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Pathophysiology of Esophageal Reflux

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Gastroesophageal reflux disease (GERD) is a common condition that affects approximately 40 million Americans.[1] Although most episodes of acid reflux are asymptomatic, up to 36% of otherwise healthy Americans suffer from heartburn at least once per month. Of that group, 7% experience heartburn as often as once per day. It has been estimated that approximately 2% of the adult population suffers from GERD, based on objective measures such as endoscopic (Figs. 8.1 to 8.3) or histological examination. The incidence of GERD increases markedly after the age of 40, and it is not uncommon for patients experiencing symptoms to wait years before seeking medical treatment.

The clinical spectrum of GERD ranges from the symptomatic postprandial heartburn to significant morbid and pathological processes such as anemia, ulcerative esophagitis (2–7%), strictures of the esophagus (4–20%), and Barrett's esophagus (10–15%) (2%).[1] Furthermore, Barrett's esophagus often progresses to esophageal carcinoma.

Etiology of GERD

GERD is attributed to a combination of conditions that increase the actual or relative presence of acid reflux in the esophagus. These conditions include transient lower esophageal sphincter (LES) relaxation, decreased LES resting tone, impaired esophageal clearance, delayed gastric emptying, decreased salivation, and impaired tissue resistance.

Lifestyle factors can also cause increased risk of reflux. Smoking, large meals, fatty foods, caffeine, pregnancy, obesity, body position, drugs, hormones, and paraplegia may all exacerbate GERD. Hiatal hernia also frequently accompanies severe GERD. The hernia may prolong transient LES relaxation and delay acid clearance due to impaired esophageal emptying. Thus, hiatal hernia may contribute to prolonged acid exposure following reflux, resulting in GERD symptoms and esophageal damage. Approximately half of the patients with GERD have some relief of their symptoms by modifying their diet and other life-style changes.

R. C. Merrell et al. (eds.), *Laparoscopic Surgery*

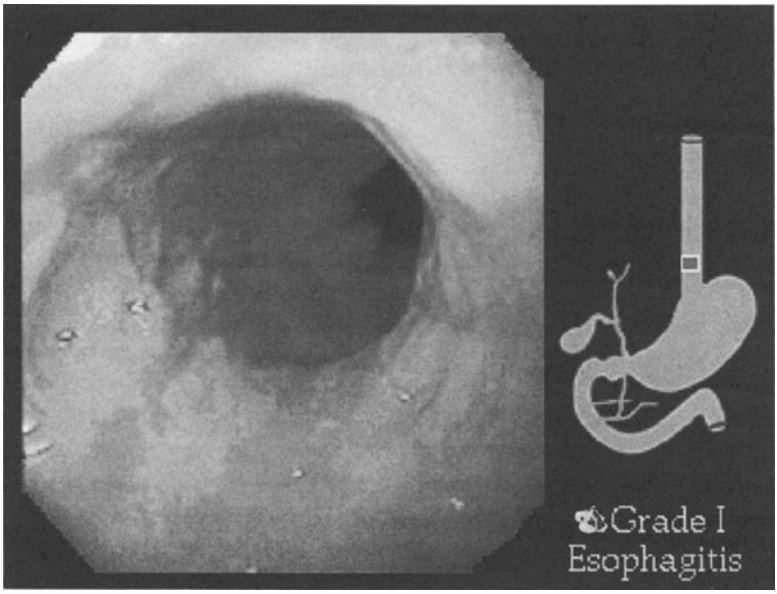

FIGURE 8.1. An endoscopic view of mild esophagitis or grade 1 esophagitis.

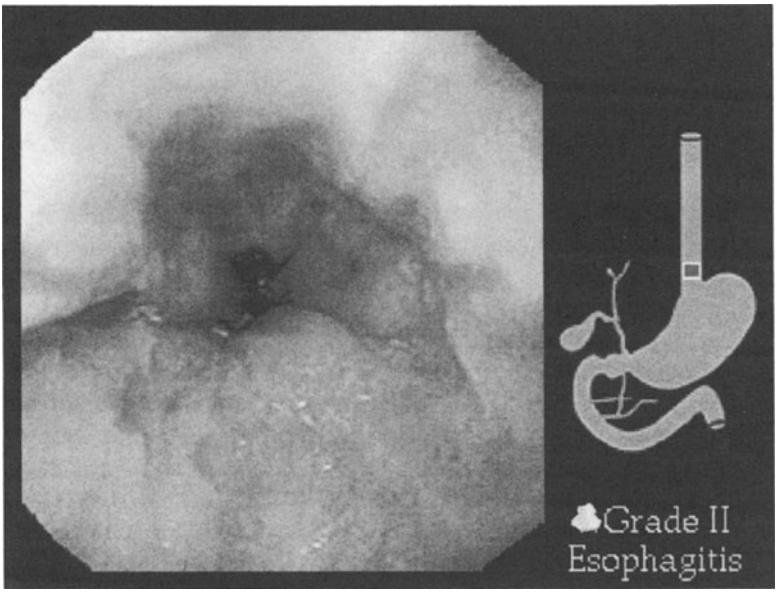

FIGURE 8.2. An endoscopic view of moderate esophagitis or grade 2 esophagitis.

