REVIEW ARTICLE

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Esophageal Motility Disorders and Gastroesophageal Reflux Disease

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Dysphagia, heartburn, regurgitation, and noncardiac chest pain are symptoms of aberrant esophageal motility and reflux disease. Gastroesophageal reflux disease (GERD) is the second most common gastrointestinal diagnosis in the ambulatory setting, the most common being abdominal pain.[1] GERD affects 18 to 28% of people living in North America.[2] Potential complications of GERD include stricture, Barrett's esophagus, and esophageal adenocarcinoma. In terms of health care costs, disorders of the esophagus consumed $18.1 billion in the year 2015 (second only to hepatitis); $12.4 billion of this spending was on acid-inhibition therapy (H_2 blockers and proton-pump inhibitors).[1] Esophageal motility disorders and GERD are benign in nature, with minimal associated mortality but a substantial effect on the quality of health.

Lower Esophageal Sphincter

The sphincter mechanism at the esophagogastric junction consists of the lower esophageal sphincter, made up of smooth muscle, and the crural diaphragm, made up of skeletal muscle — referred to as the internal and external lower esophageal sphincter, respectively. The smooth muscles of the lower esophageal sphincter, organized as clasp and sling fibers[3] (Fig. 1A), have different physiological properties and neural innervation.[4,5] Three-dimensional reconstructions of cross-sectional views of the human lower esophageal sphincter show its unique myoarchitecture.[6,7] The circular muscles of the lower esophageal sphincter cross each other at the angle of His and continue into the stomach as sling fibers; this latter portion of the lower esophageal sphincter has been known by several names, including the inner oblique layer of the stomach, the collar of Helvitus (named in 1719), and the cardiac loop of Willis (named in 1674).[8] The right crus of the diaphragm also has unique myoarchitecture; it divides into two bundles, and the muscle fascicles cross each other at the posterior–inferior and ventral–superior ends of the hiatus in a scissorlike fashion and encircle the esophagus (Fig. 1B).[7] The muscle fascicles of the external anal sphincter also cross at the dorsal and ventral ends of the anal canal.[9] Whether each sphincter in the body has unique myoarchitecture requires study, because it has important implications for how each one brings about the circumferential closure of orifices and how dysfunctional states might arise.

The lower esophageal sphincter and crural diaphragm are anatomically superimposed[10] and tightly anchored by the two leaves of phrenoesophageal ligament; these leaves originate from the surface of the diaphragm, one from the thoracic surface and the other from the abdominal surface. The two leaves are inserted into the adventitia of the esophagus and into connective tissue between the longitudinal and circular muscles.[11] The lower esophageal sphincter is innervated by the vagus (parasympathetic or inhibitory) and spinal (sympathetic or excitatory) nerves and by neurons of the myenteric plexus (excitatory and inhibitory).[12] The crural diaphragm is innervated by two phrenic nerves. The high-pressure zone of the

