Pathophysiology of Gastroesophageal Reflux Disease

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KEYWORDS

• Gastroesophageal reflux disease • Pathophysiology • Esophagogastric junction
• Esophageal sphincter

KEY POINTS

- The high-pressure zone at the esophagogastric junction is generated by the lower esophageal sphincter (LES) and the crural diaphragm.
- Transient LES relaxations are prolonged relaxations of the LES and are the main mechanism underlying gastroesophageal reflux.
- The acid pocket is the source of postprandial acid refluxate; the position of the acid pocket relative to the diaphragm is a major determinant of the acidity of the refluxate.
- Especially in patients with nonerosive reflux disease, increased permeability and dilated intercellular spaces may contribute to symptom generation.

INTRODUCTION

Although reflux of gastric contents into the esophagus is a physiologic phenomenon, increased exposure or increased perception of the refluxate may cause troublesome symptoms and/or complications, referred to as *gastroesophageal reflux disease* (GERD).[1] GERD is one of the most common digestive diseases in the Western world, with typical symptoms, such as heartburn, regurgitation, or retrosternal pain, reported by 15% to 20% of the general population.[2] Most patients have mild to moderate complaints, but increased exposure of the esophageal epithelium to noxious gastric contents may lead to complications, such as erosive esophagitis, Barrett esophagus, peptic strictures, and even esophageal carcinoma.[3,4] The different phenotypes of GERD range from nonerosive reflux disease (NERD), through reflux esophagitis and Barrett esophagus; but most patients have no abnormalities on endoscopic

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examination. Clearly, symptoms related to GERD have to be related to reflux events.[5] This relationship depends on the presence of pathologic acid exposure during 24-hour pH-metry and a positive association between symptoms and esophageal reflux episodes. In the absence of these features, patients are rather considered to suffer from functional heartburn, a functional disorder that does not belong to the GERD spectrum.

Given the high prevalence of GERD, understanding of the pathophysiology is of great importance in order to efficiently treat our patients. In this article, the authors review the major mechanisms involved in gastroesophageal reflux.

THE ESOPHAGOGASTRIC JUNCTION

The junction between the esophagus and stomach is a highly specialized region, composed of the lower esophageal sphincter (LES) and crural diaphragm.[6] Together these structures have to reassure that a bolus of food can enter into the stomach. Conversely, reflux of gastric contents across the esophagogastric junction (EGJ) into the esophagus should be prevented, with the exception of a retrograde flow of gastric contents during vomiting or venting of accumulated air during belching.[7]

The LES is a specialized thickened region of the circular muscle layer of the distal esophagus, extending over an axial distance of 3 to 4 cm. By generating a myogenic tonic resting pressure higher than the intragastric pressure, the LES provides sufficient protection against the pressure gradient between the stomach and the intrathoracic esophagus.[7] However, during straining and inspiration, this gradient increases, requiring an additional compensatory mechanism. This task is fulfilled by the crural diaphragm, which is considered the second sphincteric component of the EGJ.[6,8] The crural diaphragm forms a canal through which the esophagus enters the abdomen and is anchored to the LES by the phrenoesophageal ligament. Since the two components are anatomically superimposed, contraction of the striated muscle of the crural diaphragm during inspiration or straining exerts pressure on the LES, leading to a dynamic and powerful increase in EGJ pressure.[6] Hence, the LES and crural diaphragm are considered the internal and external sphincter of the EGJ acting in concert to prevent gastroesophageal reflux.[8,9] Under normal conditions, the EGJ fulfills this task very efficiently, except during transient LES relaxations (TLESRs) and when both sphincters (LES and crural diaphragm) are anatomically separated as in patients with a hiatal hernia.

TLESRs

TLESRs are the predominant mechanisms underlying gastroesophageal reflux, both in normal subjects and in patients with GERD.[10,11] A TLESR is a vago-vagally mediated motor pattern triggered by the activation of vagal afferents in the cardia of the stomach by various stimuli, of which gastric distension is the most important.[12] In response to gastric distention, vagal afferents are activated triggering neurons in the dorsal motor nucleus of the vagus nerve to initiate the specific motor pattern underlying TLESRs (**Fig. 1**). TLESRs are characterized by a rapid relaxation of the LES, esophageal shortening, and the inhibition of the crural diaphragm, thought to be the physiologic mechanism by which the stomach vents gas.[13] The frequency of TLESRs in patients with GERD is not different from that of normal subjects.[14] However, the occurrence of acid reflux during a TLESR is twice as high in patients with GERD, especially in those with a hiatal hernia compared with healthy controls.[15] The potential explanation for this observation is discussed later.