

Gastroesophageal Reflux Disease: Pathophysiology, Clinical Symptoms, and Diagnosis

Based on a presentation by Lin Chang, MD

Presentation Summary

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal disorders in the United States. Pathophysiology of GERD includes (1) impaired barriers to reflux: low resting lower esophageal sphincter (LES) pressure or transient LES relaxations allow gastric material to reflux into the esophagus; (2) impaired esophageal clearance, which may result in prolonged esophageal exposure to toxic refluxed material; and (3) delayed gastric emptying, which is often present and can lead to more frequent reflux. Prolonged and frequent reflux can damage the mucosa of the distal esophagus, leading to complications such as ulcerations, strictures, or Barrett's esophagus.

The chief symptom of GERD is heartburn, but respiratory symptoms or chest pain are not uncommon. In the case of patients with pulmonary disease and GERD, the cause-and-effect relationship has been difficult to establish. Diagnosis of GERD and its complica-

tions includes barium studies, endoscopy, esophageal pH monitoring, and esophageal manometry. The use of barium studies is the least expensive technique but also the least sensitive for reflux and esophagitis; they are useful primarily in diagnosing dysphagia.

Endoscopy is the gold standard for documenting esophageal injury due to GERD. If patients have no endoscopic evidence of esophagitis, 24-hour pH monitoring is useful to document acid reflux. Finally, manometry measures LES pressure and relaxation, and esophageal body contractions. This test can assess the presence of motility disorders that may underlie GERD, such as scleroderma. Esophageal manometry can also differentiate other motility disorders that may be causing symptoms that mimic those of GERD, such as diffuse esophageal spasm or achalasia. It should also be used to evaluate esophageal body contractions and peristalsis when fundoplication surgery is being considered.

Gastroesophageal reflux disease (GERD) refers to the pathologic movement of gastric contents into the esophagus resulting in symptoms of esophageal, laryngeal, and pulmonary damage. Irritating substances in the stom-

ach that can cause esophageal injury include hydrochloric acid, pepsin, bile salts, and pancreatic enzymes. The vast majority of GERD cases are due to acidic gastroesophageal reflux. The clinical spectrum of GERD consists of symptomatic gastroesophageal reflux with either gross esophageal inflammation, microscopic esophagitis, or no detectable esophageal inflammation. When inflammation can be documented,

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GERD is usually termed "reflux esophagitis."

Epidemiology

GERD is one of the most common gastrointestinal disorders evaluated by primary care physicians and gastroenterologists in the United States. More than 6 million Americans experience heartburn, the cardinal symptom of GERD, at least once a day and approximately 40% of adult Americans experience heartburn at least once a month.¹ Eighteen million Americans take antacids for heartburn more than twice a week. GERD occurs in males more frequently than in females (2 or 3:1) and in Caucasian Americans more frequently than in African Americans. Ten percent to 20% of patients who seek medical care for their reflux-induced symptoms may have serious complications such as esophageal stricture or Barrett's esophagus.

Pathogenesis

There are four major pathophysiologic mechanisms underlying GERD: lower esophageal sphincter (LES) incompetence, abnormal esophageal clearance of refluxate, esophageal exposure to damaging substances, and delayed gastric emptying.

LES Incompetence

The LES is the major anatomic barrier for the prevention of gastroesophageal reflux. This high-pressure zone has a tonic resting pressure of 10 mm Hg to 30 mm Hg. Approximately 20% of reflux patients have an abnormally low resting LES pressure (<10 mm Hg). More recently, it has been recognized that transient relaxation of the LES (TLESR) is a more important determinant of reflux than the resting pressure.^{2,3} At least 60% of patients with reflux have LES incompetence due to transient, spontaneous relaxations when the LES pressure decreases below 5 mm Hg. During TLESRs, the barrier between the stomach and esophagus is no longer adequate. TLESRs, which are independent of swallowing or distention of the esopha-

geal body, are more common after meals and can be induced by fat in the duodenum. The postprandial occurrence of TLESRs is probably due to gastric distention, which lowers LES pressure and thus allows reflux to take place.

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The role of hiatal hernia in the pathogenesis of reflux disease is controversial. The majority of patients with hiatal hernia do not have reflux esophagitis.⁴ However, most patients with esophagitis, especially if severe, do have hiatal hernias. A transient relaxation of the LES is more likely to be followed by an episode of reflux if there is a hiatal hernia pouch with retained acid than in the absence of such a pouch.⁵ Nevertheless, it is the competence of the LES and not the presence of a hiatal hernia that determines whether and how much reflux occurs.

