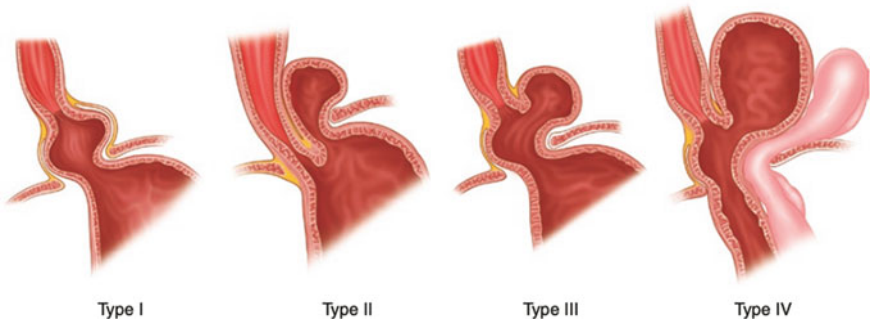

Fig. 1 Classification of hiatal hernias (Obtained from Foregut Surgery. Achalasia, Gastroesophageal Reflux Disease and Obesity. Springer 2020)

Type IV, in which another abdominal organ is projected through the mediastinum in addition to the stomach or esophagus (Fig. 1).

Medical treatment (i.e., proton pump inhibitors) is the first line of therapy for GERD. Unfortunately, some patients may still experience symptoms despite medical therapy. For patients who do not respond to medication, who are not compliant or who do not wish to maintain long term medical therapy, antireflux surgery can be indicated [2].

Robotic Antireflux Surgery

Anti-reflux surgery addresses the valvular problem at the LES, which is often combined with hiatal hernia repair. Traditionally, antireflux surgery was performed with an open approach. Currently, minimally invasive surgery is the gold standard for the surgical treatment of GERD. Robot-assisted antireflux surgery has shown better outcomes than laparoscopic approach, possibly related to the well-known advantages of the robotic platform over laparoscopy [3].

Preoperative Evaluation

All patients eligible for antireflux surgery should undergo a series of preoperative studies to confirm GERD, assess esophageal function and determine the esophagogastric anatomy. These studies include esophagogastroduodenoscopy, upper GI contrast imaging, esophageal manometry, and pH monitoring.

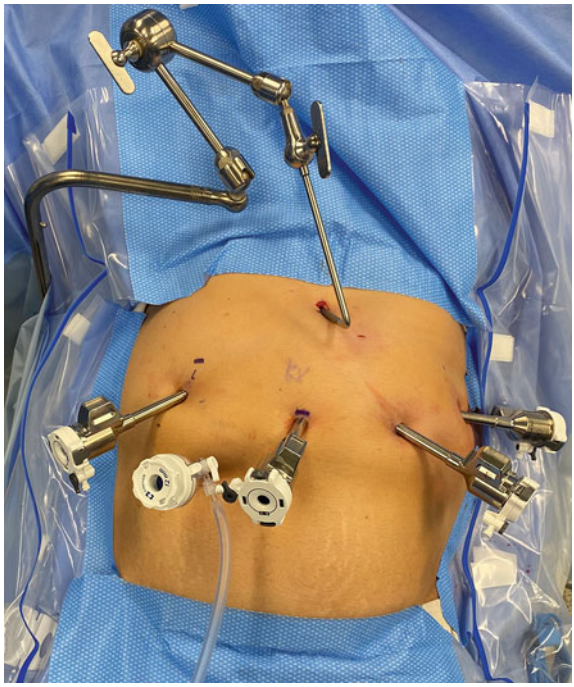

Fig. 2 Port placement

Patient Positioning and Port Placement

Reverse Trendelenburg with parted legs is the position of choice for this procedure. Once pneumoperitoneum is achieved with Veress needle at Palmer's point, the exploration of the abdominal cavity will be done by inserting a 5 mm optic trocar in the left flank. Four robotic ports are placed in straight line 5 cm above the transverse umbilical line. The scope will be positioned in the intersection of this line with the left mammary line. An additional assistant 10 mm port can be placed on the right side of the scope. A Nathanson liver retractor is used to retract the liver and allow exposure of the hiatus (Figs. 2 and 3).

Operative Technique

After the robot is correctly docked, the assistant will grab the stomach with an atraumatic laparoscopic grasper and do a firm pulling maneuver in order to partially reduce the hernia and bring the stomach from the mediastinum back to the abdominal cavity.

The left diaphragmatic pillar is initially dissected using a robotic monopolar hook. Cadiere or robotic bipolar forceps can be used alternatively. Incision of the peritoneal

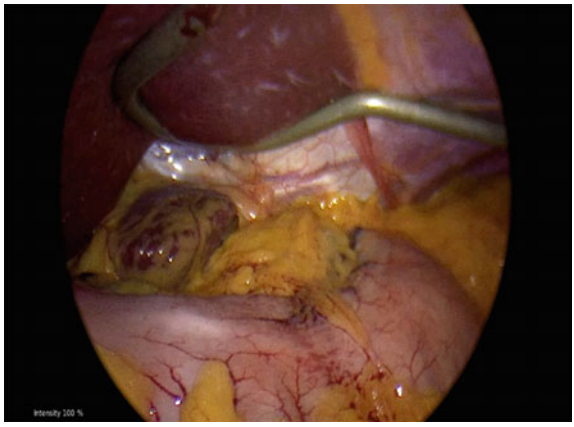

Fig. 3 Exposure of the hiatus with liver retractor

sac should be done safely over the left pillar. The left crus should be fully exposed (Figs. 4 and 5).

The phrenoesophageal membrane is incised and dissection advances towards the mediastinum to expose the lateral aspect of the hernia and avoiding injury of the anterior vagus nerve. The sac is detached starting in hour 3, progressing anteriorly towards hour 12, and then posteriorly towards hour 6.

The gastrohepatic ligament is incised and the right diaphragmatic pillar is then dissected. Conserving the integrity of the vascular and neural structures of the lesser curvature is key to avoid complications such as denervation of the stomach and gallbladder. The dissection continues until achieving complete exposure of the right crus (Fig. 6).

The mediastinal dissection proceeds laterally and posteriorly until joining the right and left planes by creating a retroesophageal window. Iatrogenic pneumothorax can be produced while dissecting the esophagus in the mediastinum. If this

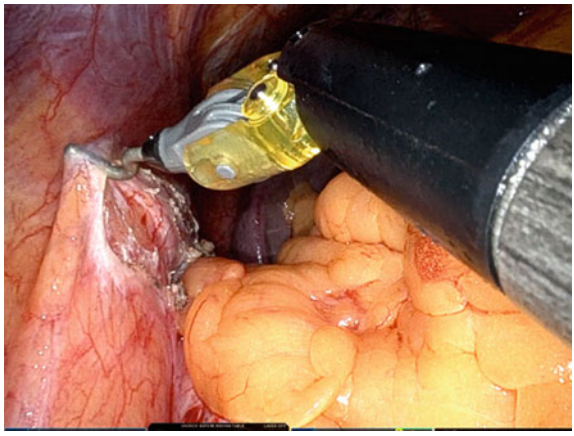

Fig. 4 Dissection of left diaphragmatic pillar with monopolar hook

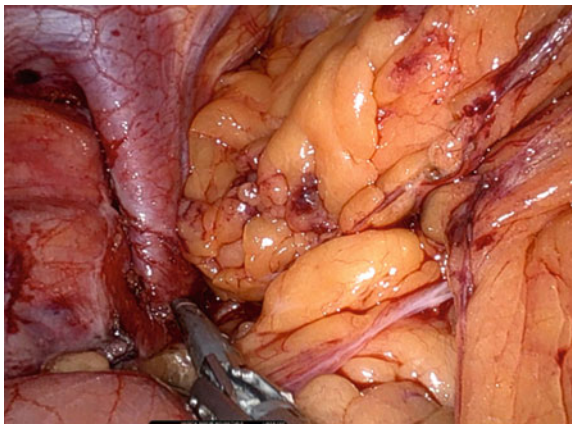

Fig. 5 Further dissection of left diaphragmatic pillar with vessel sealer

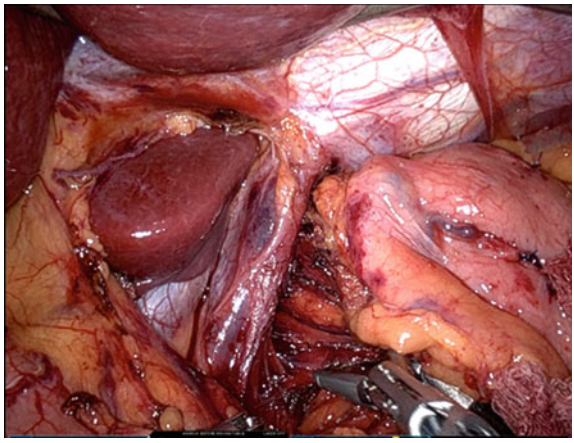

Fig. 6 Exposure of right diaphragmatic pillar

happens, this event should be communicated to the anesthesia team to adjust respiratory parameters. This complication usually does not require any further surgical maneuvers.

A Penrose drain is placed around the esophagus through the retroesophageal window, to allow further mobilization of the distal esophagus (Fig. 7). At least 3 cm of intraabdominal esophagus without tension should be obtained.

Once the hiatus is adequately exposed retracting the esophagus, the cruroplasty is performed. Posterior interrupted stitches using 2–0 polyester sutures are preferred. The pillars are often approximated with 3–4 interrupted stiches (Figs. 8 and 9).

Reinforcement of the crural closure with mesh is controversial [4]. We do not routinely place a mesh, but rather consider its use in selected cases (large hernias with poor quality crural muscles or redo operations). A biosynthetic absorbable mesh is preferred.

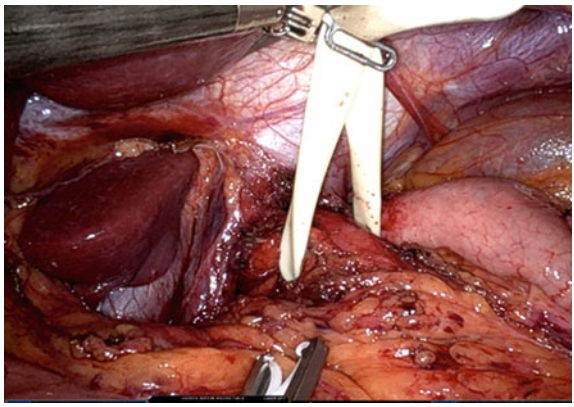

Fig. 7 The Penrose drain around the esophagus facilitates the mediastinal dissection of the distal esophagus

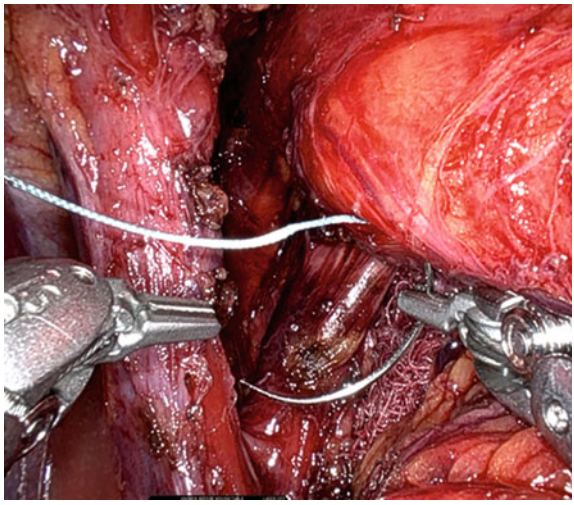

Fig. 8 Initial stitch of the cruroplasty

Once the cruroplasty is done, we start with the fundoplication. In most cases we perform a total, short, and floppy 360° wrap (Nissen fundoplication). The posterior aspect of the gastric fundus is pulled towards the right behind the esophagogastric junction. The anterior part of the gastric fundus is pulled anteriorly so it meets its posterior counterpart in the anterior side of the esophagus. Both sides of the gastric fundus are sutured together using 3 interrupted stiches of 2–0 polyester (Figs. 10, 11 and 12).

In patients with severe esophageal dismotility, a partial posterior wrap (Toupet fundoplication) is preferred.

