

CURRENT

Diagnosis & Treatment



GASTROENTEROLOGY, HEPATOLOGY, & ENDOSCOPY

second edition

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Oropharyngeal & Esophageal Motility Disorders

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► General Considerations

Oropharyngeal and esophageal motility disorders have significant impact on patients' quality of life. Mechanical and functional problems may interact to cause symptoms; thus, diagnosis of these disorders can be challenging.

Dysphagia (difficulty swallowing) must be distinguished from other symptoms such as odynophagia (pain on swallowing, suggestive of a defect in mucosal integrity, eg, from irradiation, inflammation, or infection) and aphagia (inability to swallow, generally suggestive of mechanical obstruction in patients presenting acutely). Symptoms that do not necessarily correlate with the immediate process of swallowing, such as rumination and globus sensation, should also be discerned.

Dysphagia can be differentiated into two categories: (1) oropharyngeal (also called transfer dysphagia), arising from disorders affecting the oropharynx, larynx, and upper esophageal sphincter (UES); and (2) esophageal, arising from the esophagus, lower esophageal sphincter (LES), or gastroesophageal junction. The causes of dysphagia are many, and specific entities are considered here.

Massey BT, Shaker R. Oral pharyngeal and upper esophageal sphincter motility disorders. *GI Motility Online*. Available at: <http://www.nature.com/gimo/index.html>; doi: 10.1038/gimo19, 2006.

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Wise JL, Murray IA. Oral, pharyngeal and esophageal motility disorders in systemic diseases. *GI Motility Online*. Available at: <http://www.nature.com/gimo/index.html>; doi: 10.1038/gimo40, 2006.

OROPHARYNGEAL MOTILITY DISORDERS

OROPHARYNGEAL DYSPHAGIA



ESSENTIALS OF DIAGNOSIS

- History of poor oral bolus preparation and control, difficulty in initiating a swallow, nasal and oral regurgitation, aspiration and coughing with swallowing, food sticking at the level of the throat.
- Evidence of a generalized neuromuscular disorder.
- Documentation by videofluoroscopic swallowing study (VFSS).

► General Considerations

Many neuromuscular disorders can cause dysphagia (Table 13–1). Among these are various disorders causing cortical lesions; supranuclear, nuclear, and cranial nerve lesions; defects of neurotransmission at the motor end plates; and muscular diseases.

Many patients with dysphagia are elderly and hence develop this symptom secondary to other disorders (eg, stroke). History of strokes or other neurologic illnesses, nasal regurgitation and frequent coughing immediately upon swallowing, and poor oral coordination of bolus formation or dysphonia may help suggest the greater likelihood of oropharyngeal dysphagia over esophageal dysmotility, but diagnosis, assessment of severity, and therapeutic intervention are generally guided by VFSS.

Table 13-1. Neuromuscular disorders causing oropharyngeal dysphagia.

<p>1. Diseases of cerebral cortex and brainstem</p> <p>a. With altered consciousness or dementia</p> <ul style="list-style-type: none"> • Dementias, including Alzheimer disease • Altered consciousness, metabolic encephalopathy, encephalitis, meningitis, cerebrovascular accident, brain injury <p>b. With normal cognitive functions</p> <ul style="list-style-type: none"> • Brain injury • Cerebral palsy • Rabies, tetanus, neurosyphilis • Cerebrovascular disease • Parkinson disease and other extrapyramidal lesions • Multiple sclerosis (bulbar and pseudobulbar palsy) • Amyotrophic lateral sclerosis (motor neuron disease) • Poliomyelitis and post-poliomyelitis syndrome <p>2. Diseases of cranial nerves (V, VII, IX, X, XII)</p> <p>a. Basilar meningitis (chronic inflammatory, neoplastic)</p> <p>b. Nerve injury</p> <p>c. Neuropathy (Guillain-Barré syndrome, Bell palsy, afamilial dysautonomia, sarcoid, diabetic, and other causes)</p> <p>3. Neuromuscular</p> <p>a. Myasthenia gravis</p> <p>b. Eaton-Lambert syndrome</p> <p>c. Botulinum toxin</p> <p>d. Aminoglycosides and other drugs</p> <p>4. Muscle disorders</p> <p>a. Myositis (polymyositis, dermatomyositis, sarcoidosis)</p> <p>b. Metabolic myopathy (mitochondrial myopathy, thyroid myopathy)</p> <p>c. Primary myopathies (myotonic dystrophy, oculopharyngeal myopathy)</p> <p>d. Acute and chronic radiation injury</p>

Adapted, with permission, from Goyal RK. Dysphagia. In: Fauci AS, Braunwald E, Kasper DL, et al (editors). *Harrison's Principles of Internal Medicine*, 17th ed. McGraw-Hill, 2008:237-240.

► Clinical Findings

A. Symptoms and Signs

History and physical examination provide the most valuable information in making the diagnosis. Defects in different phases of oropharyngeal swallowing should be identified by careful analysis of symptoms and signs.

Defects in the oral preparatory phase of swallowing manifest as chewing problems, oral stasis of food, inability to form a bolus, and coughing, choking, or aspiration pneumonia from regurgitation and aspiration. These symptoms occur during or immediately after the onset of swallowing. In disorders of neuromuscular dysfunction, liquids are usually more problematic than solids in causing symptoms of misdirection. On the other hand, secondary causes from oral mucosal lesions (eg, aphthous ulcers, herpetic lesions, mucositis), dental problems, or decreased saliva and xerostomia (eg, medications, Sjögren) may lead to poor processing

of the bolus and are often less problematic with moistened foods or liquids.

Generally, problems in the pharyngeal phase result in dysphagia, which the patient localizes to the throat. Often the patient makes repeated attempts to clear the throat of food or saliva.

Abnormalities of the UES phase have no distinctive symptoms, but impaired UES opening further impairs pharyngeal transport and may aggravate the symptoms of pharyngeal stasis. On the other hand, a hypotonic UES may lead to esophagopharyngeal reflux and aspiration not related to swallowing.

Because many neuromuscular structures involved in swallowing are also involved in speech, dysarthria and dysphonia are common in these patients. Moreover, patients usually have evidence of neuromuscular defects in other parts of the body. Many patients with oropharyngeal dysphagia have impaired consciousness and cognitive functions that may make evaluation difficult.

B. Videofluoroscopic Swallowing Study (VFSS)

VFSS is the study of choice for the evaluation of oropharyngeal dysphagia (Figure 13-1). VFSS allows slow-motion replay of oropharyngeal swallowing. This aids in identifying defects of the oropharyngeal phase of swallowing, which normally takes less than a second to complete. Different consistencies of food and various swallowing maneuvers can be used during the study to assess for retention or aspiration. Barium swallow or an upper gastrointestinal series is not useful in evaluation of oropharyngeal dysphagia. Plain radiographs and computed tomography (CT) scan of the neck are useful in evaluating structural lesions such as tumors and cysts. Imaging studies should be obtained prior to upper endoscopy, because pharyngeal and upper esophageal abnormalities such as diverticula and malignant strictures can perforate in this poorly visualized region.

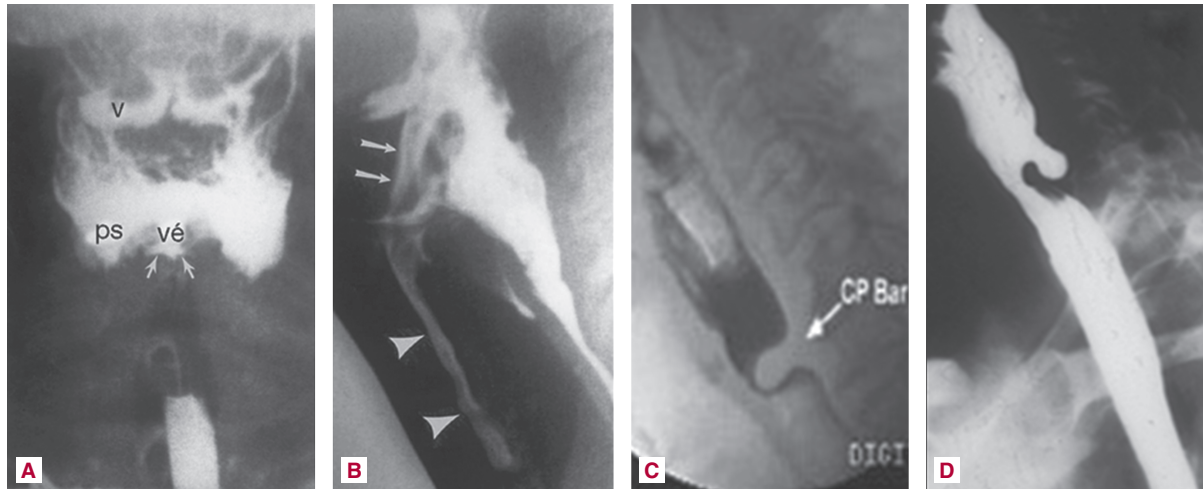
Gramigna GD. How to perform videofluoroscopic swallowing studies. *GI Motility Online*. Available at: <http://www.nature.com/gimo/index.html>; doi: 10.1038/gimo95, 2006.

C. Manometry

Because of the complex anatomy of the oral and pharyngeal passages and the speed of coordinated contractions, intraluminal manometry is not usually helpful. However, it may be useful in the evaluation of upper esophageal function and resistance to flow across the UES.

D. Videoendoscopy

Regular upper endoscopy is not helpful in the evaluation of oropharyngeal dysphagia; however, videoendoscopy, available at some specialized centers, can provide information about oropharyngeal dysfunction.



