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SURGICAL SYMPOSIUM CONTRIBUTION

Pathophysiology of Gastroesophageal Reflux Disease

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Abstract Gastroesophageal reflux disease pathophysiology is multifactorial and linked to a misbalance between the aggressiveness of the refluxate into the esophagus or adjacent organs and the failure of protective mechanisms associate or not to a defective valvular mechanism at the level of the esophagogastric junction incapable of dealing with a transdiaphragmatic pressure gradient. Antireflux mechanisms include the lower esophageal sphincter and abdominal esophagus, the diaphragm, the angle of His, the Gubaroff valve, and the phrenoesophageal membrane. Protective mechanisms include esophageal motility, saliva production, and epithelial protection. Disruption of this balance occurs most commonly due to the presence of a hiatal hernia, esophageal dysmotility, a rise in abdominal pressure (obesity), and decrease in thoracic pressure (chronic lung diseases).

Introduction

Gastroesophageal reflux disease (GERD) is defined as "a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications" [1]. The disease is highly prevalent, especially in developed countries, affecting 18–27% of the North Americans, 8–25% of Europeans, 23% of South Americans, 11% of Australians, and 2–7% of Eastern Asians [2]. This high prevalence impacts not only quality of life but also economy. The burden of GERD in the USA may reach 9–10 billion dollars/year in direct costs plus uncountable dollars in indirect costs due to decrease in productivity and days off work [3].

The understanding of GERD pathophysiology is essential to determine an optimal treatment of these patients. GERD pathophysiology is, however, complex and multifactorial, determining a tailored and individual approach for each case. Overall, it is due to a lack of balance between protective mechanisms and aggressive chemical substances, between the valvular mechanism and the transdiaphragmatic pressure gradient [4, 5].

Gastroesophageal reflux disease physiology: protection versus aggression

Previous thinking associated esophageal injury to a direct chemical damage of the mucosa by the refluxate ("acid theory"), attributed to pepsin and bile action as well [6–9]. The mucosal inflammation was due to injury to the tight junction proteins in the esophageal epithelium, resulting in increased para-cellular permeability and dilated

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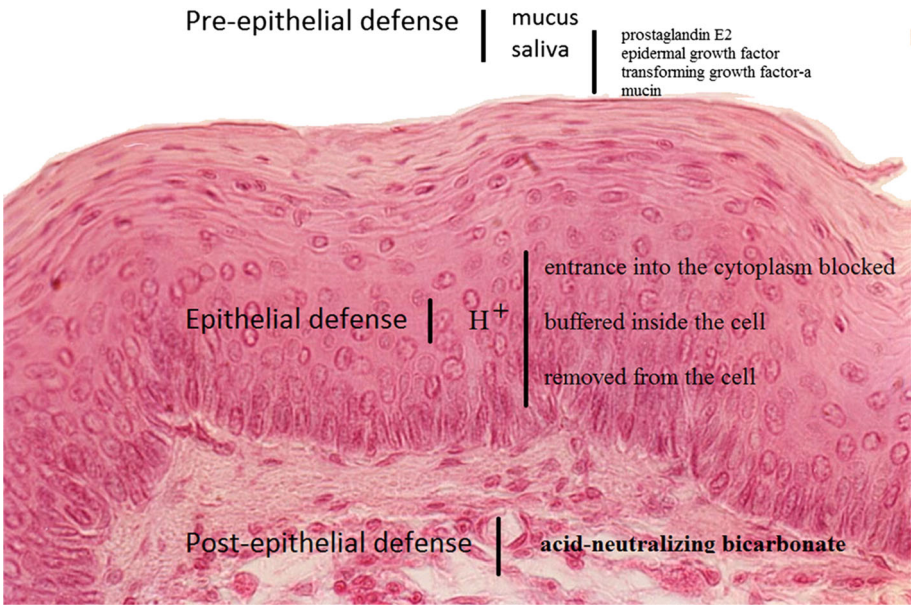

Fig. 1 Protective mechanism against noxious refluxate at the level of the esophageal mucosa

intercellular space (DIS). With DIS, noxious agents (gastric acid, bile, and pepsin) penetrate into deep basal layers of the esophageal mucosa, which produce damages in esophagus, through inflammatory mediators. This inflammation may act on nociceptors to provoke symptoms and dysmotility [6, 10–13]. This may explain GERD manifestations in the absence of mucosal damage (non-erosive form) [6, 10].

Esophageal mucosa has protective barriers defined as pre-epithelial, epithelial, and post-epithelial defenses [14, 15]. Pre-epithelial defense is represented by a minutest production of mucus by the esophagus but especially by alkaline saliva that also contains protective agents such as prostaglandin E2, epidermal growth factor, transforming growth factor-a, and mucin [14, 15]. Epithelial defense consists of dealing with hydrogen ion in three instances: (a) preventing from entering the cells; (b) buffering it with bicarbonate, proteins, and phosphate once inside the cell; and (c) removing from the cell by the action of cell membrane ion transporters (i.e., the Na+/H+ exchanger and the Na+-dependent Cl–/HCO_3–exchanger) [14, 16]. Post-epithelial defense comes from blood-born acid-neutralizing bicarbonate deriving from capillaries [14, 16] (Fig. 1).

