Chapter 3
Gastroesophageal Reflux Disease: Pathophysiology

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Abstract Gastroesophageal reflux disease (GERD) is a common disease with a variable prevalence ranging from 5 % in the Eastern population to 25 % in the West. Moreover, GERD incidence seems to be escalating.

Gastroesophageal reflux occurs daily in normal individuals (physiological reflux); however, it may become "a disease which develops when the reflux of stomach contents causes troublesome symptoms and/or complications" – or GERD – as defined by an International Consensus.

Keywords Gastroesophageal reflux disease • Pathophysiology • Acid reflux • Non-acid reflux • Esophageal manometry • Ambulatory pH

Introduction

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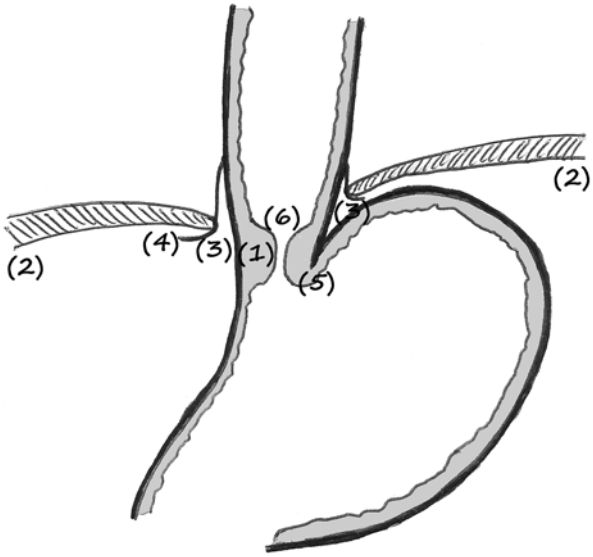

Fig. 3.1 Gastroesophageal barrier – natural antireflux mechanisms. The gastroesophageal barrier is a complex mechanism formed by different components: (*1*) the lower esophageal sphincter, which creates a high-pressure zone between the esophagus and the stomach; (*2*) the diaphragm, which acts as an external sphincter during rises in intra-abdominal pressure; (*3*) the abdominal portion of the esophagus, submitted to abdominal pressure; (*4*) the phrenoesophageal membrane, which acts transmitting the abdominal pressure high up in the mediastinum; (*5*) the angle of His, which separates between gastric fundus and cardia; and (*6*) the Gubaroff valve which represents the cushion effect of the esophageal mucosa at the gastroesophageal junction

Gastric hydrochloric acid has long been recognized as harmful to the esophagus; however, the gastroesophageal refluxate contains a variety of other noxious agents, including bile, pancreatic enzymes, and pepsin.

GERD pathophysiology is multifactorial and linked to a disbalance between the aggressiveness of the refluxate into the esophagus or adjacent organs and the failure of the esophagogastric barrier and protective mechanisms. This chronic pathologic backflow of gastroduodenal contents leads to a spectrum of symptoms, with or without tissue damage. The degree of the disease gravity depends on the frequency, duration, and quality of the exposure of the refluxate into the esophagus or adjacent organs.

This chapter reviews GERD pathophysiology.

Antireflux Mechanisms

The esophagogastric junction (EGJ) area has a specialized valve mechanism formed by the lower esophageal sphincter (LES) and abdominal esophagus, the diaphragm, the angle of His, the Gubaroff valve, and the phrenoesophageal membrane (Fig. 3.1).