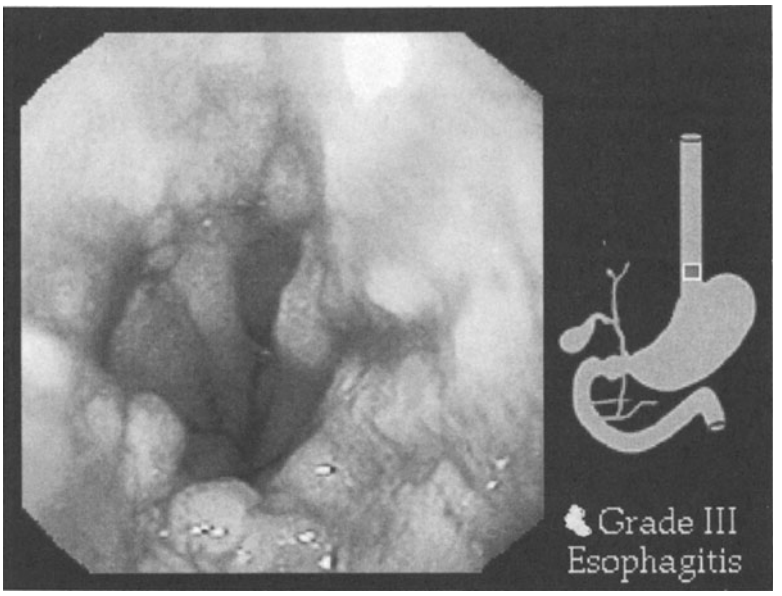

FIGURE 8.3. An endoscopic view of severe esophagitis or grade 3 esophagitis.

A careful history will often show what factors are important for individual patients. Whereas avoidance of exacerbating factors may be helpful, there are relatively little data to support lifestyle modification alone for the long-term relief of symptoms among patients with GERD.

The majority of symptomatic patients will necessitate medical therapy with acid-reducing agents. Many of these patients will have inadequate control of GERD as well as recurrent symptoms upon discontinuation of medical therapy.[2] Some 5–10% of patients who have evidence of severe esophagitis are the subgroup in which antireflux therapy should be considered.[3] Operative intervention has received renewed interest despite highly effective medical treatment because of the low morbidity of minimally invasive approaches, complications, cost concerns, and problems of compliance in protracted medical therapy for a life-long condition.

Pathophysiology of GERD

Gastroesophageal reflux is both a normal physiologic response that occurs in the general population and a pathophysiological response that can result in mild to severe symptoms. GERD can be described as any symptomatic clinical condition or change in tissue structure that results from the reflux of stomach or duodenal contents into the esophagus.

Heartburn, which is a burning sensation or discomfort behind the sternum, is the most common symptom of GERD. It is in part secondary to regurgitation of gastric contents into the esophagus.

Among patients with significant GERD, dysphagia is common and may denote stricture in the esophagus. The etiology of GERD can be attributed to such factors as transient lower esophageal sphincter (LES) relaxation, decreased LES resting tone, delayed stomach emptying, ineffective esophageal clearance, and diminished salivation. Other contributing factors include the potency of the refluxed material and the ability of the esophageal mucosa to resist injury and repair itself.

Most episodes of GERD occur during the day, usually after eating; however, some sufferers also experience reflux during sleep. Nocturnal reflux is commonly associated with a higher risk and a higher degree of esophagitis. Acid remains in the esophagus for prolonged periods because there is less swallowing at night and less saliva produced to neutralize the acid. The symptoms and severity of esophageal mucosal damage are proportional to the acidity of the refluxate and the duration of esophageal acid exposure. With rare exceptions the development of esophagitis requires the presence of acid in the refluxate.