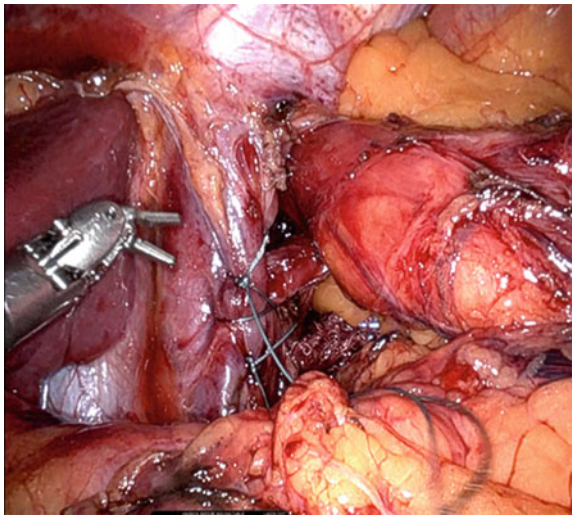

Fig. 9 The hiatus is adequately closed

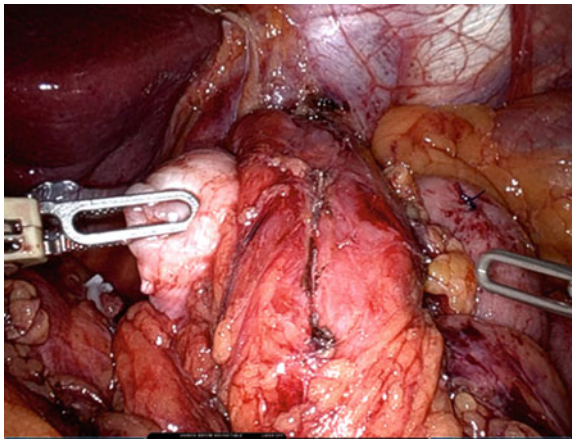

Fig. 10 The gastric fundus is pulled towards the right behind the esophagus

Postoperative Care

Patients often start with clear liquids on postoperative day 1, followed by semisolid diet before progressively moving to a solid food intake. Patients are discharged on postoperative day 2 or 3. Pharmacologic antiemetic prophylaxis is recommended during the admission to avoid excessive retching. Antireflux medical therapy is discontinued after 4 to 6 weeks.

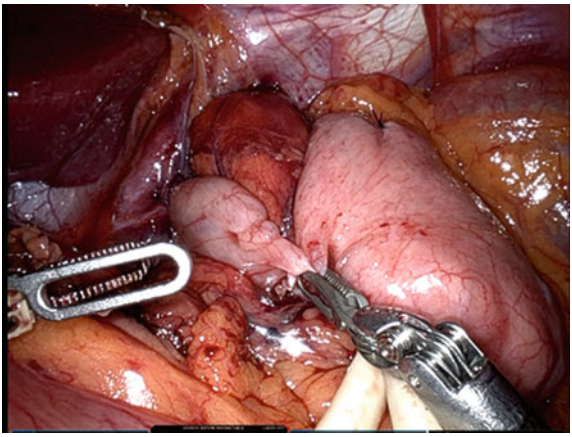

Fig. 11 Both sides of the fundoplication should be approximated without tension

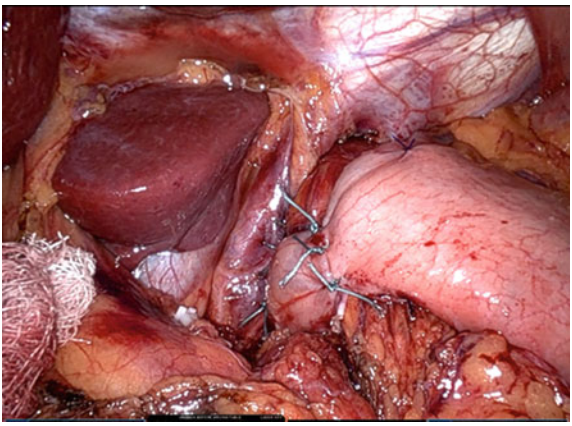

Fig. 12 Nissen fundoplication

Conclusions

Although most patients are adequately treated with medication, some will eventually require antireflux surgery. The operation addresses the valvular problem at the LES, which is often combined with hiatal hernia repair The robotic platform offers significant technical advantages over laparoscopy that help obtaining optimal surgical outcomes.

Conflicts of Interest The authors have no conflict of interest to declare.

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Gastroesophageal Reflux Disease in Obese Patients

Sofia Bertona, Manuela Monrabal Lezama, Marco G. Patti, Fernando A. M. Herbella, and Francisco Schlottmann

Abstract Obesity prevalence has exponentially increased over the last three decades, becoming a pandemic that affects a third of the global population. Obesity is an independent risk factor for gastroesophageal reflux disease (GERD). The higher incidence of GERD in obese patients is explained by several complex pathophysiologic factors such as LES abnormalities, altered trans-diaphragmatic pressure, hiatal hernia, and esophageal dysmotility among others. Although weight loss, dietary modifications, and medical therapy should be initially recommended, some patients might need surgical treatment. Roux-en-Y gastric bypass is the ideal operation for obese patients with GERD.

Keywords Obesity · GERD · Pathophysiology · Hiatal Hernia · Tran-diaphragmatic pressure

Introduction

Obesity prevalence has exponentially increased over the last three decades, becoming a pandemic that affects a third of the global population. It is a well-known risk factor for many other health conditions such as cardiovascular disease, type II diabetes and neoplasms [1, 2]. Furthermore, obesity is one of the most important independent risk factor for gastroesophageal reflux disease (GERD) [3]. Previous studies have

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already demonstrated the linear relationship between body mass index (BMI) and GERD symptoms and erosive esophagitis [4]. The incidence of GERD appears to be proportional to the degree of obesity: 23% in patients with a BMI less than 25 kg/m^2, 27% in those with a BMI between 25 and 30 kg/m^2, and a 50% in individuals with a BMI greater than 30 kg/m^2 [5].

The concern related to GERD symptoms in the obese population is not limited to their frequency, but also to the severity of the condition. Patients with obesity often experience a more severe form of GERD, characterized by a higher occurrence of erosive esophagitis and Barrett's esophagus (BE). This was demonstrated by Stein and colleagues, who reported that for each 5 unit of increase in BMI, the risk of BE increases 35%. In this context, the importance of visceral obesity seems to be greater than peripheral obesity [6, 7].

Although evidence suggests that GERD is aggravated by visceral obesity, it is also known that visceral obesity possess an increased risk for both BE and adenocarcinoma, through mechanisms that are not influenced by reflux [8, 9]. In effect, the likelihood of developing esophageal cancer (OR 4.76, 95% CI 2.96–7.66) or esophagogastric junction carcinoma (OR 3.07, 95% CI 1.89–4.99) is significantly higher in individuals who are overweight than in those with a normal BMI [10].

Obesity-related GERD pathogenesis is multifaceted and marked by a plethora of suggested mechanisms. The main pathophysiologic factors involved in the development of GERD include an increased frequency of transient lower esophageal sphincter relaxations, altered transdiaphragmatic pressure gradient, higher prevalence of hiatal hernias, esophageal dysmotility, hormonal fluctuations, and poor dietary habits (Fig. 1).

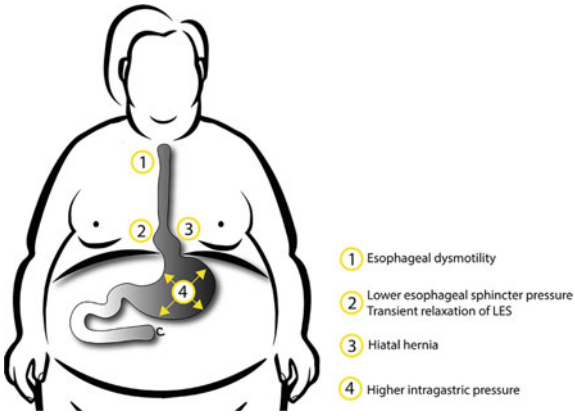

Fig. 1 Main pathophysiologic factors involved in the development of gastroesophageal reflux disease in patients with obesity (LES: lower esophageal sphincter)

Pathophysiology

Lower Esophageal Sphincter Abnormalities

The lower esophageal sphincter (LES) is a 3–4 cm longer segment of tonically contracted smooth muscle located in the lower end of the esophagus. Incompetence of the LES may be attributed to its inadequate length or suboptimal pressure. Reflux of gastric juice usually results from either a defective LES or an increased frequency of transient LES relaxations (TLESR) [11].

Compared with patients with normal weight, obese patients are significantly more likely to have a defective LES [11]. Nevertheless, a normal LES can be found in obese patients with GERD [12]. A higher frequency of TLESR seems to play a key role in these patients. The primary trigger of TLESR is thought to arise from gastric distension, specifically from the expansion of the fundus [13]. Previous research has shown that overweight and obese present increased TLESR during the post prandial period [14]. Moreover, the frequency of TLESR was strongly correlated with both BMI and waist circumference [15, 16].

The role of the angle of His is of utmost importance in the antireflux mechanism. A greater degree of acuteness in the angle of His results in a more pronounced projection of the gastric fundus towards the esophagus during gastric distension, particularly when eating. In obese individuals, the excessive deposition of adipose tissue in the gastroesophageal junction can lead to an obtuse angle, affecting this physiologic antireflux mechanism [17].

The presence of a hiatal hernia is also more common in patients with obesity. Pandolfino and colleagues using high resolution manometry showed that obese patients are at an increased risk of experiencing esophagogastric junction disruptions, which may lead to the development of a hiatal hernia. This, in conjunction with an amplified gastroesophageal pressure gradient, creates an ideal environment for the occurrence of reflux [18].

Altered Transdiaphragmatic Pressure Gradient

The majority of the esophagus is situated within the thoracic cavity under conditions of negative pressure. In contrast, the stomach is located in the abdomen and is exposed to a surge of positive pressure caused by the increase amount of intra-abdominal adiposity, resulting in higher intragastric pressure. In fact, an augmentation of 10% in intragastric pressure is observed for each point of increase in BMI [11, 19].

Obesity has also been associated with higher thoracic pressure, which can be attributed to low lung volumes resulting from limited tidal volume caused by the transmission of intraabdominal pressure and elevation of the diaphragm [20]. Obstructive sleep apnea, a common condition in the bariatric population, leads to the collapse

of the upper airway and the development of a more negative intrathoracic pressure, contributing to a prolonged period of nocturnal acid exposure in obese individuals [19, 21].

Defective Esophageal Clearance

Esophageal clearance is determined by the combined functions of salivation, gravity, and esophageal motility. Obesity is associated with not only a decrease in salivation but also esophageal dysmotility in around one quarter of individuals [22, 23]. The affected esophageal peristalsis is mostly characterized by low amplitude waves and simultaneous contractions known as ineffective esophageal motility [24].

Altered Hormone Profile

The abdominal fat is a metabolically active organ that decreases adiponectin (anti-inflammatory cytokine) and causes an increase of inflammatory agents such as leptin, interleukin-6, and tumor necrosis factor-α. These altered cytokines may contribute to the higher incidence of erosive esophagitis and BE in the obese population [25, 26]. The increased secretion of estrogen by adipose tissue also contributes to the higher prevalence of reflux symptoms in obese women. In fact, both women of reproductive age and menopausal under estrogen therapy show greater incidence of GERD, as compared to menopausal women who do not receive hormone replacement therapy [3].

Diet

The prevalence of GERD symptoms increases with the typical diet of patients with obesity: high-fat and low-fiber diet. This diet lowers the LES pressure, increases the frequency of TLESR episodes and causes delayed gastric emptying [27]. In addition, specific foods such as chocolate, caffeine, peppermint, alcohol, soft drinks, and fatty foods precipitate reflux.

Treatment of GERD in Obese Patients

Medical Therapy

Treatment of obese patients with GERD is initiated with dietary and lifestyle modifications. Recommendations include weight loss, elevation of the bed's head, discontinuation of tobacco and alcohol consumption, refraining from late night meals, and cessation of food products that exacerbate reflux symptoms (e.g., caffeine, chocolate, citrus, alcohol, spicy food) [28].