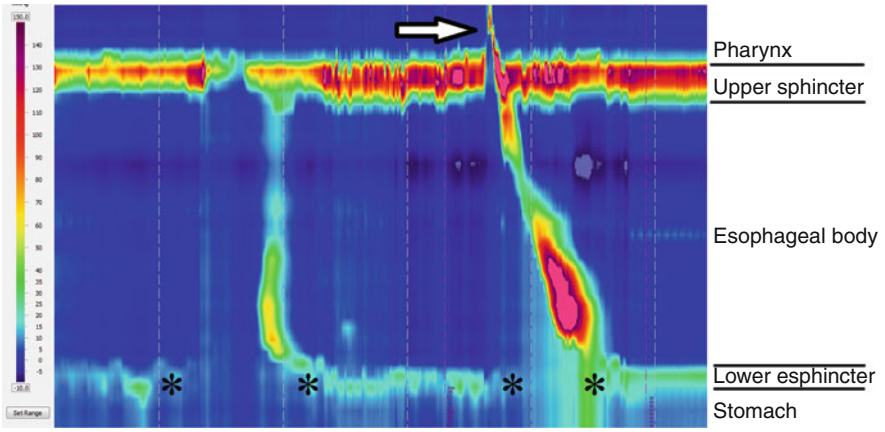

Fig. 3.2 High-resolution manometry images of the lower esophageal relaxation (between*) during transient relaxation (*left*) and swallow (*right*). The *arrow* points to swallow

Lower Esophageal Sphincter and Abdominal Esophagus

The LES creates a high-pressure zone at the level of the EGJ without a clear anatomic representation. This smooth muscle sphincter maintains a sustained tone that is disrupted only in two moments: (1) *swallowing*, to allow food transit to the stomach, and (2) *gastric fundus distention*, to allow gas ventilation and eructation.

An effective LES must have an adequate resting pressure and total and intra-abdominal length. It is intuitive that the resting pressure of the LES must be higher than the thoracoabdominal pressure gradient. Also, reflux control is linked to the extension of the LES, since gastric distension may alter the shape of the proximal stomach leading to a shorter LES. Moreover, the intra-abdominal portion of the LES is submitted to a positive abdominal pressure that forces the sphincter to collapse and close. The same mechanism applies to the presence of an abdominal portion of the esophagus, not found in a hiatal hernia (HH).

Even though most patients with GERD have a defective LES, a normal LES pressure does not exclude GERD, since the pathophysiology may be linked to abnormal relaxations.

Periodic relaxation of the LES or transient lower esophageal sphincter relaxation (TLESR) – to distinguish it from relaxation triggered by swallowing – explains physiological reflux found in normal subjects.

This relaxation is longer, and it is associated to diaphragm inhibition and contraction of the longitudinal muscular layer of the esophagus, when compared to swallow-induced relaxations (Fig. 3.2). It may contribute to reflux disease, when more frequent and prolonged. It explains the reflux seen in the 40 % of patients with GERD whose resting LES pressure is normal.