▲ **Figure 13-1.** Radiologic appearance of oropharyngeal motility disorders. **A:** Frontal view of the pharynx demonstrates aspiration of retained bolus. Note that there is retention of contrast in the valleculae (v) and piriform sinuses (ps). No swallow is taking place, yet there is entry of contrast into the laryngeal vestibule (vé) and between the vocal folds and in the ventricle (arrows). **B:** A stop-frame print from a cinepharyngogram in the lateral position shows incomplete laryngeal closure during swallowing with laryngeal penetration (arrows) and aspiration (arrowheads) down into the trachea. The bolus is passing through the open cricopharyngeus into the cervical esophagus. Degenerative change is noted in the cervical spine. **C:** Cricopharyngeal bar. **D:** Zenker diverticulum. (Reproduced, with permission, from (A) Jones B (editor): *Normal and Abnormal Swallowing: Imaging in Diagnosis and Therapy*, 2nd edition. Springer-Verlag, 2003; (B) Jones B, Donner MW (editors): *Normal and Abnormal Swallowing: Imaging in Diagnosis and Therapy*. Springer-Verlag, 1991.)

► Differential Diagnosis

Figure 13-2 is an algorithm outlining an approach to the patient with oropharyngeal dysphagia.

► Complications

The major complications of oropharyngeal dysphagia are fatal pulmonary aspiration and pneumonia, malnutrition, and weight loss.

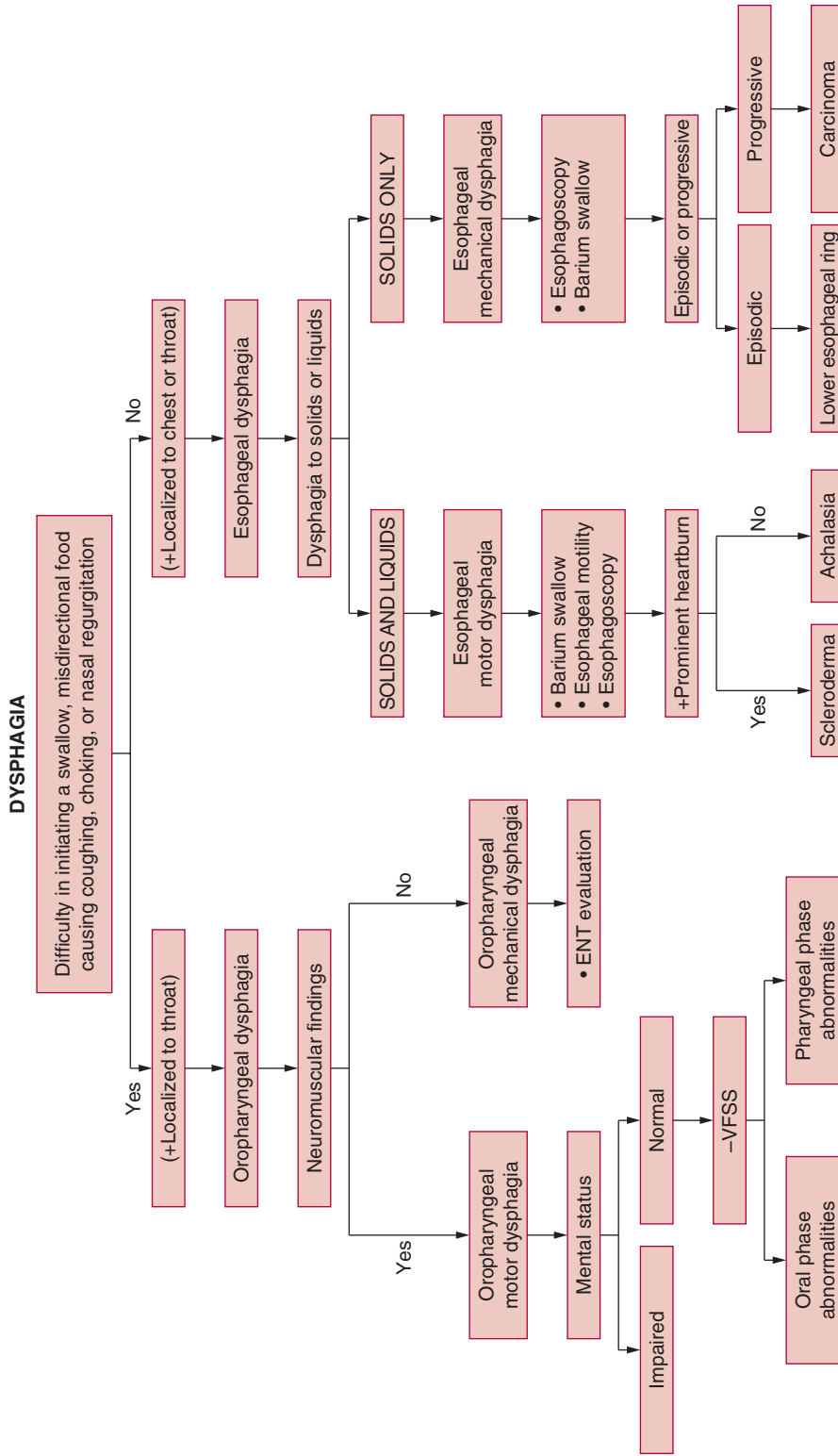
► Treatment

Evaluation and management by a deglutition team consisting of a deglutitionist (speech and swallow therapist), radiologist, gastroenterologist, otolaryngologist, and neurologist provide the best outcome in the care of these patients. Deglutitionists assess the risk of aspiration, type of food, and patient posture that is most likely to prevent aspiration and facilitate safe swallowing. Certain rehabilitative exercises to strengthen swallowing muscles may be helpful. Electrical stimulation of muscles is also being explored as a newer avenue of therapy for oropharyngeal dysphasia. Investigations are performed to

find the underlying cause of the disorder, and appropriate therapy, if available, is initiated. If safe oral feeding cannot be undertaken, a percutaneous endoscopic gastrostomy (PEG) tube is placed by a gastroenterologist. The overall management of the patient, rather than focused treatment of the swallowing difficulty, is essential for effective management.

► Course & Prognosis

Prognosis depends on the underlying cause, compliance with therapy, and prevention of acute pulmonary complications. Patients with recent cerebrovascular accidents may regain their swallowing function after 6–8 weeks. Those with diseases such as myasthenia gravis, metabolic myopathies such as thyroid disorders, polymyositis, and Parkinson disease usually respond to appropriate treatment. Other patients, such as those with muscular dystrophy, amyotrophic lateral sclerosis, and multiple sclerosis, sometimes develop recurrent aspiration pneumonia that may prove fatal.



▲ **Figure 13-2.** Algorithm outlining an approach to the patient with dysphagia. ENT, ear, nose, throat; VFSS, videofluoroscopic swallowing study.

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CRICOPHARYNGEAL ACHALASIA & CRICOPHARYNGEAL BAR

UES dysfunction has been variably defined and described. Cricopharyngeal “achalasia” is a confused and often misused term that is best avoided since the diagnosis is rarely made by manometric or electromyographic evidence to demonstrate failure of UES relaxation, but historically used when there is radiographic evidence for failed opening of the UES. UES “achalasia” should be replaced by more specific descriptions such as failed UES relaxation, cricopharyngeal spasms, and cricopharyngeal bar. The clinical presentation of these entities comprising UES dysfunction is variable, but most patients complain of food sticking in the lower third of the neck. Patients may also have heartburn, choking, and odynophagia, and less commonly dysphonia or globus sensation during swallows. These entities are considered primary if the abnormality is confined to the cricopharyngeus muscle without neurologic or systemic cause and secondary if produced by another disease process. Primary UES dysfunction, in turn, is subdivided into idiopathic and intrinsic myopathies (eg, polymyositis, inclusion body myositis, muscular dystrophy, hypothyroidism). Secondary causes include amyotrophic lateral sclerosis, polio, oculopharyngeal dysphagia, stroke, Parkinson disease, fibrosis from prior irradiation, and peripheral nerve disorders such as myasthenia gravis and diabetic neuropathy. Gastroesophageal reflux has also been suggested to cause cricopharyngeal spasm.

The diagnostic criteria for UES dysfunction are subject to much controversy. The plain radiographic appearance is not reliable in making this diagnosis, and some experts advocate highly specialized radiologic (VFSS) and solid-state manometric probe studies. However, lack of data and standardization in measurements (eg, in anteroposterior, lateral, or circumferential pressures) and the possibility of the manometric catheter eliciting cricopharyngeal spasms have thwarted its standard use. Many clinicians base their diagnosis simply on symptoms. Thus, the true incidence of UES dysfunction or UES “achalasia” is unknown but may involve 5–25% of patients being evaluated for dysphagia.

The cricopharyngeal bar is a radiologic abnormality, often equated with UES “achalasia.” However, manometric

studies in patients with cricopharyngeal bars have demonstrated generally normal UES pressure and relaxation. Thus, they are generally not associated with failed UES relaxation or cricopharyngeal spasm. Barium swallow shows a characteristic prominent projection on the posterior wall of the pharynx at the level of the lower part of the cricoid cartilage (see Figure 13–1C). A transient cricopharyngeal bar is seen in up to 5% of individuals without dysphagia undergoing upper gastrointestinal studies; it can be produced in normal individuals during a Valsalva maneuver. A persistent cricopharyngeal bar may be caused by fibrosis or frank myositis in the cricopharyngeus. Some cases have been reported with dermatomyositis or inclusion body myositis. However, muscle biopsies are not routinely taken.

Failed UES relaxation is poorly responsive to medical therapy including muscle relaxants. Cricopharyngeal myotomy is usually not helpful unless obstruction at the cricopharyngeus is demonstrated by videofluoroscopy in severely symptomatic patients, such as those with significant aspiration or weight loss. Similarly, local injection of botulinum toxin is falling out of favor with recognition that effects are short lived and the injections are rarely well confined to the affected muscles; frequent leakage outside the cricopharyngeus may result in temporary dysphonia or aspiration. However, a trial injection may be considered to aid in making the diagnosis, or for patients who are poor surgical candidates. These procedures are contraindicated in patients with cervical tumors and relatively contraindicated in those who have a fibrotic lesion after neck irradiation or who have a progressive neurologic disorder such as bulbar palsy. One exception appears to be patients with oculopharyngeal dysphagia, who appear to do well with surgical myotomy or with repeated dilations. Myotomy is also contraindicated in the presence of severe gastroesophageal reflux because it may lead to pharyngeal and pulmonary aspiration. In patients with gastroesophageal reflux, aggressive therapy with proton pump inhibitors is warranted in addition to management of the underlying disorder. The classic surgical approach is external cricopharyngeal myotomy.