Valvular mechanism versus transdiaphragmatic pressure gradient

Positive abdominal pressure tends to push gastric contents up to the esophagus. At the same time, negative thoracic pressure sucks gastric contents up. This transdiaphragmatic pressure gradient is compensated by a complex valvular mechanism at the esophagogastric junction to prevent GERD (Fig. 2). These are the components of the valvular mechanism:

Lower esophageal sphincter

The lower esophageal sphincter (LES) is a composite of different muscles spanning 2.4–4.5 cm in length that allows coordinated passage of food into the stomach and venting of gas after meals but also prevents reflux of contents back into the esophagus [17, 18].

A defective LES is found in the majority of GERD patients [18, 19]. Up to 40% of the patients, however, may have a normal LES [18, 20]. This is explained by the competence of other natural antireflux mechanisms. On the other side, a normal LES may exist in patients with GERD due to an altered transdiaphragmatic pressure gradient or to reflux during periods of relaxation, so-called transient LES relaxations (TLESR). TLESR is a phenomenon secondary to gastric distension, defined by LES relaxation occurring in the absence of swallowing, lasting more than 10 s, and associated with crural inhibition [21].

Diaphragm

The diaphragm pinches the abdominal part of the esophagus as it enters the abdomen through the hiatus, acting as an extrinsic component to the lower esophageal sphincter [5].

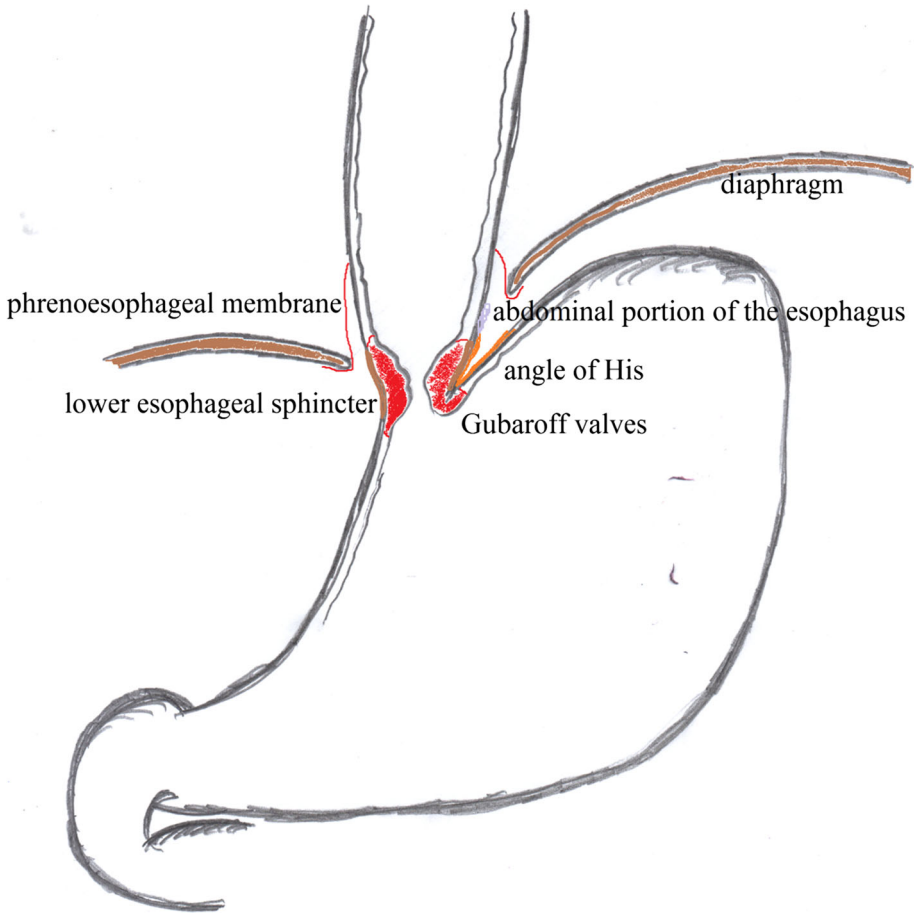

Fig. 2 Natural antireflux mechanisms at the esophagogastric junction

Abdominal part of the esophagus

The abdominal portion of the esophagus is under the positive pressure of the abdomen. This pressure forces the esophageal wall to collapse, narrowing the lumen, and preventing reflux. The longer the length of the abdominal esophagus, the better GERD control [18, 22].

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 [5].

Phrenoesophageal membrane

The phrenoesophageal membrane is a fibro-elastic 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 through the hiatus up to the insertion of the membrane in the esophagus [23].

Gubaroff valves

Gubaroff valves consist in a cushion action of the distal esophageal mucosa at the level of the esophagogastric junction [23].