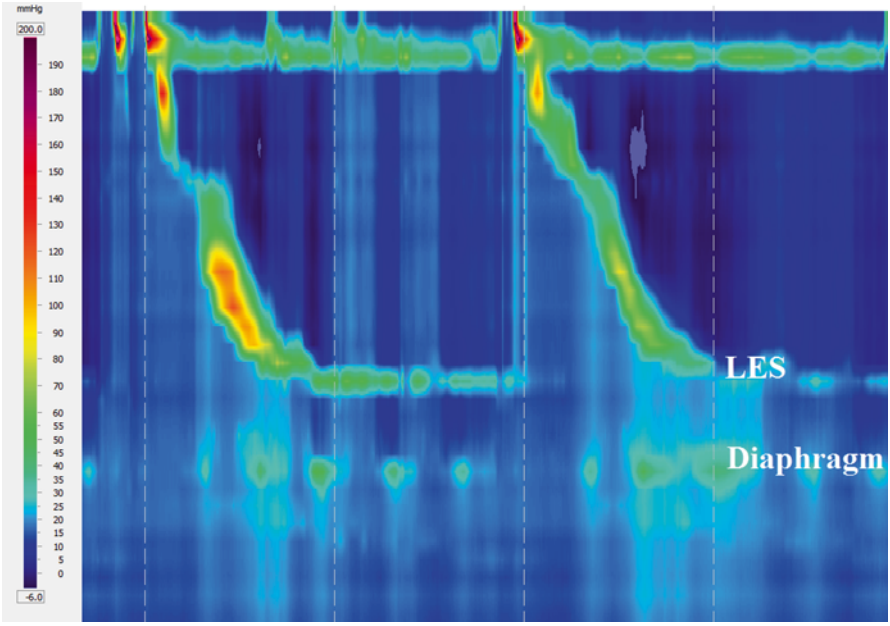

Fig. 3.3 High-resolution manometry images of two high-pressure zones at the level of the esophagogastric junction in a patient with hiatal hernia corresponding to the lower esophageal sphincter and the diaphragm. *LES* lower esophageal sphincter

Diaphragm

The esophagus crosses from the thorax to the abdomen through the esophageal hiatus formed by the right crus of the diaphragm. Thus, the esophagus is compressed during diaphragm contraction. The crus of the diaphragm provides an extrinsic component to the gastroesophageal barrier. This pinchcock action of the diaphragm is particularly important as a protection against reflux induced by sudden increases in intra-abdominal pressure.

Very interestingly, high-resolution manometry is able to show the distinct action of the diaphragm in patients with hiatal hernia (Fig. 3.3), and a high pressure zone is observed at this level even in patients after distal esophagectomy when the LES was resected.

Angle of His and Gubaroff Valves

The acute angle formed between the esophagus and the gastric fundus (His angle) creates a longer distance between the gastric fundus where the food is stored during feeding. Also, gastric distention projects the fundus in the direction of the esophagus accentuating the His angle and closing the EGJ (Fig. 3.4).

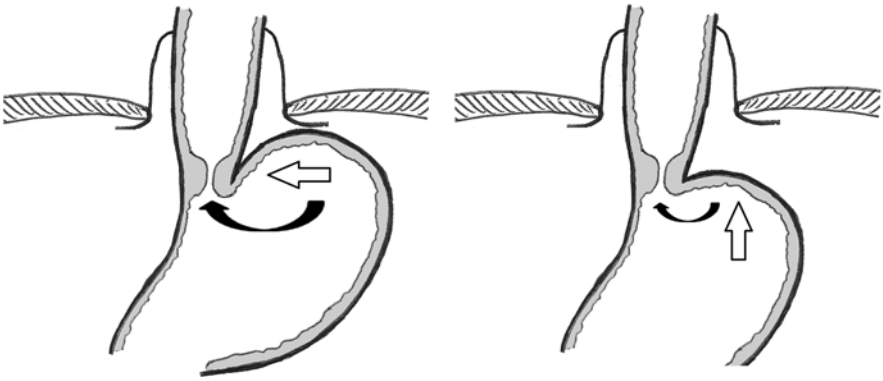

Fig. 3.4 Antireflux mechanism of the angle of His. The *white arrow* shows the vector of the intragastric pressure and the *black arrow* the path the food needs to follow to reflux with an acute His angle (physiological – *left*) or with an obtuse His angle (pathologic – *right*)

Gubaroff valves consisted in a cushion action of the distal esophageal mucosa at the level of the EGJ.

Phrenoesophageal Membrane

The phrenoesophageal membrane is a fibroelastic ligament consisting in the continuation of the transversalis fascia that leaves the diaphragm and surrounds the esophagus in a variable distance from the abdominal inlet. The membrane protects against reflux transmitting the positive abdominal pressure above the abdominal inlet into the esophageal walls. This effect creates a segment of the esophagus that is anatomically in the thorax but physiologically behaves like an abdominal segment (Fig. 3.5).

Protective Mechanisms

Some mechanisms protect the esophagus from injury when a reflux occurs.

Esophageal Clearance

The refluxate is likely to produce more mucosal injury if the contact time with the mucosa is prolonged. A rapid esophageal clearance minimizes the effect of the refluxate. Esophageal clearance is promoted by gravity, esophageal motility, and saliva production.