ZENKER DIVERTICULUM

Zenker diverticulum arises in the posterior wall of the hypopharynx, just above the cricopharyngeus muscle. The pathogenesis of Zenker diverticulum is not fully understood. It may form due to natural weakness of the pharynx (Killian triangle) associated with impaired opening of the cricopharyngeus muscle, which is often fibrotic. Barium swallow or VFSS shows characteristic findings that allow easy diagnosis (see Figure 13–1D). With time, the diverticulum may become very large. Zenker diverticulum may retain food and secretions and classically lead to halitosis, delayed regurgitation, recurrent aspiration, and pneumonia. Dysphagia is usually due to compression of a food-filled diverticulum of the esophagus. Treatment is diverticulectomy

with cricopharyngeal myotomy, and transoral approaches have also been introduced as an alternative and minimally invasive treatment.

GLOBUS PHARYNGEUS

Globus pharyngeus is a common functional disorder characterized by the persistent or intermittent nonpainful sensation of a lump or foreign body in the throat, but without any difficulty in swallowing or pain on swallowing. This disorder is more common in women than in men and is often associated with an underlying psychiatric disorder experienced during an emotional event. Some of these patients also have gastroesophageal reflux disease (GERD), and ambulatory pH monitoring or empiric trial of acid suppression is recommended. The latter has been shown to improve symptoms in a third of the patients. Findings on barium swallow are generally normal, but may discern pharyngeal dysfunction or possible cricopharyngeal bar in patients with these symptoms. Esophageal manometry also may reveal achalasia in patients with these symptoms, even when devoid of dysphagia. Results of upper endoscopy, when performed, are generally normal. However, an observational report describes improvement after ablation of cervical inlet patches, and this endoscopically often missed entity located at or just distal to the UES should be sought carefully. In most cases, treatment of globus pharyngeus consists of reassurance. Patients with concurrent psychiatric disorders, such as depression, panic, and somatization disorders, may benefit from tricyclic antidepressant therapy. Relaxation therapy has also been reported as helpful in refractory patients.

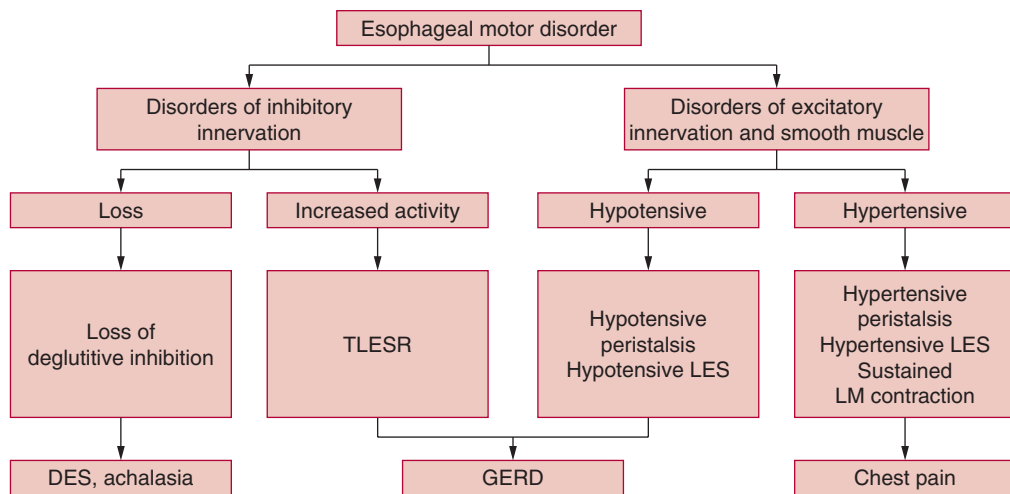
ESOPHAGEAL MOTILITY DISORDERS

Three esophageal motility disorders commonly seen in clinical practice are esophageal motor dysphagia, GERD, and esophageal chest pain. In these disorders, symptoms result from dysfunction of one or more of the mechanisms necessary for normal esophageal function.

Esophageal motility disorders are classified, depending on the involvement of one or more of the three components of esophageal peristalsis, as disorders of inhibitory innervation, excitatory innervation, or smooth muscles (Figure 13-3).

The inhibitory innervation to the esophagus consists of vagal preganglionic neurons and the postganglionic neurons in the myenteric plexus, which release vasoactive intestinal peptide (VIP) and nitric oxide. The inhibitory pathway is responsible for relaxation of the LES and the gradient of peristaltic contraction in the esophageal body. Deficiency of inhibitory innervation results in achalasia and diffuse esophageal spasm. In achalasia, both the LES and esophageal body are affected, whereas in diffuse esophageal spasm, the esophageal body is primarily affected. Increased inhibitory nerve activity is responsible for so-called transient LES relaxation (TLESR).

The excitatory innervation consists of vagal preganglionic neurons and postganglionic neurons that release acetylcholine and substance P. The excitatory nerves contribute to basal LES hypertension, hypertensive contraction, and the force of peristaltic contraction. Deficiency of the excitatory nerves causes hypotensive LES and hypotensive peristaltic contractions. The esophageal body and LES consist of phasic and tonic muscles, respectively. Phasic muscles of the esophageal body contract during peristalsis, and tonic muscles of



▲ **Figure 13-3.** Pathophysiologic classification of motor disorders of the smooth muscle portion of the esophagus. DES, diffuse esophageal spasm; GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter; LM, longitudinal muscle; TLESR, transient lower esophageal sphincter relaxation.

LES are responsible for tonic contraction. Muscle disorders may lead to hypotensive LES and hypotensive peristalsis.

In most conditions outlined below, a combination of imaging studies and intraluminal pressure measurements helps obtain an accurate clinical diagnosis.

Goyal RK. Diseases of the esophagus. In: Fauci AS, Braunwald E, Kasper DL, et al (editors). *Harrison's Principles of Internal Medicine*, 17th ed. McGraw-Hill, 2008:1847–1855.

Goyal RK, Chaudhury A. Physiology of normal esophageal motility. *J Clin Gastroenterol*. 2008;42:610–619.

Pandolfino JE, Kahrilas PJ. New technologies in the gastrointestinal clinic and research: impedance and high-resolution manometry. *World J Gastroenterol*. 2009;15:131–138.

ESOPHAGEAL MOTOR DYSPHAGIA



ESSENTIALS OF DIAGNOSIS

- ▶ Dysphagia to solids and liquids, localized to the chest or throat.
- ▶ Associated symptom of chest pain and regurgitation.
- ▶ Coughing and choking spells at night and unrelated to swallowing.
- ▶ Symptoms of GERD.
- ▶ Confirmation of abnormal motility by barium study and esophageal manometry.

▶ General Considerations

Dysphagia must be distinguished from odynophagia (pain on swallowing); the latter suggests a breach in mucosal integrity by trauma, infection, and inflammation. The role of upper endoscopy is to rule out mucosal abnormalities such as strictures, webs, malignancies, infections, and eosinophilic esophagitis. Full-column barium swallow may reveal muscular rings, which are often missed on endoscopy. Manometric studies differentiate specific motility disorders.

▶ Pathogenesis

Motor dysphagia in the thoracic esophagus occurs when deglutitive inhibition is lacking, due to loss of inhibitory nitrergic nerves, and peristaltic contractions become non-peristaltic; when the LES does not relax properly; or when the peristaltic contractions are weakened due to muscle weakness. Causes of esophageal motor dysphagia are listed in [Table 13–2](#).

Table 13–2. Causes of esophageal motor dysphagia.

<p>1. Disorders of cervical esophagus (see “Oropharyngeal Motility Disorders” in text)</p> <p>2. Disorders of thoracic esophagus</p> <p>a. Disease of smooth muscle or excitatory nerves</p> <p>(1) Weak muscle contraction or LES tone</p> <ul style="list-style-type: none"> • Idiopathic • Scleroderma and related collagen vascular diseases • Hollow visceral myopathy • Myotonic dystrophy • Metabolic neuromyopathy (amyloid, alcohol, diabetes) • Drugs—anticholinergics, smooth muscle relaxants <p>(2) Enhanced muscle contraction</p> <ul style="list-style-type: none"> • Hypertensive peristalsis (nutcracker esophagus) • Hypertensive LES, hypercontracting LES <p>b. Disorders of inhibitory innervation</p> <p>(1) Diffuse esophageal spasm</p> <p>(2) Achalasia</p> <ul style="list-style-type: none"> • Primary • Secondary (Chagas disease, carcinoma, lymphoma, neuropathic intestinal pseudo-obstruction syndrome) • Contractile (muscular) lower esophageal ring
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LES, lower esophageal sphincter. Adapted, with permission, from Goyal RK. Dysphagia. In: Fauci AS, Braunwald E, Kasper DL, et al (editors). *Harrison's Principles of Internal Medicine*, 17th ed. McGraw-Hill, 2008:237–240.

▶ Clinical Findings

A. Symptoms and Signs

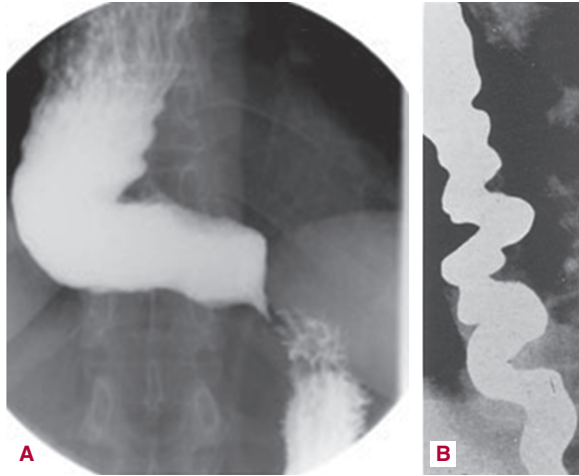
Dysphagia resulting from dysfunction of the esophageal body is described as a feeling that the swallowed bolus becomes “stuck” or “hung up” on the way down. This may be accompanied by pain or discomfort. The patient typically describes difficulty in swallowing both solids and liquids. Although most patients feel as though the bolus stops at the level of the suprasternal notch, the area of obstruction may be well below this. Many patients have associated symptoms of regurgitation and chest pain.