Almost everyone experiences a little acid reflux, particularly after meals. Acid reflux irritates the walls of the esophagus, inducing a secondary peristaltic contraction of the smooth muscle, and may produce the discomfort or pain known as heartburn. Most of the reflux episodes of the normal population are transient. After a meal, the LES usually remains closed. When it relaxes at an inappropriate time, it allows acid and food particles to reflux into the esophagus. Secondary peristalsis returns approximately 90% of the acid and food to the stomach. The LES closes again once peristalsis ends. The remaining acid in the esophagus is neutralized by successive swallowing of alkaline saliva. As long as these mechanisms remain in place the patient will not progress to gastroesophageal reflux disease.

Mechanisms of Gastroesophageal Reflux Disease

After swallowing, the LES should remain closed. Relaxation allows acid and food particles to reflux into the esophagus from the higher pressure intragastric stomach to the lower pressure intrathoracic esophagus. Among patients with GERD, gastric distention increases the frequency of transient LES relaxation, the frequency of reflux episodes, and amount of time gastric acid spends in the esophagus.

Another factor that increases esophageal acid exposure time among patients with GERD is ineffective esophageal clearance. Although peristalsis occurs, esophageal clearance is ineffective because of decreased amplitude of secondary peristaltic waves.

Patients with pathologic reflux often experience many episodes of short-duration reflux and/or several prolonged episodes where the acid may stay in the esophagus for up to several hours. Although the duration of esophageal acid exposure correlates with the frequency of symptoms, as well as with the extent and severity of esophageal mucosal injury, the degree of mucosal damage can be markedly accelerated if luminal pH is less than 2, or if conjugated bile salts are present in the refluxate.

Impaired Esophageal Clearance

Esophageal acid clearance is normally a two-step process. Peristalsis clears gastric fluid from the esophagus, and swallowed saliva neutralizes any remaining acid. Decreased amplitude of secondary peristaltic waves and segmental contractions can be demonstrated in some patients with GERD. Impaired esophageal clearance may be caused by an increase in the volume of refluxate and/or an irritant effect from a preceding reflux event. In rare cases, impaired esophageal clearance may be due to an underlying disease such as scleroderma, which combines poor tissue response with abnormal motility and abnormal sphincteric function.

Decreased Salivation

Saliva, which has a pH of 7.8–8.0, is rich in bicarbonate and can normally neutralize the residual acid coating the esophagus after a secondary peristaltic wave. Decreased salivation, therefore, can contribute to the duration of esophageal acid exposure.

Impaired Tissue Resistance

The ability of the esophageal mucosa to withstand injury can predict reflux damage. It seems to be influenced by the age and nutritional status of the individual. Tissue resistance in the esophagus consists of the membranes and intercellular junctional complexes that protect against acid injury by limiting the rate of hydrogen ions diffusing into the epithelium. The esophagus also produces bicarbonate, to buffer the acid, and mucus, which forms a protective barrier on the epithelial surface. The resistance of the esophageal mucosa to acid damage is much less than that of the stomach lining. When esophageal damage occurs, resident acid overwhelms or exceeds the local tissue resistance to digest epithelial protein.

Transient LES Relaxation

Transient LES relaxation (TLESR) is the mechanism by which reflux occurs in healthy people. Most patients with GERD have a normal resting LES tone. TLESRs are the dominant cause of reflux in these patients, occurring in up to 82% of reflux episodes. TLESRs can be induced by gastric or subthreshold pharyngeal stimulation, which initiates a vagally mediated noncholinergic inhibitory reflex in the LES. TLESRs are short-lived, usually lasting less than 30 seconds. No agent is indicated to treat GERD by preventing transient LES relaxation.

Decreased Resting Tone of LES

The lower esophageal sphincter is the primary barrier to reflux. A constantly weak, low-pressure LES allows reflux every time the pressure in the stomach exceeds that in the LES. This condition is present in a minority of GERD cases, and is usually associated with severe esophagitis.

Delayed Gastric Emptying

If gastric emptying is delayed, then the gastric fluid volume and pressure are increased. Delayed gastric emptying is believed to contribute to a small proportion of GERD cases by increasing the amount of fluid available for reflux.

Pulmonary and Wound Complications of GERD

Complications of GERD should be thought of in two categories. The first is pulmonary. These patients often present with respiratory complaints, such as shortness of breath and wheezing, and are often misdiagnosed as having asthma. Pulmonary manifestations, such as asthma, coughing, or intermittent wheezing, as well as vocal cord inflammation with hoarseness, may occur in some patients. These complications are as a result of acid reflux into the laryngeal and bronchial passages that trigger significant local inflammation. These patients' respiratory difficulties usually resolve after laparoscopic surgery.