Weight loss has the potential to mitigate symptoms due to a decline in intra-abdominal pressure and possibly due to alterations in hormonal levels. It has been demonstrated that a reduction of 3.5 kg/m^2 in BMI leads to a 40% decrease in the risk of reflux symptoms [8]. Other studies have demonstrated a significant reduction in acid exposure of the esophagus evaluated by pH monitoring following weight loss [29–32].

Proton pump inhibitors (PPIs) are the most commonly used medications for the treatment of GERD. It is uncertain if obese individuals have a different response to PPIs compared to lean individuals [33]. Currently, no evidence suggests that these patients should receive an increased dosage of medication, compared to slim patients [34].

Surgical Treatment

The use of antireflux surgery in obese individuals is controversial. While a fundoplication works mostly on the gastroesophageal barrier, pathophysiology of GERD is complex and multifaceted in these patients. In addition, chances of recurrence or failure of the operation are significantly higher due to the constant increased intra-abdominal pressure [35–37].

Bariatric surgery is indeed tempting in this scenario because patients can achieve both weight loss and GERD symptoms resolution. A Roux-en-Y gastric bypass is the ideal procedure for GERD patients with a BMI >35 kg/m because it reduces parietal cell population in the small gastric pouch (treating acid reflux) and diverts bile from the stomach through the Roux limb (treating bile reflux) [35, 37–40]. A sleeve gastrectomy is not recommended in obese patients with GERD as the amount of reflux might even increase. This operation includes several technical elements that can worsen GERD: disrupted gastric sling fibers, alterations in the angle of His, decreased LES pressure, and increased intra-gastric pressure of the narrow stomach [40].

Conclusions

The higher incidence of GERD in obese patients is explained by several complex pathophysiologic factors such as LES abnormalities, altered trans-diaphragmatic pressure, hiatal hernia, and esophageal dysmotility among others. Although weight loss, dietary modifications, and medical therapy should be initially recommended, some patients might need surgical treatment. Roux-en-Y gastric bypass is the ideal operation for obese patients with GERD.

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Conflict of Interest Sofia Bertona, Manuela Monrabal Lezama, Marco G. Patti, Fernando A.M. Herbella, and Francisco Schlottmann have no conflict of interest, financial ties or funding/support to disclose.

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Gastroesophageal Reflux Disease After Bariatric Surgery

Sarah E. Kim, Francisco Schlottmann, and Mario A. Masrur

Abstract Sleeve gastrectomy is thought to cause gastroesophageal reflux disease (GERD) due to the alteration of the valvular anatomy of the angle of His and the creation of a narrower stomach with pyloric preservation that would increase the intragastric pressure. On the other hand, Roux-en-Y gastric bypass (RYGB) is considered the ideal anti-reflux operation due to the significantly reduced number of parietal cells in the gastric pouch which reduces the risk of acid reflux. Additionally, the long Roux loop helps to prevent biliary reflux into the esophagus. However, recent research has demonstrated that some patients might develop GERD after RYGB due to diverse mechanisms (enlarged pouch, hiatal hernia, candy cane syndrome, etc.). Management of GERD after bariatric surgery is complex. Most patients can be adequately treated with medical therapy. For patients without response to medication, there are multiple available endoscopic and surgical treatment modalities that should be considered based on physiological and anatomical variables.

Keywords Gastric bypass · Sleeve gastrectomy · GERD · Proton-pump inhibitors · Endoscopy

Introduction

As the prevalence of obesity increases in the United States, complications associated to it also rises. Obesity is strongly associated with gastroesophageal reflux disease (GERD), with presence of a linear association between GERD symptoms and body mass index (BMI) [1].

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Although sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) have shown equivalent results in terms of weight loss at 5 years, these procedures have different effect on GERD [2, 3]. RYGB was previously recommended as the ideal anti-reflux surgery while SG was thought to increase likelihood of developing or worsening preexisting GERD. In this chapter, we discuss how a significant proportion of obese patients continue to suffer or develop (de novo) GERD after bariatric surgery and the various treatment modalities existing.

GERD and Obesity

GERD occurs when acid refluxes from the stomach back into the esophagus. Obesity is one the most common risk factor contributing to GERD with two- to three-fold increase likelihood to develop reflux compared to those with normal weight [4]. Similarly, moderate weight gain in patients with normal baseline weight showed to cause or worsen reflux symptoms.

Some potential mechanisms as to why obesity is associated with GERD include low basal pressure of the lower esophageal sphincter (LES), abnormal esophageal clearance, increased intra-abdominal pressure, presence of hiatal hernia, and dietary habits. An alteration in the transdiaphragmatic pressure gradient due to an increased intra-abdominal pressure is thought to be the most critical factor, as the additional abdominal fat increases the intra-abdominal pressure to modify the intragastric pressure. Prior research has shown that gastric pressure increases approximately 10% for each unit increase in BMI [5, 6]. The HUNT study further investigated the relationship between BMI reduction and GERD and concluded that weight loss is associated in a dose-dependent manner with reduction of symptoms as well as treatment success with medications [7].

When not properly treated, GERD is also associated with complications, including esophagitis, esophageal strictures, Barrett's esophagus (BE) and esophageal adenocarcinoma, asthma, sinusitis, dental erosions, and aspiration pneumonia among others.

GERD and Bariatric Surgery

SG is thought to worsen GERD due to the alteration of the valvular anatomy of the angle of His and the creation of a narrower stomach with pyloric preservation that would increase the intragastric pressure. Due to these anatomical changes, patients are likely to either develop or worsen their GERD symptoms (Fig. 1).

On the other hand, RYGB is considered the ideal anti-reflux operation due to the significantly reduced number of parietal cells in the gastric pouch, thus reducing the risk of acid reflux. Additionally, the long Roux loop helps to prevent biliary reflux into the esophagus (Fig. 2). The improvement of GERD was seen in several

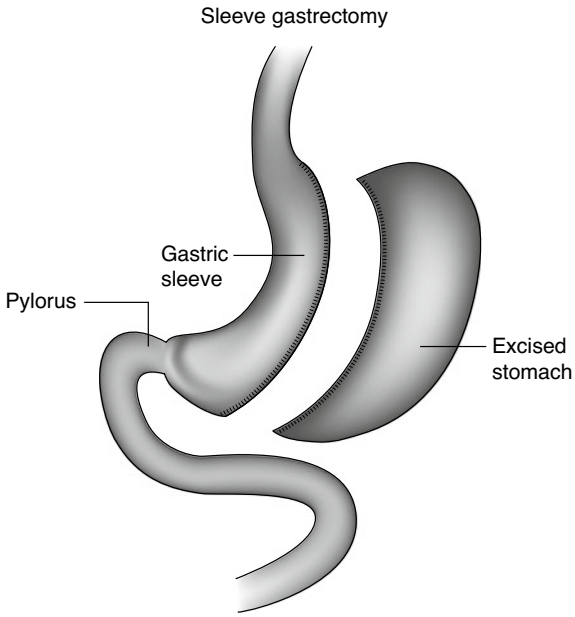

Fig. 1 Sleeve gastrectomy

studies, with patients noting decrease in symptoms as well as decrease in medication usage. However, additional studies showed that some patients had recurrence or no additional improvement, as patients reported symptoms again and required acid suppressing medications [8–10]. Another study showed that after RYGB, some patients developed hiatal hernias, enlarged pouches, and gastric pouch fistulas that were seen on radiographic imaging. Additionally, patients who underwent upper endoscopy showed esophagitis and even BE. Correspondingly, patients had hypotensive LES and hypomotility or aperistalsis seen on manometry and abnormal acid exposure on pH monitoring [11]. Other possible causes of development of GERD after RYGB include impaired esophageal clearance, large gastric pouch, candy cane syndrome, pouch stasis syndrome, short alimentary limb, and Roux-en-Y stasis syndrome. Though rare, de novo GERD can also occur after RYGB [12].

Diagnosis of GERD After Bariatric Surgery

The diagnostic work-up for GERD (both persistence/recurrence and de-novo) is based on typical symptoms (i.e., heartburn, regurgitation, dysphagia) and additional tests including upper endoscopy, esophageal manometry, and pH monitoring. In particularly after SG, barium swallow is also performed to better delineate the post-surgical anatomy, evaluate for strictures, and assess esophageal motility. Additionally, an upper endoscopy allows the direct visualization of the mucosa and gives

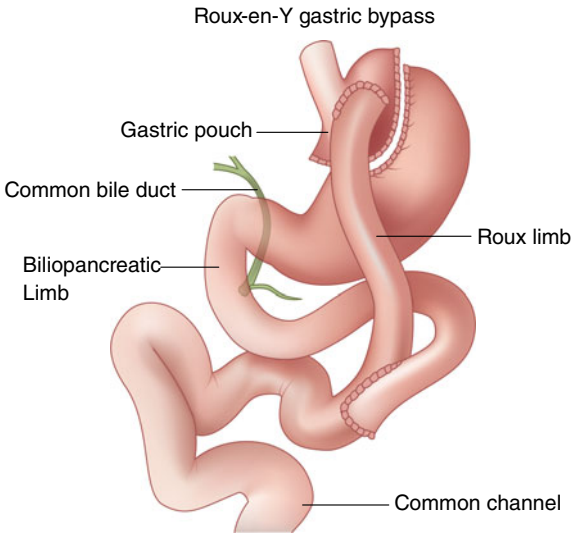

Fig. 2 Roux-en-Y gastric bypass

the ability to take tissue biopsies. Impedance testing can also be combined with pH monitoring and manometry to help characterize the amount and type of reflux.

Management of GERD After Bariatric Surgery

Medical Therapy

The initial management of GERD after bariatric surgery starts with lifestyle modifications and use of acid suppressing medications. Lifestyle modifications include avoidance of alcohol and trigger foods, tobacco cessation, elevation of head of bed, avoiding meals before bedtime, and weight loss. For patients who continue to have symptoms despite lifestyle modifications, the addition of acid suppressing medications is recommended. Proton pump inhibitors (PPIs) are currently the most effective medication for GERD with reported higher rates of healing of erosive reflux disease compared to H2 blockers [2, 13]. Despite lifestyle modification and medical therapy, some patients continue to suffer from GERD due to lack of compliance, bile reflux, improper dosage, and PPI resistance.

Endoscopic Procedures

Endoscopic procedures provide an endoluminal treatment option for patients who continue to have symptoms despite medical management. Endoscopic techniques can

provide advantages of providing additional diagnostic tools as well as a therapeutic intervention.

a. *Radiofrequency Ablation of the Lower Esophageal Sphincter*

The endoscopic radiofrequency ablation (RFA) of the LES (*Stretta Procedure*) was first described in 2000 and helps treating GERD by thickening the LES, decreasing transient lower esophageal sphincter relaxation, and reducing acid exposure. A flexible endoscopy is used to visualize the mucosa and the Stretta catheter is introduced and inflated just 1 cm proximal to the GE junction. Four needle electrodes in perpendicular positions are introduced with the tips located in the muscular layer and each needle will use radiofrequency waves to heat the tissue to 85 °C for 1 min with continuous irrigation of cold water to prevent thermal injury. Radiofrequency waves are delivered to 6 locations from 1 cm proximal to the GE junction up to 1.5 cm distally [13].

The safety and efficacy of the Stretta Procedure in patients without history of bariatric surgery has been demonstrated on multiple studies showing significant reduction in PPI use, regression of BE, improvement of GERD scores and quality of life, and reduction of acid exposure time. Esophageal perforations were reported when the procedure was first introduced, now some common complications of this procedure include gastroparesis and ulcerative esophagitis, both of which are transient and reversible. Some patients also reported dysphagia, which improved after bougie dilation. In several analyses, no reported long-term complications were noted. Currently, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) advocate the use of the Stretta Procedure for patients without history of bariatric surgery, hiatal hernia, or severe esophagitis [14]. Although there are no absolute contraindications for the procedure, some relative contraindications include pregnancy, large hiatal hernia or significant dysphagia.