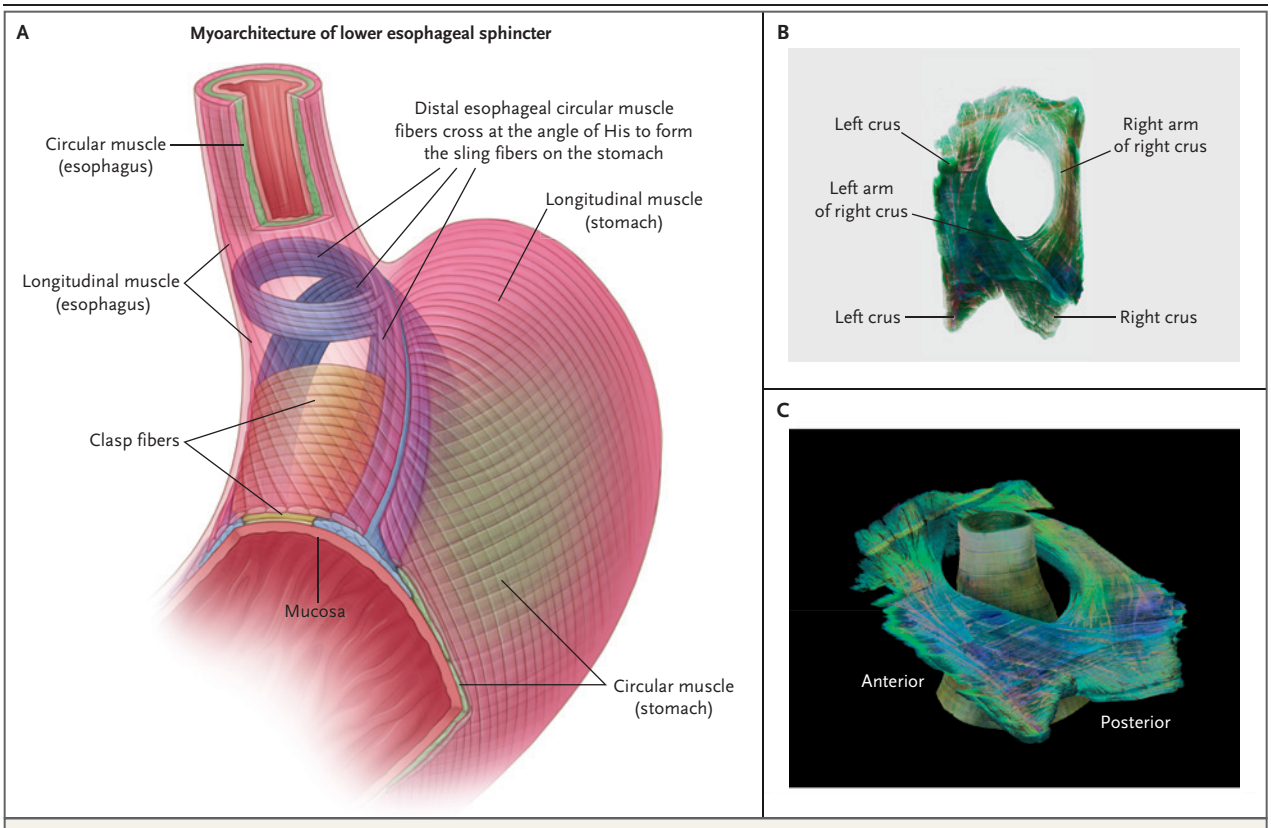

Figure 1. Myoarchitecture of the Lower Esophageal Sphincter and Hiatus.

Panel A shows the microscopic myoarchitecture of the circular and longitudinal muscle layers of the lower esophageal sphincter and stomach. The circular muscle fibers of the esophagus cross each other at the angle of His to continue as the oblique muscle fibers (innermost muscle layer of the stomach) on the ventral and dorsal surface of the stomach. Panels B and C show the microscopic anatomy of the esophageal hiatus in superior view and posterior view, respectively. The two bundles of the right crus cross each other first and then encircle the esophagus to form the esophageal hiatus at the posterior–inferior and anterior–superior ends.

lower esophageal sphincter is shorter and has higher pressures along the greater curvature of the stomach and is longer and has lower pressures in the area toward the lesser curvature. The tone of the lower esophageal sphincter is mostly myogenic.[13] Excitatory and inhibitory neurons of the myenteric plexus and many neurohumoral factors play roles in the modulation of the tone.[14] The crural diaphragm provides extrinsic "squeeze"; it increases esophagogastric junction pressure during inspiration, coughing, sneezing, or bending to guard against increases in pressure gradients between the chest and the abdomen.[15]

PHYSIOLOGY OF ESOPHAGEAL PERISTALSIS

Each volitional act of swallowing elicits relaxation of the upper and lower esophageal sphincters and any ongoing esophageal contraction (deglutitive inhibition), followed by sequential or peristaltic contraction. Repetitive swallowing at short intervals (of <4 seconds) induces sustained inhibition of the esophagus and lower esophageal sphincter and one peristaltic contraction at the end of the last swallow.[16] Neural control of skeletal and smooth muscle of the esophagus occurs through the nucleus ambiguus and dorsomotor nucleus of the vagus nerve (in the brain stem), respectively. The myenteric plexus, which contains excitatory neurons (releasing acetylcholine and substance P) and inhibitory neurons (releasing nitric oxide and vasoactive intestinal polypeptide) and is located between the circular and longitudinal muscles of the esophagus, provides the local control mechanism.[17]

During peristalsis, circular and longitudinal muscles contract and relax in a synchronous fashion, and a liquid bolus travels through the esophagus in the shape of an American football