Esophageal Clearance

Prolonged exposure to refluxed material increases the risk of complications such as frank esophagitis and stricture formation, especially in patients with LES incompetence. Esophageal clearance is an important defense mechanism to decrease the duration of contact of esophageal mucosa with gastric contents following an episode of reflux. Normally, esophageal peristalsis clears esophageal contents into the stomach. Then, saliva (bicarbonate secretion) helps neutralize the remaining volume. Gravity assists in esophageal clearance when patients are in the upright position. Up to 48% of reflux patients exhibit some degree of impaired esophageal peristalsis, either amplitude or frequency of contractions.⁶

Gastric Emptying

Delayed gastric emptying, which affects up to 60% of reflux patients,⁷ plays a role in the pathogenesis of GERD. There is a direct relationship between gastric volume and the frequency of TLESRs. The larger the gastric volume, the more frequently reflux occurs.⁸ This is because gastric distention increases the occurrence of TLESRs. The volume of gastric contents depends on the volume of food ingested, the volume of gastric secretions, and the rate of gastric emptying.⁹ This explains why patients with GERD are advised to eat small-volume meals. Delayed gastric emptying in patients with GERD is most likely related to abnormal antral motility. Pyloric incompetence may also be a factor. These disturbances may be idiopathic or secondary to an identifiable disease such as diabetes mellitus or scleroderma. Since fat adversely affects both LES pressure and gastric emptying, low-fat meals are generally recommended to individuals with GERD.

Esophageal Mucosal Resistance

Under normal conditions, the mucosa of the distal esophagus is fairly resistant to injury from refluxed gastric contents, due to the impermeability of squamous epithelium and its defensive factors such as mucus, bicarbonate prostaglandin, and epidermal growth factors. However, prolonged or repeated episodes of gastroesophageal reflux can damage the esophageal mucosa. The injurious agents in the reflux material (bile, pepsin, acid) can destroy the protective cellular proteins and thus expose unprotected layers of esophageal tissue to further damage. Esophageal inflammation results and can subsequently lead to ulcerations, strictures, and Barrett's esophagus.

Clinical Presentation

The most common symptom of GERD is heartburn. Heartburn is described as a wave-like burning sensation that ascends from the upper epigastrium, usually occurring after meals. It

tends to be aggravated or precipitated by postural changes, especially upon reclining, or increases in intra-abdominal pressure. Heartburn is commonly relieved with antacids. Other commonly encountered reflux symptoms are regurgitation, chest pain, dysphagia and odynophagia. The severity of symptoms does not correlate with severity of reflux esophagitis. For example, some patients who complain of frequent or severe symptoms may have no evidence of gross esophagitis during endoscopy. On the other hand, patients with severe esophagitis or Barrett's esophagus may have minimal reflux symptoms. Patients with underlying disordered motility can be identified by the presence of belching, early satiety, bloating, regurgitation, and nocturnal symptoms. These symptoms are important to document because they affect the choice of antireflux medications. In patients with these symptoms, prokinetic agents may be more effective than antisecretory therapy.

Extraintestinal symptoms due to reflux disease include hoarseness, wheezing, and cough. Approximately half of patients with these atypical symptoms do not complain of heartburn. Chronic laryngeal symptoms such as cough and hoarseness may be due to "reflux laryngitis," a diagnosis based on laryngoscopic findings of contact ulcer, interarytenoid erythema, plaques, and nodularity. Jacob et al¹⁰ studied the presence of proximal esophageal acid exposure in 40 reflux patients. Patients were divided into three groups based on symptoms and laryngoscopic findings: (1) persistent laryngeal symptoms (dysphonia, cough, globus sensation, frequent throat clearing, or sore throat) with laryngoscopic evidence of reflux laryngitis, (2) persistent laryngeal symptoms without laryngoscopic findings, and (3) reflux disease patients without laryngeal symptoms or laryngoscopic findings (control group). Proximal esophageal acid exposure was shown in a subset of patients with reflux disease who experienced chronic laryngeal symptoms compared with disease controls. These patients were more likely

to exhibit laryngoscopic findings consistent with acid laryngitis than GERD patients without laryngeal symptoms.