B. Radiography

Chest radiographs may show mediastinal widening and air-fluid level when a food-filled dilated esophagus is present as in long-standing achalasia. Barium swallow may show the characteristic appearance of achalasia or diffuse esophageal spasm ([Figure 13–4](#)). Radiographic studies also help in excluding mechanical causes of dysphagia. Videofluoroscopic examination of the esophagus may identify abnormalities in peristaltic sequence and in the force of peristaltic contractions.

C. Manometry and Impedance Manometry

Esophageal manometry can be used to measure the strength (amplitude), duration, and sequential nature of the contractions



▲ Figure 13-4. Radiologic appearance of motor disorders of the smooth muscle portion of the esophagus. **A:** Note the sigmoid-shaped esophagus and “bird-beaking” of the lower end in achalasia. **B:** Corkscrew appearance in diffuse esophageal spasm. (B: Used with permission from Dr. Harvey Goldstein)

of the esophageal body, as well as the resting pressure and relaxation of the LES. This technique involves passage, through the nose and into the esophagus and stomach, of a small, flexible catheter with an array of pressure sensors.

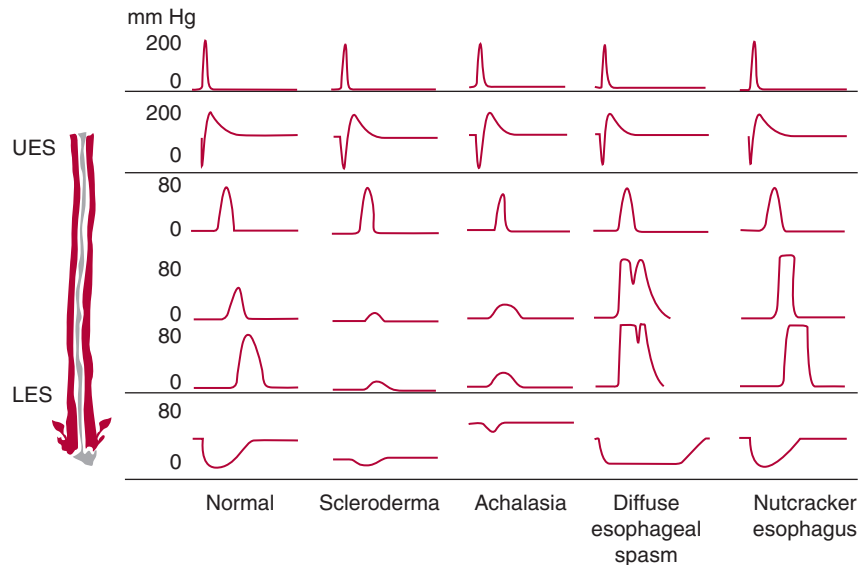
Figure 13-5 summarizes patterns of esophageal motility in normal subjects and in a variety of esophageal motility disorders. Newer manometric probes with an array of dozens of sensors (high resolution) have also helped identify some patients with weak or slow contractions near the transition zone (a variable area of interdigitating striated and smooth muscle fibers) that correlate with dysphagia. Impedance sensors in the same catheter assembly have helped correlate functional liquid and viscous bolus clearance in patients with various types of esophageal motility abnormalities, and have allowed new algorithms to analyze pressure waves.

D. Endoscopy

Endoscopy is required in most patients with esophageal motility disorders that cause dysphagia to exclude mechanical causes such as peptic stricture and other complications of an erosive esophagitis, and rule out lesions such as gastroesophageal junction adenocarcinoma that may produce secondary achalasia. Biopsies at multiple levels of the esophageal body are also often obtained to rule out eosinophilic esophagitis.

► Differential Diagnosis

Refer to Figure 13-2, which outlines an approach to the patient with dysphagia.



▲ Figure 13-5. Motility patterns in esophageal smooth muscle disorders. LES, lower esophageal sphincter; UES, upper esophageal sphincter. (Adapted, with permission, from Goyal RK: Diseases of the Esophagus. In: Fauci AS, Braunwald E, Kasper DL, et al (editors): *Harrison’s Principles of Internal Medicine*, 17th ed. McGraw-Hill, 2008.)

► Treatment

Management of esophageal motility disorders depends on the type of the disorder and its clinical consequences. (For details, see “Disorders of Inhibitory Innervation” and “Disorders of Excitatory Nerves and Smooth Muscles” later in this chapter.)

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GASTROESOPHAGEAL REFLUX DISEASE (SEE CHAPTER 11)

GERD is the most common manifestation of impaired esophageal motility and one of the most common disorders seen in clinical practice. The basic cause of GERD is incompetent antireflux barriers at the gastroesophageal junction, which normally prevents backflow of gastric acid into the stomach. Competence of the gastroesophageal barrier is the result of the intra-abdominal location of the LES, mucosal folds at the gastroesophageal junction, LES closure, reflex LES contraction, and the proper position of the diaphragmatic crura, which can be disrupted with the presence of a sliding hiatal hernia. Factors such as increased intra-abdominal pressure (that may arise, for example, from obesity), gastric stasis (that may arise, for example, from chronic diabetes or medications), and inappropriate transient relaxations of the LES can increase the likelihood of developing GERD.

The pathogenesis of gastroesophageal reflux is complicated and multifactorial. Important esophageal motor abnormalities underlying GERD are hypotensive LES, TLESR, or both. Hypotensive esophageal contractions are commonly associated with hypotensive LES and contribute to reflux-associated esophageal mucosal damage.

Although the main clinical manifestations of GERD are heartburn and regurgitation, other manifestations, including development of chronic cough and the premalignant condition of Barrett esophagus, may occur. Moreover, the majority of patients with GERD do not have symptoms. Manifestations and complications of GERD are discussed in detail in Chapter 11.

- Diamond NE. Pathophysiology of gastroesophageal reflux disease. *GI Motility Online*. Available at: <http://www.nature.com/gimo/index.html>; doi: 10.1038/gimo21, 2006.
- Falconer J. Gastro-oesophageal reflux and gastroesophageal reflux disease in infants and children. *J Fam Health Care*. 2010;20:175–177.
- Harding SM. Gastroesophageal reflux and chronic cough. *GI Motility Online*. Available at: <http://www.nature.com/gimo/index.html>; doi: 10.1038/gimo77, 2006.

ESOPHAGEAL CHEST PAIN



ESSENTIALS OF DIAGNOSIS

- Chronic symptoms.
- Rule out life-threatening conditions (eg, ischemic heart disease).
- Rule out panic disorder, related psychiatric disorders, and musculoskeletal disorders.
- Well-accepted causes are reflux esophagitis, achalasia, and diffuse esophageal spasm.
- Probable causes are hypertensive esophageal motor disorders, cervical inlet patch, sustained longitudinal muscle contraction, and esophageal hypersensitivity.

► General Considerations

Heartburn and odynophagia are classical symptoms of esophageal disease. However, some patients with esophageal disorders present with chest pain that is neither typical heartburn nor odynophagia. Esophageal chest pain may resemble cardiac chest pain. This overlap is due to the spinal primary sensory afferent that carries cardiac and esophageal nociceptive information and also innervates common cutaneous segments.

► Pathogenesis

For practical purposes, causes of chronic esophageal chest pain can be divided into well-accepted and possible causes.

A. Well-Accepted Causes of Esophageal Chest Pain

Well-established causes of chest pain are reflux esophagitis and motility disorders such as achalasia and diffuse esophageal spasm. Overall, reflux esophagitis is the most common cause of noncardiac chest pain.

B. Probable Causes of Esophageal Chest Pain

Esophageal disorders that have been proposed as causes of chest pain are hypertensive esophageal motility disorders, sustained longitudinal muscle contraction, esophageal hypersensitivity, and esophageal sensory neuropathy.

1. Hypertensive esophageal motility disorders—Some esophageal motility disorders, particularly those associated with hypertensive esophageal peristaltic contractions (so-called nutcracker esophagus), hypertensive LES, and hypercontracting LES, have been identified during manometric evaluation of patients with unexplained chest pain. Therefore, these manometric diagnoses were proposed as causing chest pain. However, a causal relationship has not been established. Moreover, a temporal association between these conditions and chest pain has not been documented, and treatment of the hypercontractile states with smooth muscle relaxants has not proved to be effective in the relief of chest pain.

2. Sustained longitudinal muscle contraction—Dynamic high-resolution endoscopic ultrasound has shown that episodes of chest pain are associated with sustained contraction of the esophageal longitudinal muscle. The longitudinal muscle contraction remains undetected by intraluminal manometry. Therefore, sustained esophageal longitudinal muscle contraction has been proposed as a cause of chest pain in patients with normal esophageal manometry. Further studies are needed to fully establish this sustained contraction as the cause of unexplained chest pain.

3. Defects in sensory nerves and pain perception—Several recent studies have suggested that the esophagus may develop sensory hypersensitivity, in which stimuli that do not normally produce pain are perceived as painful. Esophageal hypersensitivity may be a part of generalized visceral hypersensitivity. The pathophysiology of visceral hypersensitivity is not fully understood but may occur peripherally in the esophageal afferent nerves or centrally in the central nervous system. Esophageal hypersensitivity is demonstrated by showing a reduced threshold to esophageal balloon distention. Esophageal mucosal hypersensitivity can also be tested by the esophageal acid perfusion test (Bernstein test), discussed later.

► Clinical Findings

Chest pain is a common and alarming symptom. Acute chest pain syndromes are due to life-threatening conditions such as myocardial infarction, aortic dissection, pulmonary embolism, esophageal perforation, acute bolus obstruction, or penetrating esophageal ulcer. Patients with these conditions require emergent care.