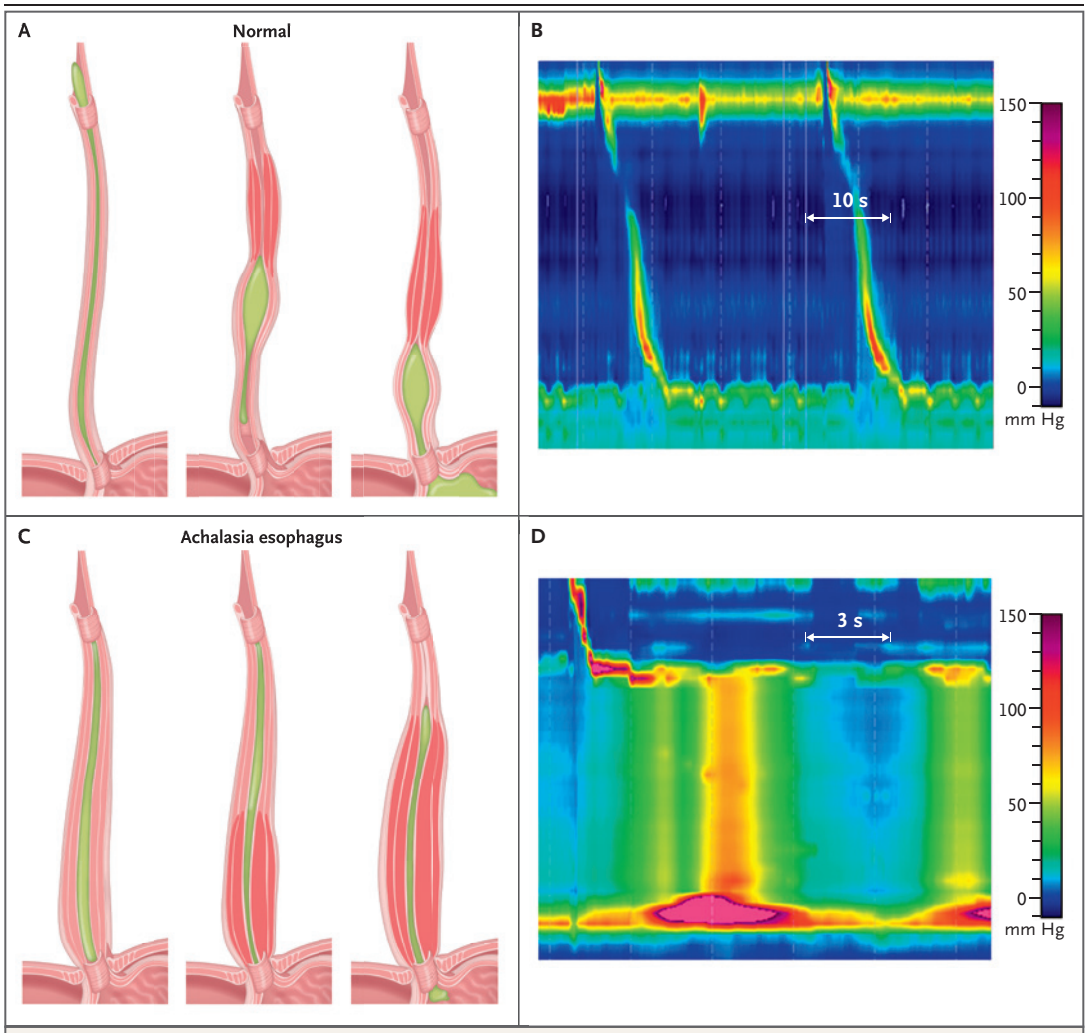

Figure 2. Esophageal Function in a Person with Normal Function and in a Patient with Achalasia Esophagus.

Contraction behind and relaxation ahead of the bolus are the essential elements of peristalsis. In a normally functioning esophagus, the bolus travels the esophagus in the shape of an American football (Panel A), and manometry shows normal lower esophageal sphincter relaxation and normal peristalsis (Panel B). In a patient with achalasia esophagus, partial esophageal emptying is seen (Panel C), and manometry shows poor lower esophageal sphincter relaxation and an absence of peristalsis (Panel D).

(Fig. 2A).[18] The fact that the bolus takes on this shape implies that similar to contraction, relaxation of the esophagus moves sequentially along the length of esophagus. Longitudinal muscle contraction in the contracted segment of the esophagus results in esophageal shortening and sliding between the circular and longitudinal muscle layers in the distended segment. Motor neurons of the myenteric plexus layers are mechanosensitive, which raises the possibility that longitudinal muscle contraction in the contracted segment of the esophagus might be responsible for the activation of mechanosensitive inhibitory motor neurons, resulting in relaxation of the circular muscles distal to the contraction and thereby leading to relaxation of the lower esophageal sphincter.[17] Esophageal distention is an important stimulus of esophageal peristalsis; a change in posture from supine to upright and the Trendelenburg position affect the amplitude of esophageal contraction and relaxation. Axial shortening of the esophagus during peristalsis and lifting of the lower esophageal sphincter (by 2 to 3 cm) are critical for relaxation of the lower esophageal sphincter; these also result in physiologic herniation of the stomach into the chest

Table 1. Primary and Secondary Esophageal Motility Disorders.

Disorder	Details
Primary or idiopathic esophageal motility disorders	
Major	
Achalasia esophagus types 1, 2, and 3	Impaired relaxation of the lower esophageal sphincter and no peristalsis
Esophagogastric junction outflow obstruction	Impaired relaxation of the lower esophageal sphincter and normal peristalsis
Distal esophageal spasm	Normal relaxation of the lower esophageal sphincter and reduced latency of distal esophageal contraction
Hypercontractility of the esophagus	Also called nutcracker or jackhammer esophagus; normal relaxation of the lower esophageal sphincter with high-amplitude peristaltic contractions
Minor	
Ineffective esophageal peristalsis	Low-amplitude esophageal contractions or fragmented esophageal peristalsis
Secondary esophageal motility disorders	
Myasthenia gravis	Low pressure of upper esophageal sphincter and esophageal muscle fatigue with repetitive swallowing
Dermatomyositis	Low pressure of upper esophageal sphincter and esophageal muscle fatigue with repetitive swallowing
Scleroderma esophagus	Low to absent pressure of lower esophageal sphincter; absence of esophageal contractions and peristalsis in smooth muscle of the esophagus
Connective-tissue disorders	Low to absent pressure of lower esophageal sphincter; absence of esophageal contractions and peristalsis in smooth muscle of the esophagus
Diabetes mellitus	Low-amplitude, multipeaked esophageal contractions and low pressure of the lower esophageal sphincter
Secondary achalasia esophagus	Associated with neoplastic infiltration of lower esophageal sphincter or Chagas' disease

that appears as a phrenic ampulla on radiologic barium swallow studies.[19] Emptying of the phrenic ampulla, which takes place more slowly than emptying of the esophagus, is not due to peristalsis; rather, it is related to descent of the lower esophageal sphincter from an intrathoracic to an intraabdominal location.[20]

ESOPHAGEAL MOTILITY DISORDERS

The esophageal motility disorders are categorized as secondary and primary disorders. The pathogenesis of secondary motility disorders is associated with systemic diseases (Table 1). Among patients with scleroderma, 70% have involvement of the esophagus, with replacement of muscles by fibrous tissue and dysfunction of the cholinergic nerves.[21,22] Loss of peristalsis and a hypotensive lower esophageal sphincter result in severe reflux disease and stricture in patients with scleroderma esophagus. Patients with diabetes mellitus have hypotensive and multipeaked esophageal peristaltic contraction related to involvement of autonomic neuropathy that may result in mild dysphagia and an increased risk of GERD.[23] Infiltration of the lower esophageal sphincter by neoplastic processes, such as adenocarcinoma of the stomach, results in secondary achalasia. Primary or idiopathic esophageal motility disorders are of interest because they are much more common than secondary esophageal motility disorders, their pathogenesis remains mysterious, and new diagnostics and therapeutic agents have been targeted toward these disorders.