Patients with GERD may also have respiratory findings such as wheezing, bronchitis, asthma, and aspiration pneumonia. Asthma symptoms are believed to be due to aspiration of refluxed gastric contents or to reflex bronchospasm mediated through cholinergic fibers elicited by esophageal acidification alone. However, the exact cause-and-effect relationship between GERD and pulmonary disease, ie, which disease precipitates the other, has been difficult to establish.¹¹ Another possibility is that neither of the two diseases causes the other, but rather that both reflux and pulmonary disease share a common risk factor, such as smoking.¹¹ When GERD is suspected as the cause of nonesophageal signs and symptoms, antireflux treatment should be instituted, although the results will depend on the accuracy of the diagnosis.

Diagnosis

Various common diagnostic tests are used to diagnose GERD; however, in most cases, a history of persistent or recurrent heartburn is usually enough evidence to make a diagnosis of GERD and initiate therapy. Diagnostic tests should be performed to confirm the diagnosis and assess for complications (eg, stricture, Barrett's esophagus) in patients with recurrent or persistent symptoms despite medical therapy or with signs of severe disease (eg, dysphagia, weight loss, gastrointestinal bleeding, respiratory symptoms). The utility of each diagnostic study is discussed below. Medicare reimbursement of these tests is listed in Table 1.

Barium Studies

Although barium studies (esophagram, cine-esophagram, and upper gastrointestinal series) are the least expensive diagnostic tests for pathologic gastroesophageal reflux, they have a low sensitivity for demonstrating reflux of barium from the stomach to the esophagus^{11,12}

and identifying esophagitis. Therefore, barium studies should not be ordered as the initial diagnostic test when GERD is suspected. However, barium studies provide a useful initial diagnostic tool when a patient presents with dysphagia. Peptic and malignant strictures, as well as other causes of dysphagia such as Zenker's diverticulum and achalasia, can be easily identified.

Endoscopy and Biopsy

Upper endoscopy with biopsy is the gold standard for documenting esophageal injury due to gastroesophageal reflux.¹¹ The degree of gross esophagitis varies from Grade I to Grade V (Table 2).¹³ Patients with heartburn due to GERD may also have normal-appearing esophageal mucosa but microscopic esophagitis demonstrated histologically.

Table 1. 1996 Medicare Reimbursement (in dollars) for Diagnostic Tests for GERD

Test	Physician Component	Hospital Fee	Total Cost
Barium esophagram	26.38	49.05	75.43
Cine-esophagram	30.87	53.91	84.78
Barium UGI	39.91	60.44	100.35
Continuous esophageal pH monitoring	113.00	31.24	144.24
Esophageal manometry	146.22	32.07	178.29
EGD without biopsy	223.27	188.73	412.00
EGD with biopsy	250.75	188.73	439.48

EGD = esophagogastroduodenoscopy; UGI = upper gastrointestinal series

Table 2. Endoscopic Grading of Esophageal Inflammation

Grade	Endoscopic Findings
0	no lesions
I	single or multiple erosions on a single fold
II	multiple erosions affecting multiple folds
III	multiple circumferential erosions
IV	ulcer, stricture, or esophageal shortening
V	Barrett's epithelium

Adapted with permission from Ollyo JB¹³

Therefore, random biopsies from the distal esophagus are obtained in these patients during upper endoscopy. Histologic features that are characteristic of reflux disease are basal cell hyperplasia and acute inflammation with infiltration of eosinophils and neutrophils. Endoscopy with biopsy also can identify other complications secondary to GERD, including Barrett's esophagus and adenocarcinoma. In addition to its diagnostic capabilities, endoscopy provides a means for therapeutic intervention, eg, dilation of a peptic stricture. Barium studies are not as accurate in diagnosing esophagitis or Barrett's esophagus.^{12,14} A 24-hour pH test can establish the presence of reflux; however, it cannot allow one to rule out other causes of heartburn or dyspepsia or to diagnose Barrett's esophagus. Thus, if complications are suspected, upper endoscopy may be a cost-effective tool when used early, because it averts the cost of other tests.⁵