Patients presenting with chronic chest pain should undergo careful clinical evaluation to classify them into the following broad groups: cardiac chest pain, musculoskeletal chest pain, psychosomatic chest pain, esophageal chest pain, and miscellaneous causes of chest pain. In the majority of patients, the origin of chest pain is easily identified and treated. However, in some patients, the origin of chest pain remains obscure.

Lee R, Mittal R. Heartburn and esophageal pain. *GI Motility Online*. Available at: <http://www.nature.com/gimo/index.html>; doi: 10.1038/gimo75, 2006.

Miwa H, Kondo T, Oshima T, Fukui H, Tomita T, Watari J. Esophageal sensation and esophageal hypersensitivity: overview from bench to bedside. *J Neurogastroenterol Motil*. 2010;16:353–362.

Prakash Gyawali C. Esophageal hypersensitivity. *Gastroenterol Hepatol*. 2010;6:497–500.

Remes-Troche JM. The hypersensitive esophagus: pathophysiology, evaluation, and treatment options. *Curr Gastroenterol Rep*. 2010;12:417–426.

► Differential Diagnosis & Treatment

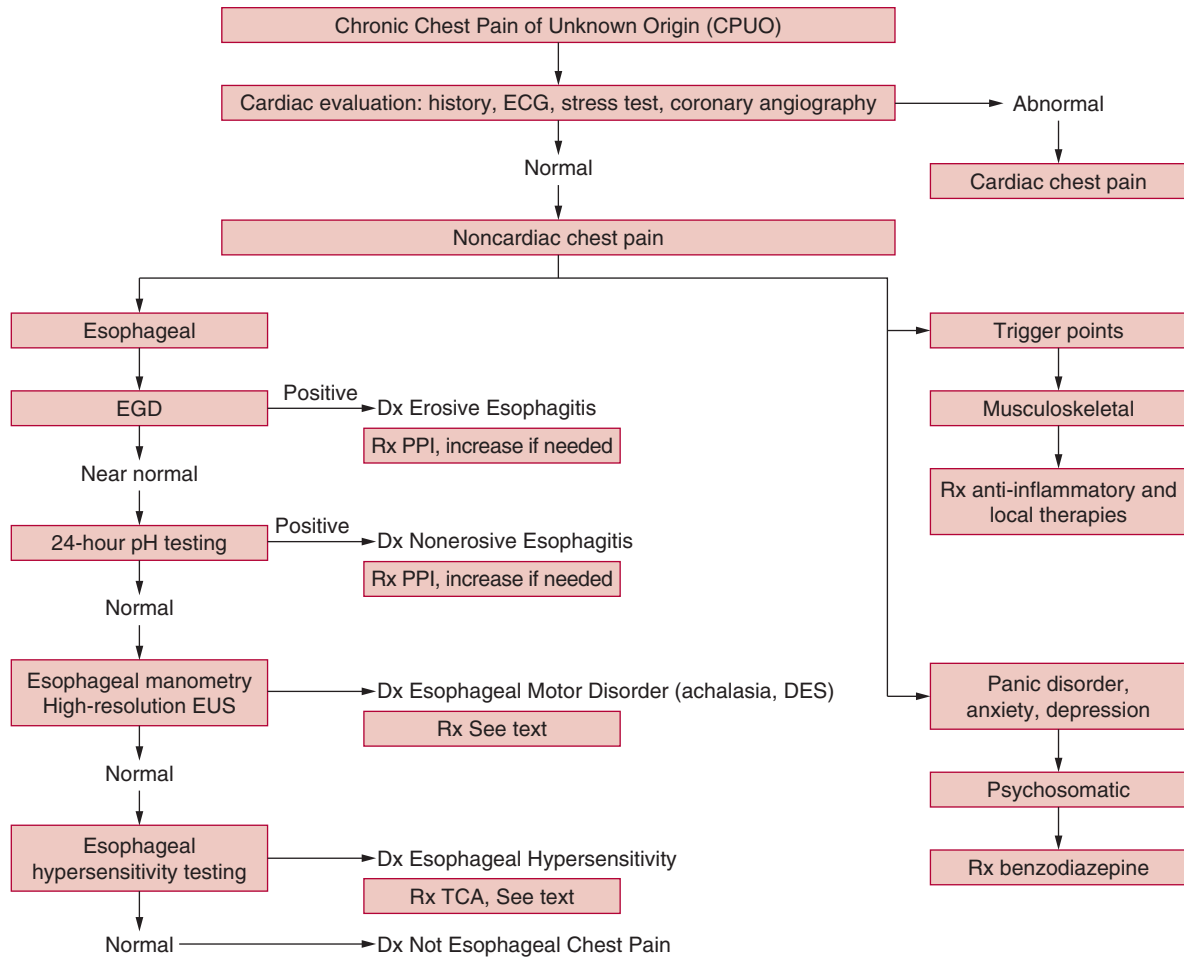
An algorithm outlining an approach to the patient with chest pain of unknown origin (CPUO) is presented in [Figure 13–6](#). A working definition of CPUO has not been developed. However, it is clear that this diagnosis should be used only after careful initial evaluation. For example, cardiac evaluation and treatment should be performed for patients with ischemic heart disease and typical symptoms of cardiac ischemia; a trial of a proton pump inhibitor should be initiated for patients suspected of having heartburn and GERD; a trial of nonsteroidal anti-inflammatory drugs (NSAIDs) and possibly skeletal muscle relaxants should be used for those with musculoskeletal disorders; and a therapeutic trial should be started for those with panic disorder.

A. Chest Pain of Unknown Origin

Patients in whom the initial evaluation does not yield a cause are identified as having CPUO. The first step in the evaluation of a patient with CPUO is to carefully exclude coronary artery disease because of the life-threatening nature of cardiac chest pain. This may require coronary angiography, which remains the gold standard, apart from careful consideration of cardiac causes of chest pain. The speculative cardiac causes of chest pain include microvascular angina or syndrome X. This diagnosis is sometimes considered in patients with atypical anginal symptoms and normal coronary arteries, especially when abnormalities are present on noninvasive tests of cardiac function such as exercise radionuclide angiography or exercise thallium scintigraphy. Similarly, mitral valve prolapse is frequently present in patients with chest pain of undetermined etiology; however, most investigators agree that it does not cause chest pain. CPUO patients in whom cardiac causes of chest pain have been excluded are identified as having non-cardiac chest pain. These patients require careful screening for esophageal, musculoskeletal, psychosomatic, and miscellaneous causes of chest pain.

B. Reflux Esophagitis

Reflux esophagitis is one of the most common causes of esophageal chest pain. Among patients with reflux, 10–20% will have chest pain alone, and reflux esophagitis remains the



▲ **Figure 13-6.** Algorithm outlining an approach to the patient with unexplained chest pain. CPUO, chest pain of unknown origin; DES, diffuse esophageal spasm; Dx, diagnosis; ECG, electrocardiogram; EGD, esophagogastroduodenoscopy; EUS, esophageal ultrasound; Rx, prescription; PPI, proton pump inhibitor; TCA, tricyclic antidepressant.

most common cause of unexplained chest pain. Therefore, the first step is to prescribe a therapeutic trial of a proton pump inhibitor if this therapy has not already been initiated. If there is no satisfactory response, the patient should undergo endoscopic examination. Esophageal erosions, ulcers, and peptic strictures provide evidence of GERD, which should be treated with a proton pump inhibitor, including high-dose therapy if needed. If no or minimal mucosal abnormalities are found, high-magnification endoscopy or narrow band image endoscopy may be performed to look for microerosions. Mucosal biopsies should be obtained in patients with negative endoscopic results. These patients should undergo pH monitoring by placement of a pH capsule in the distal esophagus. If capsule monitoring is not available, 24-hour ambulatory esophageal pH testing should be performed.

Mucosal biopsy specimens may show enlarged intercellular spaces, which are thought to represent very early mucosal damage in reflux esophagitis. Patients having abnormal mucosal biopsy and esophageal pH findings are diagnosed as having nonerosive reflux disease and treated aggressively with proton pump inhibitor therapy. Newer pH catheters with impedance have allowed assessment of volume reflux and distinction of these episodes as acidic or nonacidic.

Cho YK. How to interpret esophageal impedance pH monitoring. *J Neurogastroenterol Motil.* 2010;16:327–330. [PMID: 20680174]

Fass R, Dickman R. Nonerosive reflux disease. *GI Motility Online.* Available at: <http://www.nature.com/gimo/index.html>; doi: 10.1038/gimo42, 2006.

C. Esophageal Motility Problems & Esophageal Hypersensitivity

In patients showing no evidence of esophagitis, intraluminal manometry should be performed to evaluate for the presence of motility disorders such as early achalasia, diffuse esophageal spasm, and hypertensive esophageal motility. These disorders comprise only a small number of cases of unexplained chest pain. Patients who have normal esophageal motility should be evaluated for esophageal hypersensitivity by determining the threshold to esophageal distention by intraesophageal balloon inflation. Mucosal sensitivity may be determined by the acid perfusion test (also called the Bernstein test), in which 0.1% hydrochloric acid is perfused by catheter into the distal esophagus.

The antidepressant trazodone (100–150 mg/day), which has no direct effect on esophageal motility, has been effective in decreasing the distress of esophageal symptoms in patients with motility disorders. This suggests that underlying psychiatric problems may play a role in patients with esophageal motility abnormalities. Use of trazodone in men is limited by the side effect of priapism. Surgical myotomy has no role in the management of patients with chest pain and motility disorders other than achalasia.