High-resolution manometry performed with closely spaced pressure sensors and with pressures displayed as colored topographic plots (Fig. 2B) is the current standard for diagnosing esophageal motility disorders. Increases and decreases in the vigor of esophageal contractions in the distal esophagus, shorter latency of distal esophageal contraction, and impaired relaxation of the lower esophageal sphincter are key criteria used in the Chicago classification of primary esophageal motility disorders.[24] The classification

scheme for esophageal motility disorders is not based on histologic characteristics; whether these disorders represent a spectrum of the same disease or different disease entities remains unknown.

Impaired relaxation of the lower esophageal sphincter and absence of peristalsis are the key diagnostic criteria for achalasia esophagus. For patients with this disorder, swallowing rather than peristalsis induces the simultaneous pressure waves in the esophagus (pressurization) that are responsible for esophageal emptying, although the emptying in these patients is incomplete. On the basis of the amplitude of pressurization, achalasia esophagus has been categorized into three types that have prognostic significance — types 1, 2, and 3 — with the amplitude of pressurization increasing from type 1 to type 3. Of the three types of achalasia esophagus, type 2 has the best response to medical and surgical treatment, and type 3 has the worst response.

Distal esophageal spasm is characterized by reduced latency of distal esophageal contraction, and nutcracker (or jackhammer) esophagus is characterized by a greater-than-normal amplitude of distal esophageal contractions that are peristaltic. Low pressure of the lower esophageal sphincter and low-amplitude esophageal contractions (ineffective esophageal peristalsis) are generally associated with reflux disease.

A relatively new diagnostic technique involves a functional lumen imaging probe (FLIP) system, which can also be used to diagnose esophageal motility disorders at the time of upper endoscopy in a patient who is under sedation; this technique is associated with less catheter-related discomfort for the patient than high-resolution manometry. FLIP measures distensibility (opening and compliance) function of the lower esophageal sphincter and esophagus and the direction of peristalsis (antigrade or retrograde).[25] FLIP is also useful in assessing the completeness of myotomy in achalasia and possible tightness of Nissen's fundoplication.[26]

PATHOGENESIS OF SYMPTOMS IN ESOPHAGEAL MOTILITY DISORDERS

Dysphagia, chest pain, heartburn, and regurgitation are symptoms of esophageal motility disorders. The intensity of individual symptoms varies, depending on the diagnosis; for example, dysphagia and weight loss are prominent in achalasia, and chest pain (imitating cardiac angina, sometimes debilitating) is the presenting symptom in patients with distal esophageal spasm and hypercontractile (nutcracker or jackhammer) esophagus. Dysphagia in patients with nutcracker or jackhammer esophagus and in patients with type 3 achalasia may be related to low compliance or a lack of relaxation of the distal esophagus, which causes alteration in the bolus flow pattern in the esophagus.[27] Surgical or medical therapy targeted toward ablation of the lower esophageal sphincter only (pneumatic dilation, Heller's myotomy, or onabotulinumtoxinA injection into the lower esophageal sphincter) may not work well in these patients.[20,28] A long myotomy extending up to the aortic arch, which was used to treat diffuse esophageal spasm in the past, is a better therapeutic option for these patients.[29]

The genesis of esophageal pain and heartburn in esophageal motility disorders is multifactorial. Patients with esophageal pain have a hypersensitive and low-compliance (rigid) esophagus.[30] Many different stimuli can cause esophageal pain, including GERD, sustained contraction of longitudinal muscle,[31] low blood flow in the esophageal wall,[32] up-regulation of nociceptive receptors in esophageal mucosa (e.g., vanilloid receptor 1 and acid-sensitive ion channel), hypersensitivity of the spinal and supraspinal neural pathways,[33,34] and cortical hypervigilance.[35,36]

In advanced cases of achalasia (i.e., types 1 and 2), myenteric ganglia are completely replaced by fibrous tissue. However, in patients with type 3 (spastic) achalasia, ganglia are present but surrounded by chronic inflammatory cells — T (predominantly) and B lymphocytes. Infection with herpes simplex virus, measles virus, or human papillomavirus, because of their affinity for squamous epithelium and neurotropism in a genetically susceptible host, is thought to be the cause of autoimmune destruction of myenteric neurons.[37] Cytokines released by T lymphocytes and antineuronal antibodies that are present in the serum of patients with achalasia may cause up-regulation of genes that results in an imbalance between excitatory motor neurons (increasing activity) and inhibitory motor neurons (reducing activity) in spastic achalasia.

Ultrasound imaging of the esophagus reveals esophageal muscle hypertrophy and an increase in muscle mass; these findings are more pro-

nounced in patients with achalasia than in patients with distal esophageal spasm and more pronounced in patients with distal esophageal spasm than in patients with nutcracker esophagus (Fig. 3).[38] Studies in animals show that esophageal outflow obstruction leads to a corkscrew appearance on barium swallow examination, muscle hypertrophy,[39] inflammatory changes around the myenteric plexus,[40] and loss of inhibitory innervation,[41] findings similar to those in patients with achalasia. FLIP studies show poor distensibility of the lower esophageal sphincter in most patients with primary esophageal motility disorders.[25]

A dysfunctional lower esophageal sphincter or esophagogastric junction may be the main abnormality in all primary esophageal motility disorders, and changes in esophageal muscle and myenteric neurons are secondary to outflow obstruction caused by dysfunctional lower esophageal sphincter. Recently, abnormalities of the crural diaphragm have been reported in patients with achalasia, which raises the possibility that a dysfunctional hiatus may be one of the causes of major esophageal motility disorders.[42]

MEDICAL AND SURGICAL THERAPY FOR ESOPHAGEAL MOTILITY DISORDERS

Medical and surgical treatment methods are more effective in achalasia than in other esophageal motility disorders. Loss of peristalsis in achalasia is generally not reversible. The pharyngeal pump and gravity are adequate for propelling a swallowed bolus to the distal esophagus. Reducing resistance to outflow by a dysfunctional lower esophageal sphincter is the mainstay of treatment for achalasia esophagus. It can be achieved by several approaches: endoscopic injection of botulinum toxin into the lower esophageal sphincter, pneumatic dilatation, peroral endoscopic myotomy, and surgical myotomy.