The evidence for the use of Stretta in patients with previous bariatric surgery remains scarce. In a previous study, 15 patients who underwent Stretta for the management of refractory GERD after SG were analyzed. The reflux symptoms score at 6 months did not change significantly (42.7 vs. 41.8, $p = 0.8$), 66.7% of the patients were not satisfied with the treatment, only 20% were able to discontinue PPI use, and 13.3% finally required conversion to RYGB. Additionally, one case (6.7%) was complicated by hematemesis [15]. Unfortunately, there has not been strong evidence of the Stretta Procedure on post- RYGB patients.

b. *Anti-reflux Mucosectomy and Mucosal Ablation*

Anti-reflux mucosectomy (ARMS) aims to create submucosal fibrosis after mucosectomy at the GE junction. Both endoscopic mucosal resection and endoscopic submucosal dissection techniques can be used to perform ARMS. Anti-reflux mucosal ablation (ARMA) ablates the gastric cardiac mucosa by current or argon plasma coagulation and induces scarring formation. Overall, ARMS and ARMA have thought to have similar outcomes with ARMA having the benefit of reducing risk of perforation. The most common indication of ARMS is to treat acid-reflux when there is no associated hiatal hernia.

The safety and efficacy of ARMS in patients without bariatric surgery have been demonstrated on prior studies. For example, one study reported a significant decrease in DeMeester score at 2 months (64.4 to 24.9, $p < 0.01$) and discontinuation of PPIs in 51% of patients after 1 year. Two patients developed hemorrhage postoperatively and one patient had a minor perforation, requiring closure with clips [14]. There has been a few known case series for the use of ARMS after SG and in those cases the majority of patients had improvement of GERD without lifelong complications [16–18].

Surgical Procedures

There are several surgical options for the treatment of GERD after bariatric surgery. Currently, the standard surgical procedure for GERD after SG is conversion to RYGB. In addition, repair of hiatal hernia if detected pre- or intraoperatively is recommended at the time of index bariatric surgery.

a. *Conversion to Roux-en-Y Gastric Bypass*

RYGB has been considered the standard surgical treatment of GERD and weight loss failure after SG. The small gastric pouch helps limit acid production and reduces reflux into the esophagus because of the created anatomy.

Most patients who undergo conversion to RYGB after SG report significant and immediate improvement of GERD symptoms. In a large-scale study of 556 SG patients, 30.4% had conversion to RYGB due to GERD. The majority of patients had complete remission of their symptoms (79.7% at 1 year, 91.3% at 2 years) [19].

b. *Magnetic Sphincter Augmentation Device*

The magnetic sphincter augmentation device (LINX) is a flexible ring of small magnets that are placed around the LES with the magnetic force augmenting the barrier function of the LES (Fig. 3). The use of LINX has shown clinical improvement of GERD symptoms on multiple trials. Improvements in GERD scores and less bloating compared to the Nissen fundoplication were reported in many of these studies [20]. Long term effects also showed successful improvement in GERD with rare potential complications including migrations, erosions, and malfunctions.

Evidence supporting the use of LINX after bariatric surgery is scarce. Previous research has shown that the use of LINX in these patients is associated with significantly less PPI usage. Unfortunately, some patients develop dysphagia after the procedure requiring either device removal or endoscopic dilation [21].

c. *Ligament of Teres Cardiopexy*

The ligament of teres cardiopexy is a procedure that uses the ligamentum teres to achieve restoration of the GE junction function. The ligamentum teres is released from its umbilical connection and passed around the GE junction above the fundus to create a new sphincter and secured into place with sutures (Fig. 4).

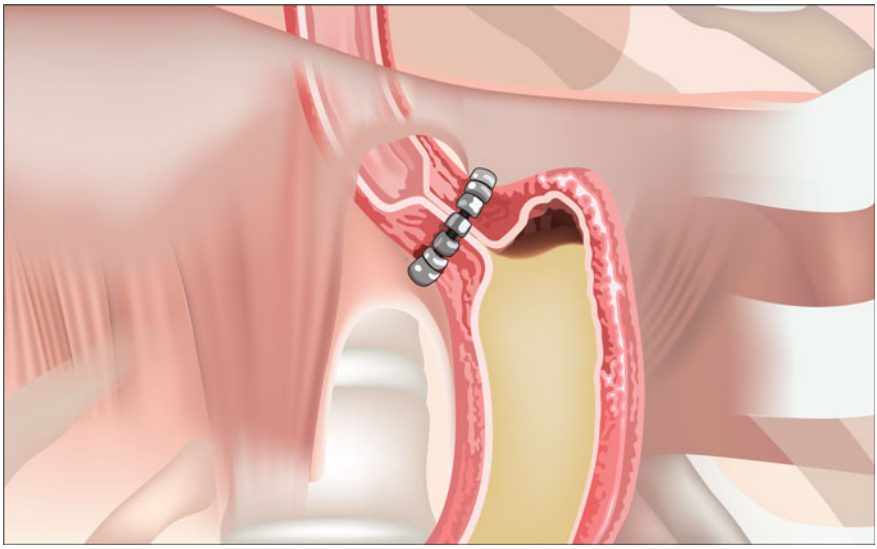

Fig. 3 Magnetic sphincter augmentation device for the treatment of GERD after sleeve gastrectomy

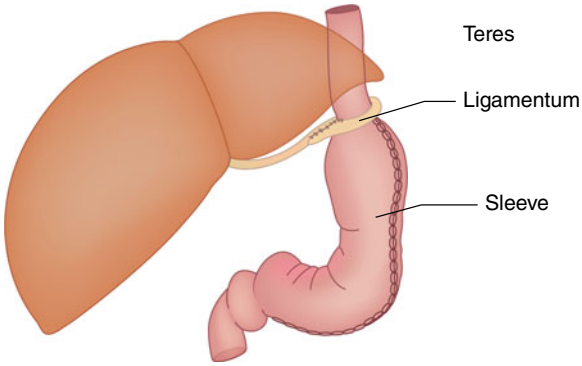

Fig. 4 Ligament of teres cardiopexy for the treatment of GERD after sleeve gastrectomy

Despite encouraging initial clinical outcomes, long-term effects in GERD symptoms remain questionable [22, 23]. There are limited studies conducted on the use of ligamentum of teres cardiopexy after bariatric surgery. The cases available report improvement of GERD symptoms, discontinued use of PPI, and no hiatal hernias or reflux on barium swallow [24, 25].

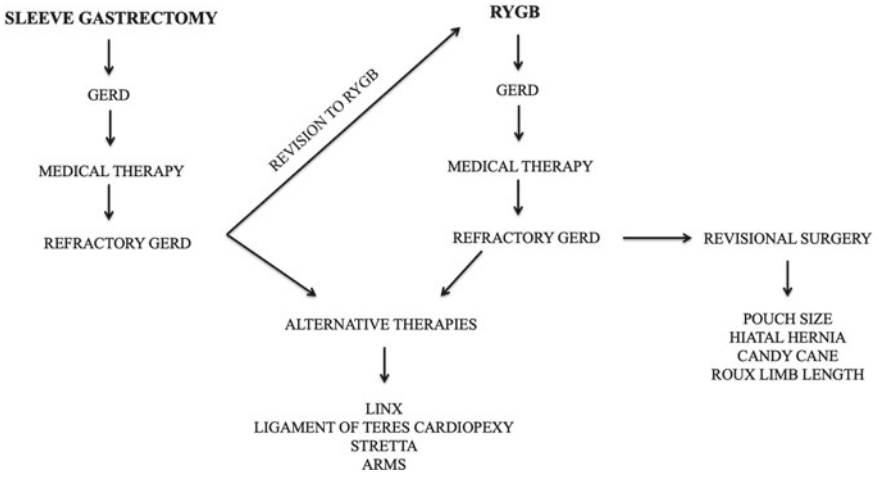

Fig. 5 Treatment algorithm for gastroesophageal reflux disease (GERD) after bariatric surgery (RYGB: Roux-en-Y gastric bypass; LINX: magnetic sphincter augmentation device; STRETTA: radiofrequency ablation of the lower esophageal sphincter; ARMS: anti-reflux mucosectomy)

Conclusions

Management of GERD after bariatric surgery is complex. Most patients can be adequately treated with medical therapy. For patients without response to medication, there are multiple endoscopic and surgical treatment modalities that should be considered based on physiological and anatomical variables (Fig. 5).

Conflict of Interests No conflict of interests to disclose.

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Failed Antireflux Surgery

Nicolette Winder, Jarrod Olafson, Francis A. Agcaoili, and Vic Velanovich

Abstract Sadly, not all antireflux operations are successful. There are several ways to define a failed antireflux procedure. These include failure in the surgeon's judgement (appropriate patient, appropriate operation, and appropriate execution of the operation), anatomical failures, and physiological failures. In this chapter, diverse types of antireflux surgery failure are thoroughly discussed along with treatment alternatives for these patients.

Keywords Antireflux surgery · Failure · Recurrence · Slipped Nissen · Hiatal hernia

Introduction

Antireflux surgery comprises a wide array of procedures that essentially entails some degree of esophagogastric fundoplication. A successful antireflux operation requires a patient who was appropriately selected for the procedure, with symptoms attributable to pathologic acid reflux. The patient was determined to have pathologic reflux caused by an incompetent lower esophageal sphincter (LES) and this reflux resulted in the patient's symptoms or other GERD-related adverse effects. The patient was physiologically fit for an abdominal operation under general anesthesia. The appropriate anti-reflux operation was chosen. The operation was well executed. The operation resulted in no acute post-operative complications. The operation led to resolution of the patient's GERD-related symptoms, corrected the pathologic acid reflux, and either eliminated or reduced the need for anti-acid medications. And finally, the operation produced no new persistent symptomatic adverse symptoms [1].

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Sadly, not all antireflux operations are successful. There are several ways to define a failed antireflux procedure. These include failure in the surgeon's judgement pertaining to the appropriate patient, appropriate operation, and appropriate execution of the operation. While we discuss each of these pitfalls in detail, we will not address acute complications following antireflux surgery that require emergent intervention including, but not limited to, esophageal perforation or gastric ischemia, nor will we address the failings of some of the less common antireflux procedures like endoluminal techniques or magnetic sphincter augmentation.

Defining What is a Failed Antireflux Operation

Surgeon Judgement in Patient Selection. Our purpose is not to review the diagnostic evaluation of the patient with symptoms of GERD or a hiatal hernia, but simply to emphasis that when these steps are not followed, a patient who could have easily been properly diagnosed will either undergo an operation that was doomed to not alleviate their symptoms or was sentenced to not undergo a potentially symptom-improving operation [2]. Such misdiagnoses include that the patient's symptoms were not related to pathological acid reflux (e.g., functional heartburn, extra-esophageal pathology, etc.), or that the patient had other underlying esophageal motility dysfunction (e.g., achalasia, ineffective esophageal motility, etc.). Some preoperative symptoms are potential predictors of poor post-operative outcomes, such as day-time, upright reflux symptoms and pre-procedure dysphagia. The patient had other gastrointestinal motility dysfunction exacerbating symptoms (e.g., gastroparesis, irritable bowel syndrome, esophageal hypersensitivity). In addition to these pathophysiological etiologies, patients may harbor psychological causes for persistent or new post-operative symptoms. For example, patients with underlying psycho-emotional disorders (e.g., anxiety, depression, chronic pain syndromes, fibromyalgia, etc.) have been shown to be prone to persistent or new symptoms [3]; although those with minor psychological conditions are less so [4].

Lastly, the wrong fundoplication may have been chosen. Although there are some differences of opinion among surgeons as to whether fundoplications should be "tailored" to an individual patient or whether partial fundoplications should always be used [5], it is incumbent on the surgeon that due consideration be given as to the fundoplication to be used.

As most of these failures have to do with the surgeon not adhering to well defined standards of patient evaluation and surgical judgement which are addressed in other chapters in this book, nothing further will be said about them.