The second series of complications after reflux disease should be thought of as wounds. These patients suffer the morbidity from a local wound in the distal esophagus. The majority of patients with GERD will have a normal appearing and histologically normal distal esophagus upon endoscopy and biopsy. Nevertheless, the appearance of mild to severe esophagitis can be

readily visualized grossly in many patients and grossly one can see that these are local wounds (Figs. 8.1 to 8.3). These wounds in patients with GERD are manifested by erythema, isolated erosions, confluent erosions, circumferential erosions, deep ulcers, esophageal stricture, or replacement of normal esophageal epithelium with abnormal (Barrett's) epithelium. In clinical terms this sequale is esophageal erosion, esophageal ulcer, esophageal stricture, or replacement of normal esophageal epithelium with abnormal (Barrett's) epithelium.

Surgical Therapy of GERD

Nissen fundoplication was reported in 1956.[4] Surgical treatment of gastroesophageal reflux and gastric fundoplication since then, have undergone numerous technical modifications and changes in attempt to reduce recurrence of GERD, and diminish side effects and complications of these operations.[5]

Although this operation has been performed for decades, it was a long-term, controlled, randomized trial of 247 patients with complicated GERD (i.e., peptic esophageal ulcer, stricture, erosive esophagitis, or Barrett's esophagus) that showed that surgical therapy was far more efficacious than medical therapy in improving the symptoms and endoscopic findings of esophagitis.[6] Furthermore, this study concluded that antireflux surgical therapy, when performed by an experienced surgeon, is a valid alternative to protracted and cumbersome medical therapy.

The first laparoscopic Nissen fundoplications (LNFP) were reported in 1991.[7,8] These reports were followed by many published small series of LNFP that gave great impetus to surgical therapy of GER and proved to have all the advances of minimally invasive surgery. The goals of laparoscopic antireflux surgical intervention remain similar to those of an open technique[9] and include: positioning and lengthening of the LES in the abdominal cavity, increasing the pressure of LES, and narrowing the crura to hold LES. These goals must be achieved, however, without jeopardizing the patients' swallowing ability.

Indications for Laparoscopic Antireflux Surgery

Although the mechanism by which antireflux surgery affects GERD is not entirely clear,[10] its effectiveness in treating a select group of patients suffering from GERD has been clearly established. Furthermore, although the indications for antireflux surgery did not change significantly in the last years, the initial success and the popularity of laparoscopic treatment, fear by the patients of long-term side effects and cost containment concerns have decreased the threshold of patients and gastroenterologists in seeking

definitive treatment of GERD. This is manifested by an increased number of these procedures performed by general surgeons.[11]

Antireflux surgery is traditionally reserved for patients who have been refractory to medical therapy.[3] Other current indications for operative intervention include noncompliance with medical therapy, recurrent strictures, laryngeal and pulmonary complications (laryngitis, bronchitis, aspiration pneumonia or asthma) and bleeding. Although antireflux procedure will arrest the reflux of acidic of alkaline gastric content into the esophagus and thus arrest the progression of metaplasia, heal ulceration, and resolve the stricture, its use in the face of Barrett's esophagus has been controversial.[12] Another group of patients where antireflux surgery is gaining momentum is in young patients who prefer surgery instead of a lifetime of exposure and the expense of medical therapy and life-style changes. Other diseases that are associated with GERD that require fundoplication include reflux-induced motility disorders, reflux after myotomy, and reflux in the severely neurologically impaired.[13] In addition to the preceding indications, the prerequisites for a successful antireflux surgery are careful patient selection, appropriate technique, and understanding of the principles of antireflux operation. Above all, the anatomy, physiology, and pathology of GERD should be mastered and integrated into the decision-making process when treating these patients surgically.[14,15]

Indications for Antireflux Surgery

In general, antireflux surgery is indicated in patients with increased esophageal exposure to gastric content, as documented by 24-hour esophageal pH studies, in patients with mechanically defective lower esophageal sphincter based on manometric studies, and in those patients with adequate esophageal contractility and peristalsis.[16] The basic indications for antireflux surgery are:

1. Failure of medical therapy
2. Noncompliance with treatment
3. Barrett's metaplasia
4. Aspiration with asthma or recurrent infection
5. Recurrent bleeding or anemia secondary to persistent esophagitis
6. Symptomatic children after 2 years of age with the GER. Antireflux surgery should be done sooner in infants who have significant morbidity from their reflux (e.g., failure to thrive or respiratory insufficiency).
7. Patients who have reflux as a consequence of their abdominal surgery. The pH of this reflux may be acidic, neutral or alkaline.
8. Reflux after esophageal myotomy
9. Motility disorders that result in reflux
10. Reflux that results in motility disorders
11. Stricture