The onabotulinumtoxinA injection provides partial symptom relief for approximately 6 months in patients with achalasia, and it can be repeated several times. OnabotulinumtoxinA injection reduces lower esophageal sphincter pressure and paralyzes the crural diaphragm; it also promotes GERD.[43] Pneumatic dilatation of the lower esophageal sphincter with a 30-mm, 35-mm, or 40-mm balloon, an outpatient procedure, is an effective treatment with efficacy similar to that of the Heller's myotomy.[44] However, dilatations need to be repeated every few years. Perforation of the esophagus (incidence, 1 to 2%) is a serious complication of pneumatic dilatation. Laparoscopic Heller's myotomy with partial fundoplication (Dor's procedure) is the treatment of choice for achalasia.[45] Peroral endoscopic myotomy has received worldwide attention,[46,47] and studies have shown that it has efficacy similar to that of Heller's myotomy.[45] The dysphagia outcomes with peroral endoscopic myotomy are better than those with pneumatic dilatation and similar to those with Heller's myotomy. GERD is more common after peroral endoscopic myotomy (40%), possibly because partial fundoplication is not possible. However, peroral endoscopic myotomy allows a long myotomy, which is needed for the treatment of achalasia type 3 and distal esophageal spasm.

Some patients have both esophageal motility disorders and GERD; hence, a brief trial course of acid-inhibition therapy is warranted in patients with predominant heartburn and chest pain. Medical therapy for spastic esophageal motility disorders with calcium-channel blockers or onabotulinumtoxinA injection into the lower esophageal sphincter works in selected patients. However, the results of controlled trials have not been uniformly positive,[48] probably because of heterogeneity of the pain mechanisms. Esophageal pain in esophageal motility disorders does not respond well to medical and surgical therapies. Dysphagia in the context of normal findings on esophagogastric duodenoscopy, biopsy, and high-resolution manometry (functional dysphagia) may respond to empirical esophageal dilatation. Esophageal motility disorders are benign disorders that rarely progress over time and lack curative treatments; hence, therapy should be conservative in mild cases. Dietary and lifestyle modifications and sublingual administration of nitroglycerine or hyoscyamine may be effective in patients with infrequent esophageal pain.

PATHOGENESIS OF GERD

GERD is a condition in which a normal physiological event is affected by an imbalance between aggressive and defensive factors (Fig. 4A). Reflux of gastric contents generally occurs through three mechanisms: transient relaxation of the lower esophageal sphincter (Fig. 4C), low