D. Musculoskeletal Chest Pain

The diagnosis of musculoskeletal chest pain may be overlooked in the initial evaluation of the patient with CPUO. Careful history and physical examination is required. Several musculoskeletal disorders may cause chest pain. Localized myofascial pain, ankylosing spondylitis, fibromyalgia, Tietze syndrome, rheumatoid arthritis, thoracic outlet syndrome, and “slipping rib” syndrome should be considered in the differential diagnosis. The diagnosis of fibromyalgia is based on at least a 3-month history of widespread pain, with more than 10–18 trigger points of tenderness on digital palpation. Patients with musculoskeletal chest pain are treated with reassurance, application of local heat, NSAIDs, and corticosteroid-lidocaine injection when appropriate. Patients with fibromyalgia may benefit from cyclobenzaprine (2.5–10 mg four times daily) or amitriptyline (10–50 mg at bedtime).

E. Psychiatric Disorders

Psychiatric disorders, including depression, anxiety, and panic disorder, may not be recognized initially as a cause of chest pain, in part because these disorders are very common in clinical practice, affecting approximately 5% of the U.S. population. Patients with symptoms of panic and anxiety should be referred to a psychiatric specialist for diagnostic evaluation and treatment. Treatment of these disorders includes antidepressants, anxiolytics, and cognitive-behavioral therapy. Many patients with these disorders require education about their disease, and gentle persuasion and reassurance that effective treatment exists, before they will accept these recommendations.

F. More Than One Cause of Chest Pain

It is important to recognize the various disorders that cause chest pain as they are very common and more than one cause may be present concurrently. For example, the incidence of GERD is markedly increased in patients with ischemic heart disease because of the overlapping risk factors for the two diseases and also because smooth muscle relaxants that are used in the treatment of coronary angina or hypertension may aggravate GERD. Similarly, patients with unexplained chest pain may be diagnosed with esophageal motility disorder, panic disorder, and microvascular angina. Moreover, many of these patients complain of characteristic chest pain during catheterization with right ventricular stimulation, suggesting a heightened visceral nociception.

► Course & Prognosis

Patients with CPUO have a normal survival rate. However, their quality of life and functional status are markedly impaired. Most patients continue to experience chest pain and functional impairment even after a diagnosis of CPUO has been made, resulting in high utilization of health care resources and associated medical costs.

Fang J, Bjorkman D. A critical approach to noncardiac chest pain: pathophysiology, diagnosis, and treatment. *Am J Gastroenterol.* 2001;96:958–968.

DISORDERS OF INHIBITORY INNERVATION

1. Achalasia



ESSENTIALS OF DIAGNOSIS

- Slowly progressive esophageal dysphagia to both solids and liquids.
- Absence of acid reflux.
- Regurgitation of undigested food without acid or bile; episodes of pneumonia.
- Chest radiograph may show a mediastinal mass with air-fluid levels.
- Barium esophagogram shows a dilated esophagus without peristalsis and a “bird beak” in the distal esophagus.
- Esophageal manometry shows nonperistalsis esophageal contractions and failure of LES relaxation on swallowing.

► General Considerations

Achalasia is a disorder of the thoracic esophagus characterized by nonperistaltic esophageal contractions and impaired relaxation of the LES in response to swallowing. It results primarily from degeneration of nitroergic inhibitory neurons in the myenteric plexus. Achalasia is an important but uncommon clinical disorder with an incidence of 1 in 100,000 persons. It most often manifests between the ages of 25 and 50 years but affects patients of all ages and both sexes. Diagnosis is generally established on the basis of radiologic findings and manometric studies, and by ruling out secondary causes such as cancer. Definitive therapy is surgical myotomy, but various medical and endoscopic treatments have been employed for symptomatic relief.

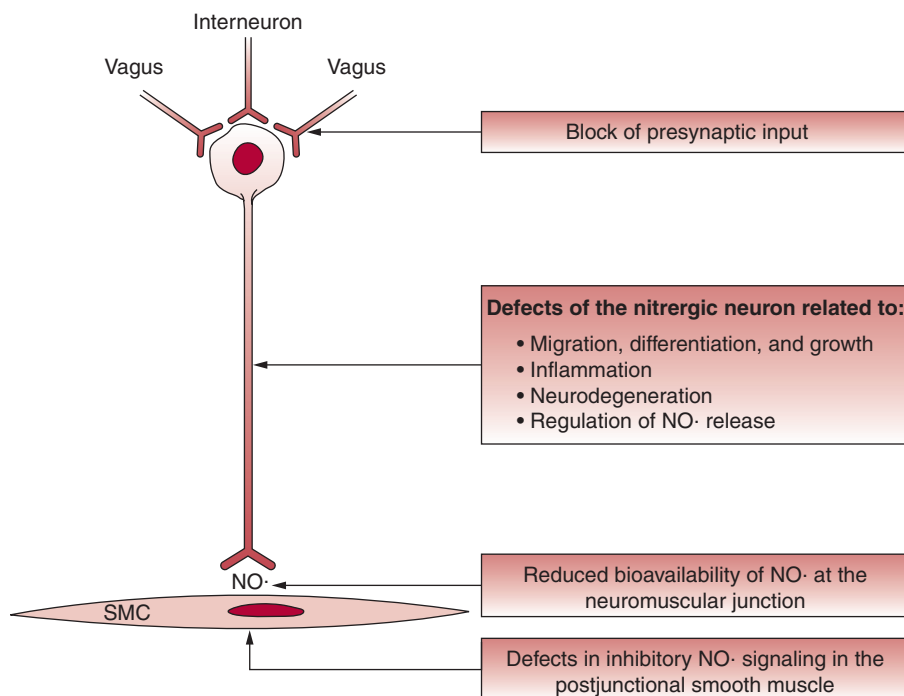
► Pathogenesis

Achalasia is associated with degeneration of postganglionic inhibitory neurons, which release nitric oxide and VIP (Figure 13-7). Postganglionic excitatory neurons may also be affected in advanced disease. Preganglionic vagal fibers and vagal nuclei may also be involved.

Most cases in the United States are of no known cause and are classified as idiopathic achalasia. A viral etiology for the inflammation has also been proposed, and elevated antibody titers to measles and varicella zoster have been described in a high proportion of patients with idiopathic achalasia. Autoimmunity has been proposed as contributing to the etiology based on observation of T-lymphocyte infiltration in the myenteric plexus, and there is a higher prevalence of the disorder in patients with certain human leukocyte antigen (HLA) types. Autoantibodies to neurons are also found in many patients with achalasia.

Familial achalasia comprises about 2–5% of all cases and generally involves an autosomal-recessive mode of inheritance, particularly in children younger than 4 years of age. In children, this may be part of the AAA syndrome (achalasia, alacrima, achlorhydria), which may also be associated with adrenocorticotropic hormone insensitivity, microcephaly, and nerve deafness. Additionally, a small percentage of patients have associated neurodegenerative diseases such as Parkinson disease and hereditary cerebellar ataxia.

Secondary achalasia refers to inhibitory neuronal degeneration caused by a known etiologic agent such as *Trypanosoma cruzi* (the causative organism in Chagas disease) and carcinoma.



▲ **Figure 13-7.** Schematic diagram of different parts of a nitroergic neuron that may be affected by various kinds of pathology, resulting in esophageal neuromuscular diseases. NO, nitric oxide.

Although the cause of primary achalasia is largely unknown, degenerative changes have been noted in the dorsal motor nucleus (Lewy bodies), along with degeneration of vagal fibers and loss of ganglion cells in the esophageal body and LES. In particular, there may be an inflammatory response, predominantly of T-cell lymphocytes. However, these changes are not consistent and may be secondary to an enteric nervous system disease involving loss of nitrergic and VIP-containing neurons (the main relaxatory mediators of the esophageal smooth muscle) and a decrease in the number of interstitial cells of Cajal. Muscular hypertrophy, possibly secondary to the denervation, and variable extent of muscle degeneration has also been described. However, these muscular and neuronal changes cannot be assessed by evaluation of mucosal biopsies obtained during endoscopy. Newer approaches are being assessed for obtaining full-thickness biopsies to facilitate evaluation of neuromuscular pathology.

Fraser H, Neshev E, Storr M, et al. A novel method of full-thickness gastric biopsy via a percutaneous, endoscopically assisted, transenteric approach. *Gastrointest Endosc.* 2010;71:831–834.
 Goyal RK, Chaudhury A. Pathogenesis of achalasia: lessons from mutant mice. *Gastroenterology.* 2010;139:1086–1090.
 Hirano I. Pathophysiology of achalasia and diffuse esophageal spasm. *GI Motility Online.* Available at: <http://www.nature.com/gimo/index.html>; doi: 10.1038/gimo22, 2006.
 Pasricha PJ, Pehlivanov ND, Gomez G, et al. Changes in the gastric enteric nervous system and muscle: a case report on two patients with diabetic gastroparesis. *BMC Gastroenterol.* 2008;8:21.

► Clinical Features

A. Symptoms and Signs

Dysphagia is the most common presenting symptom of achalasia and is present in nearly all patients. Dysphagia to both liquids and solids is characteristic of this disease; however, symptoms may initially involve primarily solids, followed by liquids. Dysphagia is mainly localized to the lower chest, although it may be localized to the neck. Generally, it is worsened by emotional stress or hurried eating. Patients often complain of taking longer to eat a meal or of drinking a large amount of liquid to clear the food from the esophagus. They may even describe having to stand up, perform the Valsalva maneuver, or arch their backs to help clear food from the esophagus.

The second most frequent presenting symptom is regurgitation of food, which is generally undigested, nonbilious, and nonacidic. Patients may wake in the middle of the night as a result of coughing or choking after regurgitation, the content of which is often described as white and foamy, arising from an inability to clear saliva from the esophagus. Chest pain and heartburn occur in approximately 40% of patients and can be misdiagnosed as GERD. However, the heartburn is generally not postprandial or responsive to antacids.

Mild weight loss is noted in approximately 85% of patients and may even mimic cancer when profound. However, the interval from the presenting symptom to the point at which the patient seeks medical attention is quite variable, sometimes extending beyond a decade.