Esophageal pH Monitoring

Continuous esophageal pH monitoring is another method of documenting gastroesophageal acid reflux. This study consists of inserting a pH probe nasally into the esophagus 5 cm above the LES and measuring esophageal pH over a 24-hour period. Esophageal pH of <4 is consistent with a reflux episode. Symptoms and meals are also recorded and can be correlated with reflux episodes. Medications can alter LES function and esophageal pH. For example, caffeine, diazepam, theophylline, and calcium channel blockers can increase the likelihood of gastroesophageal reflux by decreasing LES pressure. On the other hand, cisapride, metoclopramide, domperidone, and histamine decrease gastroesophageal reflux by increasing LES tone. The sensitivity and specificity of continuous esophageal pH monitoring range between 75% and 100%.¹⁵ This study should be reserved for patients suspected of GERD without endoscopic evidence of microscopic or macroscopic esophagitis. In these cases, the test should be performed after antise-

cretory therapy has been discontinued. Esophageal pH monitoring can also be considered in patients with documented GERD who are not responding to antireflux medications at routinely used doses. In these patients, the 24-hour pH study can be performed in the presence of antisecretory medication.

Esophageal Manometry

Esophageal manometry is conducted with a water-perfusion catheter to measure contractility of the LES, upper esophageal sphincter, and esophageal body. The catheter is passed through the nose or mouth into the esophagus. Mean LES pressure, LES relaxation with swallowing, amplitude, morphology, and peristalsis of esophageal body contractions can be measured. Because a significant number of patients with GERD have normal LES pressure (10 mm Hg to 30 mm Hg),⁶ esophageal manometry should not be used as an initial diagnostic test for reflux disease. It is more useful in differentiating other underlying esophageal motility disorders that could explain the patient's symptoms, such as achalasia or scleroderma. In many instances, esophageal manometry is requested by surgeons prior to fundoplication, especially if the patient complains of dysphagia. The presence of decreased or absent peristalsis, which could cause or be a result of long-standing severe reflux esophagitis, may alter surgical intervention.

... REFERENCES ...

1. A Gallup Organization National Survey: *Heartburn Across America*. Princeton: The Gallup Organization; 1988.
2. Dent J, Dodds WJ, Friedman RH, et al. Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. *J Clin Invest* 1980;65:256-267.
3. Dodds WJ, Dent J, Hogan WJ, et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. *N Engl J Med* 1982;307:1547-1552.
4. Ellis FH Jr. Current concepts. Esophageal hiatal hernia. *N Engl J Med* 1972;287:646-649.

5. Pope CE II. Acid-reflux disorders. *N Engl J Med* 1994;331:656-660.
6. Kahrilas PJ, Dodds WJ, Hogan WJ, et al. Esophageal peristaltic dysfunction in peptic esophagitis. *Gastroenterology* 1986;91:897-904.
7. Maddern GJ, Chatterton BE, Collins PJ, et al. Solid and liquid emptying in patients with gastro-oesophageal reflux. *Br J Surg* 1985;72:344-347.
8. McCallum RW. Gastric emptying in gastroesophageal reflux and the therapeutic role of prokinetic agents. *Gastroenterol Clin North Am* 1990;19:551-564.
9. McCallum RW, Champion MC. Physiology, diagnosis, and treatment of gastroesophageal reflux. In: McCallum RW, Champion MC, eds. *Gastrointestinal Motility Disorders: Diagnosis and Treatment*. Baltimore, MD: Williams and Wilkins; 1990:135-162.
10. Jacob P, Kahrilas PJ, Herzon G. Proximal esophageal pH-metry in patients with "reflux laryngitis." *Gastroenterology* 1991;100:305-310.
11. Orlando RC. Reflux esophagitis. In: Yamada T, Alpers DH, Owyang C, Powell DW, Silverstein FE, eds. *Textbook of Gastroenterology*. 2nd ed. Philadelphia, PA: JB Lippincott, 1995:1214-1242.
12. Ott DJ, Gelfand DW, Wu WC. Reflux esophagitis: Radiographic and endoscopic correlation. *Radiology* 1979;130:583-588.
13. Ollyo JB, Lang F, Fontolliet CH, Monnier PH. Savary-Miller's new endoscopic grading of reflux-oesophagitis: A simple, reproducible, logical, complete and useful classification. *Gastroenterology* 1990;98 (part 2):A100.
14. DeVault KR, Castell DO. Guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Arch Intern Med* 1995;155:2165-2173.
15. Glade MJ. Continuous ambulatory esophageal pH monitoring (CAEpHM) in the evaluation of patients with gastroesophageal reflux. American Medical Association; 1995.