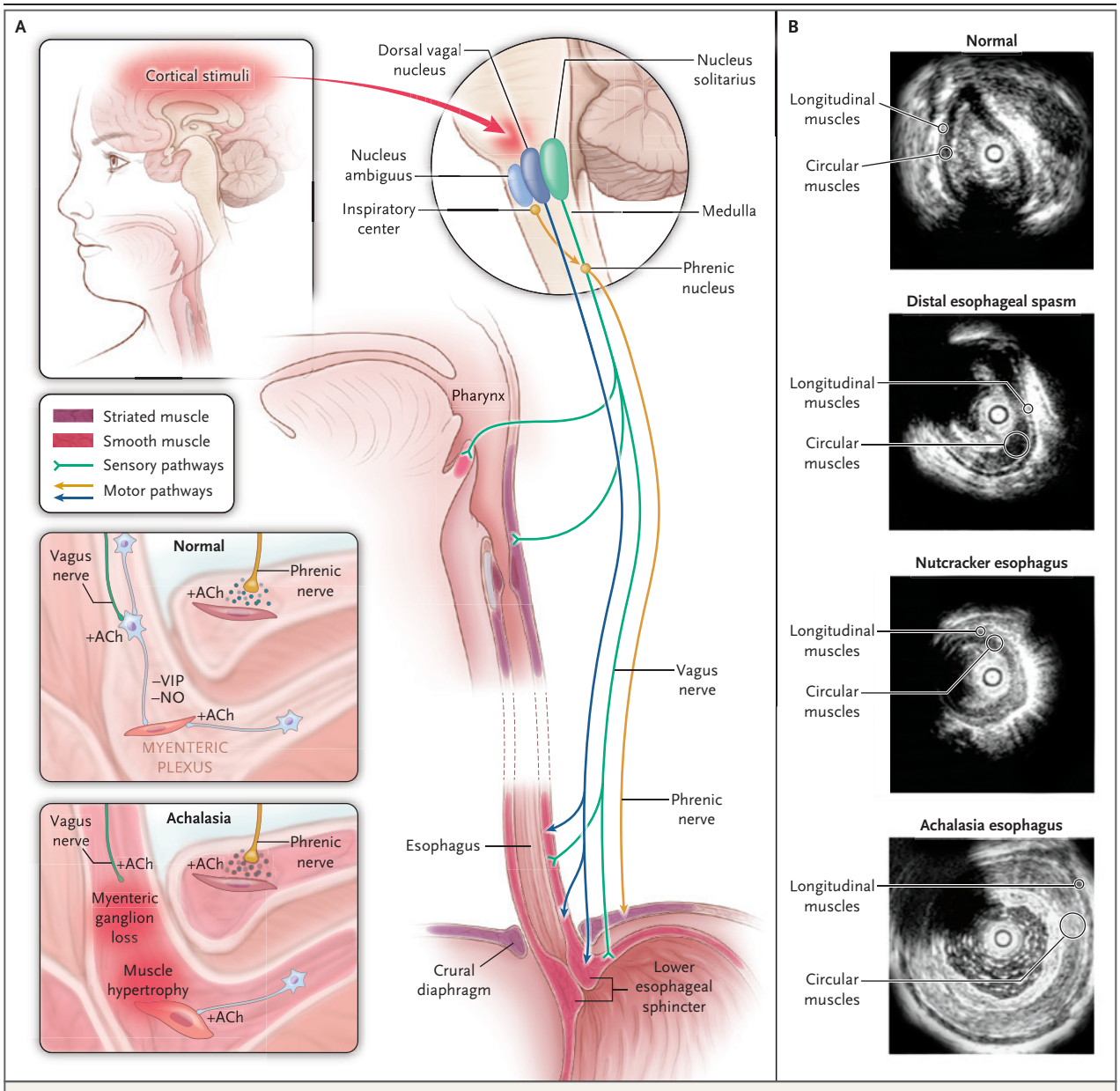

Figure 3. Pathogenesis of Esophageal Motility Disorders.

Panel A shows extrinsic (vagus) and intrinsic (myenteric plexus) innervation of the esophageal wall and the defect in patients with achalasia esophagus. ACh denotes acetylcholine, NO nitric oxide, and VIP vasoactive intestinal peptide. Panel B shows ultrasound imaging of the distal esophagus in a person with normal function, a patient with distal esophageal spasm, a patient with nutcracker esophagus, and a patient with achalasia esophagus. The muscle layer of the esophagus is thicker in patients with esophageal motility disorders; the thickest muscle is seen in patients with achalasia esophagus.

pressure of the lower esophageal sphincter, and sliding hiatus hernia.

Transient relaxation of the lower esophageal sphincter is the major mechanism underlying belching and reflux in healthy persons and in patients with GERD without hiatus hernia.[49] Transient relaxation of the lower esophageal sphincter is accompanied by longitudinal muscle contraction of the distal esophagus and inhibition of the crural diaphragm (Fig. 4C),[50] and gastric distention is the predominant stimulus of transient relaxation of the lower esophageal sphincter. Despite its importance in the pathogenesis of GERD, drugs targeting transient re-

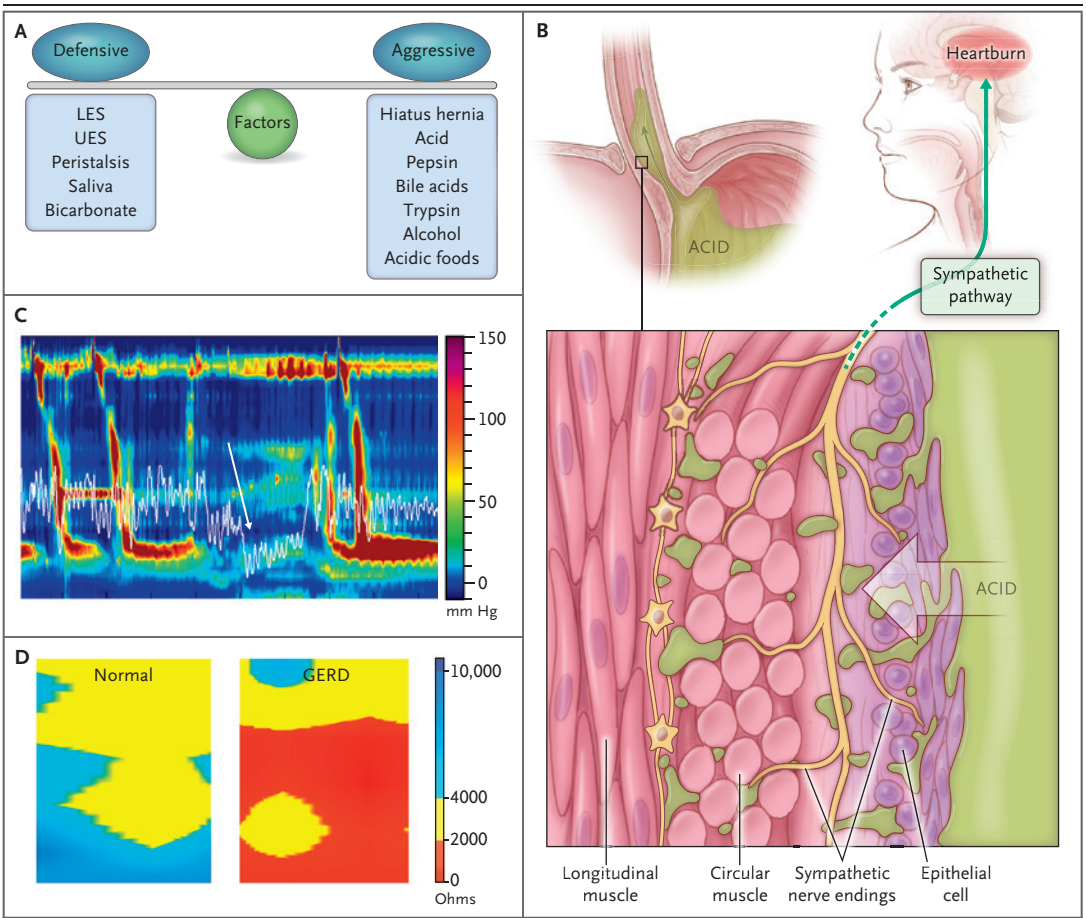

Figure 4. Pathogenesis of GERD.