Contraindications for Antireflux Surgery

The contraindications to laparoscopic Nissen fundoplication should be considered absolute, relative, or procedure specific. Absolute contraindications include those that would preclude laparotomy. The absolute contraindications to a laparoscopic antireflux surgery are:

1. Mechanical and paralytic ileus
2. Severe cardiac conduction abnormality
3. Myocardial infarction within the previous 6 months
4. Inability to tolerate general anesthesia
5. Severe pulmonary insufficiency
6. Cardiac ischemia
7. Cardiac failure
8. Coagulopathy
9. Peritonitis
10. Shock

Relative contraindications include to laparoscopic antireflux procedure include splenomegaly, an enlarged caudate lobe, an enlarged left lobe of the liver, multiple previous laparotomies, or a large portion of the stomach being tethered in the thoracic cavity. Procedure-specific contraindications include esophageal shortening, previous vagotomy, or previous gastrectomy. It must be emphasized that if there is esophageal shortening, then it will be extremely difficult to wrap the esophagus in the abdominal cavity, thereby negating the effectiveness of the procedure; therefore, if a patient has a shortened esophagus, or any of the previously mentioned surgical procedures, then a laparoscopic Nissen fundoplication should not be attempted.

Preoperative Studies

The decision for surgical antireflux procedure should not be based solely on symptoms of GERD because many upper gastrointestinal complaints are common and nonspecific, and they may accompany a variety of conditions including achalasia, diffuse esophageal spasm, cancer, peptic ulcer disease, gallstones, and coronary artery disease. Furthermore, asthma, chronic cough, chest pain, wheezing, and hoarseness may also be nonspecific, or they may represent different pathologic entities. The importance of objectively identifying which symptoms are the consequence of GERD is mandatory before any procedure is scheduled.

The evaluation of patients for antireflux surgery is independent of the choice of open versus laparoscopic technique. Many patients will have had with an upper gastrointestinal series (i.e., barium esophagram). Although this test is useful to evaluate other pathologic processes, the esophagram is

highly unspecified for GERD that will require surgical intervention. However, a lateral video esophagram, however, does provide useful information about the length of the esophagus. Nevertheless, we do not routinely recommend an esophagram for a patient with GERD.

All patients undergoing an antireflux procedure should have an esophagogastroduodenoscopy (EGD) and manometry. If a symptomatic patient has esophagitis proven by biopsy, then a 24-hour pH probe is not necessary. The degree of reflux and mucosal damage should be graded using the Savory-Miller classification.[17] If the patient does not have esophagitis on EGD, however, then a 24-hour pH probe is necessary. If the DeMeester score[16] on the 24-hour probe is greater than 30, then antireflux surgery will have greater than 90% success rate of eliminating the preoperative symptoms. If the DeMeester score is less than 30 after objective evaluation, however, then, an exhaustive work up must be completed to rule out other pathological processes. Furthermore, if the DeMeester score is less than 30 or normal, then the symptom index portion of the pH evaluation can be useful to establish candidacy for antireflux surgery. To be specific, the symptom index[18] is an objective evaluation of the percentage of the subjective symptoms compared with the objective drop in pH. This emphasizes the importance and relevance of the pH probe and 24 hour test. This has replaced the provocative Bernstein test.[19] When there is occasionally a concern of gastric emptying, radionuclide imaging should be done. This will give an indication of the ability of the stomach to empty.[12]

Manometry is necessary in all patients for two distinct reasons. First, it is required to rule out other disease processes, such as achlasia and scleroderma. Second, the results of manometry will influence the specific type of antireflux surgery. For example, patients with normal peristaltic amplitude and reflux disease are ideal candidates for a Nissen fundoplication. On the other hand, patients with weak distal esophageal contractions benefit from a partial fundoplication such as the Toupet procedure.

Summary

The widespread use of H2 blockers and the long-term use of proton pump inhibitors predicted the end for surgical procedures to correct acid reflux. Less invasive procedures employed through the laparoscope, however, have made permanent physiologic correction more worthy of consideration. No one should be enthusiastic to call a patient who has not yet really tried a course of omeprazole a medical failure. The operations are in the realm of reasonable relative to medical therapy, but they have not acquired the lead position. Most patients with GERD are perfectly managed and kept safe from harm by medical management. In the course of managing patients with GERD, however, the conditions and complications discussed

in this chapter may intervene to make the continued medical therapy unreasonable. In this regard it is a happy occasion for the GERD patient that the operations for this disease are now associated with low morbidity and superb results. The newer operations apply the same stringent scientific basis as do the more radical predecessors and for the meantime represent a powerful resource to patients and their gastroenterologists.

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