Gastroesophageal reflux disease pathology: defective valve versus challenge to the valve

GERD may occur due to a defective valve at the esophagogastric junction and/or an increased transdiaphragmatic pressure gradient overcoming the valve (Fig. 3).

Hiatal hernia

Most of the natural antireflux mechanisms are disrupted by the presence of a hiatal hernia [24]. As a consequence, hiatal hernias are associated with more severe degrees of esophagitis and to Barret's esophagus [25, 26]. The severity of the disease when hiatal hernias are present is consequence of a more extended exposure of the esophageal mucosa to the refluxate due to longer episodes of

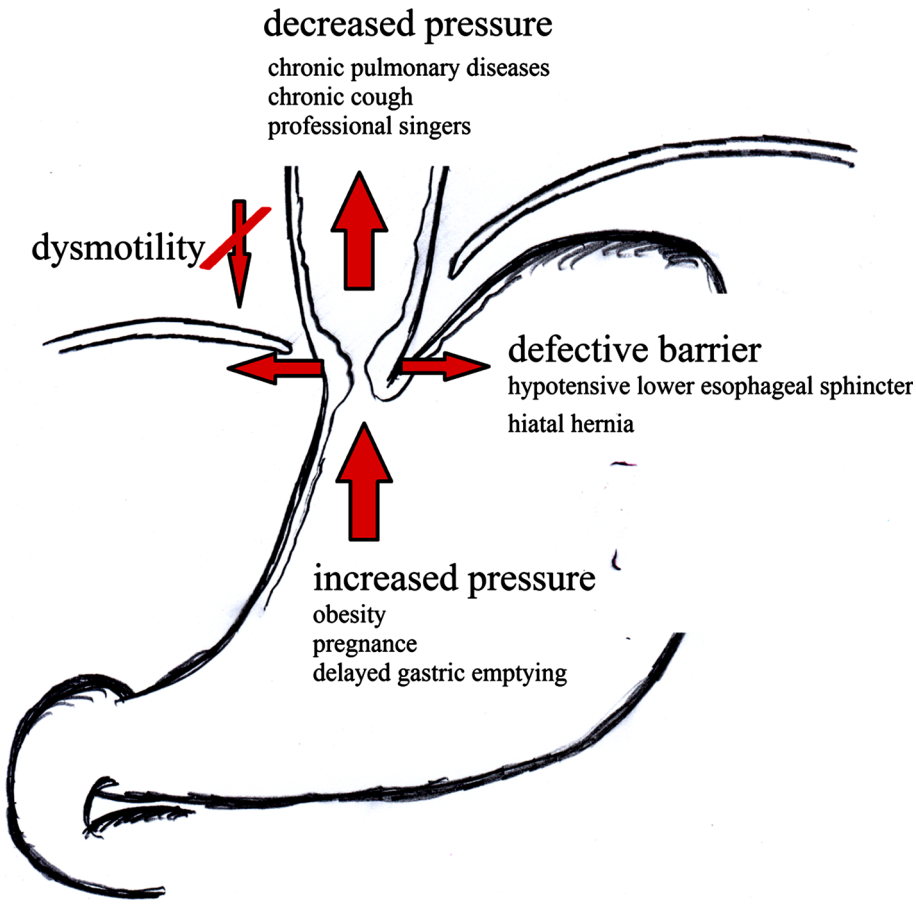

Fig. 3 Gastroesophageal reflux disease pathogenesis

reflux and decreased [25, 26]. Patients with hiatal hernia seem to have more frequent and prolonged TLESR [27]. Moreover, an enlarged post-prandial gastric acid pocket that escapes buffering by food occurs in these patients acting as a reservoir of acid to reflux [28].

Dysmotility

Esophageal clearance depends on esophageal motility to push refluxate down to the stomach again. Esophageal inflammation may lead to altered contractions. Thus, esophageal dysmotility is linked to both GERD cause and effect [29].

Dysmotility may be found in almost half of the GERD patients with 20–30% having ineffective esophageal motility [29, 30].

Increased abdominal pressure

A rise in the abdominal pressure may exceed the resting pressure of the LES. A main reason for this lack of balance is obesity. Obesity promotes a raise in abdominal pressure due to visceral adiposity. In fact, GERD is more prevalent in the obese [4, 31, 32] and it is known that for each 1-point increase in body mass index, abdominal pressure is expected to increase of 10% [33] and for each 5-point increase in body mass index, the DeMeester composite score for GERD is expect to increase of 3 points [32].

Delayed gastric emptying may be responsible for an increase in the intra-gastric pressure [5].

Decreased thoracic pressure

Many chronic pulmonary diseases are associated with a high incidence of GERD, reaching up to 70% in some series [34–36]. This may be due to an increased respiratory effort and consequent more negative thoracic pressure [35].

Conclusion

The pathophysiology of gastroesophageal reflux disease is multifactorial and linked to a lack of balance between the aggressiveness of the refluxate into the esophagus or adjacent organs and the failure of protective mechanisms associate or not to a defective valvular mechanism at the

level of the esophagogastric junction incapable of dealing with a transdiaphragmatic pressure gradient.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest to report.

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