B. Laboratory Findings

Some patients with idiopathic achalasia have increased antineuronal antibodies, including anti-Hu-1 antineuronal antibodies. Enzyme-linked immunosorbent assay (ELISA) tests, agglutination tests, and confirmatory assays, including immunofluorescence, immunoblot, Western blot, and radioimmunoprecipitation tests, may aid in identifying *T. cruzi* in patients with achalasia caused by Chagas disease.

C. Imaging Studies

Barium esophagogram, the preferred initial method of evaluation in patients with dysphagia, may reveal characteristically smooth, symmetric narrowing or “bird-beaking” of the distal esophagus, and often a dilated esophagus with no peristaltic activity and poor esophageal emptying. In severe achalasia, chest radiographs may reveal a dilated esophagus containing food, possibly air-fluid level within the esophagus in the upright position, absence of gastric air bubble, and sometimes a tubular mediastinal mass beside the aorta. Administration of a smooth muscle relaxant such as sublingual nitroglycerin or inhaled amyl nitrate may cause relaxation of the LES and distinguish achalasia from pseudo-achalasia arising from mechanical causes. Severe cases may reveal a markedly dilated and tortuous esophagus, called a sigmoid esophagus (see Figure 13–4).

D. Endoscopy

Esophagogastroduodenoscopy is not sensitive in the diagnosis of esophageal motility disorders. However, it is very useful in excluding mechanical disorders, particularly those that may be the cause of the motility disorder (eg, infiltration by gastroesophageal junction cancer, causing secondary achalasia).

E. Manometry

The diagnosis is confirmed by esophageal manometry, which typically reveals complete absence of peristalsis, incomplete LES relaxation (<50% of baseline pressure), and often but not necessarily increased lower esophageal basal tone (>30 mm Hg). Weak contractions may be noted in the esophageal body, which are simultaneous or appear simultaneous but identical if the esophageal body becomes a single lumen (common cavity effect) (see Figure 13–5). Esophageal pressures may also exceed gastric pressures when the esophagus is filled with food or fluid.

► Differential Diagnosis

The differential diagnosis of achalasia begins with the broad differential diagnosis of dysphagia and exclusion of mechanical causes of dysphagia. Strictures, benign neoplasms, vascular rings, webs, foreign bodies, and severe esophagitis (peptic, infectious, chemical, drug induced) are among the frequently encountered entities.

Achalasia must be distinguished from other motility disorders such as diffuse esophageal spasm and scleroderma that has been complicated by a peptic stricture. The next step is to determine whether it is due to an identifiable cause. These cases, termed secondary achalasia, may be due to infection with *T. cruzi* (Chagas disease) or neural degeneration as a paraneoplastic syndrome associated with many malignancies. Gastroesophageal junction carcinoma may produce myenteric plexus degeneration by local tumor invasion, resulting in achalasia. The term *pseudoachalasia* is used when there is no functional cause of achalasia but the gastroesophageal junction is narrowed due to outside compression or fibrosis and the esophageal body is dilated due to obstruction. Patients with secondary achalasia due to tumor at the gastroesophageal junction present with more recent and progressive onset of dysphagia or with progressive weight loss. Careful retroflexed inspection of the cardia and gastroesophageal junction by upper endoscopy is necessary.

► Treatment

Current options for treatment of achalasia are directed at removing the functional obstruction caused by the non-relaxing LES. However, these therapeutic modalities do not restore peristalsis. Treatment includes pharmacologic therapy, pneumatic dilation of the LES, surgical myotomy, and botulinum toxin injection therapy.

A. Pharmacologic Therapy

Sublingual nitroglycerin, calcium channel blockers, phosphodiesterase inhibitors, and anticholinergics are used to relieve the symptoms in the subset of patients who have mild symptoms without esophageal dilation, or are unable to undergo dilations or surgery.

B. Pneumatic Dilation

The disruption of muscle requires far larger diameters compared with disruption of mucosal lesions such as strictures. A 3-cm diameter balloon is used initially. Based on patient's response, successive dilations of up to 4 cm can be applied. At each session, a balloon is placed under fluoroscopic guidance to stretch the area of the gastroesophageal junction. In less than 4% of dilations, perforations occur that may require surgical repair. In experienced hands, the efficacy of pneumatic dilation and laparoscopic surgery are nearly equal, and dilation appears to be the more cost-effective initial approach.

C. Surgical Myotomy

A modified Heller cardiomyotomy of the LES and cardia results in good to excellent symptomatic relief in over 85% of patients. GERD is expected to ensue in up to 20% of patients. Myotomy can also be performed using a laparoscopic approach; this is less invasive, reduces postoperative complications, and allows a shorter hospital stay. The success of surgery does not appear to be compromised by prior botulinum or pneumatic dilation treatments.

D. Botulinum Toxin Injection

Botulinum toxin A is injected directly into the LES using an endoscope. Approximately 20–25 units of the toxin are used per injection into four quadrants in the LES. This results in reduction of lower esophageal pressures in 85% of patients. However, approximately 50% of patients relapse with symptoms over the next 6–9 months. Approximately 25% have a sustained response lasting more than 1 year. Approximately 75% of initial responders who relapse have improvement with repeat injection therapy. Because of the lower efficacy and sustained response compared with surgical myotomy, this method is often reserved for elderly patients or those with multiple medical problems.

► Course & Prognosis

Untreated, achalasia can lead to severe weight loss mimicking cancer, and respiratory complications such as stridor. Patients may develop distal esophageal diverticulum and bezoars. After surgery, patients may develop GERD, strictures, and Barrett esophagus.

Pehlivanov N, Pasricha PJ. Medical and endoscopic treatment of achalasia. *GI Motility Online*. Available at: <http://www.nature.com/gimo/index.html>; doi: 10.1038/gimo52, 2006.

2. Diffuse Esophageal Spasm



ESSENTIALS OF DIAGNOSIS

- Nonperistaltic simultaneous contractions of the esophagus.
- Dysphagia to solids and liquids and chest pain are common presenting symptoms.
- Some patients may progress to achalasia.

► General Considerations

The reported incidence of diffuse esophageal spasm depends on the diagnostic criteria used. When large amplitude of contractions is considered in the diagnosis, only 3–5% of patients undergoing manometry for suspected esophageal

motility disorders fit the diagnostic criteria. Diffuse esophageal spasm is a disorder of the thoracic esophagus resulting from impairment of inhibitory innervation. It involves the esophagus but spares the LES, leading to nonperistaltic contractions but normal LES relaxation, as evidenced on manometry. The amplitude of the contractions may be normal, increased, or decreased. Acid suppression and other medical and endoscopic treatments may alleviate symptoms. A subset of patients may progress to achalasia.

► Pathogenesis

Nonperistaltic contractions are due to loss of deglutitive inhibition associated with impaired inhibitory nerve function in the esophageal body. The amplitude of contractions involves many components, including the rebound contraction, which is dependent on the inhibitory nerves, cholinergic excitatory nerves, and myogenic factors. Loss of inhibitory nerves alone would be expected to reduce the force of contraction, whereas compensatory cholinergic and myogenic factors may lead to increased force of contraction. However, little is known about the pathology of diffuse esophageal spasm. There appears to be patchy neural degeneration localized to nerve processes rather than degeneration of nerve cell bodies, as evidenced in achalasia. Hypertrophy of the muscularis propria and associated development of distal esophageal diverticula also occur.

► Clinical Features

A. Symptoms and Signs

Chest pain, dysphagia, and regurgitation are the main presenting symptoms. Chest pain may be particularly prominent in patients with high-amplitude and protracted contractions and can occur at rest, with swallowing, or with emotional stress. The pain is generally retrosternal but can radiate to the back, sides of the chest, arms, or the jaw. Pain can last from seconds to several minutes and can mimic that of cardiac angina. Dysphagia for solids and liquids can be present. Regurgitation of food that fails to move into the stomach may occur.

B. Imaging Studies

Findings on barium swallow may be normal or show nonpropagated contractions (called tertiary contractions), particularly below the aortic arch, with the appearance of curling or multiple ripples in the wall, sacculations, and pseudodiverticula, leading to the appearance of a “corkscrew” esophagus in severe cases.

C. Manometry

The diagnosis is generally made by esophageal manometry, which reveals more than 20% of wet swallows as simultaneous

contractions. However, because the disorder is episodic, manometric findings can be entirely normal at the time of study. Simultaneous contractions must be distinguished from identical contraction patterns suggestive of a common cavity effect from functional or mechanical obstruction in the esophagus during the study. Moreover, occasional nonperistaltic contractions can occur normally. The amplitude of the nonperistaltic contractions can be increased, normal, or even decreased, and sometimes the contractions are multiphased. However, LES relaxation is normal, and normally conducted peristaltic contraction must be evidenced in at least one swallow.

Methods to provoke esophageal spasm, including cold swallows and edrophonium, can induce chest pain but may not necessarily correlate with motility changes. Thus, provocation tests have limited utility.

► Differential Diagnosis

Diffuse esophageal spasm must be distinguished from other causes of chest pain, especially cardiac ischemia. Esophageal motility disorders are an uncommon cause of noncardiac chest pain, which is more commonly caused by reflux esophagitis or visceral hypersensitivity.

► Treatment

The mainstay of therapy is reassurance, control of esophageal acidification by proton pump inhibitors or histamine receptor antagonists, and use of smooth muscle relaxants such as nitrates and calcium channel blockers. There are no controlled studies to substantiate any particular treatment modality, although smooth muscle relaxants or anticholinergic agents used for achalasia may be helpful for improving symptoms. Some studies suggest that low-dose tricyclic antidepressant therapy may be a better option for treating chest pain. Empiric bougienage has been advocated, but studies comparing large- versus small-caliber bougies showed no differences in response rate, suggestive of a placebo effect. Similarly, there have been no controlled studies to validate the use of botulinum toxin either into the LES or at intervals along the esophageal body. Long esophageal myotomy is rarely used to treat intractable dysphagia and chest pain, particularly when associated with pulsion diverticula.

► Course & Prognosis

Patients may have intermittent dysphagia and chest pain for many years without progression. A small subset of these patients (~5%) develops vigorous or classic achalasia, which should be suspected if patients develop regurgitation with worsening dysphagia.