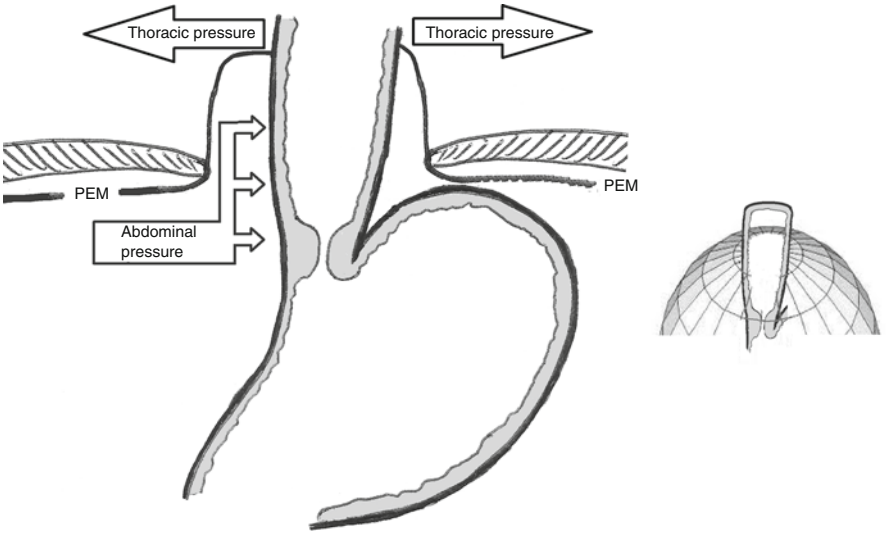

Fig. 3.5 Antireflux mechanism of the phrenoesophageal membrane. The abdominal pressure is transmitted to the insertion point of the membrane. *PEM* phrenoesophageal membrane

Esophageal Motility

Esophageal peristalsis is probably the most important component of the esophageal clearance of the refluxate. Thus, defective peristalsis is associated with more severe GERD with a higher intensity of symptoms and mucosal damage.

Saliva Production

The daily output of saliva is over 1 l. It has a dual protection effect on the esophagus: (1) mechanical, as it washes out the refluxate, and (2) chemical, as it buffers acid reflux due to the presence of bicarbonate.

Epithelial Protection

Esophageal epithelial cells have protective mechanisms against the noxious effects of reflux. These mechanisms may be divided in pre-epithelial, epithelial, or post-epithelial.

Esophageal mucus, produced by mucus cells localized at the epithelium surface and from the submucosal glands, acts as a pre-epithelial barrier against the refluxate. Under the mucus, a layer of bicarbonate-rich fluid also buffers acid that penetrates the mucus.

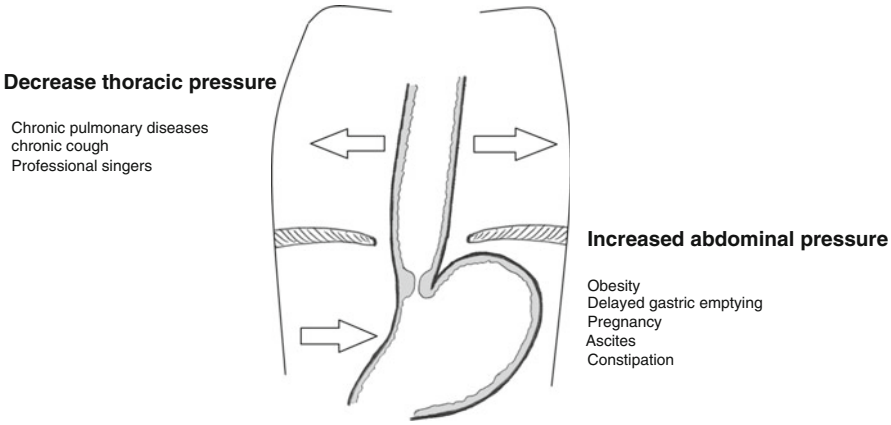

Fig. 3.6 Conditions that may affect the balance of the thoracoabdominal pressure gradient

Esophageal epithelial cells have specialized cellular membranes and intercellular junctions to prevent H+ ions to flow into the cells.