Anatomical Failures. Anatomic failures are defined as failures directly related to anatomic issues with either the fundoplication, hiatal hernia repair, or both. Fundoplication failures that will be addressed in this chapter include the poorly constructed/malpositioned/twisted fundoplication, the disrupted fundoplication, the slipped fundoplication, the tight fundoplication, the paraesophageal hernia and the

Table 1 Sources of antireflux surgery failures

Judgement failures	Anatomic failures	Physiologic failures
Failure to properly diagnose patient	Poorly constructed fundoplication	Fundoplication fatigue
Failure to identify preoperative symptoms prone to poor outcomes	Disrupted fundoplication	Progressive hiatal cicatricial stenosis
Failure to identify esophageal physiologic abnormalities	Slipped fundoplication	Bloating/inability to belch
Poor choice of fundoplication	Herniated fundoplication	Nausea/inability to vomit
Failure to identify other gastrointestinal abnormalities	Paraesophageal hernia	Gastroparesis
Failure to identify perioperative risk	Hiatal hernia recurrence	Functional gastrointestinal manifestations
Failure to identify psycho-emotional issues that may affect outcomes		

herniated fundoplication without hiatal hernia recurrence. Hiatal hernia repair failures include the herniated fundoplication, and the hiatal hernia recurrence with stomach or other organs herniated into the posterior mediastinum.

Physiological Failures. Physiological failures are defined as alterations in the patient's physiology which leads to adverse symptomatic consequences. These failures include recurrent GERD due to fundoplication "fatigue" (as opposed to anatomic fundoplication failures), bloating/inability to belch, nausea/inability to vomit, diarrhea, gastroparesis, and functional gastrointestinal outcomes which were the unintended and unpredicted result of the antireflux operation.

Table 1 lists the various types of antireflux surgery failures.

Anatomic Causes of Antireflux Surgery Failures

Figure 1 illustrates the most common types of anatomic failures. We will discuss each separately.

The Poorly Constructed Fundoplication. The principles of fundoplication construction are well known and discussed elsewhere in this book. The constructions errors made are related to not placing the fundoplication on the lower esophagus at and just superior to the gastroesophageal junction (the "malpositioned" fundoplication in Fig. 1), use of a portion of the greater curvature of the stomach inferior to the fundus, twisting of the fundoplication as it is brought posterior to the esophagus, and angulation of the fundoplication so that it "kinks" the gastroesophageal junction. Another type of poorly constructed fundoplication is the "too tight" fundoplication. This is

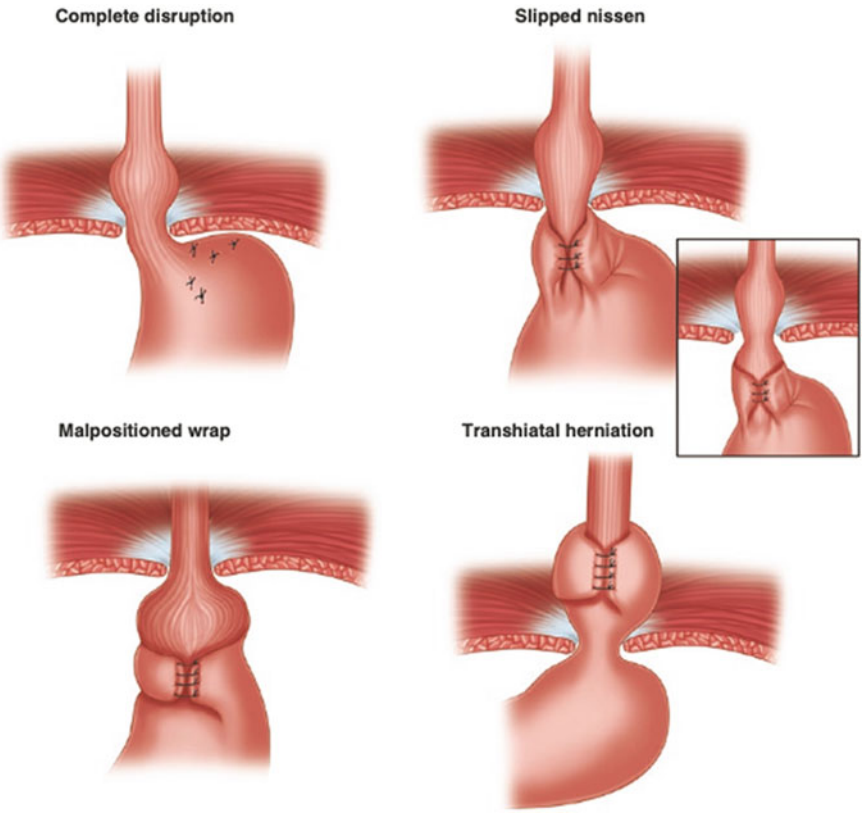

Fig. 1 Types of anatomic failures (From foregut surgery: achalasia, gastroesophageal reflux disease and obesity. Editors Marco G. Patti, Marco Di Corpo, Francisco Schlottmann. Spinger 2020)

a result of not allowing for enough fundus to construct a "floppy" fundoplication. It should be noted that a randomized, controlled trial with over 20 years of follow-up has shown that division of the short gastric vessels are not essential to creating such a wrap routinely [6], but, nevertheless, may be necessary occasionally depending on the surgeon's judgment. These construction errors will lead to persistent symptoms of GERD, dysphagia, bloating, nausea, inability to belch, and/or inability to vomit, or some combination of these symptoms.

In addition to fundoplication construction errors, errors in closure of the hiatal hernia defect can also lead to problems. The hernia defect typically needs to be repaired by approximating the left and right hiatal crura posteriorly, and occasionally anteriorly, of the esophagus such that it is neither too tight around the esophagus, nor too loose. This requires some judgement and the proper techniques discussed elsewhere in this book. Needless to say, a too tight closure will lead to dysphagia, while a too loose closure risks a herniation of the fundoplication or other intra-abdominal contents into the posterior mediastinum.

The Disrupted Fundoplication. A "disrupted" fundoplication is defined as when the sutures holding the wrap in place become untied, broken or pull through the tissue such that the fundoplication no longer functions as a competent sphincter (e.g., the "complete disruption" illustration in Fig. 1). This can be a cause of early or late failure following antireflux surgery. This early failure is generally thought to occur after an episode of increased intra-abdominal pressure causing tearing of suture resulting loosening of the wrap or complete breakdown of the fundoplication. If the patient reports an acute episode of retching or trauma it is best to investigate their anatomy with a contrasted swallow study. Within of few days of the index operation, a disrupted wrap may be safely fixed with reoperation. If this occurs further than few days after the index procedure, it is safest to wait 6–12 weeks before attempting reoperation.

The Slipped Fundoplication. A "slipped" fundoplication is defined as a fundoplication which was placed in the proper position at the gastroesophageal junction "moved" inferiorly so that the wrap is now encircling the proximal stomach (or, more likely, the proximal stomach moved superiorly through the fundoplication) (see "slipped Nissen" in Fig. 1). This can lead to a number of symptoms including recurrent heartburn, dysphagia, upper abdominal/lower chest pain and/or bloating. Timing of repair is similar to the disrupted fundoplication.

The Herniated Fundoplication with and without Hiatal Hernia Recurrence. A "herniated" fundoplication is defined as an intact fundoplication migrating superior to the esophageal hiatus into the posterior mediastinum (see "transhiatal herniation" in Fig. 1). This can occur with or without recurrence of the hiatal hernia—that is, the hiatal orifice can be of normal size with the repair intact, or the hiatal opening can be enlarged either because of disruption of the suture repair or progressive widening of the hiatus. As with a slipped fundoplication, symptoms can include recurrent heartburn, bloating, dysphagia or upper abdominal/lower chest pain. Timely of repair is similar to a disrupted fundoplication.

The Paraesphageal Hernia with and without Hiatal Hernia Recurrence. A paraesophageal hernia can occur after antireflux surgery when a portion or the stomach, usually the greater curvature, or some other intra-abdominal organ herniates through the hiatus along side (hence, "para") to the esophagus. This can occur with or without recurrence of the widening of the hiatal opening. In fact, when the hiatal repair remains intact, the risk of incarceration and strangulation of the herniated structure is much higher. These hernias can be type II (with the gastroesophageal junction and fundoplication still inferior to the hiatus in the abdomen), type III (with the gastroesophageal junction with or without an intact fundoplication migrated into the posterior mediastinum), or type IV (with some intra-abdominal organ other that the stomach in the hernia). These can also present with the same symptoms as the other types of anatomic fundoplication failures with the added risk of incarceration or strangulation.

Causes of Hiatal Hernia Recurrence. There are two basic mechanism of hiatal hernia recurrence. First is disruption of the hiatal repair either because of suture failure or

tension causing the suture to pull through the hiatal tissue. The other is progressive widening of the hiatus due to persistent transdiaphragmatic pressure leading to strain on the tissue, eventually permanently distorting the hiatal tissue [7].

Physiologic Causes of Antireflux Surgery Failures

Fundoplication "Fatigue". Following an even well performed antireflux surgery in a well selected patients, with these patient's experiencing significant improvement in their reflux symptoms, many of these patients will experience recurrence of their GERD symptoms. Some report over 50% of patients will resume proton pump inhibitors 15 years after antireflux surgery [8]. One theory with late recurrence of symptoms is that with time the wrap tends to "fatigue" or loosen around the lower esophagus allowing reflux of gastric fluid into the esophagus.

Hiatal Stenosis. Hiatal stenosis caused by excessive scar formation constricting the esophagus following antireflux surgery is one cause of post-operative dysphagia that can be difficult to differentiate. Although esophagography and esophagoscopy can both identify a stenosis, whether this is due to a too tight fundoplication or a hiatal stenosis generally cannot be determined. Sometimes, only upon reoperation can this cause be identified. The stenosis can be relieved by creating incising through the scar tissue at the anterior hiatus.

Gastroparesis. Gastroparesis is a chronic digestive disorder commonly defined by its presenting symptoms including nausea, vomiting, bloating and abdominal pain. While its pathogenesis is poorly understood, it is thought to result due to a disturbance in gastric autonomic innervation. Commonly this occurs due to diabetes, surgical compromise of the vagus nerve, or can be idiopathic. Patients with gastroparesis can be difficult to differentiate from symptomatic GERD, and in fact, gastroparesis may contribute to GERD symptoms through gastric distention causing transient LES relaxation, stimulation of gastric acid due to food residue and increased esophageal reflux due to increased gastric volume and pressure. For the purpose of this discussion, gastroparesis following antireflux surgery is thought to be due to vagal nerve injury and can be a significant cause for adverse symptoms like bloating, nausea, and vomiting. Comparing preoperative and post-operative gastric emptying studies can assist in diagnosis.

Bloating/Inability to Belch. Gas-Bloat syndrome is associated with the reduced ability to belch after fundoplication as well as increased flatulence and bloating. Several decades ago, when it was common to construct "long" "tight" fundoplications, the adage that "Nissen fundoplications turn belchers into bloating" was generally accepted. These issues generally occur immediately after surgery and improves weeks to months after. When symptoms improve over time, it is thought to be due to the post-operative inflammation and intact fundoplication. Additionally, it has been found that people with severe GERD symptoms have increased habits of

aerophagia. Pre-operatively this habit of excessive swallowing saliva and air appears to be performed to force gastric acid back into the stomach. The air then escapes through the patient's loose lower esophageal sphincter. After antireflux surgery with reinstitution of a competent lower esophageal sphincter, aerophagia causes excessive stomach distention and patient's no longer have the ability to allow the air to escape contributing to abdominal bloating and discomfort as well as increased flatulence. With retraining techniques and time these symptoms tend to improve.

Nausea/Inability to Vomit. Most nausea related to antireflux surgery is probably related to gastroparesis, although this might not necessarily be the case. In addition, this is a different issue compared to transient postoperative early satiety which is related to loss of gastric accommodation. Persistent nausea is overall uncommon, but a vexing issue. Inability to vomit is generally related to a poorly constructed fundoplication, usually a wrap that is too tight. However, many surgeons view this as a natural consequence of the operation and do not consider it an adverse event. Nevertheless, many patients do find this outcome very disturbing, so the surgeon, at a minimum, should counsel the patient of its potential occurrence.

Diarrhea. Post-operative diarrhea can significantly affect a patient's quality of life and occurs not uncommonly following antireflux surgery. Proposed mechanisms for diarrhea after antireflux include bacterial overgrowth following vagal injury and subsequent delayed gastric emptying as well as on the opposite spectrum, a form of dumping syndrome with accelerated gastric emptying and gut transit time may also lead to the observed diarrhea. Others have hypothesized that the alteration of the patient's diet (liquids or easily digested foods) following antireflux surgery may be enough to explain the noted post-operative diarrhea.