Panel A shows the balance of defensive and aggressive factors in the pathogenesis of gastroesophageal reflux disease (GERD). GERD commonly develops because of a compromise in the defensive mechanism of reduced lower esophageal sphincter (LES) pressure, hiatus hernia, and transient relaxation of the lower esophageal sphincter. UES denotes upper esophageal sphincter. Panel B shows the genesis of symptoms of heartburn and activation of the sympathetic pathway. Reflux of gastric contents causes damage to esophageal epithelium that results in widening of the intercellular spaces. Acid permeates the deeper layer of mucosa and stimulates nerves of the sympathetic pathway, resulting in a sensation of heartburn. Panel C is a manometric recording showing transient relaxation of the lower esophageal sphincter, which is the most common mechanism of reflux in patients without hiatus hernia. The arrow indicates relaxation of the lower esophageal sphincter independent of a swallow. The line tracing indicates changes in mucosal blood flow, which are likely to be related to longitudinal muscle contraction of the esophagus during transient relaxation of the lower esophageal sphincter. Panel D shows an esophageal mucosal impedance contour of mucosal integrity; mucosal damage results in lowering of mucosal impedance in patients with GERD (red indicates low mucosal integrity, yellow indicates minor changes, and blue indicates intact mucosa). The vertical dimension represents data from sensors arranged longitudinally along the esophagus, and the horizontal dimension represents data from sensors arranged around the internal circumference of the esophagus.

laxation of the lower esophageal sphincter have limited benefit and substantial adverse events.[51] Most reflux that occurs during the day occurs while the lower esophageal sphincter and the crural diaphragm are anatomically separate (sliding hiatus hernia).[52] Patients with moderate-to-severe GERD (i.e., erosive esophagitis[53] and Barrett's esophagus[54]) have hiatus hernia, which highlights its importance in GERD.

Esophageal peristalsis is important for the clearance of refluxate volume and for reducing the duration of esophageal exposure to gastric contents.[55] Abnormalities in esophageal peristalsis result in prolonged exposure of the esopha-

geal epithelium to gastroduodenal contents, which leads to esophagitis. Restoration of the esophageal pH after a reflux event also occurs through neutralization by saliva and bicarbonate-rich secretions of the esophageal submucosal glands. The clinical consequences of poor neutralization by salivary bicarbonate are seen in patients with xerostomia and Sjögren's syndrome, in whom GERD and esophageal erosions are common. The upper esophageal sphincter is the final line of defense against reflux of gastric contents into the oropharynx and possible aspiration.[56] Transition from physiologic to pathologic reflux is a consequence of defects in one or more of the defensive mechanisms.

The aggressive factors in the pathogenesis of GERD are gastroduodenal contents — that is, acid, pepsin, bile acids, and trypsin.[57] However, gastroduodenal secretions are not present in greater amounts in patients with GERD or Barrett's esophagus than in other persons.[58] Acid and pepsin together are more injurious to the esophageal epithelium than acid alone.[59] Pepsin activity is substantially reduced when the pH is greater than 4. The degree of esophageal injury in GERD parallels the increase in frequency and duration of pepsin and acid-reflux exposure (when the pH is less than 4). Acid inhibition is the cornerstone of treatment for GERD-related esophagitis. Esophageal exposure to gastroduodenal contents results in dilated intercellular spaces and increased epithelial permeability to noxious agents, which leads to symptom generation by activation of subepithelial nerve endings.[60] Studies in animal and human esophageal cell lines show that injury to the esophageal epithelium induces an inflammatory reaction in the submucosal layer, with release of cytokines that mediate injury.[61,62] Acid-sensitive receptors called transient receptor potential vanilloid type 1 (TRPV-1) receptors, which are located in the submucosal nerve endings, may be important in causing the reflux-induced symptoms. Reductions in the acidity of refluxate, rendering it less damaging to the esophageal epithelium, account for the high success rates (90 to 95%) for healing of the esophagitis with proton-pump inhibitors. Acid pocket,[63] an unneutralized acidity in the gastric cardia after meals, may explain the clinical paradox of having neutralization of gastric acid by meals as well as the presence of symptoms of GERD in the immediate postprandial state (Fig. 4B).

Obesity is a major risk factor for GERD symptoms, erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma[64]; the mechanism is increased gastric pressure that results in more transient relaxation of the lower esophageal sphincter.[65] The waist-to-hip ratio is more important than body-mass index in association with GERD.[66] Weight reduction reduces GERD symptoms and esophageal acid exposure. The role of dietary factors such as alcohol, carbonated drinks, and coffee intake in GERD is controversial.

DIAGNOSTIC AND TREATMENT STRATEGIES FOR GERD

Clinical suspicion based on a patient's report of classic symptoms of heartburn (burning sensation rising from the stomach or lower chest toward the neck or throat), usually occurring after eating large meals or spicy or citrus foods, is the typical clinical history associated with GERD. Regurgitation, defined as perception of flow or refluxed gastric contents into the pharynx, may not accompany heartburn but suggests the presence of a mechanical defect (e.g., a hiatus hernia). However, the sensitivity (30 to 76%) and specificity (62 to 96%) of such symptoms for diagnosing GERD are suboptimal[67] because of a substantial overlap in symptoms among GERD, gastroparesis, functional dyspepsia, esophageal motility disorders, and rumination syndrome. GERD can also cause angina-like pain, worsening or difficult-to-treat asthma, posterior laryngitis, chronic cough, dental erosions, and disordered sleep.[68] The relationship of these extraesophageal or atypical manifestations to GERD is often difficult to prove.