The post-epithelial protective mechanism is performed by the clearance of H+ ions to the blood.

Thoracoabdominal Gradient

The esophagus is placed in almost its totality in the thorax under a negative pressure. This promotes the upward extension of gastric contents. On the other side, the stomach lies within the positive pressure of the abdomen, compressing its walls and also forcing contents upwards. This thoracoabdominal gradient must be counterbalanced by the valve mechanism previously described, interposed between the esophagus and the stomach. An increase in abdominal (intragastric) pressure or a decrease in thoracic pressure (becoming more "negative") may alter this and lead to GERD (Fig. 3.6).

Obesity is probably the main cause for GERD due to increased abdominal pressure. It has been shown that there is a dose-response relationship between increasing body mass index (BMI) and prevalence of GERD and its complications. Abnormal gastric emptying might also contribute to GERD by increasing intragastric pressure.

The association of various pulmonary diseases and GERD has been demonstrated. It has been shown that patients with end-stage lung disease may have a prevalence of GERD in up to 70 %.

Others

Age

Although GERD symptoms are distributed equally in different ages, the prevalence and severity of GERD increase with aging. This fact may be attributed to decrease in the esophageal motility, decrease in the production of saliva, and a higher incidence of hiatal hernias.

Helicobacter pylori

Helicobacter pylori might influence GERD by leading to an atrophic gastritis and consequent achlorhydria, altering the nature of the refluxate. Some studies showed an inverse association between *H. pylori* infection and reflux esophagitis and increase in GERD symptoms after eradication of the bacteria. However, studies on the topic are not unanimous and the real interaction between GERD and *H. pylori* is still elusive.

Drugs, Diet, and Hormones

Many substances may alter the lower esophageal sphincter function and promote GERD (Table 3.1).

Table 3.1 Substances may alter the lower esophageal sphincter function and promote GERD

Drugs	Food	Hormones
Nitrates	Caffeine	Secretin
Ca++ channel blockers	Alcohol	Cholecystokinin
Morphine	Tobacco	Glucagon
Sildenafil	Chocolate	Progesterone
Meperidine	Mint	E2 prostaglandin
Beta-adrenergic agonist	Fat	
Aminophylline		
Benzodiazepines		
Barbiturates		
Tricyclic antidepressant		