Postoperative Functional Gastrointestinal Disorders. Many patients with GERD will also have other functional disorders, such as irritable bowel syndrome. These syndromes may be further exacerbated by the antireflux operation.

Evaluation of the Patient with Recurrent Symptoms After a Fundoplication

When evaluating a patient with "recurrent symptoms" it is important to perform a thorough history, physical exam and work up to precisely delineate the etiology of their symptoms. Are their symptoms the exact same as before surgery or has there been subtle changes? Over what time period have these symptoms recurred? These types of questions can allow one to not only narrow down the etiology but also help elucidate the best way to approach fixing it.

Management/Treatment

For the patient who has undergone antireflux surgery without desired symptom improvement, recurrence of symptoms, or intolerable side effects of the procedure an individualized approach to their symptomology is essential. For the patient with recurrent symptoms, following a full re-evaluation as to the etiology of failure, a discussion with the patient of medical and surgical options for management can be profitably undertaken.

If surgical management is pursued, the patient should be well counseled that recurrent antireflux surgery does have an increased risk profile. Reoperative antireflux operations have a higher complication rate, risk of conversion to open, longer operative times, and increased lengths of stay compared to the primary procedure [9]. The feared complication of iatrogenic esophagogastric perforations occurred in 11–25% of reoperations, compared with < 1% in primary operations [10]. In addition, reoperations have a higher rate of splenic injury and pneumothorax. Post-operative rates of dysphagia and gas bloat syndrome do not appear to be much different in reoperative cases. Despite these risks, patient satisfaction with these operations remains high at 89% and recurrence of symptoms in about 13% of patients at 3 months, but this is reported to increase with each subsequent reoperation [11].

In regards to choice of antireflux operation for a failed primary surgery, a similar approach can be taken to choose of operation in the initial surgery. In cases of severe esophageal dysmotility and partial fundoplication can be considered, although there is some data that a Nissen fundoplication can be performed in esophageal dysmotility without worsening of dysphagia. In patients with good esophageal motility, magnetic sphincter augmentation may provide a more durable repair than a fundoplication [12]. If inadequate esophageal length is encountered at the time of reoperation, a lengthening procedure will be required. The true incidence of short esophagus with less than 3 cm of intra-abdominal esophagus following mediastinal mobilization is unknown but thought to be about 4% of the time [12]. This is expected to be higher in patients who have previously undergone antireflux surgery with recurrent hiatal hernia although the exact rate is unknown. Therefore, reoperative antireflux operations are expected to require a Collis gastroplasty at a higher rate than initial operations.

Medical/Conservative Care for Nonoperative Adverse Events

Medical management of side effects such as mild dysphagia or gas-bloat syndrome help improve quality of life and patient satisfaction with a reflux operation. Mild dysphagia following any antireflux surgery is expected and worst in the 6 weeks immediately post-operatively due to edema. Patients should be counseled on dietary modifications such as soft foods, small meals, sitting upright and liquid intake

with solids to improve symptoms. In certain patients with persistent and significant dysphagia following dietary modifications, esophageal dilation or reoperation may be needed to improve the dysphagia. For gas-bloat syndrome, symptoms are often worst shortly following surgery and improve greatly or resolve a year later. This is thought to be due to decreased aerophagia that occurs during this time. In addition to time, symptoms can be improved with reduction in the consumption of gas producing foods or carbonated beverages.

Conclusions

Antireflux surgery is not always associated with successful outcomes. A failed antireflux procedure might be related to poor surgeon's judgement, anatomical failures, and/or physiological failures. In this chapter, diverse types of antireflux surgery failure are thoroughly discussed along with treatment alternatives for these patients. Patients with persistent or recurrent symptoms after antireflux surgery should undergo a thorough diagnostic work up to precisely delineate the etiology of the failure and plan the optimal treatment.

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Gastroesophageal Reflux Disease, Barrett's Esophagus and Beyond

Sarah E. Kim, Manuela Monrabal Lezama, and Francisco Schlottmann

Abstract Barrett's esophagus (BE) is defined as the presence of at least 1 cm of metaplastic columnar epithelium that replaces the stratified squamous epithelium normally lining the distal esophagus. Around 10% of patients affected by GERD will eventually develop BE. Patients with BE without dysplasia require endoscopic surveillance. For patients with dysplasia, endoscopic eradication therapies are recommended. Antireflux surgery should not be considered an antineoplastic therapy in patients with BE, and thereby indications for fundoplication remain the same as for GERD patients without BE. New diagnostic and therapeutic technologies are being developed to improve BE management.

Keywords Barrett's esophagus · Gastroesophageal reflux disease · Dysplasia · Radiofrequency ablation · Endoscopic surveillance

Introduction

Gastroesophageal reflux disease (GERD) is a pathological condition characterized by the chronic retrograde flow of gastric contents, leading to the manifestation of recurrent and distressing symptoms such as heartburn and regurgitation, as well as GERD-specific complications. Although the real incidence of GERD is unknown due to its underdiagnosis, it is estimated that this disease affects up to 20% of the adult population in the US, and its prevalence is increasing worldwide [1, 2]. High urbanization levels may cause more GERD in North America and Europe compared to Asia, Latin America, and the Caribbean [3].

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GERD affects patients' quality of life and is linked with higher chances of esophagitis, esophageal strictures, Barrett esophagus, and esophageal adenocarcinoma. The risk of developing GERD is increased by obesity, smoking, and genetics. While common symptoms are enough to diagnose GERD, uncommon symptoms like dysphagia and chronic cough may also appear [4].

GERD can be treated with lifestyle modifications, medication, or surgery. Weight loss and quitting smoking may be beneficial. Patients with typical GERD symptoms can be treated empirically with proton pump inhibitors (PPIs). If there is no response or unclear diagnosis, endoscopy, manometry, and pH monitoring are recommended. Furthermore, endoscopy is recommended for patients with warning symptoms of malignancy (e.g., bleeding, weight loss, dysphagia) or other risk factors for esophageal adenocarcinoma such as obesity, older age or male sex [4–6]. Laparoscopic antireflux surgery is an effective treatment alternative for selected patients after thorough and objective assessments. There are emerging endoscopic and less invasive surgical techniques that may reduce the need for long-term PPI and fundoplication, but their long-term safety and efficacy have yet to be scientifically established [5–7].

While medical therapy has shown excellent results in controlling GERD symptoms, they have not averted the malignant complications of this disease. Barrett's esophagus (BE), a condition characterized by the replacement of the normal esophageal lining with columnar epithelium, affects about 10% of individuals with GERD and approximately 1.2–5.6% of those without, with an overall incidence of 1% worldwide [7]. It is well-established that male gender, advanced age, and tobacco use are prominent factors that increase the risk of developing BE [1, 4, 7]. The histopathological progression of BE extends from metaplasia to dysplasia and has the potential to advance to adenocarcinoma in the absence of treatment. The annual incidence of esophageal adenocarcinoma (EAC) in individuals with BE is estimated to be around 0.2–0.5%. EAC, linked to chronic GERD symptoms, is one of the fastest rising cancers in the last 30 years. Despite recent improvements in treatment, survival rates remain low, with an overall 5-year survival of less than 20% [7].

Managing BE entails primarily the administration of acid-suppressive medications to reduce GERD symptoms and conducting surveillance endoscopy every 3–5 years. In the case of individuals with BE and dysplasia or early-stage cancer, endoscopic therapy involving resection and ablation is needed.

Pathophysiology

Barrett's esophagus has been traditionally defined as the presence of at least 1 cm of metaplastic columnar epithelium that replaces the stratified squamous epithelium normally lining the distal esophagus. Currently, the presence of intestinal metaplasia—columnar epithelium with goblet cells—is also needed for the diagnosis of

BE in the USA [6]. The reason that intestinal metaplasia is mandated in the definition of BE is related to the higher risk of developing cancer in columnar epithelium containing goblet cells as compared to columnar epithelium without intestinal metaplasia [8, 9]. Currently, the exact molecular pathway leading to this transformation is unknown.

Studies have shown that acid damage produces dilated intercellular spaces in the esophageal epithelium. This process reduces transepithelial resistance and increases permeability to allow molecules (as large as 20 kD) to diffuse across the epithelium, thus initiating a cascade of loss of cellular osmoregulation, edema, and eventual cell death [10, 11]. Cell death is counterbalanced by tissue reparative processes, including restitution and replication. Additionally, cells are normally under transition from columnar to squamous cells through activation of prosquamous and inactivation of procolumnar homeobox genes. This normal process, however, may also be reverse by reactivation of the opposite homeobox genes. The acid exposure may also cause a phenotypic change as columnar epithelium may have better adaptability to the acidic environment. Despite these potential pathways, the exact origin of BE remains unclear with several hypotheses including migration and differentiation of gastric cardia stem cells, differentiation of stem cell in the esophageal crypts, and migration of stem cells from the bone marrow [11–13].

While the transition between squamous and columnar epithelium likely occurs within a few years, the development of intestinal metaplasia may take over 5–10 years [14]. Once the columnar epithelium is established, the change continues by two possible pathways: "gastric differentiation" and "intestinal differentiation". Gastric differentiation is the formation of parietal cells within the glands. Intestinal differentiation is the formation of goblet cells within the columnar epithelium, which has potential for further progression into adenocarcinoma.

The inciting event that is believed to cause intestinal differentiation involves multiple exposures to noxious luminal contents, rather than to acid reflux only. Bile acids are one of the noxious luminal content exposures that were seen in previous studies to have a role in the development of intestinal metaplasia [15]. It has been previously hypothesized that in mildly acidic environments (pH 3–5), bile acids can become nonionized and cross the cell membrane. Once they cross the membrane into neutral pH (pH 7), they become ionized again and are unable to cross back, causing mitochondrial injury, cellular toxicity, and mutagenesis [16]. Bile acids, additionally, may also be related to the activation of nuclear factor kappa B (NF-kB) with production of caudal-related homeobox 2 (Cdx2) protein that leads to production of MUC2, an intestinal-type protein seen in BE [17].

It was found that COX-2, an enzyme that plays a major role in inflammatory responses, has a substantially higher expression in human BE tissues than that in adjacent squamous cells and control tissues. Also, its presence is considerably higher in EAC tissues. Inhibition of NF-κB in esophageal squamous cells inhibits cell proliferation, followed by decreased COX-2 expression. Inhibition of NF-κB expression in EAC cells reduces the expression of COX-2 and CDX-2 and improves apoptosis of EAC cells. This suggests that COX-2 may be involved in the development of BE [18].

Diagnosis of Barrett's Esophagus

Patients are screened for BE based on risk factors such as presence of hiatal hernia, chronic GERD, history of cigarette smoking, and confirmed history of first degree relative with BE or esophageal adenocarcinoma. Patients undergo screening upper endoscopy and at least 4 biopsies are obtained for every 2 cm area of suspected BE or a total of 8 biopsies. Any potential diagnosis of dysplasia seen on initial tissue imaging is confirmed by a second pathologist [6].

More advanced endoscopic imaging techniques such as electronic chromoendoscopy or laser endomicroscopy can be performed for optimized visualization of the mucosa that may increase the detection of dysplasia. Electronic chromoendoscopy can increase the detection of dysplasia with advanced imaging of mucosal and vascular patterns [19]. Confocal and volumetric laser endomicroscopy have also shown the ability for more enhanced imaging and wider sampling areas [20]. Other future directions for diagnosis may include Cytosponge, a non-endoscopic screening test with esophageal sampling via sponge, as well as biomarkers [21].

There are four categories of dysplasia: no dysplasia, indefinite for dysplasia, low grade dysplasia (LGD), and high-grade dysplasia (HGD). Patients with non-dysplastic BE have very low risk for malignant progression. A meta-analysis conducted by Desai and colleagues reported that the pooled annual incidence of adenocarcinoma in this cohort was 0.33% (95% CI 0.28–0.38) [22]. For patients with LGD, a pooled annual incidence of 0.5% for adenocarcinoma (95% CI 0.3–0.8) was described [23]. Patients with HGD present an annual incidence of adenocarcinoma of 7% (95% CI 5–8) [24].