Symptom response to a short (6-week) course of once-daily oral therapy with a proton-pump inhibitor confirms a clinical diagnosis of GERD in patients with typical or suspected atypical symptoms, with the caveat that response to placebo is common in these patients.[69] The recommendation for patients who have a response to empirical proton-pump inhibitor therapy is to taper to the lowest dose of acid suppression needed for symptom control.[70] In patients who have no response or a partial response to once-daily proton-pump inhibitor therapy, treatment often involves switching to another agent or to twice-daily dosing, although data to assess the efficacy of

salvage therapy are lacking. Despite the fact that proton-pump inhibitors are highly effective in treating acid-peptic disorders, concerns about their long-term safety have resulted in reexamination of their use in the long term.[70]

Diagnostic testing is indicated if there are any alarm symptoms such as dysphagia, weight loss, iron deficiency anemia, or bleeding. Patients with these symptoms should first undergo an upper endoscopic examination to rule out Barrett's esophagus, strictures, and cancer. Further testing is indicated if symptoms persist after 6 to 8 weeks of acid-suppressive therapy. Diagnostic methods usually include ambulatory reflux testing, esophageal manometry, and gastric emptying tests; the goal of these tests is to rule out a contribution of GERD to the patient's symptoms. Mucosal integrity tests performed during endoscopy while the patient is under sedation provide real-time determination of the integrity of the esophageal epithelia as a surrogate marker for GERD-related damage (Fig. 4D).[71,72]

PROTON-PUMP INHIBITOR–RESISTANT GERD

In the era of over-the-counter proton-pump inhibitors, the majority of patients with typical or atypical symptoms of GERD who are seen by physicians are the ones who have persistent symptoms despite taking proton-pump inhibitors. In this group, the role of diagnostic testing is to identify patients whose symptoms are not from GERD. Endoscopy is normally performed in these patients. Ambulatory impedance–pH monitoring while the patient is taking a proton-pump inhibitor may identify the small group of patients whose symptoms are from continued reflux of acid or weakly acidic gastric juice containing bile acids. A recent phase 2b trial of a drug that targets bile acids in patients with GERD whose symptoms are refractory to proton-pump inhibitor therapy showed promise for reducing symptoms of heartburn and regurgitation.[73]

Patients with proton-pump inhibitor–resistant GERD may undergo esophageal pH testing while not taking proton-pump inhibitor therapy. On the basis of the results, patients are categorized into three groups: those with abnormal acid reflux scores (i.e., an esophageal pH of less than 4 for more than 6% of the time over a period of 24 hours) (nonerosive reflux disease), those with normal acid reflux scores and a positive symptom correlation with reflux (acid-sensitive esophagus), and those with normal reflux scores and no symptom association with reflux events (functional heartburn).[74] Studies show that patients in these three groups have different responses to proton-pump inhibitors: the patients with nonerosive GERD have a better response than those in the other two groups, and those with functional heartburn have the least response. In a recent study, patients without a response to proton-pump inhibitors who had a positive symptom–reflux association on impedance–pH testing had a better response to antireflux surgery than to medical therapy.[75] High-resolution manometry has a role in defining conditions that mimic GERD — that is, achalasia, rumination syndrome, and supragastric belching. Heartburn is present in 35% of patients with achalasia. If the results of a gastric emptying test are found to be abnormal, dietary modifications and possibly prokinetic agents may be helpful.

Performed by an experienced surgeon, Nissen's fundoplication surgery is effective in treating GERD[76]; however, 10 to 20% of patients have bothersome side effects such as dysphagia, gas bloat, difficulty belching, and vomiting. Patients may be good candidates for antireflux surgery if they have concerns about long-term effects of proton-pump inhibitor therapy or if they have one of the following characteristics: recalcitrant symptoms of GERD (with GERD confirmed by proper testing), especially in patients with hiatus hernia; regurgitation symptoms that do not respond to adequate medical therapy in patients with no clinically significant gastric or esophageal motility abnormalities; or moderate-to-severe GERD associated with aspiration, asthma, recurrent pneumonia, or lung transplantation.

CONCLUSIONS

Symptoms of esophageal motility disorders and GERD are common, with myriad manifestations and a substantial effect on patients' quality of life. The pathogenesis of esophageal motility disorders involves degeneration of the inhibitory motor neurons of the myenteric plexus and muscular changes. Impaired relaxation and opening of the lower esophageal sphincter is common to all major motility disorders, and disruption of the lower esophageal sphincter by either medical or surgical means is the mainstay of treatment.

The pathogenesis of GERD involves an incom-

petent antireflux barrier, defined as low pressure of the lower esophageal sphincter, hiatus hernia, transient relaxation of the lower esophageal sphincter, and impaired esophageal peristalsis. In the absence of an effective medical therapy to enhance the competence of the lower esophageal sphincter and esophageal peristalsis, suppression of gastric acidity is the mainstay of medical treatment for GERD. A lack of response to adequate acid-inhibition therapy for suspected GERD should arouse suspicion of a non-GERD diagnosis. Recent advances in diagnostic testing for esophageal motility disorders and GERD have improved the management of these disorders.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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