3. Inappropriate Transient Lower Esophageal Sphincter Relaxation (TLESR)

Transient LES relaxation normally occurs on swallowing, belching, or vomiting reflexes. When it occurs in the absence of such activities, it has been called inappropriate transient LES relaxation or simply transient LES relaxation (TLESR). TLESR is a vagovagal inhibitory reflex that is mediated via the nitroergic inhibitory nerves to the LES. The frequency of TLESR is increased by gastric distention. Increased frequency of TLESR has been shown to be an important cause of GERD. Diagnosis of TLESR can only be made by long-term manometric recordings, which are employed mainly in research but not in common clinical practice.

Basal LES pressure is dependent on the myogenic tone of the sphincter muscle, and superimposed, counterbalancing influence of inhibitory and excitatory nerves. The force of peristaltic contraction is dependent on the contractile ability of the smooth muscle and influence of the excitatory as well as the inhibitory nerves. The inhibitory nerves are responsible not only for inhibition but also for the rebound contraction that follows the inhibition. Therefore, loss of rebound contraction can only occur if the preceding deglutitive inhibition is also lost. Disorders of TLESR that involve normal deglutitive inhibition and peristaltic sequence can be classified into hypotensive and hypertensive esophageal motility disorders and are described in the following sections.

DISORDERS OF EXCITATORY NERVES AND SMOOTH MUSCLES

1. Hypotensive Esophageal Disorders



ESSENTIALS OF DIAGNOSIS

- ▶ GERD and dysphagia.
- ▶ Hypotensive LES (LES pressure <10 mm Hg).
- ▶ Hypotensive peristaltic contractions (<30 mm Hg).

▶ General Considerations

Hypotensive esophageal disorders include hypotensive LES, hypotensive peristaltic contraction, or both. Hypotensive LES may lead to GERD, and hypotensive peristaltic contractions may lead to dysphagia, impaired esophageal clearing of refluxed material, and accentuation of GERD.

▶ Pathogenesis

Hypotensive esophageal disorders are due to either impaired excitatory innervation or impaired muscle contractility. Most cases are idiopathic, but a few are secondary to known causes.

Secondary causes include anticholinergic agents, smooth muscle relaxants, estrogens, progesterone, and pregnancy. Other important causes are connective tissue disorders, particularly scleroderma and intestinal pseudo-obstruction syndrome. The latter may be caused by muscular atrophy, disease or impairment of the cholinergic neurons, or both. Most cases of hypotensive LES are idiopathic in nature.

▶ Clinical Findings

By esophageal manometry, abnormally hypotensive peristaltic contractions are generally evidenced in the distal esophagus (consisting of smooth muscle). Low-amplitude contractions can be normal in the transition zone between striated and smooth muscle. However, high-resolution manometry and impedance have revealed a small minority of patients with dysphagia (<4% in one series) who have a larger gap of poor contractility (<20 mm Hg) and slower transit (>1 second) over this transition zone that correlated with poor bolus transit and dysphagia.

Refer to GERD and scleroderma esophagus elsewhere in this chapter.

▶ Treatment

Refer to GERD and scleroderma esophagus elsewhere in this chapter.

2. Hypertensive Esophageal Disorders



ESSENTIALS OF DIAGNOSIS

- ▶ Hypertensive LES, hypercontracting LES, and hypertensive peristalsis identified on intraluminal manometry.
- ▶ Sustained longitudinal muscle contraction diagnosed by high-frequency endoscopic ultrasound.
- ▶ Usually noted in patients being evaluated for non-cardiac chest pain or dysphagia.

▶ General Considerations

Hypercontractile syndromes include entities such as hypertensive LES, hypercontracting LES, hypertensive peristalsis (nutcracker esophagus), and sustained contraction of the esophageal longitudinal muscle.

▶ Pathogenesis

These hypercontractile states may result from overactive excitatory nerves or stress. The cause is unknown, but patients may have esophageal hypersensitivity.

► Clinical Findings

A. Symptoms and Signs

When hypertensive peristalsis or nutcracker esophagus was initially described, it was a common manometric abnormality found in patients with noncardiac chest pain. However, it is now appreciated that these episodes of high-amplitude contraction coincide poorly with chest pain and may be an epiphenomenon or perhaps a marker for hypersensitivity or a hyperreactive esophagus. Dysphagia has been reported by some patients with manometric findings of hypercontractile esophagus.

There are no physical findings specific for hypercontractile esophagus.

B. Laboratory, Imaging, and Manometric Studies

Hypertensive peristalsis is the most common manometric finding in patients referred for evaluation of noncardiac angina-like chest pain. Generally, barium studies show normal peristalsis, normal esophageal transit, and no structural esophageal disease. Esophagoscopy is also normal.

Prolonged ambulatory manometric studies reveal that some patients with hypertensive peristalsis have nonperistaltic contractions during mealtime, but not during standard wet swallows of a standard manometric study.

A subset of these patients may have inappropriate contractions of the esophageal longitudinal muscles that are poorly transduced on standard manometric evaluations but may be revealed on esophageal ultrasonography.

Specimens are rarely available for pathologic examination of these hypercontractile states, although a single report has described loss of intramural neurons in the LES of patients with isolated hypertensive LES.

As the names imply, hypertensive peristalsis, hypertensive LES, and hypercontracting LES are diagnosed manometrically. In hypertensive peristalsis, the amplitude of the peristaltic contractions exceeds 180 mm Hg or the duration of contraction exceeds 7.5 seconds. In hypertensive LES, the basal pressure of the LES exceeds 40 mm Hg. Similarly, hypercontracting LES shows prolonged and high-amplitude postrelaxation (rebound) contraction.

► Differential Diagnosis

As with achalasia, ischemic heart disease must be excluded in patients presenting with chest pain. GERD is the most common cause of atypical noncardiac chest pain and should be excluded, either with an empiric trial of proton pump inhibitor therapy or through ambulatory pH testing. Other causes of chest pain include chest wall origin, pericarditis, atelectasis, and panic attacks.

► Treatment

Anticholinergic drugs and smooth muscle relaxants (nitrates and calcium channel blockers) are often used but have

unproven value. Low-dose tricyclic antidepressants may improve chest pain in some patients, perhaps because of their modulation of visceral hypersensitivity. Cognitive-behavioral therapy has also been employed with benefit to some patients.

3. Scleroderma Esophagus



ESSENTIALS OF DIAGNOSIS

- Absent LES tone and esophageal peristalsis.
- Symptoms of GERD or dysphagia, or both.
- Respiratory compromise from aspiration or direct lung involvement.

► General Considerations

Esophageal scleroderma occurs as part of a connective tissue disorder and leads to atrophy of esophageal smooth muscle with consequent loss of LES tone and force of esophageal peristalsis. The condition occurs in 75–85% of patients with scleroderma and affects particularly woman in the 30- to 50-year age group. Patients with Raynaud phenomenon frequently have esophageal motor abnormalities.

► Pathogenesis

The cause of scleroderma is unknown, but it is thought to involve an autoimmune response. Progressive atrophy and sclerosis of the esophageal smooth muscles lead to poor peristaltic contractions in the distal esophagus and to LES incompetence. Microvessel disease in scleroderma may lead to intramural neuronal dysfunction early in the disease. Subsequently, fibrosis and atrophy of esophageal smooth muscle develop, leading to a markedly hypotensive LES and loss of peristaltic contractions in the smooth muscle segment of the esophagus.

► Clinical Findings

Diagnosis is confirmed by the presence of Raynaud phenomenon and cutaneous manifestations of scleroderma along with symptoms of dysphagia and GERD. Physiologic changes in the esophagus contribute to poor esophageal clearance and marked gastroesophageal reflux. This can result in reflux esophagitis and strictures in advanced cases. Pulmonary interstitial fibrosis can result from either direct smooth muscle involvement of the disease or from aspiration of refluxate.

A. Symptoms and Signs

Owing to LES incompetence and lack of esophageal acid clearance from lack of esophageal peristalsis, patients often

have severe GERD, leading to heartburn, regurgitation, dysphagia, and chest pain. However, symptoms can be relatively mild despite severe mucosal disease. Dysphagia may occur even in the absence of obvious skin and joint involvement, although Raynaud phenomenon is usually present.

B. Laboratory Findings

Certain autoimmune markers such as the antiendonuclear antigens and anti-ScL-70 and anticentromere antibodies may be present.

C. Imaging Studies

In advanced disease, barium swallow reveals a dilated esophagus with poor esophageal clearance and weak contractions.

D. Manometry

Manometry shows a hypotensive LES and low-amplitude peristaltic contractions in the thoracic esophagus. Sometimes, swallow-induced contractions are nonperistaltic, suggesting additional impairment of the nitroergic inhibitory nerves.

► Differential Diagnosis

In the absence of other features of a connective tissue disorder, scleroderma can be confused with primary GERD.

Cutaneous manifestations of scleroderma may be absent in up to 5% of patients. History of Raynaud phenomenon may be very useful in the diagnosis. Pulmonary fibrosis may even be attributed to repeated aspiration from GERD. In patients presenting with dysphagia, eosinophilic esophagitis should be excluded by multiple (at least five) mucosal biopsies obtained at different levels of the esophagus. Scleroderma esophagus may sometimes be confused with achalasia, particularly in patients with a dilated esophagus on barium swallow and poor peristaltic contractions in the thoracic esophagus on barium swallow or esophageal manometry. However, patulous and hypotensive LES on endoscopic and manometric findings can distinguish the two. In scleroderma, LES is usually patulous unless complicating peptic stricture is present.

► Treatment

There is no specific treatment for esophageal scleroderma. Severe reflux, which is generally the source of the patient's predominant symptoms, is treated with proton pump inhibitors, often requiring double-dose, twice-daily administration. Esophageal bougienage may be required for strictures. Generally, antireflux surgery should be avoided because of the risk of severe postoperative dysphagia. Otherwise, a partial fundoplication, generally with a Collis procedure and esophageal lengthening, is performed.