The grading of dysplasia is often inaccurate and subjective, particularly in centers lacking expert gastrointestinal pathologists. Pathologists frequently disagree on the diagnosis of LGD, leading to substantial heterogeneity in reported outcomes. Studies have reported progression rates ranging from 0.9 to 26.5% per patient-year for LGD, which is a challenging issue [24–28]. This was recently confirmed in an international study of 51 pathologists who reviewed 55 digitized biopsies, in which excellent concordance among pathologists was seen for non-dysplastic BE (NDBE) (79%) and HGD (71%), but considerably less for LGD (42%) and indefinite for dysplasia (23%) [29]. Thus, according to current guidelines, patients diagnosed with BE and dysplasia should undergo a review by two pathologists with expertise in gastrointestinal pathology, as there is a significant amount of variability in interpretation [6].

Management of Barrett's Esophagus

According to the American College of Gastroenterology, current management of BE is determined by the presence of dysplasia. For patients with BE without dysplasia, it is recommended to undergo repeat endoscopic surveillance at 3–5 years, depending

on the length of the BE. For BE indefinite for dysplasia, endoscopy should be repeated after optimization with acid suppression medication in 3–6 months. For BE with LGD, either endoscopic therapy (such as radiofrequency ablation) or repeat endoscopic surveillance every 12 months are valid alternatives. Patients with HGD or intramucosal carcinoma (T1a) should undergo endoscopic therapy [6]. Lastly, patients with submucosal cancer (T1b) should be referred for esophagectomy.

Figure 1 suggests an algorithm for the management of BE.

Endoscopic Therapies

Endoscopic eradication therapy (EET) has transformed the management of patients with BE-related dysplasia/neoplasia, providing a minimally invasive treatment approach that avoids the morbidity and mortality associated with esophagectomy [30]. EET relies on the low lymph node metastasis risk in patients with BE with high-grade dysplasia and intramucosal carcinoma [31]. Contemporary practice involves endoscopic resection of visible lesions in the BE segment, followed by ablative techniques such as radiofrequency ablation (RFA) and cryotherapy for complete eradication of dysplasia and intestinal metaplasia.

I. Photodynamic Therapy

Photodynamic therapy (PDT) involves the use of intravenous agents to make the esophageal mucosa sensitive to light. Light is applied to cause injury, with the level of tissue penetration determined by the agent and light wavelength [32]. PDT works by inducing apoptosis and producing reactive oxygen species that directly damage cancer cells [33]. It also has indirect effects by modifying tumor blood supply and boosting the patient's immune response [34]. PDT acts selectively, only at the site where the light is provided, thus accounting for fewer adverse effects than systemic treatment. This method has been proven to completely eradicate HGD and decrease occurrence of EAC; however, it seems to have a lower rate of complete histopathological remission of BE in comparison to RFA [35]. Complications of PDT include esophageal strictures, fistulization, and phototoxicity [32]. These findings led to a decline in the utilization of this method for the treatment of BE or early esophageal cancer, in favor of other ablative interventions.

II. Radiofrequency Ablation

Radiofrequency ablation (RFA) employs electrodes to apply thermal energy, causing protein coagulation and cell necrosis. RFA enables precise and consistent depth of ablation at 0.5 mm, eliminating the affected mucosal tissue [36]. Frequently, several sessions of treatments may need to be done every few months depending on the length and tissue response. Studies have demonstrated that RFA resulted in less progression of BE-LGD and similar survival rates and EAC-related deaths compared to esophagectomy in patients with HGD/intramucosal EAC [28, 30]. A meta-analysis conducted by Qumseya reported a rate of adverse events with RFA of 8.8%. These

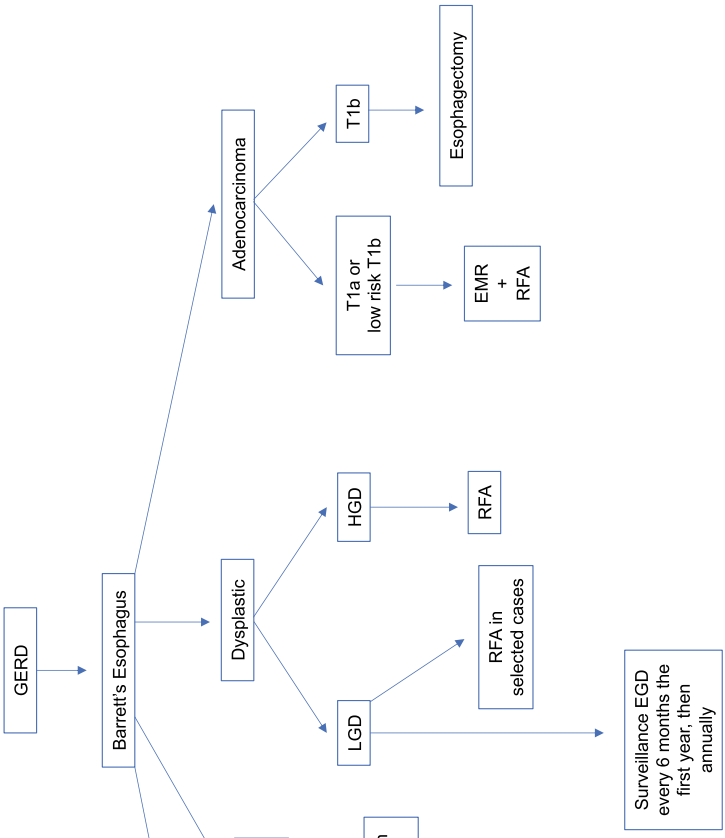

Fig. 1 Algorithm for the management of Barrett's esophagus (GERD: Gastroesophageal reflux disease; BE: Barrett's esophagus; EGD: esophagogastroduodenoscopy; LGD: low-grade dysplasia; HGD: high-grade dysplasia; RFA: radiofrequency ablation; EMA: endoscopic mucosal resection)

events include 5.6% of patients developing strictures, 1% having bleeding, and 0.6% developing perforation [13]. Due to the extensive evidence of its efficacy in multiple studies, RFA has become the most commonly utilized method of ablation [37].

III. **Cryoablation**

Cryotherapy is a technique that uses freezing and thawing to induce damage tissue. The administration of liquid nitrogen at −196° causes rapid cooling which disrupts membranes, denatures proteins, and dehydrates cells. This is followed by slow thawing that leads to hypoxia and necrosis of targeted tissue [38, 39]. Cryotherapy, unlike RFA, leaves the overall esophageal architecture intact and has been thought to be less likely to cause strictures. Preliminary research suggests that spray cryotherapy can achieve dysplasia and BE eradication rates comparable to RFA but with less postprocedural pain [40, 41]. Additionally, a meta-analysis has demonstrated that cryoballoon and spray cryotherapy may be effective for patients who did not respond to initial RFA treatment, but further research is needed to confirm this [42].

IV. **Endoscopic Mucosal Resection**

Currently, endoscopic mucosal resection (EMR) is the preferred treatment choice for patients with intramucosal adenocarcinoma without risk factors (well-differentiated tumors without lymphovascular invasion), given the low risk of lymph node metastasis in such cases [37]. Once a complete resection of the T1a adenocarcinoma is performed, the entire segment of BE should be treated with ablation therapy (RFA). Prior studies including T1a tumors have shown high rates of 5-year survival. Moreover, in patients with BE, EMR eradicated neoplasia and BE in 98.8% of patients who completed therapy per-protocol. The most common complication was the development of strictures (41.5%), which are often properly managed with dilation [43].

Esophagectomy has traditionally been recommended for T1b EAC due to high risk of lymph node metastases [44]. However, endoscopic eradication therapy (i.e. endoscopic submucosal dissection) may be an alternative for T1b EAC with superficial submucosal invasion and low-risk features [45–48]. High-risk histology is best treated with esophagectomy, unless patient is a poor surgical candidate. Discussion with a multidisciplinary team is always recommended for treating these patients.

Surgical Therapies

I. **Anti-reflux Surgery**

Proton pump inhibitors have no impact on reflux episodes; however, they do effectively modify the pH levels. Anti-reflux surgery, on the other hand, reinstates the competence of the gastroesophageal junction by impeding all gastric reflux (both acid and bile reflux) [49, 50]. Anti-reflux surgery is a treatment modality that can be effective for both GERD and BE, and is an option for patients who persist with symptoms despite medical therapy. Although several studies demonstrate a trend towards

anti-reflux surgery preventing malignant transformation of BE, the available evidence is inconclusive [51–53]. Due to lack of data and well-conducted randomized trials, anti-reflux surgery should not be recommended to prevent malignant transformation of BE. Overall, indications for anti-reflux surgery should be the same as for other GERD patients [54, 55].

II. **Esophagectomy**

Esophagectomy is the current treatment modality for medium to high risk T1b tumors. An esophagectomy removes the entire segment of Barrett's esophagus, adenocarcinoma, and regional lymph nodes. Additionally, an esophagectomy can also be considered for patients with BE refractory to endoscopic interventions or at higher cancer risk.

Conclusions

Around 10% of patients affected with GERD will eventually develop BE. Patients with BE without dysplasia require endoscopic surveillance. For patients with dysplasia, endoscopic eradication therapies are recommended. Antireflux surgery should not be considered an antineoplastic therapy in patients with BE, and thereby indications for fundoplication remain the same as for GERD patients without BE. New diagnostic and therapeutic technologies are being developed to improve BE management.

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Gastroesophageal Reflux Disease. From Heartburn to Lung Fibrosis and Beyond

Fernando A. M. Herbella, Francisco Schlottmann, and Marco G. Patti

Abstract Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive form of usual interstitial pneumonia of unknown origin which leads to pulmonary fibrosis. While the pathogenesis of IPF is probably multifactorial, there is evidence today that GERD, through episodes of micro aspiration, might play a role in the genesis and/or progression of the disease. In addition, it seems that GERD might also be implicated in the pathogenesis of the bronchiolitis obliterans syndrome (BOS), a common cause of rejection of the transplanted lungs. This chapter will review the evidence that links GERD to IPF and GERD to the BOS, discussing a possible therapeutic approach that might stop the progression of IPF or avoid the post-transplant BOS.

Keywords Gastroesophageal reflux disease · Regurgitation · Aspiration · Idiopathic pulmonary fibrosis · Pepsin · Bile acids · Bronco-alveolar lavage · Lung transplantation · Brochiolitis obliterans syndrome

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive form of usual interstitial pneumonia of unknown origin which leads to pulmonary fibrosis. IPF affects about 40,000 individuals every year in the United States, and it is an irreversible disease. Median survival after the diagnosis is between 3 and 5 years, with approximately 80% of all deaths caused by respiratory failure. Because pharmacological therapy is mostly ineffective, lung transplantation offers the only chance of survival.

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The pathophysiology of IPF involves recurrent epithelial injury and subsequent aberrant fibroblast proliferation. While the pathogenesis of this disease is probably multifactorial (genetic factors and environmental factors such as tobacco smoke), there is evidence today that gastroesophageal reflux disease (GERD) might play a role in the genesis and/or progression of the disease through repeated episodes of micro aspiration of gastric contents. In addition, it seems that GERD might also be implicated in the pathogenesis of the bronchiolitis obliterans syndrome (BOS), a common cause of rejection of the transplanted lungs.

GERD and IPF

GERD is quite common in patients with IPF. A previous study compared the reflux profile between 40 IPF patients, 40 non-IPF patients with interstitial lung disease and 50 volunteers [1]. IPF patients had significantly higher esophageal acid exposure, number of acid and weakly acidic reflux episodes, and proximal reflux compared to non-IPF patients and volunteers. Pulmonary high-resolution CT scores correlated with reflux episodes in both the distal and proximal esophagus. In addition, IPF patients had more bile acids and pepsin in the bronchoalveolar lavage fluid than non-IPF patients. These findings suggest that IPF patients are at high risk of aspiration of gastric contents, advocating the need for effective anti-reflux therapy [1]. Raghu et al. [2] studied by esophageal manometry and pH monitoring 65 consecutive patients with well-defined IPF. The prevalence of abnormal acid reflux in IPF patients was 87%, with 76 and 63% demonstrating abnormal distal and proximal esophageal acid exposure, respectively.