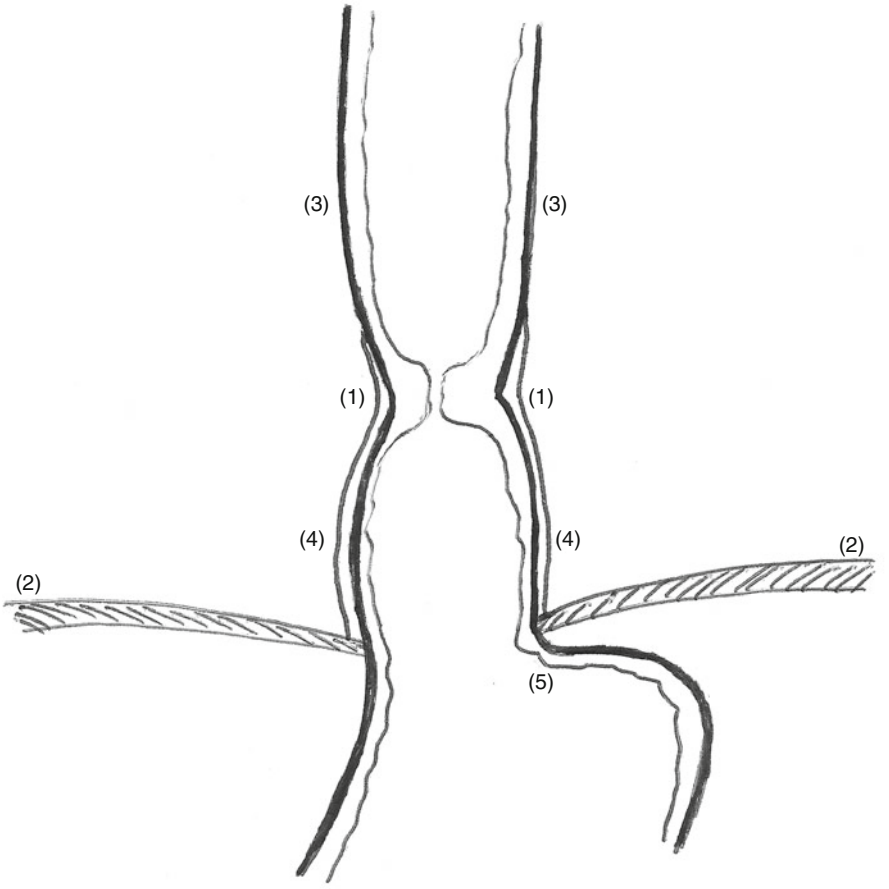

Fig. 3.7 Hiatal hernia and antireflux mechanisms. All natural antireflux mechanisms are absent or compromised when a hiatal hernia is present: (*1*) the lower esophageal sphincter is under negative thoracic pressure, (*2*) the diaphragm is below the esophagogastric junction, (*3*) the abdominal portion of the esophagus is not present, (*4*) the phrenoesophageal membrane is stretched and nonfunctional, and (*5*) the angle of His is obtuse

Hiatal Hernia

Hiatal hernia and GERD were considered synonyms in the past. Currently, it is well known that both conditions can exist independently; however, the presence and size of a hiatal hernia increase the chance of GERD by disrupting most of the natural antireflux mechanisms (Fig. 3.7). The presence and size of a hiatal hernia are also associated with more severe mucosal damage and increased acid exposure.

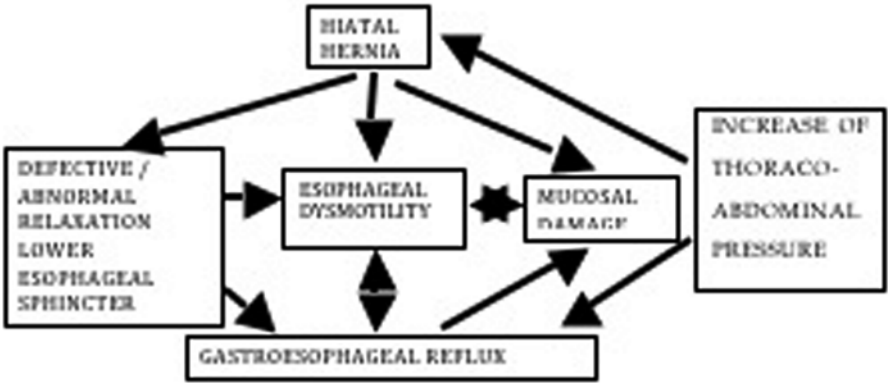

Fig. 3.8 Gastroesophageal reflux disease interaction among causative factors

Conclusions

GERD is a multifactorial disease, and there is a great interaction among causative factors (Fig. 3.8). Patients with suspected GERD must be carefully studied, and therapy should be based on the pathophysiology of the disease.

Summary

- GERD is defined as a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications.
- Gastroesophageal reflux occurs daily in normal individuals.
- GERD pathophysiology is multifactorial and linked to a disbalance between the aggressiveness of the refluxate into the esophagus or adjacent organs and the failure of the esophagogastric barrier and protective mechanisms.
- Antireflux mechanisms include the lower esophageal sphincter and abdominal esophagus, the diaphragm, the His angle, the Gubaroff valve, and the phrenoesophageal membrane.
- Protective mechanisms include esophageal motility, saliva production, and epithelial protection.
- Age, drugs, hormones, *Helicobacter pylori* infection, increased abdominal pressure (especially obesity and delayed gastric emptying), a more negative thoracic pressure, and the presence of hiatal hernia all affect GERD.

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