Physiology and Pathogenesis of Gastroesophageal Reflux Disease

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KEYWORDS

• Gastroesophageal reflux disease • GERD • Heartburn • Pathology of GERD
• Pathogenesis of GERD

KEY POINTS

- Gastroesophageal reflux disease (GERD) represents a wide range of pathologic conditions that are poorly understood.
- Reflux of gastric acid most commonly presents as heartburn, but GERD can also be associated with bile (alkaline) reflux, gastric or esophageal distention, and motility disorders.
- Pain associated with gastroesophageal reflux is secondary to the stimulation and activation of mucosal chemoreceptors by acid; the lower esophageal sphincter (LES) plays a vital role in the frequency and severity of GERD.
- Development of Barrett esophagus is believed to be due to repeated and uncontrolled acid exposure of the distal esophagus resulting in metaplasia, which can progress to dysplasia of the epithelium of the distal esophagus.

INTRODUCTION: NATURE OF THE PROBLEM

GERD is a common problem treated by primary care physicians. It is estimated that up to 20% of Americans experience symptomatic GERD weekly and that an even higher percentage of people have heartburn monthly.[1] The cost of managing a disease of this prevalence is substantial, with estimates of direct and indirect costs exceeding $14 billion in the United States, 60% of which is accounted for by medication costs.[2] Although the physiology and pathogenesis of GERD are poorly understood, heartburn, the most common symptom, occurs in most patients and is thought to be due to the stimulation and activation of mucosal chemoreceptors in the distal esophagus.[3] The

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pain associated with heartburn is usually due to gastric acid present in the esophagus, but it can also be due to bile salt irritation of the esophagus, esophageal distention, and motility disorders of the distal esophagus.[4] There has been an alarming increase in the prevalence of GERD in the United States over the past 2 decades, and although the cause is likely multifactorial and our understanding of GERD has improved, 2 factors that seem to have contributed most are the obesity epidemic and improvements in diagnostic techniques, with the routine use of endoscopy becoming more commonplace.[5,6]

The wide range of symptoms from mild to severe heartburn with or without acid exposure in combination with the multifactorial nature of GERD makes understanding this disease challenging. GERD and its associated symptoms occur as the end product of a collection of anatomic and/or physiologic abnormalities. Under normal circumstances, the intra-abdominal pressure is positive, whereas the intrathoracic pressure is negative, a physical principle that should promote reflux of gastric contents into the esophagus. Not surprisingly, small amounts of reflux occur throughout the day in everyone, but pathologic GERD is prevented by the normal anatomy and physiology of the esophagus, LES, diaphragm muscles at the hiatus, and the stomach. In general, pathologic reflux is most commonly a consequence of the breakdown of the normal reflux barrier of the LES, but it can also result from factors that increase the pressure gradient between the abdomen and thorax (eg, morbid obesity and pregnancy) or dysmotility of the esophagus, hiatus musculature, and/or the stomach. This article examines the physiology of GERD and the pathologic conditions resulting from it.

PHYSIOLOGY OF THE DISTAL ESOPHAGUS

The distal esophagus and LES are dynamic and interrelated (**Fig. 1**). The antireflux mechanism of the esophagus consists of the LES, the angle of His, and the muscle fibers of the diaphragm. The LES is 2 to 4 cm in length of the distal esophagus and is composed of tonically contracted circular smooth muscle located within the diaphragm hiatus.[7,8] Gastroesophageal reflux occurs when there is inappropriate relaxation of the LES permitting gastric acid to enter the distal esophagus, stimulating the chemoreceptors and causing irritation, leading to the manifestation of symptoms. In addition, several drugs can alter the LES tone (**Table 1**) and affect the natural defenses of the esophagus to induce heartburn; however, more commonly, many different foods can trigger heartburn (**Box 1**). As mentioned, other key contributors to reflux in addition to the drugs and foods listed are factors that increase intra-abdominal pressure, overcoming the antireflux barrier, such as pregnancy or obesity.[9]

The LES is a circular muscle layer of the distal esophagus that generates a resting pressure higher than the intra-abdominal pressure.[7] The LES resting pressure is normally sufficient to prevent reflux of gastric contents into the esophagus thereby preventing symptomatic heartburn, but during times of increased abdominal pressure (ie, Valsalva maneuver, lifting, Trendelenburg position, and pregnancy) other mechanisms aid in preventing reflux.[10] The left and right crural muscles of the diaphragm constitute the second mechanism of defense to protect the esophagus from reflux. The crural muscles and the LES are anatomically connected by the phrenoesophageal ligament (**Fig. 2**) and give the esophagus 2 distinct but interactive mechanisms to prevent reflux of stomach contents into the esophagus.[11]

Swallowing is a complex physiologic process that results in the propulsion of the food bolus from the pharynx into the esophagus and then into the stomach. This process can be started consciously or reflexively by stimulation of areas of the mouth or pharynx. Pharyngeal activity during swallowing stimulates the esophageal phase and