Patti and colleagues studied 18 patients with IPF [3]. Pathologic reflux was detected by pH monitoring in 12 patients (Group A, 66%). When compared to IPF patients who had a normal reflux profile (Group B), group A patients had more frequently a hypotensive lower esophageal sphincter (LES; 75% vs. 0%), and abnormal esophageal peristalsis (75% vs. 34%). In addition, barium swallow showed a hiatal hernia in 75% of group A patients and in none of the patients in group B. In 50% of group A patients acid refluxed all the way to the upper esophagus (20 cm above the LES). Similar results by ambulatory dual probe pH monitoring (5 and 20 cm above the LES) have been documented in IPF patients awaiting lung transplantation, with pathologic distal and proximal reflux in 78 and 33% of patients, respectively [4].

The presence of a hiatal hernia might contribute to the existence of abnormal reflux in patients with IPF. Noth et al. [5] evaluated the prevalence of hiatal hernia by blinded multidetector CT in patients with IPF and compared to that in patients with asthma and COPD. They found that hiatal hernia was more common in IPF (39%) than COPD (13.3%) or asthma (16.7%). In IPF patients, hiatal hernia correlated with a higher DeMeester score.

Based on the findings of these studies, it seems that factors that play a role in the genesis of pathologic reflux in IPF patients include the presence of a hiatal hernia,

a hypotensive LES and abnormal esophageal peristalsis. In addition, an increased transdiaphragmatic pressure gradient might contribute, particularly for determining proximal esophageal reflux [6, 7].

While the findings of the studies described above show a high prevalence of pathologic reflux in IPF patients, the mechanism and relationship of GERD to causality, progression, and treatment of IPF is still uncertain. An answer might come from the treatment of GERD to determine if abolishing the abnormal reflux may influence the progression of the disease once the diagnosis is established. Considering the elements that play a role in the abnormal reflux, it is doubtful that proton pump inhibitors (PPIs) can be an effective treatment as it is known that while they can suppress the acid production by the parietal cells, therefore changing the pH of the refluxate, they are not able to stop the reflux through an incompetent LES. Only a fundoplication, by restoring the competence of the LES, can control any type of reflux, acidic or non-acidic.

As of today, there are in the literature only a few retrospective studies and only one multicenter, prospective, and randomized trial assessing the effect of anti-reflux treatment in IPF patients with GERD [8–11]. If indeed it is true that GERD is linked to IPF, effective anti-reflux therapy should be able to alter the natural history of the disease.

Linden et al. [8] compared the outcome of 14 patients with GERD and IPF on the lung transplant list who underwent laparoscopic anti-reflux surgery (LARS) with that of a control group of 31 patients with GERD and IPF on the transplant list who did not undergo LARS. They found that in patients with IPF who underwent LARS there was stabilization of the oxygen requirement, whereas controls had a significant deterioration in oxygen requirement. Hoppo et al. [9] evaluated 19 patients with GERD and end stage lung disease before lung transplant and found that 1 year after LARS the FEV1 improved in in 85% of them, and that episodes of pneumonia and acute rejection stabilized. More recently, Lee et al. [10] assessed the effect of anti-reflux treatment—PPI or Nissen fundoplication—in a large cohort of patients with IPF. The study cohort consisted of 204 patients with IPF from the University of California San Francisco and the Mayo Clinic in Rochester. Most patients were overweight and former or current smokers. Mean forced vital capacity (FVC) was 69% predicted and the diffusing capacity for carbon monoxide (DLCO) was 47% predicted. Symptoms of GERD were present in 34% of patients; 86 were treated with PPI and 17 with H2 blocking agents. Eleven patients had a Nissen fundoplication. The study showed that use of acid reducing medications or LARS was associated with lower high resolution CT fibrosis score and longer survival time in patients from both Institutions, suggesting that gastroesophageal reflux and micro aspiration may play an important role in the pathobiology of IPF.

To properly test the hypothesis that treatment of GERD in IPF could change the natural history of the disease by altering the progression, a prospective, randomized trial was designed—the WRAP-IPF trial [11]. In this phase II NIH trial, patients with IPF and GERD were recruited from 6 academic centers in the USA. The enrolled patients had abnormal acid exposure by 24-h pH monitoring and preserved FVC. Patients with FVC below 50% predicted, a history of an acute respiratory illness in the

past 12 weeks, a BMI > 35, and severe pulmonary hypertension were excluded. The primary endpoint was change in the FVC from randomization to week 48. Twenty-nine patients were randomly assigned to receive surgery and 29 to no surgery. All patients tolerated the LARS well with no complications. Eventually, 27 patients in the surgery group and 20 in the no surgery group had a FVC measurement after 48 weeks. The results showed that there was no difference between the two groups. Acute exacerbations, respiratory-related hospitalizations, non-elective hospitalization, and lung transplantation were less common in the surgery group but without statistical significance. In summary this long-awaited controlled trial in patients with IPF and acid reflux showed that LARS was safe and well tolerated but did not show that anti-reflux surgery significantly slowed the rate of FVC decline [11]. Unfortunately, this study was not able to answer the hypothesis because of many severe flaws. The study was very underpowered as 400 patients rather than 58 were required to achieve 90% power. In addition, the effect of LARS on FVC decline and clinical events in patients with IPF and GERD might have been reduced by the near universal use of anti-acid medications in the non-surgery group. Finally, when the authors did a post-hoc exploratory analysis of the primary endpoint using Lachin worst rank analysis (an approach that assumes that missing values are informative and reflect poor outcomes) the difference between groups was significant ($p = 0.01$) and favored the surgical group [11].

In 2022 the most recent guidelines for IPF of the American Thoracic Society and other international respiratory societies were published [12]. Considering the data of the retrospective studies, and the severe limitations of the WRAP-IPF trial, it was surprising that the guidelines recommended against the use of PPI or anti-reflux surgery in patients with IPF and GERD. This recommendation was based on a very low level of evidence.

Overall, we feel there is a subgroup of IPF patients in whom pathologic reflux is documented that might benefit from anti-reflux therapy, particularly before a lung transplant: these are patients in whom proximal reflux is documented by pH monitoring or impedance, and pepsin or bile acids are detected in the broncho-alveolar lavage fluid (BALF), suggesting that aspiration of gastric contents is occurring. LARS has been shown in multiple studies to be safe and effective in controlling pathologic reflux in IPF and should be performed in selected patients before their functional status deteriorates.

GERD and Lung Transplantation

Lung transplantation is an effective therapeutic option for patients with end-stage lung disease such as IPF, as it improves the quality of life and prolongs survival. However, it is linked to a five-year survival around 50% only, much lower than other solid organ transplants such as heart (75%) and liver (70%).

This low five-year survival is due to acute rejection and chronic rejection. Acute rejection occurs during the first year after transplant and includes acute cellular

rejection and lymphocytic bronchiolitis, both eventually associated with chronic rejection. Chronic rejection manifests as bronchiolitis obliterans (BO), a form of progressive airway obstruction resulting from macrophage and fibroblast infiltration which causes fibrosis and scar formation of the small airways (Fig. 1).

The clinical equivalent of the BO is the bronchiolitis obliterans syndrome (BOS), defined as a progressive decline in the forced expiratory volume in 1 s (FEV1). BOS is the major factor determining long-term survival as it affects most patients by 5 years, eventually causing death. Immune mediated lung injury, including cellular and humoral rejection, has been recognized as the leading cause of BOS. However, non-immune mechanisms such as ischemic reperfusion injury and infection may play a role.

GERD has also been recognized as a risk factor for the development of BOS through silent aspiration of gastric contents. Bile acids and pepsin (both markers of reflux and aspiration) have been demonstrated in the BALF of lung transplant patients. D'Ovidio et al. [13] investigated 120 patients after lung transplant and found that 20 (17%) had high concentrations of bile acids in the BALF. They also noted an association between the presence of bile acids and decreased surfactant and phospholipids, suggesting that aspiration of bile acids may have impaired the innate immunity of the allograft. In addition, they demonstrated that the highest concentrations of bile acids were found in 70% of patients with early onset (< 1 year after transplant) and most severe manifestations of BOS, suggesting a temporal and dose-related relationship [13, 14].

Elevated levels of pepsin (a proteolytic enzyme) have also been identified in the BALF of patients following lung transplantation [15]. Clearly, the finding of bile acids and/or pepsin in the BALF after lung transplant shows that micro aspiration of gastric contents into the tracheobronchial tree is occurring. While GERD is present in about 50–60% of IPF patients, it is even more common after lung transplant as it affects more than 2/3 of patients. Possible factors that might play a role in the increased incidence of GERD are a vagal nerve injury, delayed gastric emptying,

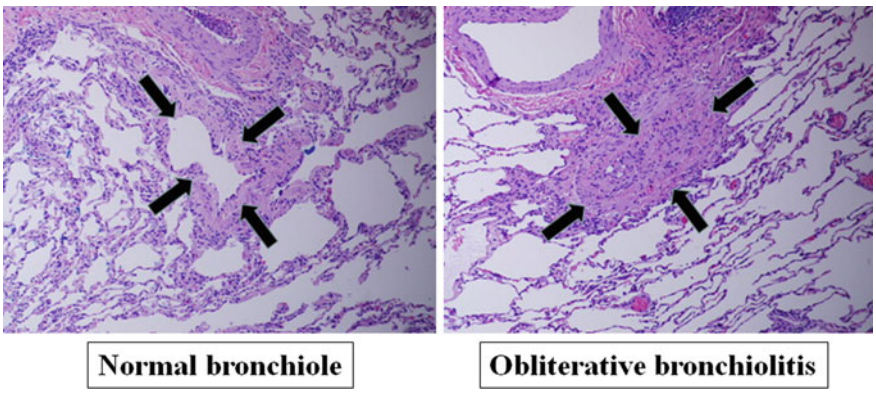

Fig. 1 Bronchiolitis obliterans

effects of immunosuppression medications, and changes in the intra-thoracic and intra-abdominal pressures.

Today it is considered standard of care in most centers where lung transplantation is performed to routinely test patients for GERD and perform a laparoscopic fundoplication before waiting for the onset of BOS. No prospective and randomized trial has ever been conducted and this approach is rather based on retrospective studies. Davis et al. [16] studied 128 patients who had esophageal function tests after lung transplantation. Abnormal pH studies were present in 93 patients (73%). Forty-three patients underwent fundoplication; of these 26 patients had BOS. After fundoplication, 16 patients had improved BOS, with 13 of these patients no longer meeting the criteria for BOS. In patients at least 6 months after lung transplantation and 6 months after fundoplication the FEV1 improved by an average of 24%. Overall actuarial survival was significantly better in patients who had either normal pH studies or who had fundoplication. Cantu et a. investigated if early fundoplication would prevent BOS and improve survival [17]. They found that patients who underwent early LARS had 100% freedom from BOS at 1 and 3 years compared to those who did not had LARS (96 and 60% at 1 and 3 years respectively). The difference in BOS translated in a difference in survival which was 100% at 1 and 3 years versus 92 and 76% in patients with no intervention. Hartwig et al. [18] subsequently showed that early LARS might preserve lung allograft function. They compared patients who had GERD and underwent LARS to patients with GERD and no intervention and demonstrated that in the non-intervention group there was a worse predicted peak and 1-year FEV1. The timing of the fundoplication is clearly important. For instance, Lo et al. [19] evaluated the impact of the timing of LARS (before and after lung transplantation) on early allograft injury and found that late LARS (> 6 months after transplant) resulted in increased risk of allograft injury compared to pre-transplant or early LARS (< 6 months).

Overall, we feel that every IPF patient should be evaluated early after lung transplant by esophageal manometry, dual probe pH monitoring and bronchoscopy with analysis of the BALF for pepsin or bile acids. LARS is safe and effective and should be performed early after the transplant. In selected patients with significant delay in gastric emptying a pyloroplasty should be added [20].

Conclusions

Selected IPF patients in whom pathologic reflux is documented might benefit from anti-reflux therapy. GERD has also been recognized as a risk factor for the development of BOS, a form of progressive airway obstruction in lung transplant recipients resulting from macrophage and fibroblast infiltration which causes fibrosis and scar formation of the small airways. Laparoscopic anti-reflux surgery is safe and effective and should be performed before or early after the lung transplant if GERD is diagnosed.

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